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Immunogenicity of Hepatitis B Vaccine Simultaneously Administered With the Expanded Programme on Immunisation (EPI)

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To assess the immunogenicity of hepatitis B vaccine simultaneously administered with the Expanded Programme on Immunisation (EPI) vaccines, a total of 300 consecutive infants, ranging in age between 6 weeks and 6 months, were alternatively assigned to the revised EPI and to EPI plus plasma-derived hepatitis B vaccine (Hevac B Pasteur). Four dosages (2 mcg or 0.5 ml each) of hepatitis B vaccine were given intramuscularly. HBsAg, anti-HBc, and anti-HBs were determined at day 0 and at day 210 in both groups by radioimmunoassay methods. The anti-HBs titre levels and geometric mean titres (GMTs) were determined at day 180 and day 210. There were three new hepatitis B virus infections in the control group and none in the study group by day 210. The seroconversion rates in the study group were 66% at day 180 and 84% at day 210, the respective GMTs being 116 and 940. Although the duration of observation is short (7 months) and the difference in the rate of infection between the two groups is not statistically significant ($P > 0.05$), the immunogenicity of the vaccine appears to be good. The simultaneous administration of hepatitis B vaccine and the EPI vaccines is logistically ideal. However, we suggest a further study using a larger dose of the Hevac B Pasteur vaccine to find out if a higher seroconversion rate than the 84% observed in this study could be achieved.

KEY WORDS: Ethiopian infants, seroconversion rates

INTRODUCTION

Hepatitis B virus (HBV) infection, both sporadic and epidemic, and its sequelae, chronic hepatitis, cirrhosis of the liver, and hepatocellular carcinoma (PHC) are common in Ethiopia [Pavlica and Samuel, 1970; Lester and Tsega, 1976; Tsega, 1977a,b; Tsega et al., 1986]. Infection with HBV in this population starts early in life, gradually rises with age, and is transmitted horizontally [Tsega, et al., 1988, 1989]. Early immunisation with hepatitis B vaccine is therefore essential in this hyperendemic area.

The human plasma-derived hepatitis B vaccine Hevac B Pasteur, or Pasteur Vaccin, has been tried extensively and has proved safe and highly immunogenic in neonates, children, and adults [Skinhoy, 1979; Szmuness et al., 1980; Maupas et al., 1981]. However, its immunogenicity within the framework of the Expanded Programme on Immunisation (EPI) [WHO, 1986] has not been studied in this part of Africa. The purpose of this study was to assess the immunogenicity of a plasma-derived hepatitis B vaccine (Hevac B Pasteur) among Ethiopian infants to be vaccinated according to the national EPI.

SUBJECTS AND METHODS

Vaccinees

Healthy infants, 6 weeks to 6 months of age, brought by consenting mothers to the Birla Paediatric Clinic of Yekatit 12 Hospital, which is included in the national EPI programme for the people of Addis Ababa, were recruited for this study. The parents of the vaccinees were informed by experienced nurses about the advantages and possible side effects of the hepatitis B vaccine as well as what was expected from them during the conduct of the vaccination programme.

Study Design

A total of 300 consecutive infants were alternately assigned to the regular EPI only (group A or control group) and to the EPI plus hepatitis B vaccine (group B or study group). Of the 150 controls, 78 were males and 72 were females. Of the 150 study subjects (hepatitis B vaccine recipients), 77 were males and 73 were females

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$P > 0.05$). The vaccination schedule was as follows: On day 0 a minimum of 4 ml of blood was taken from the femoral vein of all infants in group A (n = 150) and group B (n = 150) for baseline determination of HBsAg, anti-HBs, and anti-HBc. Both groups received the first DPT (diphtheria toxin + pertussis vaccine + tetanus toxoid) and OPV (oral polio vaccine), as recommended by the World Health Organization [WHO, 1986], but only group B was given the first dose of hepatitis B vaccine, at a different site. On day 30 and day 60 the same vaccines were administered as on day 0. On day 180, the fourth or booster dose of hepatitis B vaccine was given to group B, and a minimum of 4 ml of blood was taken. At the same time, both groups (A and B) were given measles vaccine, at different sites in the case of group B. Thus a schedule of 0, 1, 2, and 6 months was employed. On day 210, about 4 ml of venous blood was drawn from both groups, and, though not a part of EPI, yellow fever vaccine was given to each vaccinee as a justification for this last clinic visit.

Vaccination

The vaccine is a highly purified and inactivated suspension of HBsAg, derived from human plasma and adsorbed onto aluminium hydroxide, was administered intramuscularly to 150 study subjects (group B) from a glass vial containing 2 mcg or 0.5 ml (Batch No. 92291, stored at 2–8°C) at 0, 30, 60, and 180 days. HBsAg, anti-HBc, and anti-HBs were determined from the sera obtained at 0 and 210 days in both the control and study groups. Anti-HBs antibody levels and anti-HBs geometric mean titres were also determined in both groups at 0, 180, and 210 days, except the control group at 180 days. Anti-HBs levels of 10 mIU/ml or higher, as measured by radioimmunoassay (RIA), are generally considered protective, and the duration of protection against HBV infection is directly correlated with the height of anti-HBs titres achieved by immunisation [Barin et al., 1982]. Initially seronegative subjects who developed detectable anti-HBs antibody levels (>1 mIU/ml) after receiving one to four doses of the hepatitis B vaccine are regarded as seroconverters.

Laboratory Methods

Conventional radioimmunoassay tests, using AUSRIA, CORAB, AUSAB, and the AUSAB quantitation panel (Abbott Laboratories, North Chicago, Il), were employed to determine HBsAg, anti-HBc, and anti-HBs. They were performed in the Department of Medical Microbiology, Section of Clinical Virology, University of Lund, Malmo, Sweden. The results of the anti-HBs titres were expressed in International Units (mIU/ml).

Statistical Methods

The chi-squared test, without Yate's correction, was used when applicable. The geometric mean and its 95% confidence interval were used to describe the average of individual titres.

RESULTS

At the end of the vaccination schedule, i.e., by day 210, there were 18 (12%) controls and 16 (11%) study subjects who had defaulted (no reason was available for their absence). Thus, the number of controls (66 males and 66 females) and study subjects (70 males and 78 females) who completed the vaccination schedule were comparable (chi-squared = 2.0359; $P > 0.05$). Both groups were also in the same age range (6 weeks to 6 months). Furthermore, at day 0 (screening), there was no significant difference in the HBsAg, anti-HBc, and anti-HBs positivities between the controls (3/150, 52/150, and 54/149, respectively) and study subjects (1/150, 56/150, and 49/150, respectively; $P > 0.05$). It is interesting to note that all four subjects (three in the control group and one in the study subject group) who were HBsAg positive initially became negative by day 210, suggestive of contamination but not perinatal transmission.

At day 210, there were 3/132 (2.3%) controls positive for HBsAg (all newly acquired infection), while none were positive in the study subjects. This difference, however, is not statistically significant (chi-squared = 3.0802; $P > 0.05$). Similarly, as shown in Table I, there was no significant difference in anti-HBc positivity (6/132 controls and 4/134 study subjects) between the two groups (chi-squared = 3.4628; $P > 0.05$) at day 210. In both groups the anti-HBc titre levels detected at day 0 (52/150 and 56/150) were significantly reduced by day 210 (6/132 and 4/134), indicating clearance of maternal antibodies. Similarly, all initially anti-HBs-positive controls finally lost their antibody. On the other hand, 93/140 (66%) and 112/134 (84%) of the study subjects acquired anti-HBs levels greater than 10 mIU/ml, with geometric mean titres of 116 and 940 at day 180 and day 210, respectively.

The distribution of the anti-HBs values at day 0, day 180, and day 210 is shown in Table II. Following the booster dose at day 180, there was a significant rise in the level of anti-HBs and a significant increase in the rate of seroconversion (from 66% to 84%) and geometric mean titres (from 116 to 940).

DISCUSSION

The immunogenicity or seroconversion rate of 84% following vaccination of neonates with this hepatitis B vaccine, using 2 mcg (0.5 ml) and the EPI 0, 1, 2, and 6 month schedule, is satisfactory but inferior to results of previous reports (over 95% seroconversion rate) [Maupas et al., 1981; Barin et al., 1982; Lee et al., 1983], the main difference being the use of higher doses, 5–10 mcg of the same vaccine, in the latter. It has been shown that anti-HBs of maternal origin does not interfere with active immunisation and that the simultaneous administration of hepatitis B vaccine and the EPI vaccines neither enhances nor interferes with the immunogenic effect of each vaccine [Maupas et al., Beasley, 1988]. Therefore, a trial with 5 mcg [illegible]

TABLE I. Hepatitis B Virus Markers, Seroconversion, and Geometric Mean Titres (GMTs) of Anti-HBs

Time and study groups	Hepatitis B markers			Serconversion rate (%)	GMT of anti-HBs
	HBsAg	Anti-HBc	Anti-HBs		
Day 0					
Controls	3/150	52/150	54/149[a]	—	—
Study subjects	1/150	56/150	49/150	—	—
Day 180					
Controls	ND[b]	ND	ND		
Study subjects	ND	ND	93/140	66.0	116
Day 210					
Controls	3/132	6/132	0/132	—	—
Study subjects	0/134	4/134	112/134	84.0	940

[a]One sample was not enough for anti-HBs testing.
[b]ND, Not determined.

TABLE II. Levels of Anti-HBs Titres in Control and Study Subjects*

Time and levels of anti-HBs titres	Controls	Study subjects
Day 0		
10–100	21/149 (14)	16/150 (11)
101–1,000	24/149 (16)	29/150 (19)
1001–10,000	9/149 (6)	4/150 (3)
Day 180		
10–100	ND	47/140 (34)
101–1,000	ND	40/140 (29)
1001–10,000	ND	6/140 (4)
Day 210		
10–100	0/132	14/134 (10)
101–1,000	0/132	39/134 (28)
1001–10,000	0/132	48/134 (34)
>10,000	0/132	11/134 (8)

*ND, not done. Values in parentheses are percentages.

titis B vaccine may yield a better result than that observed in this study.

The occurrence of three HBsAg-positive samples in the control group and none in the hepatitis B vaccine recipients, though the observation period of 7 months is too short and the difference is not statistically significant, is in agreement with the efficacy (vaccine efficacy = attack rate unimmunised − attack rate immunised/attack rate unimmunised ×100 = 3 − 0/3 × 100 = 100%) of the hepatitis B vaccine reported by others [Barin et al., 1982]. In addition, the early occurrence of HBV infection among the control neonates is in support of early immunisation in this endemic area [Tsega et al., 1986, 1988].

As HBV infection occurs early in life, mostly by horizontal but not perinatal transmission in this country and in other parts of Africa [Botha et al., 1984, Tsega et al., 1986, 1988; Prince et al., 1985; Tabor et al., 1985], it is logical to administer hepatitis B vaccine at birth. However, deliveries in Africa often take place at home. Most countries carry out a nationwide EPI which is now revised by the World Health Organization to reduce the age of vaccination [WHO, 1986]. Furthermore, there is no known interference between hepatitis B vaccine and the EPI vaccines [Maupas et al., 1981; Beasley, 1988]. A minimum of three doses of hepatitis B vaccine is required to achieve a desirable level of anti-HBs. Therefore, simultaneous administration of hepatitis B vaccine with the EPI vaccines is most practical. Incorporating hepatitis B vaccine with EPI vaccines, if feasible, might be an even better approach.

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The clinical and hormonal (C-peptide and glucagon) profile and liability to ketoacidosis during nutritional rehabilitation in Ethiopian patients with malnutrition-related diabetes mellitus

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Summary. Cases of malnutrition-related diabetes mellitus conforming to the description of the protein deficient pancreatic diabetes type in Ethiopian patients were compared with Type 1 (insulin-dependent) and Type 2 (non-insulin-dependent) diabetic. Fourteen of 39 malnutriton-related diabetes mellitus patients had fat malabsorption compared with only two of ten Type 1 diabetic patients and one of nine control subjects. Xylose absorption was normal favouring a pancreatic cause for the malabsorption. Plasma C-peptide during oral glucose tolerance test was significantly lower than that in Type 2 diabetic patients and normal control subjects ($p < 0.01$ to 0.001) and was also consistently but not significantly higher than in Type 1 diabetic patients. Glucagon secretion patterns were similar in malnutriton-related and Type 1 diabetic patients. Of 23 new malnutrition-related diabetic patients treated with glibenclamide after nutritional rehabilitation and insulin treatment, only three responded, 14 were unresponsive but remained ketosis free for over eight days while another six developed ketoacidosis or significant ketonuria within two to six days during the trial. Sixteen unselected Type 1 diabetic patients who discontinued their insulin therapy all developed frank ketoacidosis after a mean of 5.5 days. The similarity of the malnutrition-related and Type 1 diabetes mellitus in age of onset, insulin requirement for diabetic control and appearance of ketosis-proneness in some cases, together with the similarity of C-peptide and glucagon secretion patterns suggest that the protein deficient pancreatic diabetes variant of malnutrition-related diabetes mellitus may be Type 1 diabetes mellitus modified by the background of malnutrition rather than an aetiologically separate entity. Community based studies are required to ascertain frequency and types of diabetes mellitus in malnourished populations and the role of genetics and environment in their aetiology.

Key words: Ethiopian malnutrition-related diabetes mellitus, nutritional rehabilitation, ketosis-resistance, fat malabsorption, C-peptide, glucagon.

A preliminary study of diabetes mellitus associated with malnutrition in Ethiopian patients [1] had shown that the majority were young adults from a poor socioeconomic background susbsisting on a diet inadequate in animal protein and vitamins (ascorbic acid in particular) and persistently or seasonally in food energy as well [2, 3]. Patients presented with classic symptoms of thirst, polyuria and wasting often of several months' or a few years' duration but had little or no ketoacidosis. Attempts to control their hyperglycaemia with oral agents, on admission to hospital or after initial treatment with insulin therapy, were unsuccessful in the majority of cases. However, these patients did not develop ketoacidosis after withdrawal of insulin therapy. They thus demonstrated the need for insulin and ketosis-resistance, well-known characteristics of malnutrition-related diabetes mellitus (MRDM). Of the two main variants of MRDM, i. e. the fibrocalcific pancreatic diabetes (FCPD) and the protein deficient pancreatic diabetes (PDPD also known as the Jamaica or J-type) [4] the Ethiopian cases were closer to the latter type. However, in contrast to the Jamaican and Indian patients who required 80 IU or more of insulin (at least initially) [5, 6] most of our patients responded to modest doses (50 IU or less) from the start of treatment.

The objectives of this study were to relate the clinical and hormonal (C-peptide and glucagon) responses to glu-

cose to the liability of Ethiopian MRDM patients to ketoacidosis during a period of nutritional rehabilitation. These patients would then be compared with Type 1 (insulin-dependent) and Type 2 (non-insulin-dependent) diabetic patients. An additional objective was to re-examine the possibility of treating malnutrition-related diabetic patients with oral agents after nutritional rehabilitation and some recovery of their endogenous insulin secretion.

Patients and methods

The study was conducted at the Ethiopian Nutrition Institute in Addis Ababa over a period of 22 months from June 1966. The purpose of the study was explained and agreement was obtained from each patient and normal control subject (and parents or guardians in the case of minors; minors were not included in the normal control group) participating in the study including their freedom to withdraw from the study at any stage without jeopardy to their care if they did so, in accordance with the Helsinki Declaration. Patients in each category of diabetes (see below) were included in the order in which they were seen (by J. A. and B. M.). Application of various tests, some of which were introduced during the study, was determined by their availability. All information was recorded on a protocol prepared for the purpose. In the case of the MRDM patients, the first objective of treatment was to improve their nutritional status over a period of six to eight weeks.

Classification of patients and management

MRDM. A poor socioeconomic background with any three of the following four additional characteristics: (1) Presentation with the classic symptoms of diabetes mellitus of at least three months' duration. (2) Undernourished or cachectic when first seen with a body mass index (BMI) of $< = 18$ kg/m^2. (3) Without significant ketonuria (less than + + with Ketostix). (4) Requiring insulin for diabetic control (i.e. failure to respond adequately to oral agents).

Type 1 diabetes. (1) A history of ketoacidosis on presentation. (2) Rapid development of ketoacidosis after insulin withdrawal or in the face of acute stress such as infection, trauma or surgery.

Type 2 diabetes. (1) No socioeconomic or clinical evidence of malnutrition. (2) A diagnosis of diabetes mellitus based on fasting hyperglycaemia of > 7.8 mmol/l whole blood on more than one occasion with symptoms of diabetes mellitus or whole blood glucose values of > 10 mmol/l at 2 h and at one other time during standard oral glucose tolerance test (OGTT) in asymptomatic cases. (3) Response to diet and oral agents.

Unclassified. Patients put in this category were those requiring insulin but without ketosis-proneness or malnutrition in their history or clinical findings and, provisionally, MRDM type patients with age of onset of diabetes above 40 years because they are not included in most MRDM studies.

Patients with hypertension or kidney disease, or those who were breast feeding were excluded.

Normal control subjects. The subjects chosen were adults, unrelated to the patients, with a BMI of 19–25 kg/m^2 with normal fasting blood glucose and with no family history of diabetes.

There were 55 MRDM patients, 19 with Type 1 diabetes, 18 with Type 2 diabetes and 16 normal control subjects in various components of the study.

Management during the study

All MRDM patients, and uncontrolled and new Type 1 patients were admitted to the metabolic ward of the Ethiopian Nutrition Institute for treatment. Their diet contained 113 to 120 g of protein allowing at least 1 g/kg body weight of animal protein, 96 to 116 g of fat and total energy 10,000–12,600 kJ (2,700–3,000 kcal) per day. Well-controlled Type 1 and all Type 2 diabetic patients came from their homes on the morning of the test.

Insulin treatment was initiated for MRDM patients on admission to the study. After improvement in their nutritional state (three to four weeks after admission) insulin was withdrawn for trial with glibenclamide (Daonil, Hoechst, Frankfurt, FRG). Insulin was restarted if ketoacidosis or persistent ketonuria (+ + or more on repeated testing with ketostix (Ames (Miles Ltd.), Slough, England)) occurred, or if there were recurrence and progression of the classic symptoms of diabetes despite glibenclamide treatment.

Biochemical procedures and methods

OGTT was performed within two to three weeks of admission according to the standard procedure (75 g glucose in 300 ml of water after withholding insulin from 18.00 hours the day before the test) after relief of the acute symptoms with insulin treatment. Venous blood was sampled every 30 min through an indwelling needle kept patent with heparinized 154 mmol/l NaCl. Aprotinin (Midran, Novo Industri S/C, Copenhagen, Denmark) was added to the samples for glucagon determination and all the specimens were stored at -20 °C pending hormone assay.

C-peptide and glucagon were measured by RIA in duplicate samples using reagents supplied by Novo Industri following their directions.

Stool was collected for fat determination (after appropriate treatment in those harbouring intestinal parasites), early in the study for 24 h and later for 72 h at the time of admission and repeated once or twice after nutritional improvement [7]. Normal control subjects (free of intestinal parasites) were put on the same diet as the patients for six days and stool was collected for fat determination from day 4 to day 6.

D-xylose absorption was determined using the same method [8] as in our previous study. Blood was sampled at 30 min and 60 min for serum xylose determination (normal values being > 150 mg/l at 30 min and > 250 mg/l at 60 min).

Statistical methods

The Student's *t* test was used for statistical analysis.

Results

Of a total of 63 patients, 56 males and seven females, included in the category of MRDM initially, two patients were later put in the unclassified category because their history indicated an adequate nutritional background and six others because of onset of symptoms after the age of 40 years. These patients were excluded from the hormonal studies. The age pattern is shown in Table 1.

Clinical and biochemical findings

As shown in Table 2, MRDM patients had many of the physical characteristics associated with malnutrition which were not seen in Type 1 patients although a BMI of

Table 1. Age at onset in malnutrition-related diabetes (MRDM), Type 1 (insulin-dependent) diabetes and Type 2 (non-insulin-dependent) diabetes

Age	MRDM		Type 1 diabetes		Type 2 diabetes	
	M	F	M	F	M	F
10–19	19	3	7	3	0	0
20–29	18	2	6	1	0	0
30–39	13	2	1	0	1	0
40–49	4	0	0	0	8	2
50 +	2	0	0	0	5	3
Total	56	7	14	4	14	5

Table 2. Clinical and biochemical findings in 55 (+ 6 patients aged 40 years and above) new malnutrition related diabetes mellitus patients

	Present
Parotid enlargement	35 + 2[a]
Scalp hair changes	11 + 2
Oedema with skin changes	9 + 1
Without skin changes	2 + 1
Scabies	7 + 2
Intestinal parasites	13 + 3
Amoebic liver abscess	1
Elevated transaminases (44)	17 + 1
Elevated alkaline phos (44)	7 + 2
Haemoglobin (49) < 120 g/l	11 + 2

( ) = total number tested when less than 55. Numbers after plus sign apply to the 6 patients aged 40 years and above.
[a] Unrecorded in 5 cases: all other cases normal or above the given value as applicable

Table 3. D-xylose absorption in relation to stool fat in malnutrition related diabetes (MRDM)[a], Type 1 (insulin-dependent) diabetes and normal control subjects

Stool fat	MRDM	Type 1	Normal control subjects
Normal	9 (16 + 3)	(9)	(9)
Abnormal[b]	6 (14)	(2)	(1)
Abnormal[c]	6 (9 + 3)	(0)	(0)
	21 (39 + 6)	(11)	(10)

[a] Including three patients of six over 40 years of age; [b] Without intestinal parasites; [c] With intestinal parasites. Numbers in parentheses indicate the total number of subjects in each group in relation to stool fat; numbers before the parentheses indicate the number who had the D-xylose test Numbers after the plus signs indicate patients aged 40 years and above

< 18 kg/m^2 was also found in some of these patients. Most of the MRDM patients described significant weight loss occurring after the onset of diabetic symptoms. The mean initial BMI of 24 new MRDM patients was 15.60 ± 1.45 kg/m^2. There were no MRDM patients with clinical evidence of liver disease at the time of admission to the study but 17 of 47 patients had mild elevation of transaminases, seven (aged 18 years and above) had isolated elevation of alkaline phosphatase and two patients showed elevation of both. Of 10 Type 1 patients tested none showed these abnormalities. Haemoglobin was 120 g/l or less in 12 of 49 MRDM patients. Fat malabsorption (Table 3) was found in 23 of 39 (plus three patients over 40 years old) unselected MRDM patients of them without intestinal parasites. This abnormality was found in only two of 10 Type 1 patients and one of nine control subjects tested. D-xylose absorption was normal in all 12 MRDM patients with excess faecal fat who were tested. Two previously well-nourished but subsequently cachectic Type 2 patients also showed fat malabsorption.

C-peptide and glucagon patterns during OGTT (Tables 4a and b)

The mean C-peptide values of MRDM patients were higher than those of Type 1 patients, although the difference was not significant; they were, however, significantly lower than those in Type 2 patients and normal control subjects ($p < 0.01$ to 0.001 at various times during OGTT in each case). The values were highest in the mild MRDM cases (who responded to the oral agent) approximating those of Type 2 diabetic patients, lowest in the severe group (those who showed ketosis-proneness) being indistinguishable from Type 1 diabetic patients, and intermediate in the intermediate group (those who required insulin but were ketosis-resistant on insulin interruption). The glucagon secretion patterns were similar in MRDM and Type 1 diabetes. The values for the ratio of C-peptide to glucose concentration showed a reversal of the relation of C-peptide levels between Type 2 and normal control subjects.

Response to treatment

Weight gain in MRDM patients was from 1.1 to 5.4 kg/m^2 on insulin and diet in those who stayed at the Ethiopian Nutrition Institute for four weeks or more except in three patients whose desire for food was reduced by painful neuropathy. The clinical manifestations of malnutrition resolved including reduction in size or disappearance of the parotid enlargement. In three patients who had soft offensive stools the physical characteristics of the stool returned to normal and the fat content also diminished. Abnormal liver function also resolved or improved and there was improvement in haemoglobin levels.

Trial on oral agent (Table 5)

The mean BMI of 24 MRDM patients at the start of oral agent therapy was 18.67 ± 1.55 kg/m^2 vs 15.6 ± 1.45 kg/m^2 at the time of admission ($p < 0.001$). The mean duration of the trial was 8.9 days. Only three patients responded and only one had an initial BMI of < 18 kg/m^2. Manifestations of ketoacidosis appeared in two patients and persistent moderate ketonuria in one other within two to four days of starting the oral agent. Another three developed ketonuria without progression to ketoacidosis from day six of treatment while 17 did not show any evidence of ketosis for the duration of their trial as shown in Table 5 but had fasting blood glucose values persistently

Table 4a. C-peptide values (nmol/l) during oral glucose tolerance test in all three types of diabetes mellitus

Time hours	Malnutrition-related diabetes mellitus	Type 1 (insulin-dependent)	Type 2 (non-insulin-dependent)	Normal control subjects
0	0.21 ± 0.13 (22)	0.15 ± 0.09 (11)	0.57 ± 0.38 (8)	0.41 ± 0.11 (8)
0.5	0.23 ± 0.15 (22)	0.17 ± 0.09 (11)	0.60 ± 0.44 (8)	0.55 ± 0.11 (8)
1.0	0.25 ± 0.14 (22)	0.19 ± 0.12 (11)	0.69 ± 0.47 (8)	0.57 ± 0.13 (8)
1.5	0.29 ± 0.16 (22)	0.20 ± 0.14 (11)	0.68 ± 0.43 (8)	0.55 ± 0.14 (8)
2.0	0.30 ± 0.19 (22)	0.23 ± 0.13 (10)	0.71 ± 0.45 (8)	0.52 ± 0.12 (8)
2.5	0.29 ± 0.19 (16)	0.20 ± 0.00 (8)	0.79 ± 0.45 (6)	0.53 ± 0.13 (7)
3.0	0.31 ± 0.20 (15)	0.24 ± 0.14 (8)	0.81 ± 0.45 (6)	0.52 ± 0.13 (7)

Numbers in parentheses indicate number of individuals tested

Table 4b. Glucagon values (nmol/l) during oral glucose tolerance test in the three types of diabetes

Time hours	Malnutrition-related diabetes mellitus	Type 1 (insulin-dependent)	Type 2 (non-insulin-dependent)	Normal control subjects
0	52.3 ± 15.3 (14)	48.3 ± 3.3 (5)	73.2 ± 24.0 (5)	53.5 ± 9.6 (5)
0.5	52.4 ± 17.7 (14)	48.0 ± 13.2 (5)	63.8 ± 3.8 (5)	42.4 ± 24.5 (5)
1.0	54.3 ± 20.0 (14)	50.6 ± 11.3 (5)	62.5 ± 10.9 (5)	43.7 ± 14.4 (5)
1.5	52.2 ± 20.5 (14)	49.0 ± 6.0 (5)	65.0 ± 14.0 (5)	40.5 ± 36.4 (5)
2.0	52.3 ± 16.5 (14)	49.6 ± 7.5 (5)	62.0 ± 14.6 (5)	33.3 ± 26.2 (5)
2.5	44.2 ± 10.3 (12)	56.9 ± 13.4 (4)	64.5 ± 17.2 (5)	20.7 ± 14.5 (4)
3.0	46.3 ± 8.1 (12)	43.3 ± 6.8 (4)	56.7 ± 12.0 (5)	26.5 ± 10.7 (4)

Numbers in parentheses indicate number of individuals tested

Table 5. Duration of insulin withdrawal

Days off insulin	No. of cases	No. showing ketosis*
< 4	24*	3
5–9	20	3
10–14	17	0
15 +	5	0

* Includes ketoacidosis and persistent ketonuria of + + or more;
* 1 patient withdrew from the trial after the 3rd day

>11.1 mmol/l, recurrence of polyuria and polydipsia and decline of body weight. The mean age of onset of diabetes of the six patients who developed ketoacidosis or persistent ketonuria during the trial with glibenclamide was 19.7 years, BMI at the time of the trial was 19.2 kg/m² (increase in BMI 1.0–5.4 kg/m²) while the mean age of onset of the 17 who remained ketosis-free during the trial was 23.0 years, the mean BMI was 18.5 kg/m² (increase in BMI 1.0–4.8 kg/m²). There was no significant difference between patients in either age of onset of diabetes ($t = 1.092$, $p > 0.3$) or BMI at the time of the trial with oral agent ($t = 0.914$, $p > 0.3$). In 17 recorded episodes of frank ketoacidosis in 16 Type 1 patients who interrupted their insulin treatment for a variety of reasons, the median interval between interruption of injections and appearance of ketoacidosis was three days and the mean was 5.5 days, the difference between median and mean being due to one patient in whom the interval was recorded as 30 days.

Discussion

We have no ready explanation for the great preponderance of male subjects with MRDM seen in our present and previous studies although other studies have also shown a preponderance of male patients [9]. Most of the MRDM patients were from rural areas and this may mean that debilitated female patients are more reluctant to undertake the long journey to hospital or there may be a true preponderance of males with this type of diabetes. In agreement with our earlier findings [1], the diabetic patients from a poor socioeconomic environment not only had a low BMI but the other well-known indicators of malnutrition such as parotid enlargement, hair and skin changes, pitting oedema, anaemia (aggravated in some cases by parasitic infestation) and also abnormal liver function tests. These findings are similar to those described by Zuidema from Indonesia [10] with the difference being that among his cases a significant number had pancreatic calcification while, so far, this feature is lacking in Ethiopian MRDM. In our patients the abnormalities improved or resolved during treatment but the severity of the diabetes did not improve in the majority with respect to insulin need for diabetic control.

Excess stool fat, not attributable to intestinal parasites, was found in 14 of 39 MRDM patients. This confirms our previous finding of malabsorption in association with MRDM [1]. D-xylose absorption was normal in all 21 patients who had the test. This does not by itself rule out intestinal abnormality but favours pancreatic pathology in conjunction with the postmortem findings in two previous MRDM cases both showing marked reduction in pancreatic size with fibrosis and in one case with areas of polymorphonuclear, lymphocytic and plasma cell infiltration in the acini and islet tissues.

However, exocrine pancreatic pathology (though not pancreatic calcification) also occurs in the Type 1 and Type 2 diabetes [11–13]. On the other hand, malabsorption was more common in the MRDM than in Type 1 diabetic patients in this study suggesting an interaction between malnutrition, which is common in Ethiopia [2, 3]

and the diabetes in causing the pancreatic damage and producing a condition which, in its most severe form, is akin to kwashiorkor. This hypothesis is strengthened because regression of the parotid enlargement and reduction of the stool fat in some of the patients during treatment suggest that the pancreatic abnormality is partially reversible.

On the other hand, ketoacidosis is not restricted to Type 1 diabetes since it can occur in diabetes developing after near-total pancreatectomy [14] and in the FCPD variant of MRDM [15]. Therefore, based on clinical characteristics alone, even ketoacidosis cannot provide conclusive evidence of the aetiological category of the diabetes [16].

Concerning ketosis-resistance in MRDM, this study has confirmed our earlier findings and those of others [1, 2, 15] that the majority of patients exhibit this characteristic on insulin withdrawal in comparison to Type 1 diabetic patients, even after a significant gain in body weight, for a longer period than the average Type 1 patient although our patients were not withdrawn from insulin for as long as those in the study by Ahuja et al. [17]. Furthermore, the serum carnitine level of Ethiopian diabetic patients was not found to be significantly lower than that of normal control subjects although the nutritional state of the patients tested is not obvious in the report [18].

Weight gain during nutritional rehabilitation in the six MRDM patients who developed ketoacidosis or significant ketonuria and the 17 who did not was similar and glucagon secretion patterns in MRDM and Type 1 diabetes were also similar. On the other hand, the C-peptide in the MRDM group was consistently (though not significantly) higher than that in the Type 1 group. Furthermore, in the MRDM group it was highest in the oral agent responsive group and lowest in the ketosis-prone group. These findings are in favour of residual insulin secretion as the main factor for ketosis-resistance in MRDM. But aggravation of carnitine and body fat depletion in the course of the diabetes could be contributory factors. However, levels indistinguishable from those with Type 1 diabetes as well as wide variations in basal and stimulated levels similar to those found in this study have been reported in MRDM [19, 20]. These differences may be partly due to differences in the nutritional and metabolic status of the patients when the test is done. In addition, the possibility, also applying to our study, that ketosis-prone patients from rural areas are less likely to reach medical care because of rapid progression to ketoacidosis, thus contributing an inherent bias in the clinical identification of MRDM.

The geography of diabetes [21, 22] shows that MRDM is confined to tropical countries where malnutrition is common and in most of these countries it is peculiar to the poorer segment of the population but such an association does not necessarily indicate a cause-effect relationship. Therefore, the aetiology of MRDM remains unresolved [23].

On the basis of several characteristics including onset in youth, insulin treatment required and ketosis-proneness, developing in some cases during the natural history or after nutritional rehabilitation and the glucagon and C-peptide levels, the PDPD variant of MRDM could be considered a mild form or variant of Type 1 diabetes peculiar to malnourished populations rather than an aetiologically separate entity. In addition, a limited study of the HLA pattern in MRDM patients has shown a significantly higher frequency of HLA-DR3 than in non-diabetic control subjects and similar to that in Type 1 diabetes in the same population [24]. However, a definitive answer to its identity requires more extensive community-based studies to ascertain frequency and type of diabetes in malnourished populations and the role of genetics and environment in their aetiology.

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Characteristics of Serogroup A Neisseria meningitidis Responsible for an Epidemic in Ethiopia, 1988–89

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In September 1988, an epidemic of meningococcal disease started in Ethiopia. 21 Neisseria meningitidis isolates recovered from patients in Addis Ababa and towns 200 km south of the capital were characterized by serogrouping, serotyping, testing of susceptibility to antibiotics, restriction endonuclease fingerprinting, and multilocus enzyme electrophoresis. The 21 isolates were essentially homogeneous for all properties tested and belonged to clone III–1 of serogroup A N. meningitidis, which was also responsible for the epidemics in Saudi Arabia in 1987 and in Sudan and Chad in 1988.

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INTRODUCTION

In the "meningitis belt" of Africa which extends from Burkina Faso in the West to Ethiopia in the East (1), major epidemics of meningococcal disease occur periodically, every 8 to 12 years (2). Several outbreaks of meningococcal meningitis have earlier been reported from different parts of Ethiopia including the capital, Addis Ababa (3–6). The majority of these outbreaks have occurred in the north, north-west, and parts of the central regions of the country which fall within the "meningitis belt" (4). Characteristically, most of these outbreaks took place in the hot dry months of March to June.

In September 1988 an epidemic started in Addis Ababa and reached its peak in the months of February–March 1989. The epidemic first spread in the regions around Addis Ababa and the southern parts of the country. Later, sporadic outbreaks were reported from all over the country. The Tikur Anbessa Teaching Hospital in Addis Ababa treated 278 adult patients between January and June 1989, with a case-fatality rate of 21% (7).

We here present a characterization of meningococcal isolates recovered during the recent epidemic from patients in Addis Ababa and the Rift Valley lake regions of central Ethiopia.

MATERIALS AND METHODS

Cerebrospinal fluids (CSF) were collected from patients with meningitis and/or septicaemia admitted at the Tikur Anbessa Hospital (30 patients) and the Health Centers around Zeway town, 170 km south of Addis Ababa (20 patients). The patients were between 14 and 50 years of age, with 40% in the age group 14–19. The CSF samples were cultured on chocolate agar plates. Isolates of Neisseria meningitidis were subcultured and the selected samples stored at −20°C. Before shipment to Norway, the isolates were cultured on chocolate agar plates and inoculated into Stuart's transport medium. Of 40 cultures sent to Norway, N. meningitidis was successfully recovered from 21.

Serogrouping was performed by slide agglutination with commercial antisera (Wellcome Reagents Ltd., Beckenham, UK) specific for the A, B, C, W135, X, Y, and Z polysaccharides, and by whole-cell ELISA with a monoclonal antibody against serogroup A (14-1-A) provided by Dr W. D. Zollinger.

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Serotyping was performed by the whole-cell ELISA procedure (8) with monoclonal antibodies against serotypes 4 (15-1-P4), 21 (14-1-P21), serosubtypes P1.1 (9-1-P1.1), P1.2 (3-1-P1.2), P1.3 (12-1-P1.3), P1.15 (2-1-P1.15), and P1.16 (3-1-P1.16) provided by Dr Zollinger; with monoclonal antibodies against serotype 4 (MN14G21.17) and serosubtype P1.9 (MN5 A10F), provided by Dr J. T. Poolman; and with monoclonal antibodies against serotype 4 (2303 C5) from Dr C. E. Frasch.

Antibiotic sensitivity testing for sulfadiazine, benzylpenicillin, chloramphenicol, rifampicin, minocycline and ceftriaxone were determined by the agar dilution method. Relative penicillin resistance was also tested with disc diffusion (9). Beta-lactamase activity was looked for applying the acidometric and chromogenic cephalosporin tests (10).

Electrophoresis of enzymes was performed as described by Selander et al. (11). Multilocus enzyme genotype of the isolates was compared to those of reference serogroup A strains (12) provided by Dr M. Achtman.

Restriction endonuclease fingerprinting of chromosomal DNA (RE) was performed as described by Bjorvatn et al. (13), using restriction endonucleases *Eco*RI and *Hin*dIII. All strains were tested at least twice. RE patterns were reproducible except for occasional doubling of bands that previously had appeared single, or weakening or strengthening of bands in a few particular locations.

RESULTS

The characteristics of the 21 isolates are given in Table I. All strains were serogroup A, serotype 21/4: P1.9. Three isolates reacted weakly or not at all with one (15-1-P4) of the 3 monoclonal antibodies against serotype 4, but all strongly bound the 2 other serotype 4 monoclonal antibodies and the serotype 21 monoclonal antibody.

All the isolates were resistant to sulfadiazine: 19 isolates had a MIC of sulfadiazine of 200 µg/ml and the remaining 2 differed by only one dilution step (100 µg/ml and 400 µg/ml, respectively). No beta-lactamase activity was detected and all the isolates proved fully sensitive to benzylpenicillin, chloramphenicol and ceftriaxone. No resistance against minocycline or rifampicin was detected by screening the isolates at drug concentrations of 1.0 and 0.25 µg/ml, respectively.

The 21 isolates belonged to the same clone as demonstrated by their identical multilocus genotypes. The electromorphs at all 14 enzyme assayed were similar to those of isolates assigned to clone III-1 by Olyhoek et al. (12).

Following *Eco*RI or *Hin*dIII digestion, the electrophoresed fragments of chromosomal DNA formed patterns consisting of approximately 45 typically located bands. For 6 strains, *Eco*RI digestion produced only a limited number of bands which prompted retesting with *Hin*dIII.

Table I. *Characteristics of 21 isolates of N. meningitidis from Ethiopia*

Property tested	Laboratory findings
Serogroup	A
Serotype: serosubtype	21/4[a]: P1.9
MIC sulfonamide	200 µg/ml[b]
Electrophoretic type[c]	1 4 5 6 4 1 3 2 1 8 2 3 2 2
Restriction endonuclease fingerprinting	Identical patterns[d]

[a] 3/21 isolates bound weakly or not at all monoclonal antibody 15-1-P4. All bound 14-1-P21, MN14G21.17, and 2303 C5.

[b] MIC of sulfadiazine for 2 isolates were 100 and 400 µg/ml, respectively.

[c] Electromorphs at the following enzymes in given sequence: malic enzyme, glucose 6-phosphate dehydrogenase, peptidase, isocitrate dehydrogenase, aconitase, 2 glutamate dehydrogenases, alcohol dehydrogenase, fumarase, alkaline phosphatase, 2 indophenol oxidases, adenylate kinase, and an unknown dehydrogenase.

[d] 19/21 proven, 2/21 likely identity.

Complete clarification was thereby obtained in 4 of these cases, whereas the remaining 2 strains showed a small number of bands, albeit at typical locations. Hence, 19 strains had similar patterns indicating genetic identity or close clonal relationships. Identity of the remaining 2 strains is highly likely although not proven with this method.

DISCUSSION

The recent epidemic of meningitis in Ethiopia has 2 distinct characteristics that distinguishes it from previous outbreaks. Firstly, previously unaffected regions in the southern and eastern parts of the country have now been involved. Thus, the borders of the "meningitis belt" within Ethiopia are changing and extending. Secondly, whereas epidemics in the past appeared in the hot, dry months of March to June, the recent outbreak started in September and continued with peaks in the months of February and March. Scattered cases were still seen in August, the rainy month of the year.

As expected during an epidemic, the 21 N. meningitidis isolates exhibited very similar traits and represented a single clone, namely III-1. No difference was seen between strains from Addis Ababa and the Zewai area.

Clone III-1 had been responsible for epidemics in Finland and Brazil in the mid 1970s (12). Recently, meningococci of clone III-1 reached Saudi Arabia where they caused an outbreak among Haj pilgrims in Mecca in 1987 (2). Subsequently, clone III-1 caused severe epidemics in Sudan and Chad in 1988 (2, 14, 15). We show here that the recent outbreaks of meningitis in Ethiopia were also caused by clone III-1. Surveillance of the spread of this virulent clone to other African countries in the "meningitis belt" is warranted. In fact, preliminary results indicate that clone III-1 already has reached the Gambia (Bjorvatn & Caugant; unpublished data).

The isolates were resistant to sulfadiazine confirming that sulfonamides no longer have a place in the treatment or prophylaxis of meningococcal meningitis. The demonstration that the strains were sensitive to penicillin and chloramphenicol is essential to management of cases in developing countries (16).

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Study of family history among parents and siblings of Ethiopian diabetics: a preliminary report

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Summary

218 diabetic probands and 300 non-diabetic controls were interviewed for history of diabetes mellitus in their parents and siblings. The prevalence of diabetes mellitus among blood relatives of probands and controls differed significantly. The study also showed that NIDDM probands had more positive family history of diabetes than IDDM ones. The overall findings of this study indicated that heredity has an important role in the genesis of diabetes mellitus in Ethiopian diabetics.

Introduction

The study of heredity of diabetes mellitus in black Africans is limited. There are no twin studies to the best of our knowledge. Gelfand and Forbes (1963) reported, from Harare Hospital, that heredity does not play a role in African diabetics. He found only one case with positive family history out of 50 diabetic probands. He concluded that most African diabetics were suffering from pancreatic calcifications, liver diseases, or siderosis and believed that urbanization contributed to the genesis of diabetes mellitus in the African. Osuntokun *et al.* (1971), in Nigeria, found 2.4% positive family history from 832 diabetics and noted that most patients were unwilling to give family history. Wicks and Jones (1974) made a comparative study of Africans with Caucasians. Their findings indicated that 32% of the Africans were suffering from secondary diabetes and of 107 diabetic probands, only 5 (4.6%) had family history of diabetes among their relatives. Wicks *et al.* (1973) in another study made an observation that urbanization and 'sucrose load' was an important factor in the genesis of diabetes mellitus in African diabetics. These observations implied that environmental factors and not heredity were operative in the genesis of diabetes mellitus. Campbell (1963) made a family study among Zulu diabetics and found that 4% of his patients gave positive family history. Omar and Asmal (1983) made a family study of diabetics in Africans and Indians in Natal, South Africa, and found that family history of diabetes mellitus was more common in NIDDM in both Indians (80%) and Africans (37%) than in IDDM and controls. This is interesting in that the importance of heredity in the genesis of diabetes mellitus in Africans was revealed in that particular study.

We report here the results of a study conducted to shed light on the relative contribution genetic factors play in the pathogenesis of diabetes mellitus in Ethiopian diabetics.

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Materials and methods

A total of 218 unselected diabetics attending the Diabetic Clinic of Tikur Anbessa Hospital and 300 non-diabetic patients seen at the medical out-patients were interviewed for family history of diabetes among their parents and siblings using a prospectively prepared protocol for this purpose. In addition, inquiry was made for other relatives who are known to be diabetic. Diabetic patients with liver diseases, pancreatitis and other 'known conditions and syndromes that are known to be aetiologically related to the secondary diabetic state' were

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excluded. With regard to family history of diabetes three answer options included were 'yes' for definite positive family history, 'no' for definite negative family history, and 'I do not know' for uncertainty of such family history. The diabetics were categorized as IDDM or NIDDM according to WHO (1980) criteria for the classification of diabetes. The Z-test was used in the statistical analysis.

Results

218 diabetic probands and 300 controls were included in this study. There were 90 males and 128 females in the diabetic group. The controls comprised 162 males and 138 females. Age ranged from 10 to 68 years for the diabetics and the controls had an age range of 13–75 with a mean age of 38.5 and 31 years for diabetics and controls respectively. The major tribal groups were represented in both the diabetics and controls, but not in the same proportion as their numbers in the general population (Table 1). The majority of the diabetics and controls came from the city of Addis Ababa. The office workers and housewives constituted the main occupational groups in diabetics as well as in controls. The two groups were generally comparable in respect to age, tribal group, urban or rural residence and occupation. There were 71 IDDM and 147 NIDDM in the study group. These had 436 parents and 984 siblings on whom information was sought. Definite information was not obtained on 113 (8%) individuals (50 fathers, 50 mothers, 11 brothers and 2 sisters). We were able to get definite 'yes' or 'no' responses on 92% of the diabetics. Of the controls, 97.8% gave definite 'yes' or 'no' responses. There was a significant difference between diabetics and controls in being definite in their answers regarding family history of diabetes ($Z=7.71$; $P=0.001$).

Forty-two (19%) of 218 diabetic probands and five (1.6%) of the controls had a history of diabetes mellitus in their parents and/or siblings. The difference is significant ($Z=6.32$; $P=0.01$). When second-degree relatives are included the difference becomes even more significant. Fifty-eight (27%) of diabetic probands and six (2%) of the controls had positive family history for diabetes mellitus ($Z=8.32$; $P=0.001$).

Comparing NIDDM with IDDM showed that 39 (27%) NIDDM and three (4%) IDDM had a family history of diabetes mellitus and the difference was significant ($Z=5.3$; $P=0.01$). When second-degree relatives are included we found that 51 (34%) NIDDM and seven (10%) IDDM had affected parents and/or siblings or second-degree relatives. The difference was significant: ($Z=4.17$; $P=0.001$). Table 2 summarizes the statistical values of the comparison between various groups. In this study we did not come across diabetic twins or connubial diabetics.

Table 1. Distribution of diabetics and controls according to tribal groups

Tribal groups	Diabetics	Controls
Amhara	131	140
Oromo	22	59
Tigre	22	38
Gurage	14	28
Others	8	11

Table 2. Prevalence of positive family history of diabetes mellitus

	Total no.	No. (and percentage) positive in first-degree relatives (a)	No. (and percentage) positive in first and second-degree relatives (b)	Statistical values	
				Z	P
Controls	300	5 (1.6)	6 (2.0)	(a) 6.32	0.001
Diabetics	218	42 (19.0)	58 (27.6)	(b) 8.32	0.0001
NIDDM	147	39 (27)	51 (34)	(a) 5.3	0.001
IDDM	71	3 (4)	7 (10)	(b) 4.37	0.001

Table 3. Distribution of diabetic probands according to type of diabetes, sex and tribe

	IDDM		NIDDM	
	Male	Female	Male	Female
Amhara	15	20	30	65
Oromo	6	5	3	8
Tigre	8	6	4	4
Gurage	5	4	5	0
Others	4	0	2	2

The Amhara tribal group, which is numerically the largest group, showed a difference when compared with the others. The number of NIDDM in the Amhara's was quite large when compared with the IDDM. The other groups did not have such a high ratio of NIDDM to IDDM. In this preliminary study we made no systematic sampling of the tribal groups and the Amhara, although in the majority in the general population, is over represented in this particular survey. No definite conclusion can be made at this stage (Table 3).

Discussion

Family history of diabetes was positive in 27% of our diabetic probands and 2% of the controls. The higher prevalence of a family history in diabetics compared with those of controls accords with results of other studies (Rimoin 1967; Pincus & White 1933). This study also showed that a family history of NIDDM appears to be more common than for IDDM, and again this is in agreement with studies of Tattersall and Fajans (1975). Kadiki *et al.* (1988) found a positive family history in 23.7% of diabetics in Benghazi, Libya. In the rest of Africa, except one study reported by Omar and Asmal (1983) from Natal, South Africa, family studies did not give such a high figure. It was reported by Lester (1980) that 7.64% of Ethiopian diabetics have positive family history. We believe this is too low a figure and a recent report also indicated 29% positive family history in the same city but in another hospital (Mengistu 1987). Lester (1988) reported 18.2% positive family history among her registered diabetics.

Although there was a degree of reticence regarding family history among diabetics as compared with controls (92 *vs* 98.7%), there was a relatively good response among our diabetics. We believe that the genetic factors involved in the pathogenesis of diabetes mellitus in this country is the same as elsewhere but careful and case-controlled studies are required.

Acknowledgement

We are grateful to Dr Asmerom Kidane for the statistical analysis of our data.

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KNOWLEDGE AND APPLICATION OF ESSENTIAL NATIONAL DRUG LISTS AMONG HEALTH PROFESSIONALS IN ADDIS ABABA

Teodros Leka* and Yohannes Jorge**

It is a well known fact that proper understanding and clear identification ... obstacles in the implementation of essential drug policy and rational ... drugs is the backbone for achieving pertinent and radical solutions to the ... This study examines the knowledge and application of Essential and National ... drug lists.

INTRODUCTION

Drugs can be loosely defined as medical substances in the treatment and prevention of diseases. They include locally prepared remedies as well as highly purified pharmaceuticals, synthesized in modern factories. Whatever their form, drugs play an important role in health care service.

In most of the modern societies, people and health workers have considered the free market of drugs a condition for higher quality of health system. Less attention was given to the quality of the products, and to the safety and efficacy of drugs.

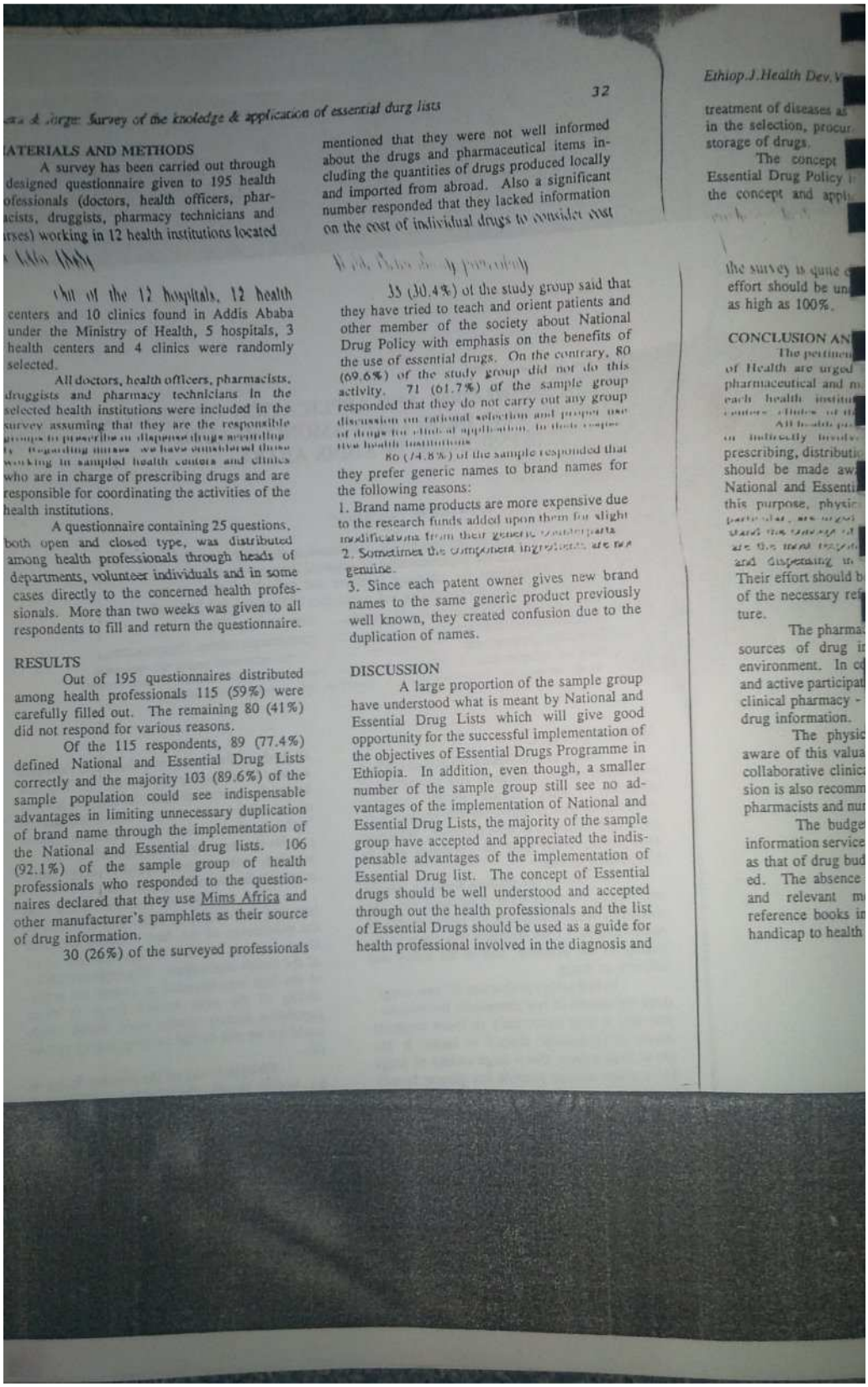
In fact a high proportion of "new drugs" does not consist of real therapeutic innovations - and this is true particularly in those countries where governmental control is loose. It has never been proven that a large variety of drugs for a given disease provide any greater benefit for public health than a more selected number of products. On the contrary, the existence of a large number of drugs may cause confusion at all levels of the therapeutic chain and represent a waste of manpower and money (1). The idea behind the concept of essential drugs is not that of depriving health workers and customers the 'right' to choose drugs and treatment, but to provide the majority of the population with effective, safe and less expensive drugs easily accessible for better drug treatments.

The concept of essential drugs was launched in Ethiopia in 1985, and followed by the publication of the first National Essential Drugs List and sub-lists for the different levels of the health institutions. The implementation of the lists was intended to extend the accessibility of the most needed drugs to those population sectors whose basic health needs could not be met by the existing supply system (3).

Ethiopia is one of the member states of the World Health Organization (WHO) that accepted the essential drug policy and drafted its own National and Essential drug lists. But, as it is true with other third world countries, the National and Essential drug lists have certain implementation problems.

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ATERIALS AND METHODS

A survey has been carried out through designed questionnaire given to 195 health ofessionals (doctors, health officers, phar- acists, druggists, pharmacy technicians and irses) working in 12 health institutions located

... Addis Ababa

... out of the 12 hospitals, 12 health centers and 10 clinics found in Addis Ababa under the Ministry of Health, 5 hospitals, 3 health centers and 4 clinics were randomly selected.

All doctors, health officers, pharmacists, druggists and pharmacy technicians in the selected health institutions were included in the survey assuming that they are the responsible groups to prescribe or dispense drugs according ... Regarding nurses we have considered those working in sampled health centers and clinics who are in charge of prescribing drugs and are responsible for coordinating the activities of the health institutions.

A questionnaire containing 25 questions, both open and closed type, was distributed among health professionals through heads of departments, volunteer individuals and in some cases directly to the concerned health profes- sionals. More than two weeks was given to all respondents to fill and return the questionnaire.

RESULTS

Out of 195 questionnaires distributed among health professionals 115 (59%) were carefully filled out. The remaining 80 (41%) did not respond for various reasons.

Of the 115 respondents, 89 (77.4%) defined National and Essential Drug Lists correctly and the majority 103 (89.6%) of the sample population could see indispensable advantages in limiting unnecessary duplication of brand name through the implementation of the National and Essential drug lists. 106 (92.1%) of the sample group of health professionals who responded to the question- naires declared that they use Mims Africa and other manufacturer's pamphlets as their source of drug information.

30 (26%) of the surveyed professionals mentioned that they were not well informed about the drugs and pharmaceutical items in- cluding the quantities of drugs produced locally and imported from abroad. Also a significant number responded that they lacked information on the cost of individual drugs to consider cost

... to teach and orient patients ...

35 (30.4%) of the study group said that they have tried to teach and orient patients and other member of the society about National Drug Policy with emphasis on the benefits of the use of essential drugs. On the contrary, 80 (69.6%) of the study group did not do this activity. 71 (61.7%) of the sample group responded that they do not carry out any group discussion on rational selection and proper use of drugs for clinical application in their respec- tive health institutions.

80 (74.8%) of the sample responded that they prefer generic names to brand names for the following reasons:

1. Brand name products are more expensive due to the research funds added upon them for slight modifications from their generic counterparts
2. Sometimes the component ingredients are not genuine.
3. Since each patent owner gives new brand names to the same generic product previously well known, they created confusion due to the duplication of names.

DISCUSSION

A large proportion of the sample group have understood what is meant by National and Essential Drug Lists which will give good opportunity for the successful implementation of the objectives of Essential Drugs Programme in Ethiopia. In addition, even though, a smaller number of the sample group still see no ad- vantages of the implementation of National and Essential Drug Lists, the majority of the sample group have accepted and appreciated the indis- pensable advantages of the implementation of Essential Drug list. The concept of Essential drugs should be well understood and accepted through out the health professionals and the list of Essential Drugs should be used as a guide for health professional involved in the diagnosis and

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CONCLUSION AN...

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treatment of diseases as well as those concerned in the selection, procurement, distribution and storage of drugs.

The concept and implementation of Essential Drug Policy is obviously linked with the concept and application of generic drug products. In this aspect the result obtained in the survey is quite encouraging and still further effort should be undertaken to make the result as high as 100%.

CONCLUSION AND RECOMMENDATIONS

The pertinent authorities of the Ministry of Health are urged to provide the necessary pharmaceutical and medical reference books in each health institutions - hospitals, health centers, clinics -of the country.

All health professionals who are directly or indirectly involved in activities such as prescribing, distribution and dispensing of drugs should be made aware of the importance of National and Essential drug lists. To achieve this purpose, physicians and pharmacists, in particular, are urged to do their best to understand the concept of essential drugs, since they are the most responsible groups in prescribing and dispensing in the clinical environment. Their effort should be backed with the provision of the necessary reference materials and literature.

The pharmacists should act as the main sources of drug information in the clinical environment. In collaboration with physicians and active participation in the implementation of clinical pharmacy - they could be the center for drug information.

The physicians also should be well aware of this valuable and beneficial aspect of collaborative clinical work. A clinical discussion is also recommended to include physicians, pharmacists and nurses of pertinent departments.

The budget for the provision of drug information service should be considered as vital as that of drug budget and properly implemented. The absence of drug information service and recent medical and pharmaceutical reference books in health institutions can be a handicap to health professionals who would like to update their knowledge. This is particularly true of hospital pharmacists.

All pertinent health professionals of the country should be involved in teaching and orienting the public, patients and professionals about importance of Essential Drug Policy and its implementation. In addition to this, they are required to carry out organized clinical group discussions on drugs among themselves.

Prescriptions are recommended to be written in generic names rather than in brand names for the benefit of patients and for proper implementation of the Essential Drug Policy.

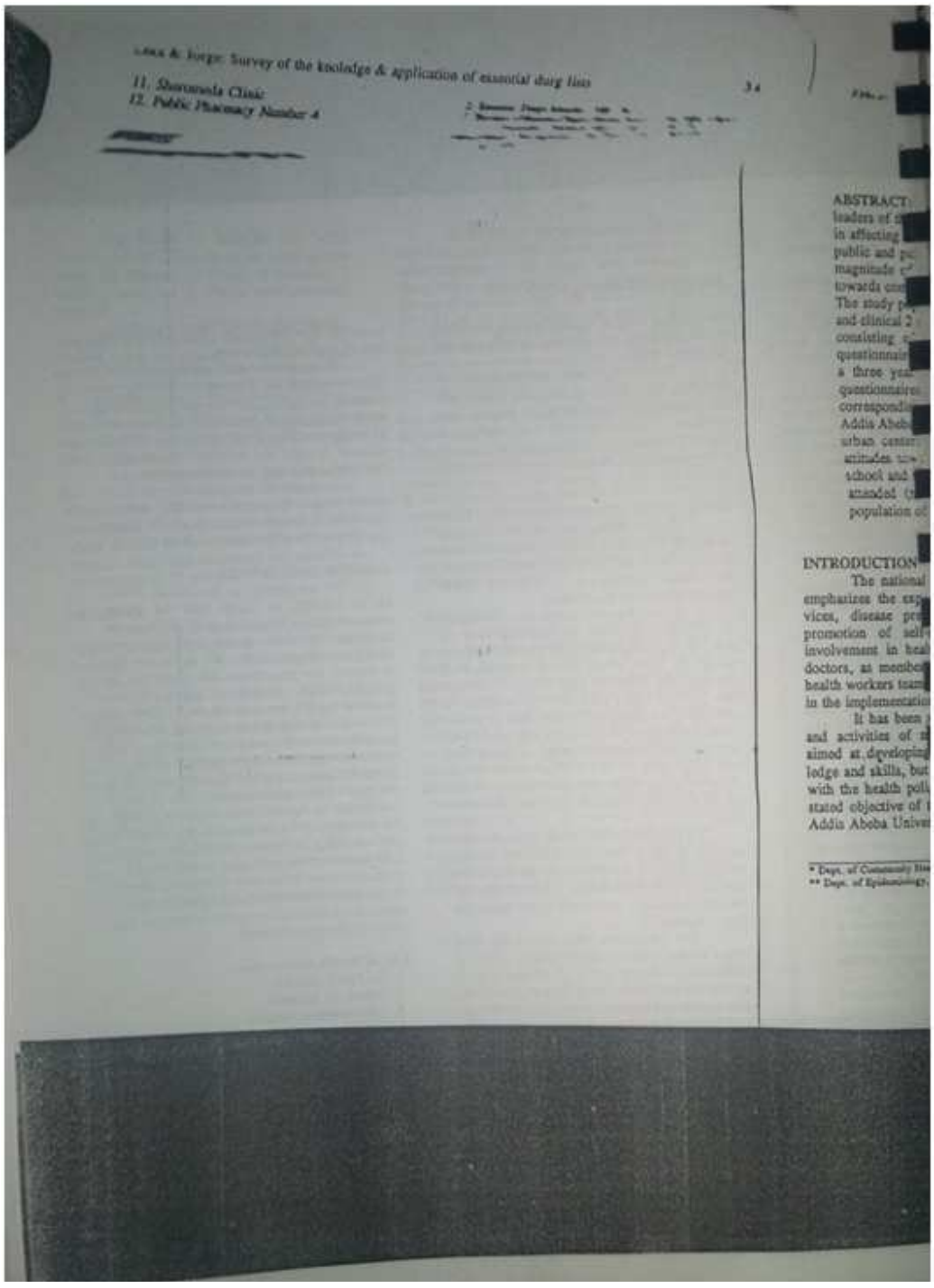
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List of Health Institutions

1. St. Paul's Hospital
2. Yekatit 12 Hospital
3. Tikur Anbessa Hospital
4. Ethio-Swedish Pediatric Hospital
5. Minilik II Hospital
6. Karanchis Health Center
7. Anbessa Clinic
8. Addis Beer Clinic
9. EELPA Clinic
10. Arada Clinic

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11. Shewarnela Clinic
12. Public Pharmacy Number 4

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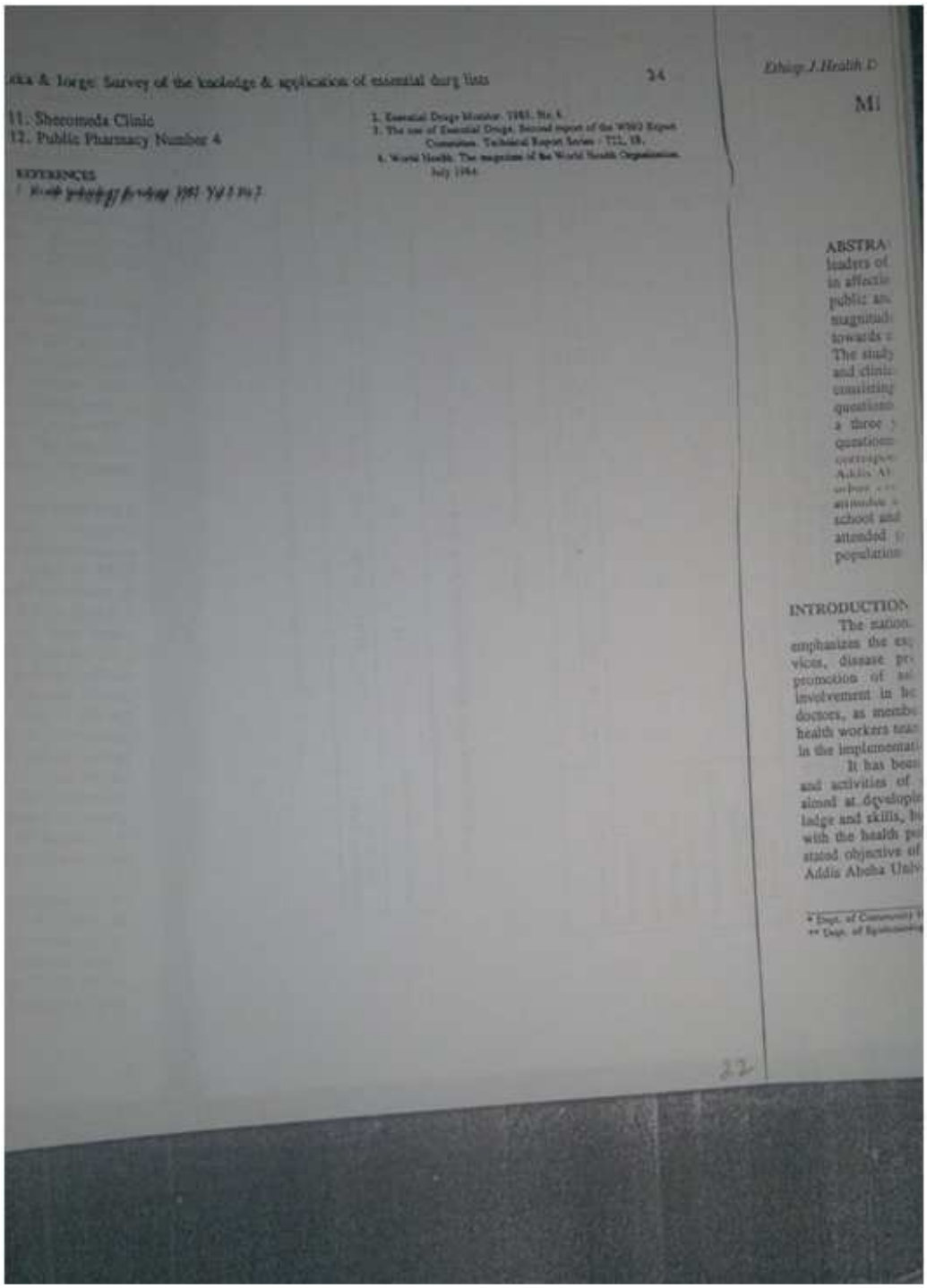
ABSTRACT:

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INTRODUCTION

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ABSTRA
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INTRODUCTION
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Amir sultan (MD), 2014

TABLE 1. Plasma levels of phenytoin in Ethiopian epileptics in Addis Ababa

Phenytoin level in µg/ml	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	>50	Total
Number of patients	7	7	18	16	13	14	4	3	3	2	2	89*

* 90% of patients were taking phenytoin in a dose of 300 mg p.o. daily.

TABLE 2. Phenytoin side effects

Side effects	Plasma Phenytoin Level (µg/ml)										Percent of patients
	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	>40	Total	
Nystagmus	-	-	1	2	3	2	3	2	5	18	20.2
Ataxia	-	-	1	1	2	3	-	-	6	13	14.6
Hirsutism, skin rash, acne	-	1	2	3	3	-	-	1	-	10	11.2
Gingival hypertrophy	2	2	3	5	4	5	2	2	2	27	30.3
Lymphadenopathy	-	-	1	-	1	1	-	-	-	3	3.4
Total number of patients	7	7	18	16	13	14	4	3	7	89*	

* 66 (74%) patients were on combination of phenytoin and phenobarbitone
6 (26%) patients taking phenytoin singly and 25 (37.8%) patients taking combinations of phenytoin and phenobarbitone had motor disturbances ($p>0.10$).

seen in 31 (34.8%) of the patients. Dysmorphic and idiosyncratic side effects including gum hypertrophy, hirsutism, acne and rash were observed in 37 (41.6%) of the patients. Three patients had lymphadenopathy.

Nystagmus usually appeared at phenytoin levels above 20 ug/ml but has been observed with concentrations as low as 15 ug/ml. Ataxia was most common above 30 ug/ml and drowsiness was seen in patients with levels of 40 ug/ml and over.

As shown in Table 3, of the 60 patients who were taking both phenytoin and phenobarbitone and in whom seizure control was documented, 34 (56.6%) were seizure free for the last two months. If one takes phenytoin level as a marker, seizure control was lowest (27.7%) with plasma levels below 10 ug/ml. Only 58.3% of patients who had plasma levels of phenytoin above 30 ug/ml were controlled.

Table 4 shows control of seizures with single or combined anticonvulsant therapy. Control of seizures was documented in 108 patients. Sixty (55.6%), were on combined drug therapy (phenobarbitone and phenytoin) and 48 (44.8%) on phenytoin or phenobarbitone. Seizure control was achieved in 37 (77.1%) of patients on a single drug as opposed to 34 (56.6%) on combination, a statistically significant difference ($p < 0.05$) The overall control rate was 66.%.

Table 5 compares findings from different studies of low serum calcium and high alkaline phosphatase in epileptic patients taking anticonvulsant drugs. In our study 30.6% and 26.5% had low serum calcium and high alkaline phosphatase levels respectively.

The renal function tests were normal in all the patients investigated. No case of megaloblastic anaemia was encountered. Electroencephalographic findings were normal in 19.5%, borderline in 21%, and abnormal in 59.5% of patients.

DISCUSSION

In Ethiopia, as in the rest of Africa, where resources are limited, there are only a few basic anticonvulsants available to treat epileptics. Phenobarbitone and phenytoin were the only anticonvulsants available to poor patients with generalized seizures.

Although phenytoin has been a drug of first choice in the treatment of the major epilepsies, it has several important disadvantages including a narrow therapeutic ratio with a potentially wide variety of adverse effects associated with its acute and chronic use. Furthermore, its kinetics in man make it a difficult drug to use in practice, because of a non-linear relationship between dose and serum level (4-6).

Phenobarbitone, on the other hand, is a very cheap and effective anticonvulsant, which, however, has the side effects of sedation and intellectual depression.

Although facilities for routine drug level determinations are not available in Ethiopia, such determinations have been documented to be invaluable in the judicious and rational use of anticonvulsants.

The plasma levels of both anticonvulsant drugs varied widely from patient to patient although most patients were prescribed similar standard doses of the drugs. As only 38.2% of patients taking phenytoin and 52% of patients on phenobarbitone had plasma levels in the therapeutic range, it is clear that more efficient therapeutic use of the drugs would be obtained by monitoring drug levels. Our results confirm the observations from various studies that patients on a standard dose of phenytoin have a wide scatter of plasma levels (7-10).

The frequency of side effects in our patients, most of whom (74%) were on combination of phenytoin and phenobarbitone, is higher, but not statistically significantly so ($p > 0.10$), than the figures in previous studies which dealt with single drug therapy

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TABLE 3. Patients on phenytoin and phenobarbitoen seizure-free for the last two months

Plasma phenytoin level (μg/ml)	0-9	10-19	20-29	30-39	>40	Total
Total number of patients	11	21	16	6	6	60
Number of patients seizure free	3	12	12	3	4	34(56.7%)

TABLE 4. Seizure control: Single drug versus combined drug therapy

Anticonvulsalt	Total number of patients	Number of patients seizure free		p value
Phenytoin	16	12 (75%)	77.1%	
Phenobarbitone	32	25 (78.1%)		
Combined phenytoin and phenobarbitone	60	34 (56.7%)	56.7%	p<0.05

TABLE 5. Serum calcium and alkaline phosphatase levels in epileptic patients taking anticonvulsant drugs

	Number of patients	Low serum calcium % of patients	High serum alkaline phosphatase % of patients
1. Richens and Rowe Europe (1970)	160 (adults)	22.5	29.0
2. Hunter (1971) Europe	105 (children)	30.0	24.0
3. Apantaku (1975) Nigeria	52	-	30.8
4. Present study Ethiopia (1988)	49 (adults)	30.6	26.5

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(11,12). Motor disturbances observed by Mattson *et al* (11) for phenobarbitone and phenytoin when taken singly were seen in 24% and 28% of patients respectively. Dysmorphic and idiosyncratic side effects occurred in 11% on phenobarbitone and 22% on phenytoin. These toxic effects, especially motor disturbances which occurred in 26% of our patients when phenytoin was singly taken and in 37.8% when combinations of phenytoin and phenobarbitone were used, were most likely the cumulative adverse effects of the combined drug therapy. Ramsay (12), in his comparative study of carbamazepine and phenytoin, found major side effects in 23% of his patients in each study group. Minor side effects were common with both drugs, nystagmus being the most common.

Motor disturbance in the 20-30 ug/ml plasma phenytoin range were seen in 37% of the patients and were not significantly different from a rate of 34.8% for all patients taking phenytoin. In contrast, control of seizures was maximal (75%) with plasma concentration of 20-30 ug/ml. This implies that, in situations of failure of control, an attempt should be made to adjust the dosage of phenytoin to attain plasma concentrations which give maximal effect without significantly increased side effects. From this study one is able to conclude that the standard recommended dosage of phenytoin is satisfactory for Ethiopian patients.

On the other hand, Osuntokun (13) stated that side effects were relatively uncommon in Africans taking anticonvulsants. Megaloblastic anaemia was encountered extremely rarely. There have also been suggestions that black skin and abundant sunshine may protect the African against anticonvulsant-induced osteomalacia (14). In this study we found side effects similar in magnitude to those in other reports (11,12,15,16).

This study has also inadvertently shown that seizure control was better in those single drug therapy, an approach which has been supported by the studies of Reynolds (17) and Schmidt (18).

A relatively close correlation between toxic symptoms and signs and serum drug levels is noted in this study. Similar findings were observed in previous studies by Kutt *et al* (19) and Haerer and Grace (20).

It is known that excessive phenytoin may paradoxically aggravate epilepsy and even precipitate status epilepticus (21). This is an important point to consider in some of our patients who had plasma levels of phenytoin greater than 40 ug/ml and yet were not controlled.

In this study, phenobarbitone was the most commonly prescribed anticonvulsant drug, followed by phenytoin. In its study in 35 developing countries, the WHO-sponsored Commission of Antiepileptic Drugs (AEDS) found heterogenous distribution and availability of antiepileptic drugs. Similarly in Ethiopia, only the older drugs, such as phenobarbitone, are available to most patients (22).

Although most patients claimed to have taken their medication regularly, we have evidence, through information from relatives, that 20% of those with low drug levels were not fully compliant.

Even though this study is a cross-sectional study during long term treatment, our results support the recent policy of treating epileptics with a single drug whenever possible and also re-emphasize the value of monitoring plasma levels of anticonvulsants for optimization of seizure control. Needless to say, a consistent and reliable supply of basic anticonvulsants should be available to African epileptics at a fairly low cost. In addition to giving the poor epileptic the confidence of leading a relatively seizure-free life, this would also avoid the use of multiple drugs in the control of seizures. Multiple drug therapy carries a higher risk of chronic toxicity, and the evaluation of the individual

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effects of each drug is made extremely difficult.

Acknowledgements

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PROLONGED PARESIS IN A PRIMIGRAVIDA DURING AND AFTER CAESAREAN SECTION

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ABSTRACT. A primigravida, who had a Caesarean section because of cervical dystocia and relative cephalo-pelvic disproportion, in Nov. 1988 in Yekatit 12 Hospital, Addis Ababa, remained relaxed and without spontaneous respiration for about four hours after the completion of the operation, requiring assisted respiration. This condition is the result of a decreased plasma cholinesterase (PCE) activity which is responsible for the breaking down of succinylcholine used in general anaesthesia as a muscle relaxant. Although the incidence of PCE deficiency in our population is not known, it should be remembered that such a complication may be seen in hospitals where operations are carried out using succinylcholine as a muscle relaxant.

INTRODUCTION

Just after the introduction of succinylcholine into clinical practice almost four decades ago, there were reports of prolonged apnoea in association with its use (1-3).

In the majority of cases, this condition was encountered in individuals who subsequently were found to have a low plasma cholinesterase (PCE) activity or a familial peculiarity of this enzyme (4-6).

As a result of using succinylcholine as a muscle relaxant in surgical anaesthesia, the existence of genetically determined variants of PCE was recognized (7-9).

Succinylcholine blocks the action of acetylcholine on voluntary muscles and so produces relaxation. The effect of this drug is usually short (3 to 5 minutes) and after some time most of it is metabolised by the action of PCE so that the tone of muscles, including those of respiration, returns to normal. However, certain individuals remain relaxed and without spontaneous respiration for a prolonged period.

CASE REPORT

M.Z., a 25-year old primigravida, was admitted to the Department of Obstetrics and Gynaecology, Yekatit 12 Hospital, Addis Ababa on November 4, 1988 at 39 to 40 weeks' gestation, in the first stage of labour. She was previously in good health and from the sixteenth week of pregnancy had had regular antenatal care. She had never had surgery before and had no history of myasthenia gravis or other neuromuscular disorders. She had never taken any medication before admission.

On physical examination, she was a healthy looking woman in no distress. Vital signs on admission were as follows: blood pressure 115/70-mmHg., pulse 80/min., temperature 36.5°C and respiratory rate 24/min. There were no abnormal findings in the cardiorespiratory system. Her weight was 50kg. Neurological examination was normal.

Labour did not progress normally, with marked delay of the first stage. A decision was made to deliver the

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patient abdominally because of cervical dystocia and relative cephalopelvic disproportion. The patient underwent Caesarean section and for general anaesthesia received diazepam 10mg, atropine 0.6mg, ketamine 250mg and succinylcholine 100mg. Respiration was maintained with oxygen and 0.5% halothane. Ventilation was controlled manually. vital signs during operation were: blood pressure 130/80 mm, pulse 128/min., temperature 37°C, and respiratory rate 28/min.

A baby girl with apgar scores of 5 and 8, weighing 3Kg., was delivered. Although the operation was completed within 40 min., the patient remained apnoeic. Artificial ventilation was required for four hours before the patient could be extubated safely. During this period of apnoea, she was incapable of independent breathing, but heard some of the conversation around her. Blood was not transfused. Vital signs after the patient resumed spontaneous respiration were blood pressure 130/80 mmHg, pulse 100/min., temperature 37°C, and respiratory rate 26/min.

Peripheral nerve stimulation to demonstrate neuromuscular block and determination of arterial blood gases could not be done.

Urine analysis, complete blood count, blood urea nitrogen, creatinine, liver function tests and chest radiograph were within normal limits. The patient was discharged after ten days in hospital in good condition.

At the National Research Institute of Health, in the Department od Drug Control and Toxicology, the PCE level was determined by Michel's method (10). On both December 15 and 22, 1988, the PCE level was 48 MU (normal range is 50 - 140 MU).

Inhibition studies to determine the genotype of PCE of the patient were not carried out. It was impossible to investigate the family of this patient for PCE levels as they live in Wollo Administrative Region.

DISCUSSION

Since PCE is genetically determined, its production is controlled by a locus on a gene. This locus can be represented by the symbol E_1 and the normal PCE by E_1^U and the atypical (abnormally inherited) gene as E_1^A. The genetically determined major variants of PCE can also be expressed by combination of allelemorphic genes.

Individuals who are normal homozygotes (E_1^U Eu - genotype) for the enzyme hydrolyse succinylcholine rapidly. Those individuals who are heterozygous break down the drug more slowly and may be in need of controlled artificial ventilation for a prolonged period. However, prolonged apnoea was observed in individuals homozygous for the normal enzyme at Caesarean section (11). In the same study, pregnant women, close to term and heterozygous for the normal and atypical enzyme, are said to be sensitive to succinylcholine.

Individuals homozygous for the atypical gene ($E_1^AE_1^A$) are rare: Kalow's and Churchill-Davidson's reports (12,13) estimated one of 2850 and one of 2400 cases of prolonged apnoea respectively.

The effect of pregnancy on a decreased level of PCE is well documented (14 - 18), but in a recent report Howard et al (19) suggest an initial fall in the activity of the enzyme which returns to normal values during late pregnancy.

Our patient received the recommended dose of succinylcholine and ketamine twice. This is a common practice as the drugs' activity in solution diminishes with time. According to Lee (20), prolonged apnoea could result if succinylcholine is given at 3 to 5 times the recommended dose. Ketamine, it was reported, augments the action of succinylcholine (21), but it has been shown that a single dose of ketamine potentiates the neuromuscular blocking effect of d-tubocurarine, but not that of succinylcholine (22).

Our patient has a PCE level on the low side of the normal range, received no blood transfusion, and artificial ventilation for a period of four hours was adequate to bring her to independent respiration. We presume that some genotypic abnormality of the enzyme might have been responsible for this complication.

When such a problem is encountered, patients should be artificially ventilated until the slow break down of succinylcholine has been completed. In order to provide cholinesterase, fresh blood or plasma transfusion is recommended to hasten the recovery (23). Nowadays, commercial cholinesterase preparations are available and could be administered to overcome prolonged apnoea (24,25).

Metabolism of succinylcholine can also be impaired when there is a deficiency of the enzyme due to liver disease, malnutrition, burns, etc (26), apart from conditions in which the enzyme is genetically atypical (27, 28). The patient had no debilitating disease.

Although prolonged apnoea due to either decreased PCE activity or a genetically determined atypical variant of the enzyme has not been reported previously in our population, it should be remembered that such a complication may be seen in hospitals where operations are carried out using succinylcholine as a muscle relaxant.

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HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION IN PATIENTS WITH LYMPHOID NEOPLASIA

Milkias Shamebo, MD

ABSTRACT. Forty-four patients with lymphoid neoplasia 37 males and 7 females aged 15 to 75 years, were seen in the Department of Internal Medicine, Tikur Anbessa (Black Lion) Hospital, Addis Ababa, Ethiopia, between January and December 1988. Twenty-seven (61.4%) had non-Hodgkin's lymphoma, eleven (25%) Hodgkin's disease and six (13.6%) chronic lymphocytic leukaemia. Six (22.2%) of the non-Hodgkin's lymphoma, one (9.1%) of the Hodgkin's disease and none of the chronic lymphocytic leukaemia cases had positive enzyme linked immunosorbant assay (ELISA) and Western Blot tests for human immunodeficiency virus (HIV) infection. Of the 6 non-Hodgkin's lymphoma patients with HIV infection, five had extra-nodal involvement - four of the gastrointestinal tract, including the oropharyax, and one of the cervix uteri. Four of these six had clinically advanced disease at the time of presentation and histologically three patients had intermediate and three high grade malignancy. Two of the patients have died within two months of diagnosis, one is lost to follow up, and three patients are still alive and well 12 to 46 months after diagnosis. The HIV positive patient with Hodgkin's disease had stage IV E disease involving the pancreas with mixed cellularity histology, and died seven months after diagnosis. Diffuse, aggressive non-Hodgkin's lymphoma and possibly atypical aggressive Hodgkin's disease, may be indicator diseases for AIDS in HIV seropositive individuals.

INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) was first reported in the USA in 1981 (1), and by late 1989 had affected 186,846 victims in 152 countries (2). The persons at risk of acquiring human immunodeficiency virus (HIV) infection in the USA and Western Europe are homosexual males, intravenous drug abusers and recipients of blood products infected with HIV (3-5). In Africa, however, AIDS cases are seen among heterosexuals who have multiple sexual partners (6-7), and by October 31, 1989, 32,105 cases had been reported to the World Health Organization (WHO) from 48 countries of this continent (2).

In Ethiopia, serosurveys conducted among prostitutes and their clients, reported in 1987, showed a prevalence rate of HIV antibodies of 7% (8). In addition, a serosurvey conducted on a large population from different parts of Ethiopia and in hospital patients has shown a tendency to increasing rates of HIV infection since 1984 (9). Clinical cases of AIDS have been documented in Ethiopians since 1986 (10). The total number of AIDS cases reported to the AIDS Control and Prevention Office in the Ministry of Health, Addis Ababa reached 236 in 1989 (2).

The initial criteria by the Center for Disease Control (CDC) for the diagnosis of AIDS were the occurrence of opportunistic infections or Kaposi's sarcoma with unexplained immunosuppression (11). Subsequently, however, many investigators (12-

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17) have reported the frequent occurrence of non-Hodgkin's lymphoma and the sporadic occurrence of Hodgkin's disease and T-cell chronic lymphocytic leukaemia in persons with AIDS, AIDS related complex and those at increased risk for AIDS, necessitating some modifications in the CDC criteria for the diagnosis of AIDS (18, 19).

The present study was conducted to find out the prevalence of HIV infection among patients with lymphoid neoplasia in Addis Ababa and characterize their clinical presentation, histology and prognosis.

PATIENTS AND METHODS

Forty-four patients with lymphoid neoplasia, 37 males and 7 females aged 15 to 75 years, seen as inpatients in the Department of Internal Medicine and followed by the haematology referral clinic of Tikur Anbessa Hospital, Addis Ababa, Ethiopia, were tested for the presence of HIV infection between January and December 1988. Twenty patients were newly diagnosed and twenty four had been followed for 3 months to 8 years. Non-Hodgkin's lymphoma and Hodgkin's disease were diagnosed by staining lymph node and other tissues with haematoxylin and eosin (20). Chronic lymphocytic leukaemia was diagnosed if the absolute lymphocyte count was more than 5,000 per mm^3, with the characteristic peripheral blood film findings (21).

The working formulation for clinical usage (22) was used to categorize non-Hodgkin's lymphoma into low, intermediate and high grade malingnancy. The Rye's histologic classification (23) was used to classify Hodgkin's disease. Clinical staging was according to Ann Arbor (24) for lymphomas and Rai et al (25) for chronic lymphocytic leukaemia.

The chemotherapeutic agents used were cyclophosphamide, vincristine (Oncovin) and prednisolone (COP), according to Schien et al (26) or cyclophosphamide, hydroxydaunomycin (Adriamycin), vincristine and prednisolone (CHOP) according to McVarley (27) for non-Hodgkin's lymphoma. Hodgkin's disease was treated with cyclophosphamide, with or without prenisolone (29).

The tests for HIV antibodies, enzymelinked immunosorbant assay (ELISA) (Wellcozyme anti-HTLV III, Wellcome Diagnostics, Dartford, U.K.) and Western Immune Blot (Bio/Rad, Novapath, Modespo, California, USA) were performed at the National Research Institute of Health, Addis Ababa, Ethiopia.

RESULTS

The clinical and pathological characteristics and the distribution of HIV prevalence among the 44 lymphoid neoplasia patients is shown in Tables 1 and 2. There were 37 males and 7 females (M:F 5.3:1) with mean age of 42.8 years (range 15-75). Most patients presented with advanced disease. Non-Hodgkin's lymphoma constituted 61.4% of all lymphoid neoplasia while Hodgkin's diseasse and chronic lymphocytic leukaemia accounted for 25% and 13.6% respectively. No cases diagnosed before 1985 were HIV antibody positive. The first HIV positive case was verified in a non-Hodgkin's lymphoma patient diagnosed in 1985. Most cases were diagnosed in 1987 (Table 2). Overall, six (22.2%) of the non-Hodgkin's lymphoma, one (9.1%) of the Hodgkin's disease and none of the chronic lymphocytic leukaemia cases had HIV antibodies.

The clinical characteristics of the lymphoid neoplasia patients with HIV infection are shown in Table 3. There were five males and two females. The age range was 26 to

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TABLE 1. Clinical and pathological characteristics of 44 lymphoid neoplasia patients at Tikur Anbessa Hospital, Addis Ababa.

	Number of Patients			
	Non-Hodgkin's lymphoma	Hodgkin's disease	Chronic lymphocytic leukaemia	Total
Sex M/F	21/6	10/1	6/0	37/7
Age, mean (range) yrs	42.5(15-75)	34.9(18-60)	51.2(40-67)	42.8(15-75)
Stage: I	2	1	-	
II	4	4	1	
III	15	4	2	
IV	6	2	3	
Histology: Low grade		6	[1]LP 2	
Intermediate		13	[2]MC 6	
			[3]NS 2	
High grade		7	[4]LD 1	
Unclassifiable		1	--	

[1]LP Lymphocyte predominance, [2]MC Mixed cellularity, [3]NS Nodular Sclerosis
[4]LD Lymphocyte depletion

TABLE 2. HIV infection in lymphoid neoplasia patients

Year of diagnosis of the lymphoid neoplasia	Type of lymphoid neoplasia			
	Non-Hodgkin's lymphoma	Hodgkin's disease	Chronic lymphocytic leukaemia	Total
	Number HIV Positive/Total number			
1981-1984	0/2	0/2	-	0/4
1985	1/1	0/1	0/2	1/4
1986	1/2	-	0/1	1/3
1987	3/7	1/5	0/1	4/13
1988	1/15	0/3	0/2	1/20
Total 1981-1988	6/27	1/11	0/6	7/44

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TABLE 3. Clinical characteristics of lymphoid neoplasia patients with HIV infection.

Patient	Date of diagnosis of lymphoid neoplasia	Age	Sex	Diagnosis	Presenting symptoms and signs
1	March 1985	32	M	Gastric NHL[1]	Hematamesis and molena
2	October 1986	26	F	Mesenteric NHL and TB[2] (pulmonary)	Abdominal mass, fever, sweating and weight loss
3	November 1987	35	M	Nodal NHL	Lymphadenopathy fever and weight loss
4	December 1987	57	M	Gastric NHL	Dyspepsia, fever and weight loss
5	December 1987	75	M	Tonsillar NHL	Dysphagia, fever and weight loss
6	August 1987	46	M	Pancreatic HD[3]	Weight loss, fever, sweating, jaundice and lymphadenopathy terminally
7	April 1988	47	F	Cervix NHL	postmenopausal vaginal bleeding, fever, sweating, weight loss

[1]NHL: Non-Hodgkin's lymphoma: [2]TB: Tuberculosis
[3]HD: Hodgkin's disease

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TABLE 4. Clinical stage, histology, treatment and outcome of lymphoid neoplasia patients with HIV infection

Patient	Diagnosis	Clinical Stage	Extra-nodal site involved	Histology	Treatment	Survival as at Dec. 1988
1	NHL	IE	Stomach	Diffuse, mixed, large and small cell	Surgery and COP[1]	Alive 46+ months
2	NHL	IE	Mesentery	Immunoblastic	Surgery & COP	Alive 26+ months
3	NHL	IIB	-	Diffuse, mixed, large and small cell	COP	Alive 12+ months
4	NHL	IVB	Liver and stomach	Diffuse, mixed large and small cell	None	Died, 2 month
5	NHL	IIE	Tonsils	Immunoblastic	Surgery and COP	Lost to follow-up after 6 months
6	HD	IVB	Pancreas	Mixed cellularity	Surgery, RT[2] and C-MOPP[3]	Died, 7 months
7	NHL	IVE	Cervix uteri	Small noncleaved cell	Surgery + CHOP[4]	Died 1 month

[1]COP: Cyclophosphamide, vincristine (Oncovine), prednisolone, [2]RT: Radiotherapy
[3]C-MOPP: Cyclophosphamide, vincristin (Oncovine), procarbazine, prednisolone
[4]CHOP: Cyclophosphamide, hydroxyldaunomycin (Adriamycin), vincristine (Acriamycin)

TABLE 5. Haematological data in lymphoid neoplasia patients with HIV infection

Patient	Hgb(gm%)	WBC/Lymphocyte (per mm^3)	Platelets (per mm^3)	ESR(mm/hr)
1	10.3	5800/2900	155,000	62
2	10.3	3400/680	110,000	20
3	15.7	10000/3800	150,000	43
4	11.4	3500/840	100,000	117
5	11.8	5400/1890	110,000	52
6	11.9	6000/1890	105,000	24
7	11.1	4500/1575	150,000	125

[1]H: Haemoglobin, [2]WBC: White blood cells, [3]ESR: Erythrocyte sedimentation rate

75 years with mean of 45.4. Except for one young lady from Asmara, all were residents of Addis Ababa. Two were single at the time of diagnosis of non-Hodgkin's lymphoma, while the rest were married with children. There were 3 civil servants, two merchants, one salesman and one housewife. None of the patients belonged to the known risk groups for HIV infection. One of the non-Hodgkin's lymphoma patients developed tuberculosis during the course of her illness and responded well to antituberculosis treatment.

Two patients with non-Hodgkin's lymphoma had clinical stage IE disease, both with involvement of the gastrointestinal tract (Table 4). Three patients had stages III or IV non-Hodgkin's lymphoma. Only one patient had disease confined to the lymph nodes. The only HIV-positive patient with Hodgkin's disease presented with an abdominal mass, progressive weight loss, fever, sweating and jaundice. Laparotomy revealed mixed cellularity Hodgkin's disease involving the head of the pancreas.

The histology of the non-Hodgkin's lymphomas was diffuse, mixed large and small cell (intermediate malignancy) in 3 patients, non-Burkitt type immunoblastic in 2, and small noncleaved cell in 1. All non-Hodgkin's lymphoma patients with extranodal involvement (except patient 4) had combined treatment with surgery and chemotherapy, while the patient with nodal disease only was treated with chemotherapy alone. Two patients died within two months of diagnosis, one was lost after follow-up for six months, three are alive and in good condition for 12-46 months after diagnosis. The patient with Hodgkin's disease was treated with surgery, radiotherapy to the pancreas and systemic chemotherapy. He died of progressive disease within seven months of diagnosis.

Haematological parameters in the seven patients are shown in Table 5. All but one had moderate anaemia (mean haemoglobin 11.8 gm%). Total lymphocyte count ranged from 680 to 3800/mm^3 (mean 1939/mm^3). It was not possible to measure T4/T8 ratio. The platelet counts were only moderately decreased ranging from 100,000 to 155,000/mm^3 (mean 119,000/mm^3). Bone marrow examination in four patients did not show any infiltration by malignant cells.

DISCUSSION

Neoplasia in the population at high risk for AIDS has been more frequently reported during the last five to six years. In addition to the opportunistic infections, Kaposi's sarcoma, non-Hodgkin's lymphoma and other tumours showed significantly higher incidence in homosexual men and intravenous drug abusers than in the general population. It now appears that the immune deficiency resulting from the initial infection with HIV may provide the opportunity for a second infection, not only with opportunistic micro-organisms producing severe systemic diseases but also with oncogenic viruses inducing specific types of neoplasia (13).

The resulting neoplastic diseases are not only more common in the groups at high risk for AIDS, but also different in their clinical presentation, histology, clinical course and response to therapy compared to those seen in the general population (17).

In this series of forty-four lymphoid neoplasia patients, HIV infection was found in 7 (15.9%). Six had non-Hodgkin's lymphoma and one had Hodgkin's disease, similar to previous observations (13,17). Four of the non-Hodgkin's lymphoma patients had advanced stage III disease and five extranodal involvement at the time of presentation. The gastrointestinal tract, including the oropharynx, was involved in four of the five. The other patient had involvement

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of the cervix uteri, an unusual site for lymphoma. There was no central nervous system or bone marrow involvement identified in this series in contrast to observations by other workers (12, 17).

The histology of this small group of patients with non-Hodgkin's lymphoma was of either intermediate grade (diffuse, large and small cell) or high grade malignancy (immunoblastic and small non-cleaved cell). Some authors have observed that low grade malignancies may occur in individuals with AIDS (12), but a recent report from a multicentre study suggested that the lymphomas were usually of high grade malignancy with small, non-cleaved, immunoblastic plasmacytoid, or large cell lymphoma (17).

The number of patients in this series is too small to make a meaningful analysis of clinical presentation and survival. It is known that patients with AIDS-associated non-Hodgkin's lymphomas survive for shorter periods compared to those without AIDS (22), and that survival is affected significantly by the histologic type (17).

There was one case of Hodgkin's disease in a 46 year old man who had involvement of an unusual organ (the pancreas), a rapid downhill course to death only seven months after diagnosis, in spite of aggressive treatment with surgery, radiotherapy and combined chemotherapy. Since 1984, there have been reports of individual or small groups of HIV positive Hodgkin's disease cases from several institutions (14, 15, 17). Most of these patients, like ours, had advanced disease (stage III or IV) and B symptoms. These clinical findings contrast markedly with those of Hodgkin's disease unassociated with AIDS which is usually asymptomatic and localized to a single lymph node group at presentation (17). Our patient had mixed cellularity histology as did most patients in the literature. Again, in marked contrast to classical Hodgkin's disease, most patients with AIDS-associated Hodgkin's disease, have an aggressive rapidly fatal clinical course.

None of the patients with chronic lymphocytic leukaemia in this series had evidence of HIV infection; there were three cases of T-cell chronic lymphocytic leukaemia in a recent report (17).

It has been suggested that diffuse, intermediate grade, aggressive non-Hodgkin's lymphoma be included as an indicator disease for the diagnosis of AIDS in HIV positive persons (30), and possibly also atypical, aggressive Hodgkin's disease (17). The cases reported here lend support to this suggestion.

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LEUKAEMIA IN ADULT ETHIOPIANS

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ABSTRACT. *The pattern of leukaemias in adult Ethiopians admitted to Tikur Anbessa (Black Lion) Hospital, a teaching and referral hospital in Addis Ababa, Ethiopia, from January 1982 to December 1985 is analyzed. There were a total of 7969 medical admissions, of which 180 (2.3%) were for leukaemia. The age range was 14 to 80 years, with a mean of 37.6 years. The male : female ratio was 2.3 : 1. The commonest type of leukaemia was chronic myeloid leukaemia (CML) 57.8%, acute leukaemias and chronic lymphatic leukaemia (CLL) accounted for 21.1% each. Of the acute leukaemias, 53.3% were lymphoblastic (ALL) while 46.7% were acute myeloblastic (AML). Most patients came from Addis Ababa (30.6%) and Shoa (28.9%) regions. The overall incidence of leukaemia in Addis Ababa population was estimated at 1.95 ± 0.79/100,000/year at 95% confidence interval. The purpose of this study is to attempt a detailed description of leukaemias in Ethiopian patients and compare the findings with similar studies from other countries. Leukaemias are commoner than previously thought, and warrant further study in the community so that management, especially of acute forms, can be improved.*

INTRODUCTION

Leukaemias occur world-wide; the incidence of these diseases, however, appears to be different in various countries. In the United States of America (USA) and Western Europe, the incidence of leukaemias is 9.0/100,000 population/year (1). It is said that in USA, leukaemias were less common in blacks than in whites (1). Reports from Africa in the 1960's had suggested that leukaemias were uncommon (2), the likely reason being underdiagnosis (1,2), and other reports suggested that African children resisted leukaemia (3). Subsequent retrospective and prospective studies, however, have shown that leukaemias were more frequent than previously suggested (4-12). Analyses of medical admissions to various Ethiopian hospitals in the 1960's reported very low figures for leukaemias (13-17). A more recent analysis of haematological disease admissions found a higher proportion of leukaemias among medical admissions (18). The aim of this prospective study is to attempt a detailed description of leukaemias in terms of incidence, types, distribution by age, sex and geographic regions and to compare the findings with similar studies from other countries.

PATIENTS AND METHODS

This study is based on the analysis of 180 consecutive new cases of leukaemia admitted to the adult medical wards of the Tikur Anbessa (Black Lion) Hospital, Addis Ababa University's teaching and referral hospital, between Juanuary 1982 and December 1987. One patient with chronic lympho-

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cytic leukaemia (CLL) seen in the gynaecology department was included. No patients were seen in the surgical department during the study period. Leukaemia cases from other hospitals whose bone marrows were reviewed by the author were not included in this study. All patients with the diagnosis of leukaemia were admitted for investigations and management.

The age, sex, address, date of diagnosis and type of leukaemia of each patient as well as the clinical, haematological, biochemical, radiological and bone marrow aspiration results were recorded prospectively. The diagnosis of leukaemia was based on clinical and haematological findings, mainly on the morphology of peripheral blood and bone marrow stained by Wright's stain (19).

The population figures for Addis Ababa were obtained from the data of the 1984 population census of the Central Statistical Office (20). To estimate the crude incidence of leukaemia for Addis Ababa, all leukaemia cases (adults and children) from Addis Ababa Hospitals (including Tikur Anbessa) diagnosed during the study period were included. To avoid duplication of cases, patients were identified by their particulars, i.e. name, age and sex.

RESULTS

During the study period, there were a total of 7969 admissions to the medical wards of the Tikur Anbessa Hospital of which 180 (2.3%) were for leukaemias. There were 126 males and 54 females, giving male : female ratio of 2.3 : 1. The age range was 14-80 years (mean 37.6 years).

Table 1 shows annual proportions of leukaemia over the six years. The proportion has ranged from 1.4% to 3.3% of medical admissions, with an overall rate of 2.3%. There was a steady rise since 1983 but a sharper one in 1987 to a maximum of 52 cases, mainly due to an increase in the number of chronic leukaemias.

A rough estimate of crude incidence in Addis Ababa was calculated by using the annual number of cases of leukaemia documented in all Addis Ababa hospitals, including childhood cases. There were 172 cases of leukaemia from other Addis Ababa hospitals and the overall estimated crude incidence rate, at 95% confidence interval, was 1.95 ± 0.79 (1.62-2.74)/100,000/ year.

Table 2 shows the age and sex distribution of leukaemias in adults. Almost 75% of leukaemias occurred below the age of 50 years and more commonly in males than females. The male to female ratios for ALL, CML and CLL were 3 : 1, 0.8 : 1, 1.9 : 1 and 11.6 : 1 respectively.

The age groups and types of leukaemia are shown in Table 3. Acute lymphoblastic leukaemia (ALL) and acute myeloblastic leukaemia (AML) occurred almost equally, respectively 11.1% and 10.0% of all cases. Patients with ALL were younger than those with AML. 16/20 (80%) of ALL patients were less than 30 years old (mean 24.9 years) while 7/18 (39%) of AML cases were less than 30 (mean 36). Chronic myeloid leukaemia (CML) was the commonest type of leukaemia, 104 cases (57.8%), and it commonly occurred below the age of 50 years (mean 35.6 years). Chronic lymphatic leukaemia (CLL) occurred in the age group above 40 years (mean 53.8 years) and accounted for 21.1% of all leukaemias.

The geographic distribution of the leukaemia cases seen is shown in Table 4. Most patients came from Addis Ababa 55/180 (30.6%) and Shoa 52/180 (28.9%). It is noteworthy that most patients with acute leukaemia 24/32 (63.3%) were from Addis Ababa, while a higher proportion of the chronic leukaemia cases came from Shoa 48/142 (33.8%) and other regions 63/142 (44.4%).

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TABLE 1. Annual leukaemia admissions in relation to medical admissions Tikur Anbessa Hospital, Addis Ababa, Ethiopia, 1982-1987

Year	Types and number of leukaemia					No. of medical admissions	% leukaemia admissions
	ALL	AML	CML	CLL*	Total		
1982	6	2	23	2	33	1434	2.3
1983	1	2	3	7	13	928	1.4
1984	2	1	15	2	20	1428	1.4
1985	3	8	12	8	31	1347	2.3
1986	4	3	19	5	31	1240	2.5
1987	4	2	32	14	52	1592	3.3
Total	20	18	104	38	180	7969	2.3

* Includes one case of hairy cell leukaemia
ALL - Acute lymphoblastic leukaemia
AML - Acute myelogenous leukaemia
CML - Chronic myelogenous leukaemia
CLL - Chronic lymphocytic leukaemia

TABLE 2. Age and sex distribution of patients with leukaemia

Age group * (years)	Sex		Total	
	Male	Female	No.	%
11 - 20	9	7	16	8.9
21 - 30	30	17	47	26.1
31 - 40	27	12	39	21.7
41 - 50	21	10	31	17.2
51 - 60	23	5	28	15.6
61 - 70	11	3	14	7.8
Over 70	5	-	5	2.7
Total	126	54	180	100.0

* Children are seen in Ethio-Swedish and Birla Paediatric Clinics.

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TABLE 3. Age groups and types of leukaemia

Age groups * (years)	Types of leukaemia				Total	
	ALL	AML	CML	CLL*	No.	%
11 - 20	6	2	8	-	16	8.9
21 - 30	10	5	32	-	47	26.1
31 - 40	2	4	29	4	39	21.7
41 - 50	-	3	18	10	31	17.2
51 - 60	2	3	13	10	28	15.6
61 - 70	-	1	4	9	14	7.8
Over 70	-	-	-	5	5	2.7
Total	20	18	104	38	180	100.0

* Children are seen in Ethio-Swedish or Birla Paediatric Clinics.
* Includes one case of hairy cell leukaemia

TABLE 4. Distribution of leukaemias cases seen in Tikur Anbessa hospital, Addis Ababa, by geographic region.

Region	Types of leukaemia				Total	
	ALL	AML	CML	CLL*	No.	%
Addis Ababa	15	11	20	11	55	30.6
Shoa	2	2	35	13	52	28.9
Gojjam	1	1	8	5	15	8.3
Sidamo	1	-	8	3	12	6.8
Arsi	1	-	7	2	10	5.6
Wollo	-	1	7	1	9	5.0
Hararghe	-	-	6	1	7	3.8
Wollega	-	1	4	1	6	3.3
Eritrea	1	2	1	-	4	2.2
Kaffa	-	-	3	1	4	2.2
Tigrai	-	-	2	-	2	1.1
Illubabor	-	-	2	-	2	1.1
Bale	-	-	1	-	1	0.6
Assab Admin. Region	1	-	-	-	1	0.6
Total	20	18	104	38	180	100.0

* Includes one case of hairy cell leukaemia (HCL)

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TABLE 5. Distribution of types of leukaemias reported from various countries.

Author(s) (Ref.)	Country	Acute leukaemia	% type of leukaemia		Total no. of cases
			CML	CLL	
Kasili et al (4)	Kenya	54.2	25.4	16.2	456
Eissen (11)	Nigeria	19.5	40.0	40.5	182
Davies (3)	Uganda	9.9	48.8	41.3	121
Gunz et al (1)	Caucasions	60.0	15.0	25.0	-
Ahmed et al (7)	Sudan	42.2	42.5	13.3	256
Levy (8)	Zimbabwe	49.5	30.0	20.5	127
Booth et al (23)	Papua New Guinea	71.0	27.0	2.0	173
Lester (15)	Ethiopia	24.2	48.5	12.1	33
Present Series	Ethiopia	21.1	57.8	21.1	180

Note: Childhood leukaemias are included in all these studies except those of Levy (8) and Lester (15), and the present study.

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DISCUSSION

In this study, leukaemias accounted for 2.3% of all medical admissions to the Tikur Anbessa Hospital during six years. Previously in Ethiopia leukaemias had been reported in 0-0.3% of medical admissions (13-17). The higher rate in this study may be due to referral of cases to this hospital, rather than actual increase in the number of cases of leukaemia. The rough estimate made of the crude incidence of leukaemias in Addis Ababa was 1.95 ± 0.79/100,000/year. This figure is much less than figures from USA, Europe and Australia where the incidence is 9.0/100,000/year (1). The findings in this study are similar to those from Kenya, 3.4/100,000/year (4) and Nigeria, 2.7/100,000/year (21), but higher than that from Papua, New Guinea, 0.79/100,000/year (22). The low figures in this study and in other developing countries may be due to underdiagnosis or misdiagnosis. This is especially true for acute leukaemias, as up to 30% of the cases in this series were misdiagnosed at the time of admission. The other reason may be that the patients die at home before reaching health institutions. This may be the reason for the paucity of acute leukaemia cases from the regions; those from Addis Ababa may more quickly reach hospitals, and hebhce the relatively higher number of acute leukaemia cases from the city.

The overall male:female ratio was 2.3 : 1. This is a higher figure than reported from Zimbabwe (8) and in Caucasians (1). It is said that male : female ratio for chronic lymphocytic leukaemia in Caucasians is 2 : 1 (1), while in Nigeria the females predominate (11,12): in this study, however, it was 11.6 : 1. There is no good explanation for this other than the possibility that males may be visiting health institutions more frequently than females as this is a well known phenomenon in developing countries. This distribution of the different types of leukaemias are compared with those reported by different authors from different countries in Table 5.

The places of residence of the patients is shown in Table 4. Most patients (60%) came from Addis Ababa and Shoa regions. This is in keeping with the observation of MacMahon (23) that referral hospitals attract patients from the regions in close proximity to them.

In conclusion, leukaemias are much more commonly seen in Ethiopians than was previously reported. This may be due to increase in correct diagnosis rather than to increase in their incidence. Therefore, further study in the community is warranted, especially to strengthen the management of the acute leukaemias.

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Ceftriaxone in the Treatment of Septicaemia due to MultipleDrug Resistant Bacteria

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SUMMARY

Ceftriaxone, a highly effective, B- Lactamase resistant broad spectrum parenteral cephalosporin was used in the treatment of 26 consecutive patients with clinically and/or bacteriologically resistant infections at the Addis Ababa University Tikur Anbessa and Ethio-Swedish Paediatric Teaching Hospitals. The patients who had failed to respond to a combination of two or more previously appropriate antibiotics were treated with ceftriaxone administered in two divided doses (daily 50 - 100 mg/kg) in children and a single dose of 2 -3 gm in adults for an average duration of 9.9 days. Of the 21 evaluable cases 16 (76%) were cured, three died and two developed superinfection with *Pseudomonas* and *Staphylococcus* species.

Primary pathogenic bacteria were eradicated from all the 21 bacteraemic patients on the third day of therapy. Twelve of the 21 patients had serious underlying conditions. Except for the two superinfections, the results of the trial confirm that ceftriaxone is a very potent and effective agent in the treatment of resistant bacteraemic infections. No significant adverse effect of the drug was encountered during the therapy.

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INTRODUCTION

Ceftriaxone is a B-lactamase stable third generation cephalosporin, active against a broad range of pathogenic bacteria. These include gram positive and gram negative cocci (except interococci and methicillin-resistant staphylococci), enteric gram negative bacilli and many anaerobes[1,2]. The drug can be useful especially for infections caused by multiple drug resistant *Enterobacteriaceae* or other pathogens of hospital acquired (nosocomial) infections[3].

The prolonged serum half-life of eight hours, longer than any currently available cephalosporins, allows one or two daily administration without loss of efficacy over a 24-hour period[4,5,6].

In health institutions with acute material and manpower shortages, a highly potent broad spectrum antibiotic, that can be administered effectively once or twice a day, is a very attractive alternative to the usual standard therapy. Thus, this open non-comparative trial on resistant bacteraemic infection was undertaken to test the efficacy and adverse effects, if any, of the drug under local conditions in hospitalized Ethiopian patients.

MATERIALS AND METHODS

All age groups with serious bacteraemic infections that failed to respond to other appropriate antibiotics, or for which there were no alternative drugs due to toxicity, unavailability were included. Failure of previous therapy was defined as absence of improvement after seven days of treatment and or demonstration of resistance of the pathogen to the drug being administered. Exclusion criteria were pregnancy, *in-vitro* ceftriaxone resistance and known hypersensitivity to cephalosporins or penicillins.

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The staff and residents of Tikur Anbessa and Ethio-Swedish Paediatric hospitals in Addis Ababa, were requested to contact the study group when they encountered clinically and/or bacteriologically resistant infections in their wards. Informed consent was obtained from the patient or guardian in the case of children. Diagnosis of septicaemia was made on the basis of two or more positive blood cultures. Sensitivity to ceftriaxone was determined by the standard Kirby-Bauer method[7] with discs containing 30ug of the drug. Growth inhibition zone diameter of more than 16 mm indicated sensitivity. The drug, ceftriaxone (Rocephin) and its discs for sensitivity testing were kindly supplied by courtesy of Hoffmann La Roche & Co., Basle, Switzerland.

Cure was considered only if the patient became afebrile, all signs and symptoms of infection disappeared and blood cultures became negative. Improvement was taken as partial resolution of symptoms and signs. It was graded as failure when no improvement was apparent or clinical condition deteriorated after four days of therapy.

Bacteriological grades consisted of (1) bacteriological cure when the offending pathogenic bacteria were eradicated during and following therapy, in which case, duration of observation lasted only two days after the end of treatment; (2) emergence of resistant strain; and (3) superinfection by another pathogen.

From November 1986 to October 1987, 200 cases with suspected septicaemia were referred. After investigations, 26 patients who satisfied the criteria were included into the study. The age of the patient ranged from nine days to 52 years, composed of 16 paediatric age and 10 adults. There was equal (13) distribution by sex. Five of the patients were not evaluated.

Ceftriaxone was administered by a slow intravenous injection in a dosage of 50 - 100 mg/kg/day in two divided doses in children and 2 - 3 gm/day in a single daily injection in adults. Once therapy started, cultures were repeated within 72 hours, every fourth day thereafter, and 48 hours after completion of treatment, when clinically appropriate. Other laboratory follow up consisted of haemoglobin, total and differential leucocyte count, and sedimentation rate every third day.

RESULTS

Twenty-six patients were entered into the study. Five were not evaluable. Three of the five patients, though clinically septic, did not have bacteraemia. The first of these had CSF - fistula after stab wound on the posterior neck. *Pseudomonas* species was grown from the cerebrospinal fluid after two weeks course of gentamicin and ampicillin combination. Ceftriaxone also failed to eradicate the infection despite *in-vitro* sensitivity. The patient's recurrent pseudomonas meningitis was successfully treated with a combination of gentamicin and ceftriaxone. The second patient had postoperative right hip arthritis caused by *Proteus mirabilis* cultured from pus discharge and was successfully treated with a four-week course. The third had *Citrobacter* species grown from only a single culture of blood, thus failing to satisfy the definition of septicaemia. He was successfully treated with a nine-day course of ceftriaxone.

The fourth case had *Klebsiella pneumoniae* bacteraemia and died on the third day of therapy from gangrenous intestine before the effect of the drug could be assessed. The fifth patient had intravenous catheter-related bacteraemia due to *Staphylococcus aureus* sensitive to penicillin and cephalosporin. Ceftriaxone was administered before trial of appropriate first line drugs.

Twenty-one of the patients that were evaluable consisted of 13 paediatric and eight adult cases. In terms of sex, the evaluable subset comprised eleven males and ten females. Their age ranged from nine days to 52 years, with a mean of 254.6 days for paediatrics and a mean of 34.6 years for adults. All patients, except two, were given appropriate antibiotics in adequate doses for seven or more days. The two patients deteriorated after four days on antibiotics. Blood culture grew organisms resistant to the antibiotic being administered. All the 21 patients received two or more previous drugs (average 2.78, median 2) for an average duration of 13.6 days and a median of 12 days. The mean duration of hospital stay before initiation of ceftriaxone was 17.2 days, median 12 days, and range of four-50 days. All the patients, except one, received gentamicin combined with other antibiotics in adequate doses.

Twelve of the patients, evenly distributed be-

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tween paediatric patients and adults, had serious underlying conditions. Among the paediatric patients, three were pre-term infants. The other three had second degree burn, malnutrition, and operating for bone fracture. Six of the eight adults had the following conditions: recent operations for hepatic hydatid cyst (2), hepatoma and recent operation for ruptured uterus (1), diabetic ketoacidosis (1), diabetes mellitus with cirrhosis of the liver (1), and tuberculosis spondylitis (1).

In those that responded favourably, fever subsided in one-four days in the majority of cases. Sixteen were cured at the end of follow up that lasted only two days after the end of ceftriaxone treatment.

Of the remaining five patients, three died during or at the end of therapy. Two had superinfection with resistant *Staphylococcus aureus* and *Pseudomonas* species on the third and ninth day of therapy, respectively.

The first death occurred due to infection by *Salmonella* group B that was resistant to chloramphenicol and cotrimoxazole. It was sensitive to ceftriaxone and negative culture indicated that the bacteria were eradicated from blood on the third day of therapy. However, the patient died on the fourth day from intestinal haemorrhage and paralytic ileus. The second death occurred from advanced cirrhosis and hepatoma two weeks after the end of therapy. The patient had secondary pseudomonas septicaemia that originated from infected operation wound. It was sensitive to ceftriaxone *in-vitro*.

Two sets of blood cultures on the third and seventh days did not grow organisms. Post-mortem examination failed to show evidence of abscesses or septicaemia. The third patient had *K. pneumoniae* sepsis that was also grown from urine culture. She initially became afebrile and all signs of infection subsided. Follow up cultures were negative. But after a few days, she developed high grade fever followed by repeated convulsions, lapsed into coma, and died in one week. CSF and blood remained negative on subsequent culture. Since post-mortem study was refused, the cause of death was not ascertained. Her underlying illness was tuberculous spondylitis with evidence of increased intracranial pressure associated with paraparesis and incontinence.

Initial pathogens were eradicated in all 21 evaluable cases. The types of bacteria isolated are listed in Table I. Clinically, of the 21 cases that could be evaluated, 16 were cured and three improved initially but died later for reasons pointed out earlier. There were two failures.

TABLE I - Types of bacteria isolated

Type	Number
Klebsiella pneumoniae	9
Pseudomonas species	5
Salmonella Group B	2
Enterobacter agglomerans	2
Escherichia coli	1
Proteus mirabilis	1
Serratia species	1
Total isolates	21

DISCUSSION

Ceftriaxone, a very potent parenteral broad spectrum cephalosporin, was administered to eight adults and 13 paediatric patients. Because of its exceptionally prolonged half-life, administration of the drug was done once or twice a day.

Results were very good with a cure rate of 76 pc (16/21) and 100pc (21/21) eradication of primary pathogen. Two of the three deaths are probably attributable to serious underlying illness. In the third death, there was complete eradication of the pathogen and an initial clinical improvement. The cause of death could not be ascertained. The cure rate is lower than the 86 pc reported by Baumgartner *et al* [3] in their large series of refractory bacteraemia infections. However, our cases have more serious underlying conditions than theirs.

The occurrence of resistant *Pseudomonas* and *Staphylococcus aureus* is the main deficiency. Probably, the drug should not be the first choice in infections caused by these organisms. In this study, Gram negative organisms were the main cause of bacteraemia. The predominance of multi-drug resistant *K. pneumoniae*, including to gentamicin, in paediatrics (6/13) may be related to the high incidence of infection by this organism in the obstetric/gynaecological

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ward[8]. Although the excellent activity of the drug against resistant *K. pneumoniae* and *Enterobacteriaceae* is a welcome finding, urgent action is needed to define the size and nature of the problem in these institutions.

Except two cases of mild diarrhoea, no clinical or haematological adverse effects were recorded.

Though the series is small, ceftriaxone has proved to be effective in the treatment of resistant infections in these large teaching hospitals including infections for which gentamicin was ineffective.

The high cure rate of all the five cases of Pseudomonas infections may be related to the rare or non-usage of cephalosporins in these hospitals and hence the prevailing strains being susceptible.

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COMMUNITY-BASED STUDY OF NEUROLOGICAL DISORDERS IN ETHIOPIA: DEVELOPMENT OF A SCREENING INSTRUMENT

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ABSTRACT. This paper describes the development of a screening instrument for a community-based neuroepidemiological survey in a rural community in Ethiopia. A pilot study in 1984 to pre-test the questionnaires developed revealed that epilepsy, poliomyelitis, mental retardation and speech disturbances were the most common neurological disorders among the 3,000 rural inhabitants surveyed. The study suggested that a base-population of about 50,000 was required for a future major epidemiological survey to identify rare neurological disorders.

INTRODUCTION

For any country to deliver appropriate and adequate health services to its people, it must possess accurate data on the pattern and prevalence of diseases. This is even more relevant in a developing country such as Ethiopia, where there are limited resources and limited trained manpower to run preventive and intervention programmes. Such information is best obtained in well executed population based epidemiological studies.

In recent years attention has been drawn to the need for neuroepidemiological studies. A screening instrument for neuroepidemiological surveys was developed in 1981 under the auspices of the Neurosciences Programme of the World Health Organization (1). Subsequently, studies undertaken in Nigeria (2-4), Ecuador (5) and China (6,7) have been reported. These studies have contributed to the understanding of prevalence of neurological disorders in different parts of the world.

In 1983/84 we developed a protocol for an epidemiological study to determine the prevalence of neurological disorders in an Ethiopian rural community. This paper describes the methods used in the development of the screening instruments and the pilot studies which were performed to pre-test them. The results of the studies were also used to determine the population size required for the major neuroepidemiological survey that will follow.

MATERIAL AND METHODS

The first questionnaire prepared was for collection of demographic data (Figure 1). In its design there was an assumption based on previous experience that villagers in our rural communities were unable to give correct and detailed information on the characteristics of all household members unless we used methods that would systematize their recall capabilities. We found that going through a list of the members of the household in an age/chronological order, starting with the head of the household, followed by the wife and children, and finally other relations, was the most efficient approach. For instance, the results of asking

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the head of the household to tell the number of children under a certain age or belonging to a certain sex were often inaccurate and unreliable. Information required on every member of the household was: relation to head of the household, age and sex, marital status, number of wives, ethnicity, literacy, duration of residence and condition of health at the time of the interview. General information on diet was also registered.

The second questionnaire developed (Figure 2) was aimed at separating those with neurological disorders from those identified by the first questionnaire as having an illness. The questionnaire was simplified and addressed itself to the specific disorders that had been chosen as important and identifiable in a reasonably accurate manner. Thus, headaches and low-back pains were excluded because information obtained on them was too subjective and often unreliable. The neurological symptoms included were mental retardation, speech disturbances, loss of consciousness, seizure, convulsion, motor weakness, movement disorders, walking difficulty and sensory disturbances. There were direct questions on leprosy and other chronic non-neurological diseases.

The third and major questionnaire (Figure 3) contained the neurological enquiries. It was completed on all those patients identified as having neurological disorders. It documented the age, sex and occupation of the patients, and also the consumption of the neurotoxic pulse, *Lathyrus sativus*. For each of the neurological disorders considered, there were questions on the age and manner of onset and a search for specific and related characteristics. In addition, the familial occurrence of the disorder identified, condition at the time of birth, history of trauma, diabetes and/or excess consumption of alcohol by the patients were documented. For those with epilepsy, an additional questionnaire was prepared, obtaining detailed information of characteristics of the seizures and the socioeconomic status of the affected person.

While the questionnaires were being prepared, polished and translated into Amharic, the official Ethiopian language, the enumerators were carefully recruited among the local secondary school graduates. Recruitment criteria included sound knowledge of the local customs, culture and dialects as well as previous experience in similar field surveys. They were trained on the concept of door-to-door field survey and the use of questionnaires in a neuroepidemiological study. Their training took four months, including mock sessions where they were made to complete questionnaires while interviewing their instructors (neurologist and the field supervisor) who posed as rural "heads of households" having different types of neurological disorders. These classroom exercises and interviews of villagers in field situations were carried out repeatedly until the neurologists were convinced that each of the enumerators had understood what he or she was supposed to do and had also mastered the art of interviewing and completing questionnaires correctly. In addition, experts from the demographic section of the Ethiopian Central Statistics Office instructed the enumerators on the basic art of simple mapping of villages.

The enumerators were given practical demonstrations on recognizing signs and symptoms of the neurological disorders they were supposed to identify. They were also shown cases of diseases that could simulate and be confused with neurological conditions.

Their supervisor, a Health Officer,

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spent two months attached to the Neurology Unit of the Department of Internal Medicine of the Tkur Anbessa Teaching Hospital in Addis Ababa. His practical instruction in recognizing neurological symptoms and signs was given by neurologists.

The enumerators were instructed and encouraged to observe signs, and to perform simple neurological examinations. Their observations and superficial examinations, as well as doubtful cases encountered during the interviews, were counterchecked by an experienced field supervisor with medical training.

Figure 4 shows the study model planned for the neuroepidemiological survey; it is similar to the one proposed by Schoenberg (8), but includes some modifications of our own. Emphasis was placed on the completeness of the forms being administered by the enumerators, whose honesty and accuracy in the conduct of the clinical interviews was periodically checked confidentially. Neurologists regularly examined all those with suspected neurological disorders, in order to validate the diagnoses.

The first pilot study was carried out in April 1983 in the small town of Koshe (Pop. 2,700), 185 km south of Addis Ababa. In this survey the first set of questionnaires developed were tested. There were a number of problems encountered both in the design of the questionnaires and their administration by the enumerators. Based on the experiences gained, revisions of the questionnaires and improvement of the field survey logistics were made.

The second pilot study was subsequently undertaken in the town of Adami Tulu in April 1984 (Figure 5). Adami Tulu is a small town (Pop. 3,000) situated on the major Ethiopian south-bound road, about 170 km from Addis Ababa. It is a town at the periphery of the proposed research area of the Meskan and Mareko subdistrict (Figure 5), with characteristics similar to the community to be studied. After consent was obtained from the administrative officials, the town was mapped and the houses were numbered with chalk. Mill-houses, schools, worship centres and administrative offices were excluded. The enumerators then conducted a door-to-door interview of heads of households. In polygamous marriages, a second wife was considered the head of household if she occupied an independent house. All neurological cases identified by the enumerators were examined by neurologists.

From 4 urban dwellers' and 2 peasant associations within the project subdistrict of Meskan and Mareko, a neurologist with the help of four medical officers selected 20 consecutive households, each with known neurological disorders (epilepsy, poliomyelitis and mental retardation) irrespective of the severity of the condition. Equal numbers of households without diseases were also chosen. Enumerators without prior knowledge of the village were assigned to make a door-to-door interview of all the households identified by the neurologist. This exercise was used to determine the sensitivity and specificity of the screening instrument.

In spite of the modification in our protocol and logistics in the implementation of the neuroepidemiological survey, the screening instruments have adhered to the guide lines laid down by Schoenberg (8). As suggested by Osuntokun et al. (2), attempts have been made to achieve a degree of uniformity with other protocols, principally WHO's, in order to allow comparisons of neurological disorders in developing countries.

RESULTS

Of the total population of Adami

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Tulu, 2747 inhabitants (92%) were included in the survey. The rest could not be reached on repeated visits within the limited time available for the pilot survey because the families had either gone to fields for the seasonal pepper harvest or to the market place. There were 5.3 persons per household; 81.5% of the inhabitants were Muslims and 37.8% belonged to the Gurage ethnic group.

Table 1 shows the age and sex distribution in the town. Nearly 60% of the inhabitants were under the age of 20 years. The median age of the population was 15.7 years. A slight preponderance of females (96/100) was found. These census data were similar to the national figures for Ethiopia (9).

Forty-four persons (1.7%) with neurological disorders were identified in the rural town surveyed. Epilepsy, mental retardation and poliomyelitis were the most common disorders (Table 2).

As shown in Table 3, the sensitivity and specificity of the screening instrument varied between types of neurological disorders. However, for the common neurological disorders that were chosen, the sensitivity and specificity of the screening instrument were 91% and 85% respectively.

What transpired from the pilot studies was the need, in the preparatory phase, to repeatedly modify the different questionnaires until statements that are easily understood and interpreted by the rural population were designed. This was particularly true of an epidemiological study of neurological disorders, such as ours, where the nature of symptoms could be difficult to appreciate and describe.

In this context, sensory symptoms posed a formidable problem. Information on sensory deficits was difficult to extract from a patient unless the deficit was very obvious, as in leprosy. In actual fact, our trained enumerators themselves had difficulties in appreciating subtle sensory symptomatologies, as in distal peripheral neuropathies. Villagers tended to use numbness or burning sensation and "rheumatic pain" indiscriminately. The enumerators were therefore instructed to consult their supervisor, and to bring to the attention of neurologists all cases with doubtful sensory symptoms.

DISCUSSION

It is estimated that over 90% of the Ethiopian population live in rural areas. The country's health care delivery is organized in a system of health stations and centres in the rural areas, and of regional and central hospitals in the capitals of the administrative regions and in Addis Ababa, the national capital. The rural health facilities are still inadequate and unevenly distributed. Given these deficiencies, there is a need to devise ways of maximizing the health care of the population within the existing health infrastructure. To this end, as Osuntokun et al (2) have convincingly argued, Ethiopia, like all other developing countries, requires accurate information from community based epidemiological studies, in order to facilitate setting of priorities.

As this pilot study demonstrates, neurological disorders like epilepsy, polomyelitis and mental retardation are not uncommon in the country (Table 2). In a small survey in western Ethiopia, Giel (10) estimated the prevalence of epilepsy at between 5 and 8 per thousand.

Assuming a prevalence of epilepsy of 5 per thousand, there are at least 230,000 persons with epilepsy in Ethiopia. From our hospital based experience, we estimate that less than 5 per cent are taking any kind of anti-convulsant therapy. The majority

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of the rural-based health facilities do not stock even phenobarbital, which is a very inexpensive drug to treat epilepsy, a disease that carries a lot of social stigma. Thus, epilepsy remains a neglected problem in the health care system of the country.

In a school survey undertaken in Accra, Ghana residual poliomyelitis was found to have a prevalence rate of 5.8 per 1,000 (11). Residual poliomyelitis in Ethiopia is common, if we judge from the large numbers of cases seen among children coming to medical centres all over the country.

It was against this background that our neuroepidemiological study was conceived. A slight departure from the neuroepidemiological protocol developed by WHO (1) was necessitated by the very elaborate and complicated nature of the protocol. Our simplified questionnaires proved in practice convenient for administration by enumerators. The forms developed were easy to carry about and complete at the village level by enumerators who had to cover long distances either on foot or horseback.

The experience we gained from this exercise was that questionnaires to be administered by the enumerators had to be simple and yet maintain a high degree of sensitivity and reasonable specificity. It must be emphasized that there is a need to assume that the villagers in an African rural setting cannot easily recall vital information and events leading to disease, unless appropriate methods to help in the recall process are designed. This, of course, has to be done within the cultural, educational and socioeconomic background of the community being studied.

For instance, our rural community had difficulties in differentiating finer details of onset and progression of symptoms. The defining of relapses and remissions was difficult to get across to the villagers. We therefore settled on confining ourselves to the acute and gradual qualifications of onset. In a country where previous reports (12, 13) have shown that demyelinating diseases like multiple sclerosis are very rare, this decision would not significantly affect the overall results of a neuropeidemiological study.

We were quite aware that, under the diagnoses of blindness, deafness, movement disorders and walking difficulties (Figure 3), enumerators would include both neurological and many cases of non-neurological cause. We welcomed this, because it was a safety measure to ensure that the genuine neurological cases were not being missed. All these cases were later examined by neurologists who identified the truly neurological cases.

It was felt that another more specific screening protocol would be required for migraine headaches and chronic low-back pain. We found that, if these conditions were to have been included in our protocol, there would be a need for a neurologist to do most of the clinical interviews in order to validate diagnoses. This is also the observation of Osuntokun et al (3), in their study of migraine in a Nigerian community. Chang et al in China (6) used teams of neurologists and nurses, supervised by a senior neurologist, to undertake a community-based study of the problem of headache. In our neuroepidemiological study, we had decided to work within Schoenbergs concept of "neurology with few neurologists" (8); hence the emphasis of this exercise on trained enumerators under the close supervision of neurologists.

Based on the results of the prevalence rates in this pilot study, we decided to survey a randomly sampled 30% of the population of 182,000

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in the sub-district of Meskan and Mareko, so that this large population base would enable us to determine age-, sex-, and ethnic specific prevalence rates of neurological disorders as suggested by Schoenberg (8). Such a large sample size would also enable us to identify disorders such as hereditary neuropathies, myopathies and Parkinson's disease, which have been documented as rare among Africans (4,14,15). The major neuroepidemiological survey of the inhabitants from randomly selected Peasants' and Urban Dwellers' Associations of the subdistrict of Meskan and Mareko was launched in 1986, after careful planning of the logistics for the door to door survey covering an area of 1,500 sq. km.

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Date	Peasants' Association: Identity code	ID CODE, House hold	Name of head of Household (HH)	No. of wives		Name of informant				
					STAPLE DIET	Maize	TEF*	WHEAT*	KOCHO*	GUAYA*

CHARACTERISTICS OF HOUSEHOLD MEMBERS

S. No.	Name of member of H.H.	Relation to H.H.	Sex	Age	Religion	Ethnic group	Literacy	Duration (Years)	Condition		Comments
									Healthy	Ill	
01											
02											
03											
04											
05											
06											
07											
08											
09											
10											
11											
12											
13											
14											
15											
16											
17											

FIGURE 1. Questionnaire on characterstics of household members

* Tef : Eragrostis tef Kocho : Ensete ventricosum guaya : Lathyrus sativus

Date	Interviewer	Peasants' Assoc.	House No.	Filing No.

NEUROLOGICAL SYMPTOMS

Is there anyone in the household who has or had the following symptoms?

	NO	YES	NAME (ID CODE)	Number of persons
Severe mental retardation				
Speech disturbance				
Unconsciousnes fit. esp. with frothing, biting of tongue or incontinence of urine				
Sudden jerking movements				
Blindness				
Deafness				
Movement disorder of arm				
Movement disorder of leg				
Movement disorder of face				
Walking difficulty				
Numbness feet / hand				
Is there anyone in the household who has leprosy				
For someone with one of these symptoms please fill Questionnaire on neurological symptoms (Figure 3)				
Chronic disease but none of the above symptoms				What ?

FIGURE 2. Questionnaire on neurological symptoms

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Name of person	AGE	SEX	Identity of Person	Date	Interviewer	Parent's Assoc.	House no:	Filing no:

	YES	NO	AGEAT ONSET	SYMPTOMS		IN CASE OF SYMPTOMS	COMMENTS
				Acute	Gradual		
MENTAL DISABILITY						HEAD CIRCUMFERENCE NORMAL ☐ SMALL ☐ BIG ☐ URINARY INCONTINENCE NO ☐ YES ☐	
SPEECH DISTURBANCE						SPEAKS NOT ☐ A FEW WORDS ☐ SLURS ☐ STAMMERS ☐ STRANGE SPEAKING ☐	
UNCONSCIOUS FITS						IF THE PERSON HAS HAD UNCONSCIOUSNESS FITS AND/OR OCCASIONAL SUDDEN JERKY MOVEMENTS, PLEASE COMPILETE THE EPILEPSY FORMES	
SUDDEN JERKY MOVEMENT	R L						
BLINDNESS	R L						
DEAFNESS	R L						
MOVEMENT DISTURBANCE : ARM	R L					PARALYSIS SHAKING/STRANGE MOVEMENTS DE FORMED JOINT SPINE ☐ ☐ ☐ ☐ ☐ ☐	
-"- -"- : LEG	R L						
-"- -"- HEAD/FACE	R L						
WALKING DIFFICULTY	R L					CAN NOT WALK ☐ WALKS WITH AID ☐ WITHOUT AID BUT WITH DIFFICULTY ☐ WITH SLIGHT DIFFICULTY ☐	
NUMBNESS ARM/HAND	R L					LEPROSY YES ☐ NO ☐	
-"- LEG/FOOT	R L						

SAME DISEASE/SYMPTOM IN RELATIVES: NO ☐ YES ☐ IF YES; NAME;.....

TRAUMA BEFORE ONSET OF SYMPTOMS: NO ☐ YES ☐ IF YES; HEAD ☐ SPINE ☐ OTHER .....

DELIVERY OFTHE AFFECTED INDIVIDUAL: HOME ☐ HOSPITAL ☐ HEALTH CENTRE ☐ KNOWN COMPLICATION:

KNOWN COMPLICATION: NO ☐ YES ☐

HISTORY OF EXCESSIVE ALCOHOL INTAKE NO ☐ YES ☐

HISTORY OF DIABETES MELLITUS NO ☐ YES ☐

FIGURE 3. Questionnaire for detailed neurological interview.

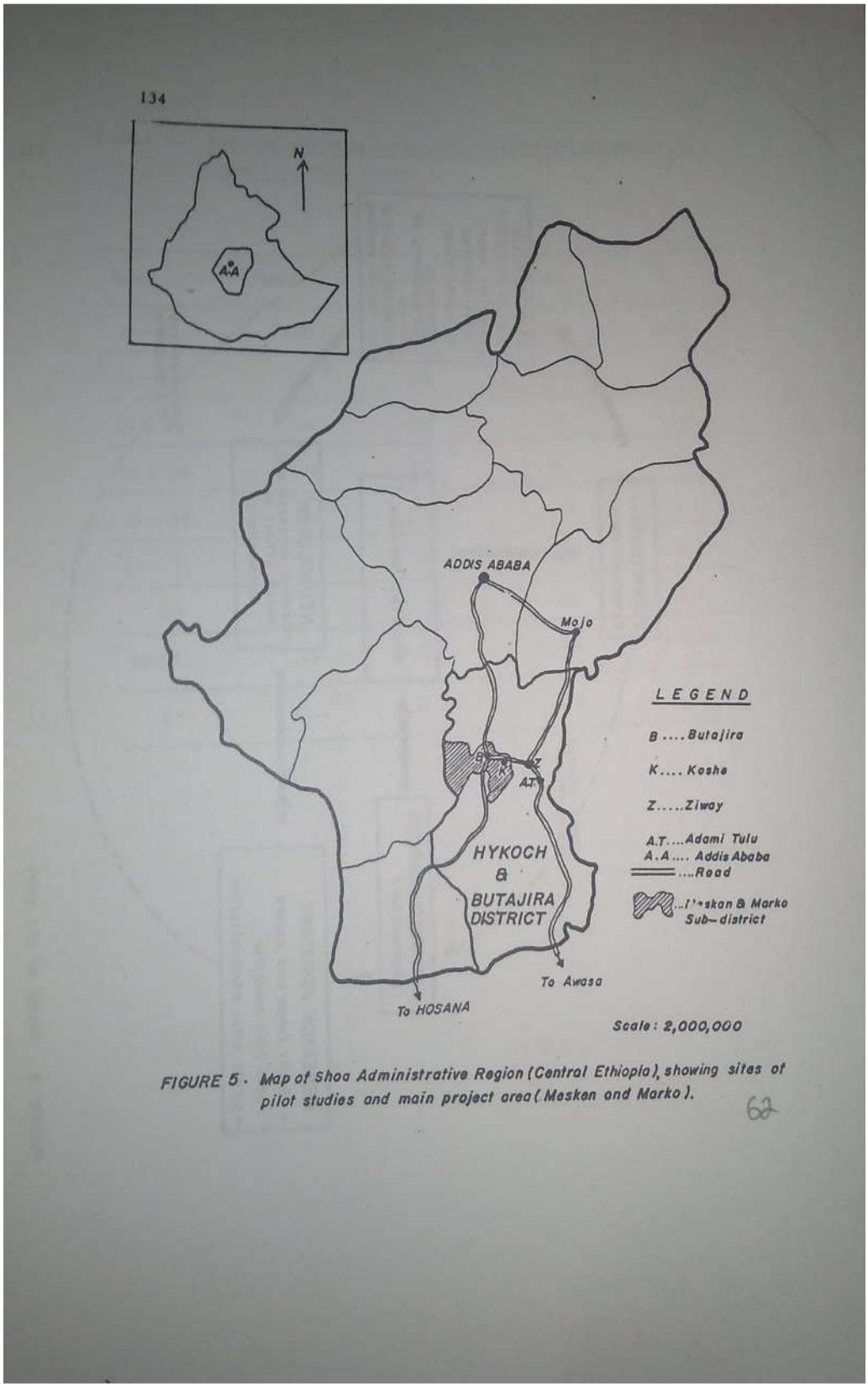


FIGURE 5 · Map of Shoa Administrative Region (Central Ethiopia), showing sites of pilot studies and main project area (Meskan and Marko).

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FIGURE 4 . Model of the study

TABLE 1. Age and sex distribution of the screened population of Adami Tulu Pilot Project

Age	Male	Female	Total	%
0 - 9	465	462	927	33.8
10 - 19	335	339	674	24.5
20 - 29	124	192	316	11.5
30 - 39	176	181	357	13.0
40 - 49	111	72	183	6.7
50 - 59	63	64	127	4.6
60+	77	86	163	5.9
TOTAL	1,351	1,396	2,747	100.00
%	49.2	50.8	100	

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TABLE 2. Prevalence ratio of identified neurological disorders in Adami Tulu

	Number	Prevalence (cases/10,000
Epilepsy	14	51
Mental retardation	7	25
Speech disturbance	6	22
Poliomyelitis	5	18
Neuropathy	4	15
Polyneuropathy	1	
Leprosy	2	
Bell's Palsy	1	
Hemiparesis (Cerebrovascular Accident)	1	4
Deafness(perceptive)	1	4
Ataxia	1	4
Tremor (essential)	1	4

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Table 3. Sensitivity and specificity of the neurological screening instrument in three common neurological conditions

DIAGNOSIS	SENSITIVITY* %	SPECIFICITY** %
EPILEPSY	93	90
MENTAL RETARDATION	88	75
POLIOMYELITIS	92	90
ALL CASES	91	85

$$*\text{Sensitivity} = \frac{\text{True positives}}{\text{True positives + false negative}}$$

$$**\text{Specificity} = \frac{\text{True negative}}{\text{True negatives + false positives}}$$

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Paraplegia

Neurological Complications of Endemic Skeletal Fluorosis, with Special Emphasis on Radiculo-Myelopathy

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Summary

The results of surveys carried out between 1976 and 1985 in the fluorosis-endemic area of the Ethiopian Rift Valley is summarised, with emphasis on the neurological complications resulting from the crippling osteofluorosis. The neurological manifestations in the forms of myelopathy with and without radiculopathy (respectively 72% and 28%) occurred after exposure to high fluoride (> 4 ppm) for longer than 10 years. These deficits were clearly found to be a consequence of fluoride deposition in bones, resulting in generalised sclerosis and osteophytosis, with reduction in the diameter of the intervertebral foramina and of the spinal canal. Advanced osteosclerosis commonly causes severe spastic quadriparesis in flexion, accompanied by distressing spasms and urinary incontinence. The dilemma of these medical problems in relation to the agro-industrial economic developments of the Ethiopian Rift Valley is discussed.
Key words: *Skeletal fluorosis; Paraparesis; Radiculo-myelopathy.*

Chronic fluorine intoxication has been documented to occur as a result of ingestion of large quantities of fluoride-rich waters over many years (World Health Organization, 1970), as well as in occupational exposure in those engaged in aluminium production, magnesium foundries, fluorspar processing, and superphosphate (Hodge and Smith, 1977).

Osteofluorosis and its complications, related to high-fluoride water consumption, have particularly gained attention in India (Siddiqui, 1955; Singh and Jolly, 1961; Jolly *et al.*, 1968). Similar reports, but mainly on endemic dental fluorosis, have appeared also from the African continent, the majority from East African Rift Valley regions (Smith *et al.*, 1953; Moller *et al.*, 1970; Nair and Manji, 1982; Tekle-Haimanot *et al.*, 1987).

In a previous study we reported on the epidemiology of endemic fluorosis in the Ethiopian Rift Valley (Tekle-Haimanot *et al.*, 1987). This is a follow-up report on the neurological complications of skeletal fluorosis, predominantly in the forms of radiculo-myelopathies observed in the same region.

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Materials, subjects and methods

The Rift Valley, extending from north to south of the country, forms the volcanic breakline in the highland regions of Ethiopia. It extends south into Kenya and Tanzania, and north across the Red Sea and the Gulf of Akaba into the Dead Sea. The Ethiopian Rift Valley lies between 500 and 1800 m above sea level. It is hot and dry, with mean temperatures of 23 to 38°C. The Rift Valley has a number of agro-industrial establishments, the most important being two sugar estates (Wonji-Shoa and Metahara), where 30 000 people live.

Between 1976 and 1983, 530 workers were retired from Wonji-Shoa sugar estates at the age of 45 to 50 years because of inability to perform physically strenuous jobs. These workers were examined for evidence of skeletal fluorosis.

In August 1984, a medical board evaluated a further 300 workers of the Wonji-Shoa sugar estates who had presented with complaints of pains and aches, stiffness and progressive kyphosis suggestive of skeletal fluorosis. The medical board, of which the author was a member, examined these workers for evidence of skeletal fluorosis and neurological complications.

From March to December 1985, two clinical surveys were undertaken in 13 villages and towns to assess the extent and magnitude of endemic fluorosis in the Rift Valley. All persons with abnormal posture and deformities, confined to bed, were given general and detailed neurological examinations according to a pre-set protocol.

From the three clinical surveys, on all subjects with the diagnosis of skeletal fluorosis, the following data were recorded: sex, age, place of birth, length of residence in the study area, and the sources of drinking-water (piped water, stream, pond or irrigation canal), as well as subjective symptoms when relevant.

All identified subjects had radiological examinations of the spine and other bones. The radiological features were classified according to Roholm (1937): first stage—involvement of the spinal column and pelvis, and roughening and blurring of bony trabaculae; second stage—blurring of bone, and uneven contours; and third stage—bones showing the appearance of marble, with woolly configuration. The bones of the extremities show irregular periosteal thickening, and calcification of ligaments and muscular attachments.

Table I Prevalence of advanced skeletal fluorosis and neurological complications in the Ethiopian Rift Valley

Survey area/year	Fluoride in drinking water (ppm)	Symptomatic persons	Clinical/radiological fluorosis		Neurological manifestations	
			No.	(%)	No.	(%)
Wonji/Shoa 1976–1983	3·7–17·7	530	244	(46)	3	(0·6)
Wonji/Shoa 1984	3·7–17·7	300	195	(65)	39	(13)
Alem Tena 1984	9·0	30	15	(50)	3	(10)
Sami Berta 1984	9·0	18	10	(56)	2	(11)

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After the surveys, those with neurological manifestations were followed up for a further 2 years. Five persons who developed overt neurological complications during the follow-up period were also included in this study.

Samples of drinking water from representative sites in the Rift Valley were analysed for fluoride content at the laboratory of the Wonji Sugar Estate Hospital, using ion analyser Orion Research Specific Ionometer. This has already been reported (Tekle-Haimanot *et al.*, 1987).

Results

The water supplies in the Rift Valley came mainly from boreholes with a depth of from 10 to 100 metres; the majority were deep boreholes. Fluoride levels from these boreholes ranged from 1·0 mg/litre to 36 mg/litre (or parts per million, ppm). The sugar estates that had the highest population densities recorded high fluoride levels: Wonji-Shoa 3·7 ppm to 17·7 ppm, and Metahara 2·4 to 7·0 ppm.

As shown in Table I, three areas (Wonji-Shoa, Alem Tena and Sami Berta) were identified as having occupants with clinically manifested skeletal fluorosis with neurological complications. The Wonji-Shoa sugar estates, the longest existing agro-industrial establishments in Ethiopia, recorded the highest number of cases of skeletal fluorosis and neurological complications. The prevalence showed a tendency to increase with the duration of residence in high fluoride areas.

Table II Neurological manifestations in 47 cases of advanced skeletal fluorosis

Neurological lesion	Sex		Bedridden state	Incontinence of urine	Patchy sensory deficit	Decreased	Decreased
	Male	Female					
Cervical radiculo-myelopathy	15	1	2	1	6	12	5
Cervical myelopathy (pure)	6	—	3	3	—	5	2
Cervical radiculopathy	5	1	—	—	4	—	1
Cervicodorsal radiculo-myelopathy	3		1	—	1	1	1
Dorsal radiculo-myelopathy	8	1	2	1	2	4	2
Dorsal myelopathy (pure)	5		2	2	—	4	1
Dorsal radiculopathy	2		—	—	1	—	1
Total and (%)	44(94)	3(6)	10(21)	7(15)	14(30)	26(53)	13(28)

The neurological complications shown in Table II include predominantly radiculo-myelopathies (80%); the majority of those involved the cervical region (66%). 'Pure' myelopathies were found in 21%. It is to be noted that, in osteofluorosis, it is often difficult to differentiate between radicular and myelopathic symptoms. In fluorotic radiculo-myelopathies generally, sensory symptoms are not very prominent.

The sensory symptoms tend to be patchy except when radicular pain in the upper limb is referred along a dermatome, or when cord compression is encountered. However, vibration sensation is reduced in about one third of those affected.

Spinal cord compression with thoracic sensory levels was found in 4 patients, two of whom underwent laminectomy. They had spastic paraparesis, sensory levels and severe painful abdominal muscle and leg spasms. Myelogram was difficult because of the difficulty of entering the subarachnoid space during lumbar puncture. The thickened bones and calcified ligaments made the laminectomies technically very difficult. The spinal canals in both cases were found to be

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narrowed by marked osteophytosis, with severe compression of the spinal cord. Following the laminectomy, however, there was appreciable relief from the painful spasms, and some improvement of the paraparesis. The amelioration lasted for 2 to 3 years. Those who developed neurological complications were persons from fluorosis-endemic areas who had consumed water from deep wells with fluoride levels higher than 4 ppm, for periods of more than 10 years. At Wonji, the first evidence of skeletal fluorosis was documented in the early 1970s, 20 years after the establishment of the sugar estate.

Varying degrees of loss of hearing to high frequencies were found in 13% of affected persons. This cochlear eight nerve dysfunction, associated with skeletal fluorosis, has also been observed by Siddiqui (1955). The pathogenesis is most probably related to sclerosis of auditory ossicles.

Skeletal fluorosis affected males (94%) rather than females. The affected persons were those engaged in physically strenuous duties performed in hot environments, such as agricultural workers exposed to the sun in the fields, and factory workers such as those stationed at the sugar boilers, where the surrounding temperatures reach 45 to 48°C. No women were engaged in similar duties.

Patients with skeletal fluorosis complicated by neurological deficits had varying periods for the development of their symptoms. However, in the majority, it was possible to register a uniform history of insidious onset with a very slow progression, except in 2 patients who developed cervical myelopathic signs after trivial falls. Of the patients, 21% ended in a bedridden state after various different periods of progression.

Decompressive laminectomies in osteofluorotic cord compression resulted in reasonable initial improvement, which unfortunately was short-lived. Both patients, over time, developed recurrence of symptoms and advanced paraparesis, as they continued to live in the same endemic areas, consuming the high fluoride water. In many people affected by skeletal fluorosis, we have seen a gradual improvement of symptoms, following relocation of domicile to areas where the water has a normal fluoride composition. We have also observed that over a period of 3 to 5 years some patients have had an arrest of the progression of the condition, and in some patients there has been improvement of the neurological symptoms in patients who have changed to and have strictly adhered to the consumption of defluoridated water in the sugar estates.

Different degrees of radiological changes were found in the patients studied. Those with neurological sequelae exhibited the most severe third stage of radiological features, with osteophytosis and marked spinal canal narrowing (Fig. 1).

Although most of the patients affected came from low socioeconomical groups, the nutritional status of the majority was satisfactory. Overt malnutrition was not recorded.

Discussion

The involvement of the nervous system in skeletal fluorosis was reported in India as early as 1937 (Shortt *et al.*, 1937), but the detailed description of the neurological deficits and the resultant syndromes appeared in the 1950s and 1960s (Siddiqui, 1955; Singh and Jolly, 1961; Jolly *et al.*, 1968). There have also been scattered

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Figure 1 X-Rays of the cervical and lumbosacral spine of a patient with mild quadriparesis, showing marked osteophytosis and narrowing of the cervical spinal canal.

reports from Britain (Webb-Peploe and Bradley, 1966) and from the United States (Goldman *et al.*, 1971).

In Ethiopia, dental fluorosis was recognised as early as 1954 in the Rift Valley, particularly at the Wonji-Shoa sugar estates established in 1951. However, attention was drawn to skeletal fluorosis only in 1971, when the first spine X-rays were critically reviewed for evidence of skeletal involvement by abnormal deposition of fluoride. A case report of neurofluorotic myelopathy from the same area was published in 1974 (Lester, 1974). Subsequently, further similar cases were recognised.

With fluoride levels above 4 ppm, most of our patients developed neurological complications after 15 years of exposure. Corresponding observations have also been reported by Singh and Jolly (1970).

Associated factors, such as hot climate, sex, occupations, protein malnutrition and calcium deficiency have been incriminated as playing important roles in the development of skeletal fluorosis.

In our experience, high fluoride content in drinking water appears to play the most determinant role, as was observed by Reddy (1979). However, men doing manual labour in hot environments appear to be more susceptible to advanced osteosclerosis with neurological complications. Similar observations have been recorded by Siddiqui (1955) and Singh *et al.* (1961b).

The effect of high fluoride intake in children was not as obvious as in adults. Some cases of knock knees and bow legs, similar to those seen in India

(Krissnamachari and Krishnaswamy, 1974) and in Tanzania (Grech, 1966), were seen in the early 1970s at Wonji-Shoa sugar estate.

However, the incidence of such disorders diminished gradually, probably as the result of the active programme of defluoridation of drinking water undertaken in the estates. Although radiologically evident skeletal fluorosis has been observed in children living in endemic areas (Krissnamachari and Krishnaswamy, 1974), it is now well documented that crippling fluorosis is not commonly encountered in children, but appears late in adulthood (Christie, 1980).

Before the onset of overt neurological symptoms, a person with skeletal fluorosis develops progressive bone pains and stiffness of the whole body. Squatting, particularly when defecating, becomes very troublesome. Standing up from a sitting position, and sitting up in bed, become increasingly difficult.

At the stage when neurological symptoms and signs become manifested, the affected persons have marked kyphosis, with stiffness and restriction of movement

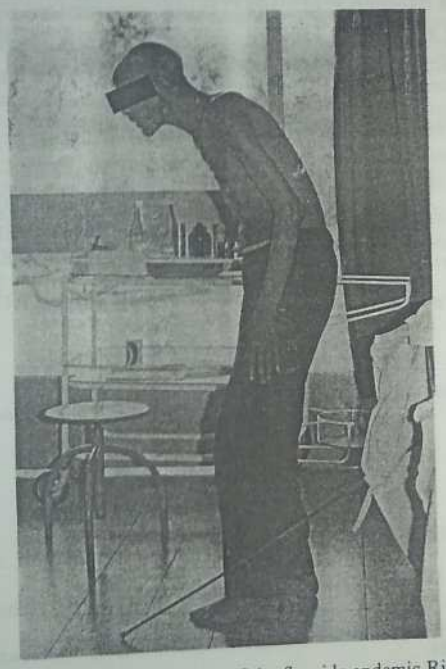


Figure 2 A 52-year-old factory-worker resident of the fluoride endemic Rift Valley for the last 31 years, with marked stiffness and fixed posture. He is unable to extend his neck and cannot squat. The whole body moves as a block during changing of position. He has weakness of the upper limbs and a spastic paraparesis.

of the whole body, which moves as a unit during postural changes (Fig. 2). Flexion deformity of the hip and knees and fixation of the chest wall are typically seen.

In the progressive cervical radiculo-myelopathy that develops insidiously, the common predominant neurological picture usually consists of marked wasting and atrophy of the small muscles of the hands, in addition to spastic paraparesis or quadriparesis, often in flexion. To a lesser extent, similar atrophies are seen in the 72

lower limbs. In some patients, widespread fasciculation may be confused with motor neuron disease.

In advanced stages of neurofluorosis, the clinical picture is rather uniform, with complete incapacitation and the bedridden state of severe spastic paraparesis, or quadriparesis with incontinence of urine and flexor spasms. Hyperreflexia, with absent abdominal reflexes and extensor plantar responses with or without patellar and ankle clonus confirms long tract involvement.

The pathogenesis of the neurological sequelae of osteofluorosis is fairly straightforward, as was shown by the post-mortem study by Singh *et al.* (1961a) on a macerated skeleton, in which fluorotic changes resulted in considerable encroachment on the diameter of the intervertebral foramina and spinal canal.

These changes tend to be most marked in the cervical region. This explains the clinical similarity of neurofluorosis to cervical spondylosis. Two of our patients gave histories of minor traumas to the neck before the onset of their quadriparesis. This may well be accurate, as Symonds has described the importance of minor trauma causing cord injury in a situation of spinal canal narrowing by cervical spondylosis (Symonds, 1953).

Progressive idiopathic and predominantly motor myelopathy, as described elsewhere in tropical countries (Roman *et al.*, 1985) is also encountered in Ethiopia (Jenik *et al.*, 1981; Rynberg *et al.*, 1988). This may, in some instances, be confused with the myelopathy of osteofluorosis, unless one is aware of the patient's area of origin and residence.

The prevention of skeletal fluorosis depends on obtaining alternative sources of low-fluoride drinking water; and includes defluoridation plants. Both of these are quite expensive for a poor country like Ethiopia. Although some defluoridation plants have been started in the sugar estates, more and more patients with osteofluorosis, with crippling neurological complications, are bound to be seen in the future.

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Epidemiological pattern of leprosy in Ethiopia: a review of the control programmes

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Summary Leprosy control started in a limited area of Ethiopia in 1956. Extended coverage of the country was achieved in the early seventies. Review of the data from the control projects since 1976 revealed that leprosy is a disease of the Ethiopian highlands where prevalence rates as high as 7 per thousand have been recorded in some provinces, while the cumulative national average for the last 13 years was 2·6 per thousand. The paucibacillary form was predominant. However, unlike other African countries, a relatively high proportion of multibacillary leprosy was found in Ethiopia. The male-to-female ratio was 2:1 with the highest prevalence in the 15–44 years age bracket. Detection rates for new cases have shown a gradual decline since 1982, a year before multiple drug therapy (MDT) was introduced into the country. For the last 5 years the number of new cases has stabilized at 4700/year. These trends probably reflect a general reduction in the prevalence of leprosy in the country, while the conspicuous decline in 1982 is most likely related to discharge of cases during screening before MDT. The new villagization policy of Ethiopia with its effective reorganization of the populations is believed to make control programmes and supervision of MDT easier and presumably more effective. Similarly, more reliable prevalence and incidence studies could be undertaken with success.

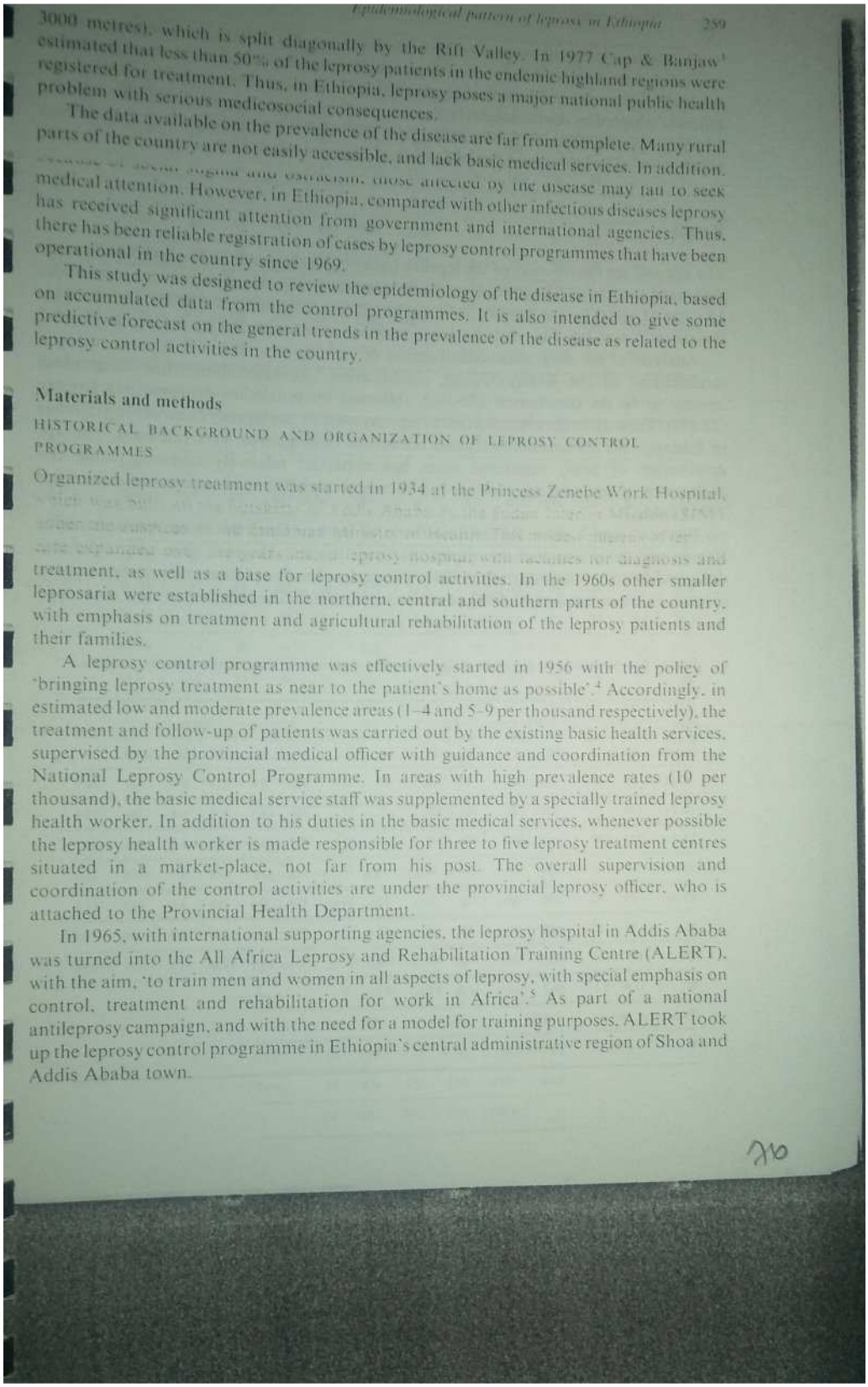
Introduction

Over 10 million people in the world are estimated to have leprosy. Only 50% are registered cases and of these, 12% are found in Africa. Ethiopia belongs to the endemic regions of the continent, with prevalence rates of 1·0–1·9.[1] Situated in the north-eastern part of the continent, Ethiopia covers an area of 1·25 million sq.km, and has a population of 46 million.[2] The topography of the country is dominated by the high central plateau (2000–

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3000 metres), which is split diagonally by the Rift Valley. In 1977 Cap & Banjaw[3] estimated that less than 50% of the leprosy patients in the endemic highland regions were registered for treatment. Thus, in Ethiopia, leprosy poses a major national public health problem with serious medicosocial consequences.

The data available on the prevalence of the disease are far from complete. Many rural parts of the country are not easily accessible, and lack basic medical services. In addition, because of social stigma and ostracism, those affected by the disease may fail to seek medical attention. However, in Ethiopia, compared with other infectious diseases leprosy has received significant attention from government and international agencies. Thus, there has been reliable registration of cases by leprosy control programmes that have been operational in the country since 1969.

This study was designed to review the epidemiology of the disease in Ethiopia, based on accumulated data from the control programmes. It is also intended to give some predictive forecast on the general trends in the prevalence of the disease as related to the leprosy control activities in the country.

Materials and methods

HISTORICAL BACKGROUND AND ORGANIZATION OF LEPROSY CONTROL PROGRAMMES

Organized leprosy treatment was started in 1934 at the Princess Zenebe Work Hospital, [illegible] under the auspices of the Ethiopian Red Cross. This [illegible] was expanded [illegible] leprosy hospital with facilities for diagnosis and treatment, as well as a base for leprosy control activities. In the 1960s other smaller leprosaria were established in the northern, central and southern parts of the country, with emphasis on treatment and agricultural rehabilitation of the leprosy patients and their families.

A leprosy control programme was effectively started in 1956 with the policy of 'bringing leprosy treatment as near to the patient's home as possible'.[4] Accordingly, in estimated low and moderate prevalence areas (1–4 and 5–9 per thousand respectively), the treatment and follow-up of patients was carried out by the existing basic health services, supervised by the provincial medical officer with guidance and coordination from the National Leprosy Control Programme. In areas with high prevalence rates (10 per thousand), the basic medical service staff was supplemented by a specially trained leprosy health worker. In addition to his duties in the basic medical services, whenever possible the leprosy health worker is made responsible for three to five leprosy treatment centres situated in a market-place, not far from his post. The overall supervision and coordination of the control activities are under the provincial leprosy officer, who is attached to the Provincial Health Department.

In 1965, with international supporting agencies, the leprosy hospital in Addis Ababa was turned into the All Africa Leprosy and Rehabilitation Training Centre (ALERT), with the aim, 'to train men and women in all aspects of leprosy, with special emphasis on control, treatment and rehabilitation for work in Africa'.[5] As part of a national antileprosy campaign, and with the need for a model for training purposes, ALERT took up the leprosy control programme in Ethiopia's central administrative region of Shoa and Addis Ababa town.

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All patients received monotherapy with dapsone until 1970, when the first cases of resistance were reported.[6] Subsequently, multiple drugs were used in the management of selected resistant cases. Multiple drug therapy (MDT), as recommended by WHO,[7] was officially adopted by the Ethiopian leprosy control programmes in 1983. In this study, the 13 years' records, since 1976, of the National and ALERT leprosy control programmes are reviewed. The Ethiopian Central Statistics Office provided the national census figures.

Results

The age and sex distribution of the leprosy patients, as shown in Table 1, is based on the records of the ALERT Leprosy Control Programme (1984–88). Ten per cent were under 15 years of age. The age group 15–44 was predominantly affected (70%). The male-to-female ratio was 2:1. This distribution is similar to that reported by Adamu & Naafs.[8]

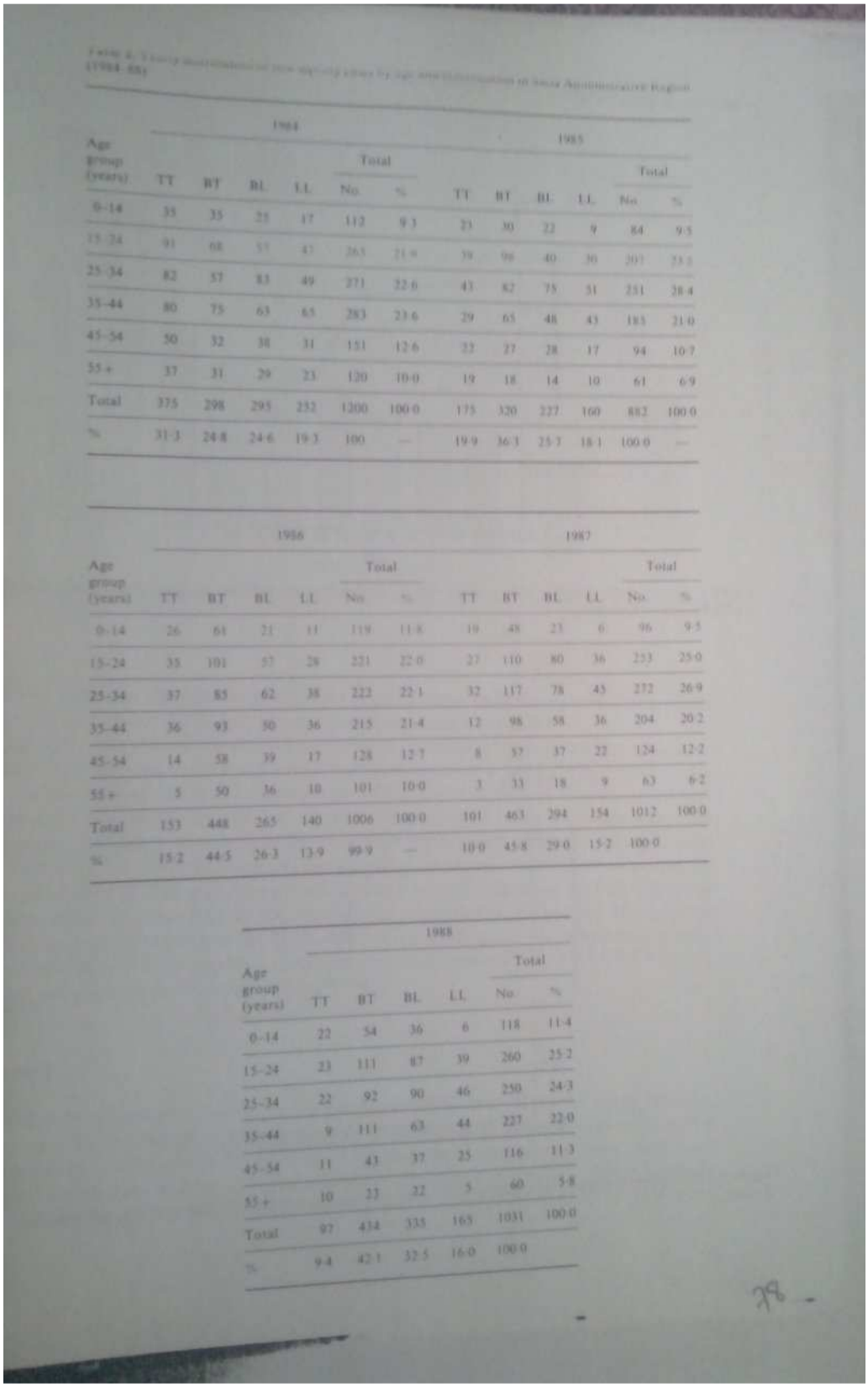
Analysis of the diagnostic classification of leprosy over the last 5 years, using a modification of the Ridley–Jopling classification,[9] revealed borderline–tuberculoid leprosy to be the commonest (38·3%), followed by borderline–lepromatous leprosy (27·6%) (Table 1). In the classification of leprosy used by the leprosy control programmes in Ethiopia, the indeterminate (I) and borderline (BB) groups were not used. The age distribution of newly registered cases has remained relatively constant while the proportion of lepromatous patients has shown an increase over successive years since 1986 (Table 2).

Figures 1 and 2 show the detection rate of leprosy from the Shoa Administrative Region and the whole country respectively over the last 13 years. One sees a definite decline of detection rates starting in 1982. The decline forms a plateau over the last 5 years (Figure 2), at an average of 4700 new cases per year.[10] The number of new cases will

Table 1. Distribution of new leprosy cases by age, sex and classification in the Shoa Administrative Region (1984–88)

Age group (years)	TT		BT		BL		LL		Total					
	M	F	M	F	M	F	M	F	M	%	F	%	M+F	%
0–14	79	46	128	100	71	56	27	22	305	5·9	224	4·4	529	10·3
15–24	139	76	300	188	201	120	110	70	750	14·6	454	8·9	1204	23·5
25–34	129	87	264	169	256	132	144	85	793	15·5	473	9·2	1266	24·7
35–44	119	47	288	154	208	74	154	70	769	15·0	345	6·7	1114	21·7
45–54	73	32	155	62	128	51	73	39	429	8·4	184	3·6	613	11·9
55+	47	27	106	49	90	29	42	15	285	5·5	120	2·3	405	7·9
Total	586	315	1241	722	954	462	550	301	3331	64·9	1800	35·1	5131	100·0
%	11·4	6·1	24·2	14·1	18·6	9·0	10·7	5·9						
Total	901		1963		1416		851							
%	17·6		38·2		27·6		16·6							

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1984

Age group (years)	TT	BT	BL	LL	Total No.	Total %
0–14	35	35	25	17	112	9·3
15–24	91	68	57	43	263	21·9
25–34	82	57	83	49	271	22·6
35–44	80	75	63	65	283	23·6
45–54	50	32	38	31	151	12·6
55+	37	31	29	23	120	10·0
Total	375	298	295	232	1200	100·0
%	31·3	24·8	24·6	19·3	100	—

1985

Age group (years)	TT	BT	BL	LL	Total No.	Total %
0–14	23	30	22	9	84	9·5
15–24	59	98	40	30	207	23·5
25–34	43	82	75	51	251	28·4
35–44	29	65	48	43	185	21·0
45–54	22	27	28	17	94	10·7
55+	19	18	14	10	61	6·9
Total	175	320	227	160	882	100·0
%	19·9	36·3	25·7	18·1	100·0	—

1986

Age group (years)	TT	BT	BL	LL	Total No.	Total %
0–14	26	61	21	11	119	11·8
15–24	35	101	57	28	221	22·0
25–34	37	85	62	38	222	22·1
35–44	36	93	50	36	215	21·4
45–54	14	58	39	17	128	12·7
55+	5	50	36	10	101	10·0
Total	153	448	265	140	1006	100·0
%	15·2	44·5	26·3	13·9	99·9	—

1987

Age group (years)	TT	BT	BL	LL	Total No.	Total %
0–14	19	48	23	6	96	9·5
15–24	27	110	80	36	253	25·0
25–34	32	117	78	45	272	26·9
35–44	12	98	58	36	204	20·2
45–54	8	57	37	22	124	12·2
55+	3	33	18	9	63	6·2
Total	101	463	294	154	1012	100·0
%	10·0	45·8	29·0	15·2	100·0	

1988

Age group (years)	TT	BT	BL	LL	Total No.	Total %
0–14	22	54	36	6	118	11·4
15–24	23	111	87	39	260	25·2
25–34	22	92	90	46	250	24·3
35–44	9	111	63	44	227	22·0
45–54	11	43	37	25	116	11·3
55+	10	23	22	5	60	5·8
Total	97	434	335	165	1031	100·0
%	9·4	42·1	32·5	16·0	100·0	

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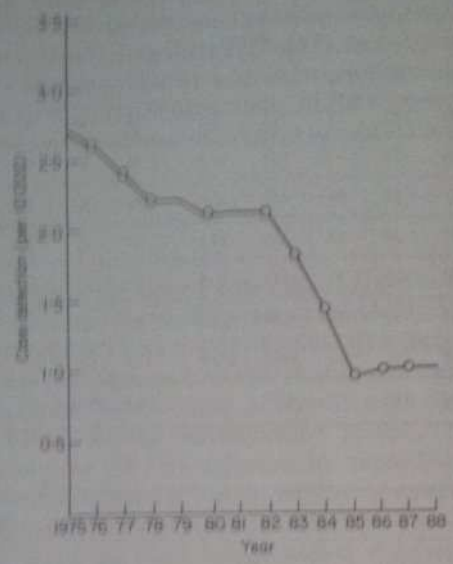


Figure 1. Leprosy case detection rate in Shoa Administrative Region, 1975–88. (*Source*: Annual Reports, ALERT Leprosy Control.)

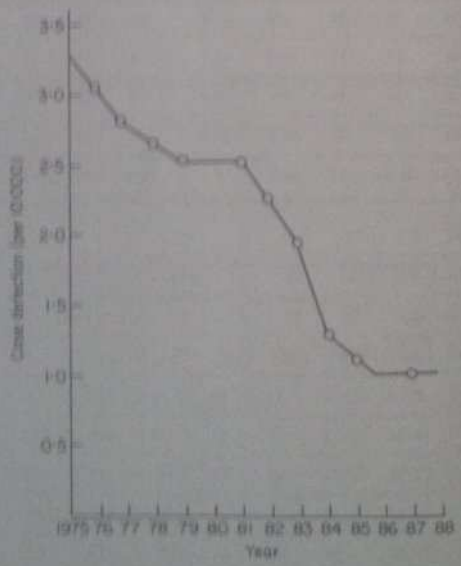


Figure 2. Leprosy case detection rate in Ethiopia, 1975–88. (*Source*: Annual Reports, National Leprosy Control Project.)

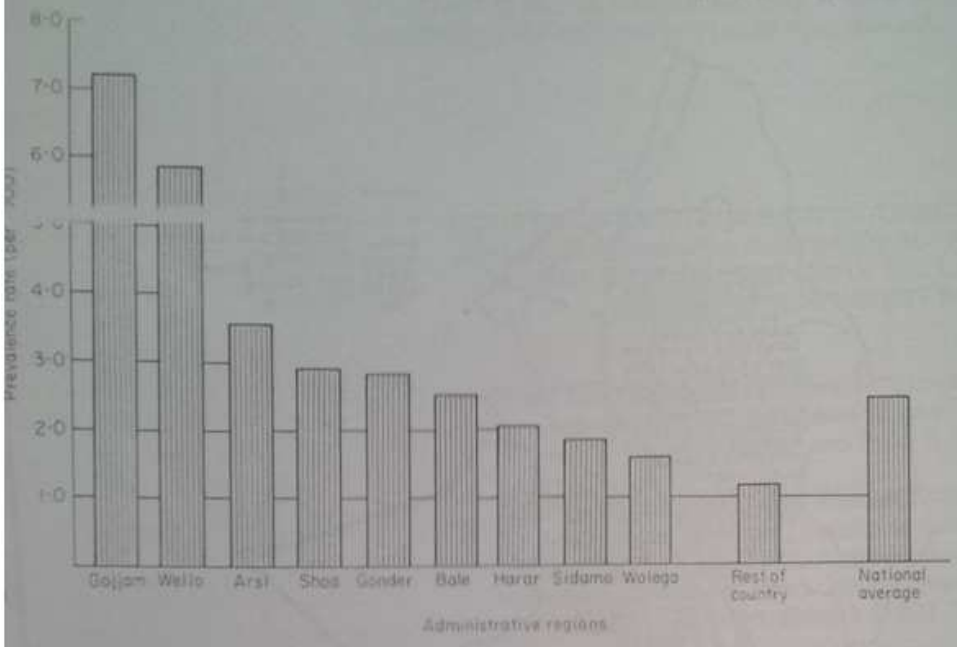


Figure 3. Prevalence rate of leprosy in the different administrative regions of Ethiopia (Source: Annual Report [illegible])

robably remain at the same level for some years to come, until the real effect of multiple drug therapy is expected to halt the transmission of the disease.

Figure 3 represents the prevalence pattern in the different administrative regions, as ompared to the national average of 2·6 per thousand over 6 years (1976–81) two years rior to the start of MDT. The prevalence of leprosy is highest in Gojjam and Wello (north-west and north-east of the country, respectively) while moderate rates are bserved in Arsi, Shoa, Gonder and Bale (respectively of south, central, north and south-st Ethiopia). As shown in Figure 4, these hyperendemic and endemic areas occupy the ighland regions of Ethiopia. The prevalence rates in the lowlands of the Rift Valley are ry low, except in some densely populated areas (the districts of Yifat and Timuga, and aikoch and Butajira) within the Shoa Administrative Region, where hyperendemicity (prevalence rates 1·5–7·8 per thousand) has been documented by the ALERT Leprosy Control programme in the years 1981 to 1986.[11]

Discussion

idemiological studies of leprosy have been very difficult to make for many reasons, particularly because leprosy patients are self-selected groups, not representative of the pulation as a whole.[12] Previous prevalence and incidence studies have used both sical examination and verbal recall in data collection and analysis. These methods ve been criticized for bias and variability. Population-based studies to determine

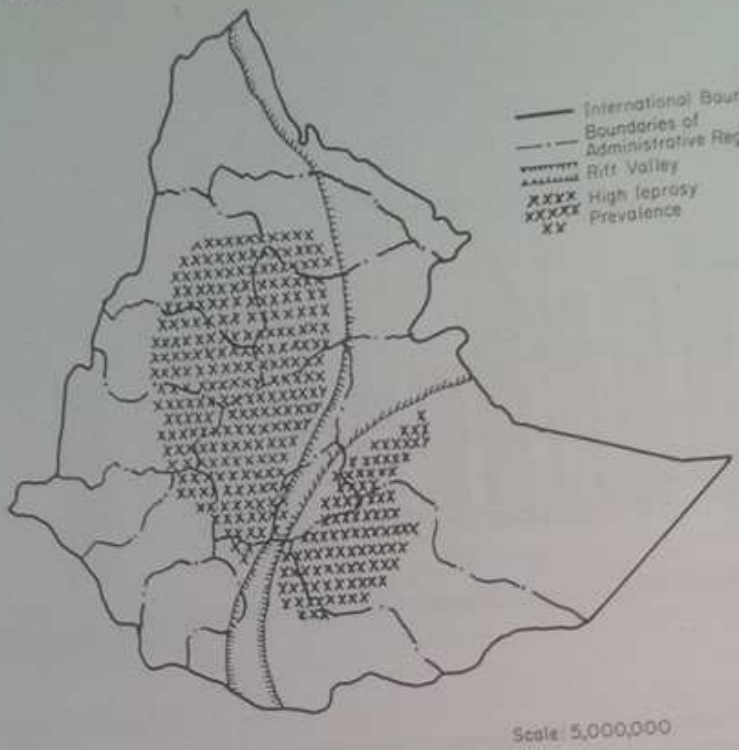


Figure 4. Ethiopia—showing areas of high leprosy prevalence corresponding to the highland regions of the country.

prevalence are very few and certainly not yet available for Ethiopia. We are therefore forced to rely on the information gathered by Control Projects.

Leprosy in Africa is characterized by a low proportion of lepromatous cases.[13] However, as shown in this study, there is a significantly high prevalence of the multibacillary form of leprosy in Ethiopia, sufficient to make the distribution different from the rest of Africa.

As observed by Schaller,[14] and later Cap & Banjaw,[3] this study clearly demonstrates that leprosy is endemic over the highland regions of the country, but also affects a few of the districts of the Shoa Administrative Region (central Ethiopia) which lie either bordering or within the Rift Valley.

One study[15] found a high prevalence of leprosy in the lowland Mendi district within the Blue Nile Valley of western Ethiopia. It suggested that the previous endemic leprosy situation in the highlands had been overshadowed by tuberculosis prevalence; nevertheless, there was an ongoing leprosy epidemic in the lowlands.

Except for these isolated endemic areas, for Ethiopia at large, leprosy is a disease of the highland regions. However, it is interesting that this geographical distribution is contrary to the findings of one study[16] in Malawi, which found a five-fold increase in the

PATTERN OF *LATHYRUS SATIVUS* (GRASS PEA) CONSUMPTION AND *BETA-N*-OXALYL-α-ß-DIAMINOPROPRIONIC ACID (ß-ODAP) CONTENT OF FOOD SAMPLES IN THE LATHYRISM ENDEMIC REGION OF NORTHWEST ETHIOPIA

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ABSTRACT

Grass pea, a legume whose consumption is associated with human lathyrism, is an important food crop among the poorer sectors of society in many parts of Ethiopia. A nutritional survey, focussing on the preparation and consumption of grass pea, in 224 families of two villages of a lathyrism endemic area in northwestern Ethiopia has been undertaken. Grass pea is grown in only one of the two villages. Raw as well as cooked food samples were collected and the levels of ß-ODAP determined by the OPT method. Grass pea foods were also prepared in the laboratory following methods used in the villages and analyzed for their toxin level to derive information if certain procedures were capable of reducing the level of toxin. Steeping grass pea in excess water leaches out *ca* 30% of the ß-ODAP. Grass pea bread (*kitta*) and roasted seeds (*kollo*) showed elevated levels of ß-ODAP compared to the seeds used in the preparation of these foods. Lower levels of ß-ODAP were found in boiled snacks (*nifro*) and the flour form (*shiro*).

KEY WORDS: Grass pea, *Lathyrus sativus,* Lathyrism, Paraparesis, ß-N-oxalyl-L-α,ß-diaminopropionic acid (ß-ODAP)

INTRODUCTION

Lathyrism, which is characterized by spastic paraparesis, is a neurotoxic disorder caused by excessive consumption of chickling or grass pea (*Lathyrus sativus*) (1,2).

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Epidemiological pattern of leprosy in Ethiopia: a review of the control programmes

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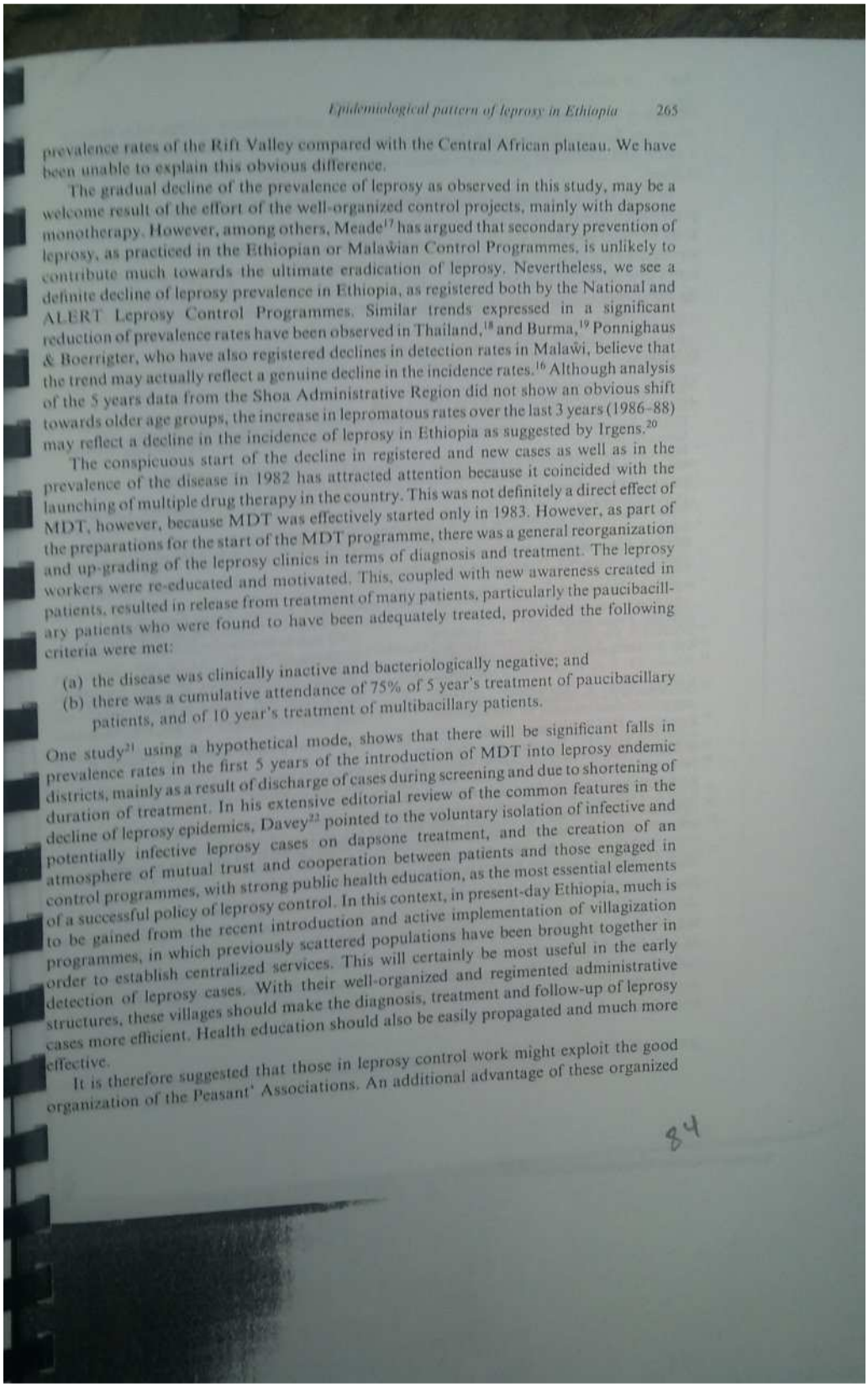
Summary Leprosy control started in a limited area of Ethiopia in 1956. Extended coverage of the country was achieved in the early seventies. Review of the data from the control projects since 1976 revealed that leprosy is a disease of the Ethiopian highlands where prevalence rates as high as 7 per thousand have been recorded in some provinces, while the cumulative national average for the last 13 years was 2·6 per thousand. The paucibacillary form was predominant. However, unlike other African countries, a relatively high proportion of multibacillary leprosy was found in Ethiopia. The male-to-female ratio was 2:1 with the highest prevalence in the 15–44 years age bracket. Detection rates for new cases have shown a gradual decline since 1982, a year before multiple drug therapy (MDT) was introduced into the country. For the last 5 years the number of new cases has stabilized at 4700/year. These trends probably reflect a general reduction in the prevalence of leprosy in the country, while the conspicuous decline in 1982 is most likely related to discharge of cases during screening before MDT. The new villagization policy of Ethiopia with its effective reorganization of the populations is believed to make control programmes and supervision of MDT easier and presumably more effective. Similarly, more reliable prevalence and incidence studies could be undertaken with success.

Introduction

Over 10 million people in the world are estimated to have leprosy. Only 50% are registered cases and of these, 12% are found in Africa. Ethiopia belongs to the endemic regions of the continent, with prevalence rates of 1·0–1·9.[1] Situated in the north-eastern part of the continent, Ethiopia covers an area of 1·25 million sq.km, and has a population of 46 million.[2] The topography of the country is dominated by the high central plateau (2000–

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prevalence rates of the Rift Valley compared with the Central African plateau. We have been unable to explain this obvious difference.

The gradual decline of the prevalence of leprosy as observed in this study, may be a welcome result of the effort of the well-organized control projects, mainly with dapsone monotherapy. However, among others, Meade[17] has argued that secondary prevention of leprosy, as practiced in the Ethiopian or Malawian Control Programmes, is unlikely to contribute much towards the ultimate eradication of leprosy. Nevertheless, we see a definite decline of leprosy prevalence in Ethiopia, as registered both by the National and ALERT Leprosy Control Programmes. Similar trends expressed in a significant reduction of prevalence rates have been observed in Thailand,[18] and Burma,[19] Ponnighaus & Boerrigter, who have also registered declines in detection rates in Malawi, believe that the trend may actually reflect a genuine decline in the incidence rates.[16] Although analysis of the 5 years data from the Shoa Administrative Region did not show an obvious shift towards older age groups, the increase in lepromatous rates over the last 3 years (1986–88) may reflect a decline in the incidence of leprosy in Ethiopia as suggested by Irgens.[20]

The conspicuous start of the decline in registered and new cases as well as in the prevalence of the disease in 1982 has attracted attention because it coincided with the launching of multiple drug therapy in the country. This was not definitely a direct effect of MDT, however, because MDT was effectively started only in 1983. However, as part of the preparations for the start of the MDT programme, there was a general reorganization and up-grading of the leprosy clinics in terms of diagnosis and treatment. The leprosy workers were re-educated and motivated. This, coupled with new awareness created in patients, resulted in release from treatment of many patients, particularly the paucibacillary patients who were found to have been adequately treated, provided the following criteria were met:

(a) the disease was clinically inactive and bacteriologically negative; and
(b) there was a cumulative attendance of 75% of 5 year's treatment of paucibacillary patients, and of 10 year's treatment of multibacillary patients.

One study[21] using a hypothetical mode, shows that there will be significant falls in prevalence rates in the first 5 years of the introduction of MDT into leprosy endemic districts, mainly as a result of discharge of cases during screening and due to shortening of duration of treatment. In his extensive editorial review of the common features in the decline of leprosy epidemics, Davey[22] pointed to the voluntary isolation of infective and potentially infective leprosy cases on dapsone treatment, and the creation of an atmosphere of mutual trust and cooperation between patients and those engaged in control programmes, with strong public health education, as the most essential elements of a successful policy of leprosy control. In this context, in present-day Ethiopia, much is to be gained from the recent introduction and active implementation of villagization programmes, in which previously scattered populations have been brought together in order to establish centralized services. This will certainly be most useful in the early detection of leprosy cases. With their well-organized and regimented administrative structures, these villages should make the diagnosis, treatment and follow-up of leprosy cases more efficient. Health education should also be easily propagated and much more effective.

It is therefore suggested that those in leprosy control work might exploit the good organization of the Peasant' Associations. An additional advantage of these organized

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villages is the possibility of conducting prevalence and incidence studies with limited resources. Such studies should be both accurate and reliable, because they will be based on a stable and controlled population whose social and economical characteristics are well defined.

In spite of Ethiopia's other priorities for dealing with communicable diseases of higher prevalences, leprosy has gained recognition and an advantageous position, with relatively good financial resources for it's control activities. Working closely with the basic medical services and the Peasant Associations, an operationally efficient control programme, with active case detection and MDT, can achieve a further and more significant reduction in the prevalence of leprosy in the country.

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Mekonnen Abebe and Redda Tekle Haimanot. 1990. *Ethiop. Med. J. 28, 53*

CEREBROVASCULAR ACCIDENTS IN ETHIOPIA

Mekonnen Abebe, MD and Redda Tekle Haimanot MD, FRCP(C)

ABSTRACT. *The causes, risk factors and outcome of cerebrovascular accidents (CVA) in 150 patients admitted to Tikur Anbessa Hospital, Addis Ababa, Ethiopia, between 1983 and 1985 were studied. Cerebral thrombosis was the commonest cause of CVA (50.7%), followed by cerebral haemorrhage (24%) and cerebral embolism (15%). The single most important risk factor for CVA was hypertension. Mortality was highest with cerebral haemorrhage (89.4%) and lowest with cerebral embolism (13%). An important measure which could reduce the incidence of CVA is the vigorous and sustained control of hypertension.*

INTRODUCTION

Cerebrovascular accident (CVA), or stroke, is not uncommon among African blacks (1,2) and is a frequent cause of morbidity and mortality in Ethiopia. In a retrospective analysis of two years' medical admissions to two teaching hospitals in Addis Ababa, Abraham and Abdulkadir reported that CVA accounted for 23.6% of all neurological admissions (3). In an attempt to identify the clinical profiles, causes, risk factors and outcome of CVA in Ethiopians this prospective study was undertaken.

MATERIALS AND METHODS

One hundred fifty consecutive CVA patients who were admitted to the Tikur Anbessa Teaching Hospital, Addis Ababa, Ethiopia, from 1983 to 1985 were included in this study. They represented 2.2% of 6971 new medical admissions during the same period. The hospital serves mainly the city of Addis Ababa, with a population of 1.5 million; however, referred cases from different parts of the country are also seen. The patients were examined by one of the authors on the day of admission and daily for the first three days and then weekly, or as needed, until discharge. A few patients were later followed on an out-patient basis.

The criteria for identification and classification of stroke cases were as follows:

1. *Cerebral haemorrhage:* rapid evolution of focal neurological signs, rapid progression to coma, signs of meningeal irritation, elevated blood pressure and headache.
2. *Cerebral thrombosis:* a slow gradual development of focal neurological signs, which lasted more than 24 hours, with relative preservation of consciousness.
3. *Cerebral embolism:* sudden onset of neurological signs in patients with atrial fibrillation, valvular disease or significant atherosclerotic changes in the relevant carotid artery.
4. *"Undetermined":* if the history of onset and residual deficit was sufficiently well documented to ensure a high probability that a stroke had occurred but there were incomplete clinical data to subcatagorize the type of stroke further.
5. *Transient ischaemic attack (TIA):* sudden onset of focal neurologic signs with

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complete remission within 24 hours.

6. *Subarachnoid haemorrhage:* sudden onset of severe headache, with only a relatively momentary disturbance of consciousness, and signs of meningeal irritation, in the absence of focal neurologic signs, with subhyaloid haemorrage.

Investigations included haematological indices, serum urea, creatinine, cholesterol, triglycerides and VDRL, fasting blood glucose, urinalysis, cerebrospinal fluid (CSF) analysis, electrocardiography, and skull and chest X-rays.

A diagnosis of hypertension was made when the diastolic blood pressure (BP) was found to be equal to or above 95 mm Hg, and/or the systolic BP equal to or above 160 mm Hg on three consecutive readings (4).

Patients who had clinical and investigatory evidence of space occupying lesions, including subdural haematomata, were excluded from the study.

RESULTS

Table 1 shows that non-embolic ischaemic vascular disease (NEIVD), or cerebral thrombosis, was the most common causes of CVA and totalled 50.6% of all cases, followed by cerebral haemorrhage and cerebral embolism which accounted for 24% and 15% of the cases respectively.

Table 2 summarizes the sex and age distribution of the subjects. Overall, the male to female ratio was 1.2 : 1. Cerebral haemorrhage and cerebral thrombosis affected a higher proportion of males, while cerebral embolism was more commonly found in females. The peak age range for cerebral thrombosis was 60 to 79 years, and for cerebral haemorrhage 40 to 59 years.

In Table 3 are listed the predisposing risk factors for NEIVD. Hypertension was by far the commonest predisposing factor (50%) for NEIVD. All patients with cerebral haemorrhage had documented hypertension during hospitalization. History of known hypertension was obtained in 57.8% of cases of cerebral thrombosis and 63.8% of cases with cerebral haemorrhage. In those who gave a history of hypertension the duration was less than ten years in the majority of the cases (73.9%). Of those with cerebral haemorrhage, twenty-four (68.8%) had diastolic BP greater than 120 mm Hg. The same number had a systolic BP greater than 200 mm Hg. The highest BP recorded was 280/160 mm Hg. None of the patients were receiving regular treatment and follow-up of their hypertension.

Diabetes mellitus was seen in eight patients (5.3%), previously undiagnosed in two of them. All of the patients who had diabetes mellitus also had hypertension. A history of transient ischaemic attacks (TIAs) was obtained in nine patients with thrombotic stroke, all in the carotid artery distribution. A family history of CVA was documented in five patients, three with NEIVD and two with cerebral haemorrhage. Five patients (3.3%) were smoking cigarettes, and four of them had associated hypertension. One patient was taking oral contraceptive pills when she developed a thrombotic CVA.

All patients with cerebral emobolism were of low socio-economic status. In 13 patients (56.5%), cardiac disease had been documented for a period ranging from one to eighteen years. In 16 patients (69.5%) the embolism was secondary to rheumatic mitral alve disease. Two patients had congestive cardiomyopathy with cardiac arrhythmias. Arteriosclerotic heart disease associated with rhythm disturbance was found in two patients. Three patients presented with atrial fibrillation and emolic phenomena, but no specific cardiac lesion was detected..

Headache was a common accompaniment of CVA. Sixty per cent of patients with cerebral haemorrhage, 51.6% with NEIVD,

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TABLE 1: Causes of cerebrovascular accidents in 150 Ethiopian patients.

Causes	Number of Patients	%
Cerebral thrombosis	76	50.7
Cerebral haemorrhage	36	24.0
Cerebral embolism	23	15.3
Migraine	4	2.7
Syphilitic vasculitis	2	1.3
Typhoid "	2	1.3
Tuberculous "	1	0.7
Undetermined aetiology	6	14.0
Total	150	100.0

TABLE 2. Sex and age distribution of 135 Ethiopian patients with cerebrovascular accidents

Age group	Cerebral thrombosis			Cerebral haemorrhage			Cerebral embolism		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
<20	-	-	-	-	-	-	1	3	4
20-39	5	6	11	2	-	2	4	3	7
40-59	14	11	25	19	7	26	4	3	7
60-79	19	15	34	2	5	7	1	2	3
>80	3	3	6	-	1	1	-	2	2
Total	41	35	76	23	13	36	10	13	23

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TABLE 3. Occurrence of known risk factors for cerebral thrombosis in 76 patients.

Risk Factor	Number of patients
Hypertension	38
Transient ischaemic attack	9
Cigarette smoking	5
Diabetes mellitus	4
Elevated blood lipids	4*
Family histroy of CVA	3
Oral contraceptive pills	1
Systemic atherosclerosis with polycythemia	1

* Analysis was performed in only 59 patients.

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and 21.7% with cerebral embolism had headache. The mode of onset of the CVA was sudden in all patients with cerebral haemorrhage and emolism, while it was reportedly gradual or occurred during sleep in about 58.5% of patients with cerebral thrombosis. A history of stressful situations was obtained in the majority of cases with cerebral haemorrhage. An altered state of consciousness was more common in cerebral haemorrhage. 38.9% with cerebral haemorrhage, 14.5% with NEIVD, and 13% with cerebral embolism were unconscious at the time of hospital admission. New onset generalized seizure disorders occurred in eight patients, five with cerebral thrombosis and three with cerebral haemorrhage. Seven patients presented with a second episode of CVA, the time interval ranging from 1 to 10 years: three of these patients died and one developed pseudobulbar palsy.

Using the Keith-Wagener classification (5), seven out of 150 patients had funduscopic abnormalities, four had grade I, and one patient each had grade, II, III and IV hypertensive retinopathy. Haematologic studies were normal in all except six patients who had anaemia and concurrently elevated BUN and creatinine levels.

Serum cholesterol and triglyceride levels were determined in 59 of the 76 patients with cerebral thrombosis, and were found to be elevated in 4.

CFS analysis was done in 34 patients with cerebral thrombosis and 23 patients with cerebral haemorrhage. It was either bloody or xanthochromic in all who had haemorrhage, while it was clear and acellular in those with NEIVD. Electrocardiographic signs of left ventricular hypertrophy were detected in eight patients with cerebral haemorrhage and four patients with cerebral thrombosis. Non-specific ST and T wave changes were seen in seven patients.

The outcome varied according to the type of CVA: 89.4% with cerebral haemorrhage, 17.4% with cerebral embolism and 17.1% with cerebral thrombosis died while in hospital. Factors contributing to death were pneumonia in 10 and sepsis of different sources in another 10 patients. Of the 76 patients with NEIVD, 55 experienced gradual improvement and were discharged in stable condition, while 8 others had no change in their neurologic deficits. Anticoagulant therapy was not given to patients with cerebral embolism due to lack of drugs and facilities for the determination of prothrombin and partial thromboplastin time during the study period.

There were four young patients, three male and one female, aged from 19 to 28 years, who presented with CVA and a history compatible with migraine. Investigations in these patients were normal. They were all discharged improved on analgesics and physiotherapy. Two young patients developed fever and headaches which were later followed by hemiparesis. The first patient had fever and headache for two weeks and the hemiparesis occurred in hospital, while in the second case the hemiparesis occurred a week after the fever and headaches. Investigations revealed high titres of agglutinins against somatic and flagellar antigens of *Salmonella typhi*. CSF studies were normal in both cases, except for a mildly elevated protein. Both patients improved markedly on chloramphenicol.

Two young male patients presented with the sudden onset of hemiplegia and strongly reactive CSF and serum VDRL. Follwoing initiation of penicillin treatment they showed considerable improvement. Another young male patient suddenly became hemiparetic while in a classroom. He had had a low grade fever and headache for a few days prior to the CVA. Examination revealed a conscious patient with a left hemiparesis and slight neck rigidity. Investigations showed a high sedimentation rate, strongly reactive Mantoux test, and xanthochromic CSF with high protein and low glucose.

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At autopsy, tuberculous spondylitis with psoas abscess, tuberculous meningitis and a large frontal cortical infarct with periarteritis and minimal enarteritis were found.

In five of six patients, four males and two females, aged 28 to 65 years, there were no predisposing risk factors for CVA, examinations showed no other abnormalities except for hemiplegia in all, and investigations revealed no clue to the aetiology of the sudden neurologic deficit. The sixth patient was a 38 year-old male patient who was known to have insulin-dependent diabetes mellitus for 2 years, and was admitted to hospital with sudden hemiplegia and altered level of consciousness. He was found to have diabetic ketoacidosis which was effectively treated, but the neurologic deficit persisted. We were uncertain of the cause of the CVA, but probably it was ischaemic.

DISCUSSION

This study found that cerebral thrombosis is by far the commonest type of CVA, which is similar to reports from different parts of Africa (1,2,6,). In the absence of sophisticated neuroimaging facilities, the differentiation of various types of CVA is obviously very difficult. However, clinical criteria based on history and neurologic findings are considered to be fairly reliable in establising the mechanism of stroke, i.e. distinguishing among infarcts, subarachnoid and parenchymatous haemorrhages (7). In this study we relied mainly on the history and a careful neurological evaluation. CSF analysis was done only in 57 patients (51%) with cerebral thrombosis and cerebral haemorrhage. It was also done in 4 patients with cerebral embolism and 5 patients with miscellaneous causes of CVA. In the rest, CSF results were not available because of contraindications to lumbar puncture (23 cases), and logistic problems in the laboratory such as incomplete results (11 cases). Thirty patients refused the procedure.

The peak age for cerebral thrombosis was 60 to 69 years, and 40 to 49 years for cerebral haemorrhage. 42% of patients in this series were below the age of 50 years, which is similar to a report from Nigeria (6). Males (63.9%) were more likely to develop cerebral haemorrhage than cerebral thrombosis.

Although some patients and their relatives were not willing to disclose their income, on the whole members of the different socioeconomic strata were similarly affected, except for those who developed embolic stroke, most of whom were of low socioeconomic status. Members of the major ethnic groups in the country were similarly represented.

Hypertension was the single most common risk factor in haemorrhagic and thrombotic strokes. A number of studies (8), including the Framingham study (9), have unequivocally shown hypertension to be most powerful risk factor in stroke. A recent study which analyzed the risk factors for stroke in a cohort of men born in 1913 confirmed the role of elevated blood pressure as the principal risk factor for CVA (10). The higher preponderance of CVA in male patients might have been a reflection of the common occurrence of hypertension in Ethiopian males (11) or the fact that male sex is a risk factor, as shown in other studies (12). The outstanding problem in this series was that none of the patients who were known to have hypertension before stroke had received proper treatment or regular follow-up. Blood pressure control has been shown to be effective in the prevention of both fatal and nonfatal cerebrovascular events (13).

Of all 150 patients 7.3% were cigarette smokers, but most of these patients had either hypertension, diabetes mellitus or both as well. A significant relationship has not been found between smoking habits and the incidence of either cerebral haemorrhage

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cerebral infarction in other studies (13). betes mellitus was found in 4.6% of ients with CVA in this series. Previous udies from Ethiopia have reported 4% and 8% (14). Although a number of dies considered diabetes mellitus a gnificant independent risk factor (15), ent ones have not confirmed this (10,16). um cholesterol and triglyceride levles ere high in four of the 59 patients (6.8%) ith cerebral thrombosis. Three of these tients had hypertension and the fourth d hypertension and diabetes mellitus, ndicating that the serum lipid level was not kely to have been an independent risk ctor in this series. Three of the patients were over the age of 50, which makes it even less significant as blood lipid levels hay be high past this age (17). Increased erum lipids have generally not been associated with an increased risk of stroke.

Evidence indicates that a maternal history of stroke is a significant and independent risk factor (10). In this series there was a family history of stroke in five patients, in three on the maternal side. TIAs probably occurred in 11.8% of cases who later developed cerebral thrombosis, all in the territory of the internal carotid arteries. Analysis of the patient's history was used to exclude other symptoms and diseases, and yet these transient neurologic deficitis were often neglected and were not clearly recalled by patients, and may account for the low figure. Summary of data from a number of studies indicates that about 25 to 30% of patients with TIAs will have cerebral infarction within 5 years (18). TIAs constitute the most significant warning event for cerebral infarction.

The clinical presentations of the different types of stroke were similar to reports by other authors. The onset of thrombotic stroke was reportedly sudden in 41.5% of cases, while it was sudden in all patients with cerebral haemorrhage and embolism. Coma was more frequent in cerebral haemorrhage and least common in cerebral embolism, which is at variance with the report by Osuntokun (6).

Although a high mortality rate of 40% has been reported by Lester among 180 CVA patients in Addis Ababa (14), the overall mortality of 28.6% in this series is comparable to the 23% found by Abraham and Abdulkadir (3) and similar to other African reports (6,19). However, these African CVA mortality rates are much higher than those reported from Europe, for example, 16% from Swedish general medical wards (20). Mortality was very high in case of cerebral haemorrhage (89.4%) and lower in cerebral thrombosis (17%) and cerebral embolism (13%). At this point it is worth emphasizing the public health importance of hypertension, which was the sole important risk factor for haemorrhagic CVA identified in this study. The prevention of stroke requires correction of the precursors of stroke in susceptible individuals, and the single most important measure is vigorous and sustained control of hypertention (13).

It is worth discussing the less common causes of CVA in this study. The presentation of the four young patients who developed stroke during or after episodes of severe headache, similar to the ones they had in the past, is informative. There is a large literature associating migraine with permanent neurological sequelae. In most of these reports (21), as in ours, the association of CVA with the migraine attacks was circumstantial.

Infections as causes of CVA are reported mainly from developing countries (22,23). Cerebrovascular neurosyphilis is responsible for stroke in different parts of Africa, with reported figures ranging from 3.5 to 27% (23). In our series, although the figure is low (1.3%) syphilitic arteritis should be considered in young patients presenting with stroke. Typhoid fever was presumed to be the cause of CVA in two patients, which indicates the need for early diagnosis and

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treatment of this condision to prevent complications (220. Cerebral arteritis due to tuberculosis is a well recognized entity (23,24). The autopsy proven case in this series alerts us to the possibility of CVA as the initial and sole manifestation of tuberculosis.

An unusual finding in this study is the rarity of subarachnoid haemorrage. We did not encounter a single patient with subarachnoid haemorrhage during the study period. In our experience over the last ten years we have noted that it is uncommon, which is in contrast to reports from other parts of Africa (6,8). We might have mistaken subarachnoid haemorrhage for intracerebral haemorrhage when the presentations were hemispheric neurologic deficits as aneurysms, especially located at the bifurcation of the middle cerebral artery may rupture out into the temporal lobe and up into the frontal and parietal lobes and occasionally present a picture of primary parenchymatous haemorrhage (25).

This hospital-based study does not necessarily reflect the true prevalence of CVA in the country, but it shows that it is a major medical problem. It will be interesting to carry out a similar study in the future when computerised tomography (CT scan and magnetic resonance imaging (MRI) studies become available.

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PLASMA LEVEL DISTRIBUTION, EFFECT AND TOXICITY OF ANTIEPILEPTIC DRUGS AMONG ETHIOPIAN EPILEPTICS

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ABSTRACT. *Plasma phenytoin and phenobarbitone levels were estimated in 123 adult Ethiopian epileptics by gas-liquid chromatography. Thirty four (38.2%) of the patients on phenytoin, and 52 (52%) of those on phenobarbitone, had plasma levels in the conventional therapeutic ranges of 10-20ug/ml and 10-30ug/ml respectively. Of the 89 patients who were taking phenytoin either singly or combined with phenobarbitone, motor disturbances (ataxia and nystagmus) were seen in 31 (34.8%) and dysmorphic and idiosyncratic side effects including gum hypertrophy, hirsutism, acne and skin rash in 37 (41.6%). Subnormal serum calcium levels were noted in 15 (30.6%) and high alkaline phosphatase was found in 13 (26.5%). Phenobarbitone was found to be an effective anticonvulsant (78.1% seizure control rate), with adverse effects of sedation and intellectual depression. Seizure control was achieved in 77.1% of patients on a single drug as opposed to 55.6% on combination of phenytoin and phenobarbitone ($p < 0.05$). The overall seizure control rate was 66%.*

INTRODUCTION

Epilepsy is a common neurological disorder in Ethiopia as in the rest of Africa. Morbidity surveys from Ethiopia by Giel (1) in 1970 gave an estimate of 5 per thousand in an urban area and 8 per thousand in a rural community. A hospital based prospective study by Tekle-Haimanot (2) showed grand mal to be the commonest clinical type of epilepsy (60.1%). In Ethiopia, phenobarbitone and phenytoin are the two widely used anticonvulsants for generalized seizures.

The purpose of this study was to determine the pattern of phenytoin and phenobarbitone plasma levels in adult Ethiopian epileptics, and to evaluate compliance and side effects in patients taking the two anticonvulsants, in order to suggest guidelines for appropriate follow-up of epileptic patients in the context of the local situation.

PATIENTS AND METHODS

Adult epileptics of both sexes with grand mal epilepsy attending the neurology referral clinic of the Tikur Anbessa teaching hospital were selected on the basis of a history of continuous anticonvulsant treatment for several months. Some patients had been given combined phenobarbitone and phenytoin therapy when a single drug failed to control their seizures according to reports from the patient or his/her relatives. Because of occasional unavailability of phenytoin for freely treated patients, many of them who came from distant and remote areas were put on two anticonvulsants to assure continuation of treatment on at least

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one drug. In this group of patients a smaller dose of phenobarbitone (60-100 mg. at night) was added to the standard phenytoin daily dose of 300 mg. It is to be noted that, during the study period, there was a continuous supply of both drugs. Patients who could afford to buy the drugs and were reliable, intelligent and compliant were put on single drug treatment. This situation incidentally created two groups of patients: those taking a single drug and those on combined drug therapy, thus allowing comparison of the control of seizures in the two groups.

History and physical examination were documented in all patients according to a preset protocol. Laboratory investigations included: haemogram, liver function tests, serum calcium and alkaline phosphatase blood urea nitrogen (BUN), creatinine and fasting blood glucose. All patients had electroencephalographic (EEG) recordings at least on one occasion.

After informed consent, blood samples for drug levels were drawn from each patient between 10 a.m. and 12 noon, and the plasma separated immediately by centrifugation and stored in a deep freeze until extraction and chromatographic analysis was done a few hours later. Gas-liquid chromatography as modified by Kupferberg (3) was used for the simultaneous determination of both phenytoin and phenobarbitone, at the Chemistry Department of the Addis Ababa University. Control of seizures in this study was defined as a seizure-free period of two or more months. Compliance was discussed with each individual patient and only those patients who claimed to have taken their drugs regularly for at least four weeks prior to drug level determination were included in the study.

RESULTS

There were a total of 123 patients, 72 males and 51 females: of these patients 78% were between the ages of 10 and 39 years. Eighty nine patients were taking phenytoin either singly or combined with phenobarbitone. There were 23 taking phenytoin alone and 34 phenobarbitone alone. One hundred patients were taking phenobarbitone either singly or combined with phenytoin. The mean durations of treatment for those taking phenobarbitone and phenytoin were 3.8 years (range 3 months – 20 years) and 3 years (range 2 months – 20 years) respectively.

Ninety percent of the patients taking phenytoin were taking the drug in a dose of 300 mg p.o. daily, and 10% 200 mg daily.

Table 1 shows the plasma level distribution of phenytoin in 89 patients. Thirty four (38.2%) patients had plasma levels of phenytoin in the therapeutic range of 10 – 20 ug/ml. Fourteen (15.7%) had levels below and 41 (46.1%) above the conventional therapeutic levels.

Of the 100 patients who were taking phenobarbitone either singly or combined with phenytoin, 52% had phenobarbitone levels in the therapeutic range of 10-30 ug/ml. Twenty percent had levels above 30 ug/ml and 28% had levels below 10 ug/ml.

Among 32 patients who were taking phenobarbitone alone, 28 patients were taking the drug in doses ranging between 60 and 100 mg per day. Thirteen patients (46.4%) were taking daily doses of 100 mg. Only 4 patients were taking doses exceeding 100 mg/day. The overall seizure control rate was 78.1%. Dosages between 90 and 200 mg daily resulted in 83% seizure-free state. The side effects included drowsiness in 8 patients (25%), altered mood in 4, hyperactivity in 2, altered cognitive function in 2 and nystagmus in one.

The side effects of phenytoin in 89 patients are shown in Table 2. Sixty six (74%) of these patients were taking phenytoin combined with phenobarbitone, whereas 23 were taking the drug alone. Motor disturbances (ataxia and nystagmus) were

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TABLE 1. Plasma levels of phenytoin in Ethiopian epileptics in Addis Ababa

Phenytoin level in μg/ml	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	>50	Total
Number of patients	7	7	18	16	13	14	4	3	3	2	2	89*

* 90% of patients were taking phenytoin in a dose of 300 mg p.o. daily.

TABLE 2. Phenytoin side effects

Side effects	Plasma Phenytoin Level (μg/ml)											Percent of patients
	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	>40	Total		
Nystagmus	-	-	1	2	3	2	3	2	5	18		20.2
Ataxia	-	-	1	1	2	3	-	-	6	13		14.6
Hirsutism, skin rash, acne	1	1	2	3	3	-	-	1	-	10		11.2
Gingival hypertrophy	2	2	3	5	4	5	2	2	2	27		30.3
Lymphadenopathy	-	-	1	-	1	1	-	-	-	3		3.4
Total number of patients	7	7	18	16	13	14	4	3	7	89*		

* 66 (74%) patients were on combination of phenytoin and phenobarbitone
6 (26%) patients taking phenytoin singly and 25 (37.8%) patients taking combinations of phenytoin and phenobarbitone had motor disturbances (p>0.10).

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seen in 31 (34.8%) of the patients. Dysmorphic and idiosyncratic side effects including gum hypertrophy, hirsutism, acne and rash were observed in 37 (41.6%) of the patients. Three patients had lymphadenopathy.

Nystagmus usually appeared at phenytoin levels above 20 ug/ml but has been observed with concentrations as low as 15 ug/ml. Ataxia was most common above 30 ug/ml and drowsiness was seen in patients with levels of 40 ug/ml and over.

As shown in Table 3, of the 60 patients who were taking both phenytoin and phenobarbitone and in whom seizure control was documented, 34 (56.6%) were seizure free for the last two months. If one takes phenytoin level as a marker, seizure control was lowest (27.7%) with plasma levels below 10 ug/ml. Only 58.3% of patients who had plasma levels of phenytoin above 30 ug/ml were controlled.

Table 4 shows control of seizures with single or combined anticonvulsant therapy. Control of seizures was documented in 108 patients. Sixty (55.6%), were on combined drug therapy (phenobarbitone and phenytoin) and 48 (44.8%) on phenytoin or phenobarbitone. Seizure control was achieved in 37 (77.1%) of patients on a single drug as opposed to 34 (56.6%) on combination, a statistically significant difference ($p < 0.05$) The overall control rate was 66.%.

Table 5 compares findings from different studies of low serum calcium and high alkaline phosphatase in epileptic patients taking anticonvulsant drugs. In our study 30.6% and 26.5% had low serum calcium and high alkaline phosphatase levels respectively.

The renal function tests were normal in all the patients investigated. No case of megaloblastic anaemia was encountered. Electroencephalographic findings were normal in 19.5%, borderline in 21%, and abnormal in 59.5% of patients.

DISCUSSION

In Ethiopia, as in the rest of Africa, where resources are limited, there are only a few basic anticonvulsants available to treat epileptics. Phenobarbitone and phenytoin were the only anticonvulsants available to poor patients with generalized seizures.

Although phenytoin has been a drug of first choice in the treatment of the major epilepsies, it has several important disadvantages including a narrow therapeutic ratio with a potentially wide variety of adverse effects associated with its acute and chronic use. Furthermore, its kinetics in man make it a difficult drug to use in practice, because of a non-linear relationship between dose and serum level (4-6).

Phenobarbitone, on the other hand, is a very cheap and effective anticonvulsant, which, however, has the side effects of sedation and intellectual depression.

Although facilities for routine drug level determinations are not available in Ethiopia, such determinations have been documented to be invaluable in the judicious and rational use of anticonvulsants.

The plasma levels of both anticonvulsant drugs varied widely from patient to patient although most patients were prescribed similar standard doses of the drugs. As only 38.2% of patients taking phenytoin and 52% of patients on phenobarbitone had plasma levels in the therapeutic range, it is clear that more efficient therapeutic use of the drugs would be obtained by monitoring drug levels. Our results confirm the observations from various studies that patients on a standard dose of phenytoin have a wide scatter of plasma levels (7-10).

The frequency of side effects in our patients, most of whom (74%) were on combination of phenytoin and phenobarbitone, is higher, but not statistically significantly so ($p > 0.10$), than the figures in previous studies which dealt with single drug therapy

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TABLE 3. Patients on phenytoin and phenobarbitoen seizure-free for the last two months

Plasma phenytoin level (µg/ml)	0-9	10-19	20-29	30-39	>40	Total
Total number of patients	11	21	16	6	6	60
Number of patients seizure free	3	12	12	3	4	34(56.7%)

TABLE 4. Seizure control: Single drug versus combined drug therapy

Anticonvulsalt	Total number of patients	Number of patients seizure free		p value
Phenytoin	16	12 (75%)	77.1%	
Phenobarbitone	32	25 (78.1%)		
Combined phenytoin and phenobarbitone	60	34 (56.7%)	56.7%	p<0.05

TABLE 5. Serum calcium and alkaline phosphatase levels in epileptic patients taking anticonvulsant drugs

	Number of patients	Low serum calcium % of patients	High serum alkaline phosphatase % of patients
1. Richens and Rowe Europe (1970)	160 (adults)	22.5	29.0
2. Hunter (1971) Europe	105 (children)	30.0	24.0
3. Apantaku (1975) Nigeria	52	-	30.8
4. Present study Ethiopia (1988)	49 (adults)	30.6	26.5

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(11,12). Motor disturbances observed by Mattson *et al* (11) for phenobarbitone and phenytoin when taken singly were seen in 24% and 28% of patients respectively. Dysmorphic and idiosyncratic side effects occurred in 11% on phenobarbitone and 22% on phenytoin. These toxic effects, especially motor disturbances which occurred in 26% of our patients when phenytoin was singly taken and in 37.8% when combinations of phenytoin and phenobarbitone were used, were most likely the cumulative adverse effects of the combined drug therapy. Ramsay (12), in his comparative study of carbamazepine and phenytoin, found major side effects in 23% of his patients in each study group. Minor side effects were common with both drugs, nystagmus being the most common.

Motor disturbance in the 20-30 ug/ml plasma phenytoin range were seen in 37% of the patients and were not significantly different from a rate of 34.8% for all patients taking phenytoin. In contrast, control of seizures was maximal (75%) with plasma concentration of 20-30 ug/ml. This implies that, in situations of failure of control, an attempt should be made to adjust the dosage of phenytoin to attain plasma concentrations which give maximal effect without significantly increased side effects. From this study one is able to conclude that the standard recommended dosage of phenytoin is satisfactory for Ethiopian patients.

On the other hand, Osuntokun (13) stated that side effects were relatively uncommon in Africans taking anticonvulsants. Megaloblastic anaemia was encountered extremely rarely. There have also been suggestions that black skin and abundant sunshine may protect the African against anticonvulsant-induced osteomalacia (14). In this study we found side effects similar in magnitude to those in other reports (11,12,15,16).

This study has also inadvertently shown that seizure control was better in those single drug therapy, an approach which has been supported by the studies of Reynolds (17) and Schmidt (18).

A relatively close correlation between toxic symptoms and signs and serum drug levels is noted in this study. Similar findings were observed in previous studies by Kutt *et al* (19) and Haerer and Grace (20).

It is known that excessive phenytoin may paradoxically aggravate epilepsy and even precipitate status epilepticus (21). This is an important point to consider in some of our patients who had plasma levels of phenytoin greater than 40 ug/ml and yet were not controlled.

In this study, phenobarbitone was the most commonly prescribed anticonvulsant drug, followed by phenytoin. In its study in 35 developing countries, the WHO-sponsored Commission of Antiepileptic Drugs (AEDS) found heterogenous distribution and availability of antiepileptic drugs. Similarly in Ethiopia, only the older drugs, such as phenobarbitone, are available to most patients (22).

Although most patients claimed to have taken their medication regularly, we have evidence, through information from relatives, that 20% of those with low drug levels were not fully compliant.

Even though this study is a cross-sectional study during long term treatment, our results support the recent policy of treating epileptics with a single drug whenever possible and also re-emphasize the value of monitoring plasma levels of anticonvulsants for optimization of seizure control. Needless to say, a consistent and reliable supply of basic anticonvulsants should be available to African epileptics at a fairly low cost. In addition to giving the poor epileptic the confidence of leading a relatively seizure-free life, this would also avoid the use of multiple drugs in the control of seizures. Multiple drug therapy carries a higher risk of chronic toxicity, and the evaluation of the individual

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effects of each drug is made extremely difficult.

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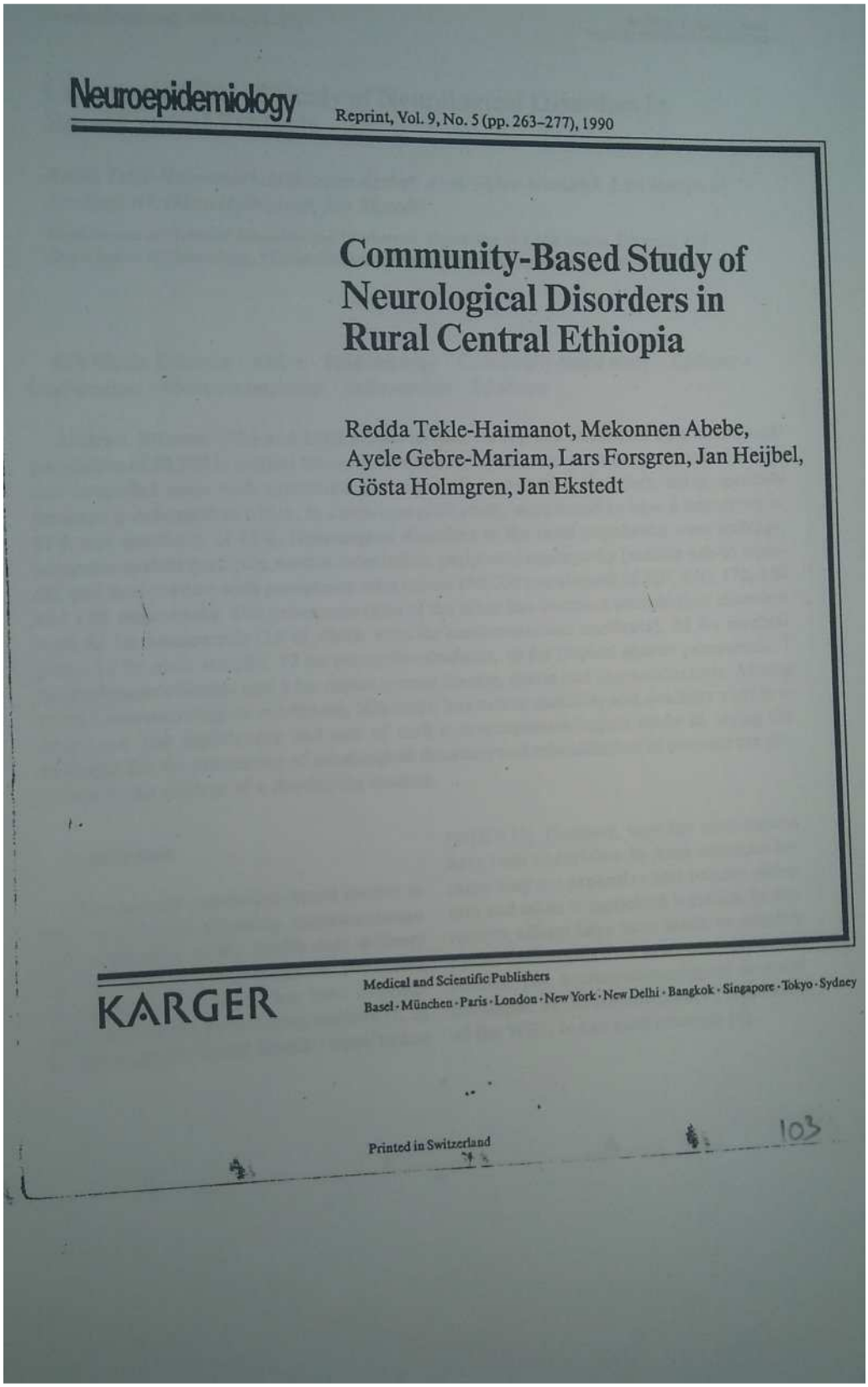
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Community-Based Study of Neurological Disorders in Rural Central Ethiopia

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Abstract. Between 1986 and 1988 a door-to-door survey was conducted on a stable rural population of 60,820 in central Ethiopia. Trained lay health workers made a complete census and identified cases with symptoms and signs of neurological disorders, using specially designed questionnaires which, in a previous pilot study, were found to have a sensitivity of 91% and specificity of 85%. Neurological disorders in the rural population were epilepsy, postpoliomyelitis paralysis, mental retardation, peripheral neuropathy (mainly due to leprosy), and deaf-mutism with prevalence rates (cases/100,000 population) of 520, 240, 170, 150 and 130, respectively. The prevalence rates of the other less common neurological disorders were 62 for hemiparesis (15 of which were for cerebrovascular accidents), 20 for cerebral palsy, 16 for optic atrophy, 12 for perceptive deafness, 10 for tropical spastic paraparesis, 7 for Parkinson's disease and 5 for motor neuron disease, ataxia and chorea/athetosis. Among related non-neurological conditions, blindness, locomotor disability and deafness were predominant. The significance and role of such a neuroepidemiological study in laying the strategies for the prevention of neurological disorders and rehabilitation of patients are discussed in the context of a developing country.

Introduction

The value of population-based studies in the cost-effective planning, implementation and evaluation of the health care delivery systems of developing countries pertaining to neurological disorders has been convincingly pointed out by different workers [1, 2] as well as by the World Health Organization (WHO) [3]. However, very few such studies have been undertaken in these countries because they are expensive and require elaborate and often complicated logistics. In this respect, efforts have been made to simplify the methodologies used in community-based studies. The neuroepidemiological protocol developed by the Neurosciences Programme of the WHO is one such example [4].

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Ethiopia, situated in the north-eastern horn of Africa, occupies an area of 1.25 million km², and has an estimated population of 46 million. Ninety percent of the population is rural [5]. Like the majority of developing countries, Ethiopia is faced with the serious public health problems of malnutrition, deficiency states and a high prevalence of communicable diseases. These problems, coupled with inadequate and inequitably distributed health delivery services particularly in the rural areas, have resulted in high morbidity and mortality, as reflected by the high infant mortality rate of 144/1,000 population [6].

From hospital-based experiences, neurological disorders are not uncommon in Ethiopia [7]. However, their prevalence has not been accurately determined. Cognizant of this need, we devised and tested a screening instrument for a neuroepidemiological study to be performed by lay health workers under the supervision of neurologists. The research protocol and questionnaire produced and the pilot study undertaken to pretest it have been described in a previous communication [8].

Our current paper reports the results of the major door-to-door survey undertaken in the subdistrict of Meskan and Mareko, involving a sampled population of 60,820 persons.

Material and Methods

Study Area

At the time of this survey Ethiopia was divided into 14 administrative regions which, in turn, were subdivided into districts *(awraja)*. The subdistrict *(woreda)* formed the smallest administrative unit.

Our study was carried out in the rural subdistrict of Meskan and Mareko of the Haykoch and Butajira district within the central Administrative Region of Shoa (fig. 1). The subdistrict is situated 130 km south of Addis Ababa, the national capital. The total population of the subdistrict was 181,883 [5]. The population is organized into peasant and urban dwellers' associations. There are three towns with 6 urban dwellers' associations and 82 peasant associations (villages) in the subdistrict. Topographically the subdistrict is divided into highlands in the north, and lowlands in the south. The ethnic groups found in the surveyed areas were Oromo, Amhara, Kembata, Tigre and Gurage. The Gurage ethnic group, with the sub-ethnic groups of Meskan, Mareko, Silti and Sodo, was the predominant one. The main occupation of the inhabitants is plough cultivation of maize, sorghum, wheat and teff *(Eragrostis tef)*. The highlanders cultivate enset *(Ensete ventricosum)*, a false banana. The core of the underground part of the plant is used to produce the staple diet of *kocho*. The lowlanders eat mainly bread made from maize flour.

The subdistrict is served by a health center, which is run by nurses and situated in Butajira town (population 13,688), the administrative center of the subdistrict. There are two additional satellite health stations in the subdistrict.

Survey Area

Figure 2 schematically represents the logistics used in our neuroepidemiological study. Using a table of random numbers, a 30% random sample of the peasant associations was taken. The survey was carried out in 25 of the 82 peasant associations and the three towns within the subdistrict. All households within the selected associations were surveyed, resulting in the inclusion of 60,820 inhabitants.

Two pilot surveys were carried out in communities near the project area. These pilot studies were used to improve on the logistics of the epidemiological studies as well as on the protocol questionnaires.

Before launching the project, the aims and goals of the survey were explained to administrative officials at all levels. Consent and collaboration was obtained from community leaders of the associations every time our research teams entered a village. There was good cooperation from everyone involved. The chairmen of the associations and their committees knew the inhabitants of their villages very well, and greatly assisted our enumerators in the collection of the necessary information. They also contributed a great deal by ensuring that all informants were present and did

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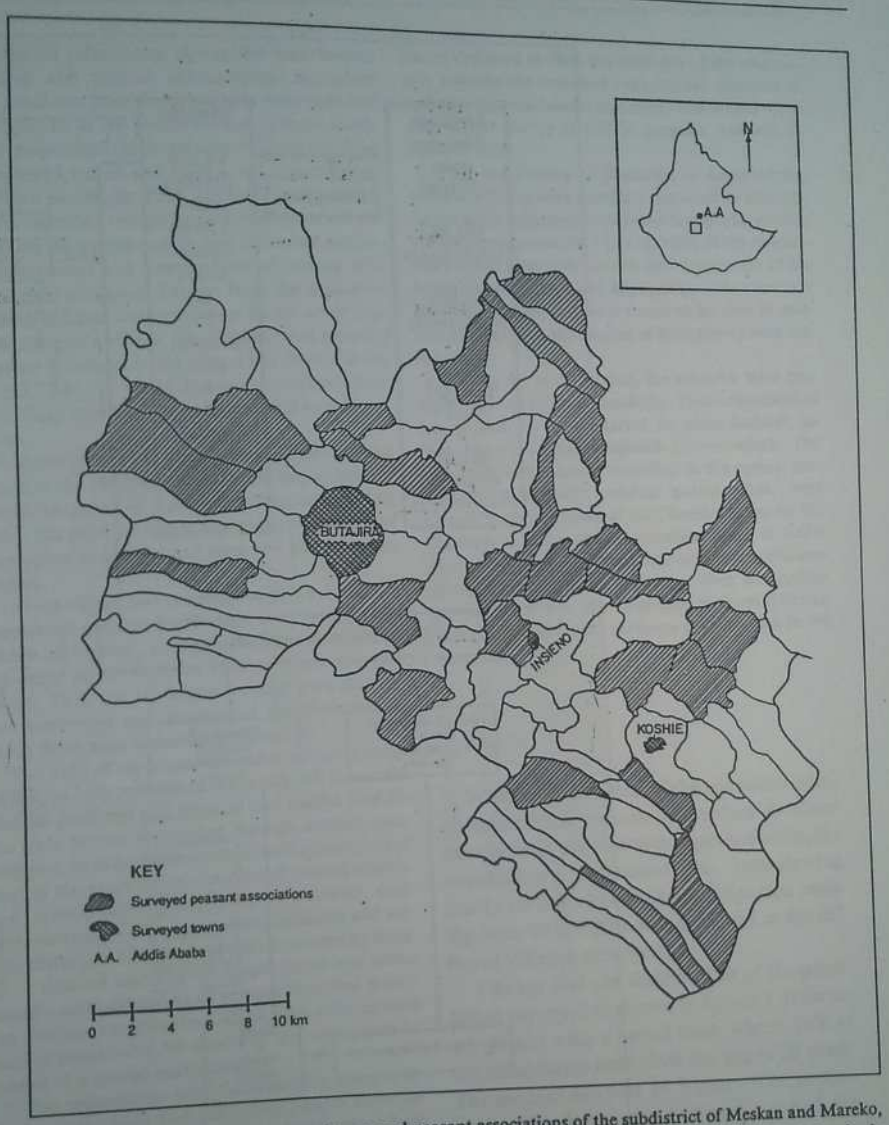


Fig. 1. Map showing the surveyed town and peasant associations of the subdistrict of Meskan and Mareko, Shoa administrative region, central Ethiopia. Butajira town is situated at latitude 8° 7′ N and longitude 38° 23′ E.

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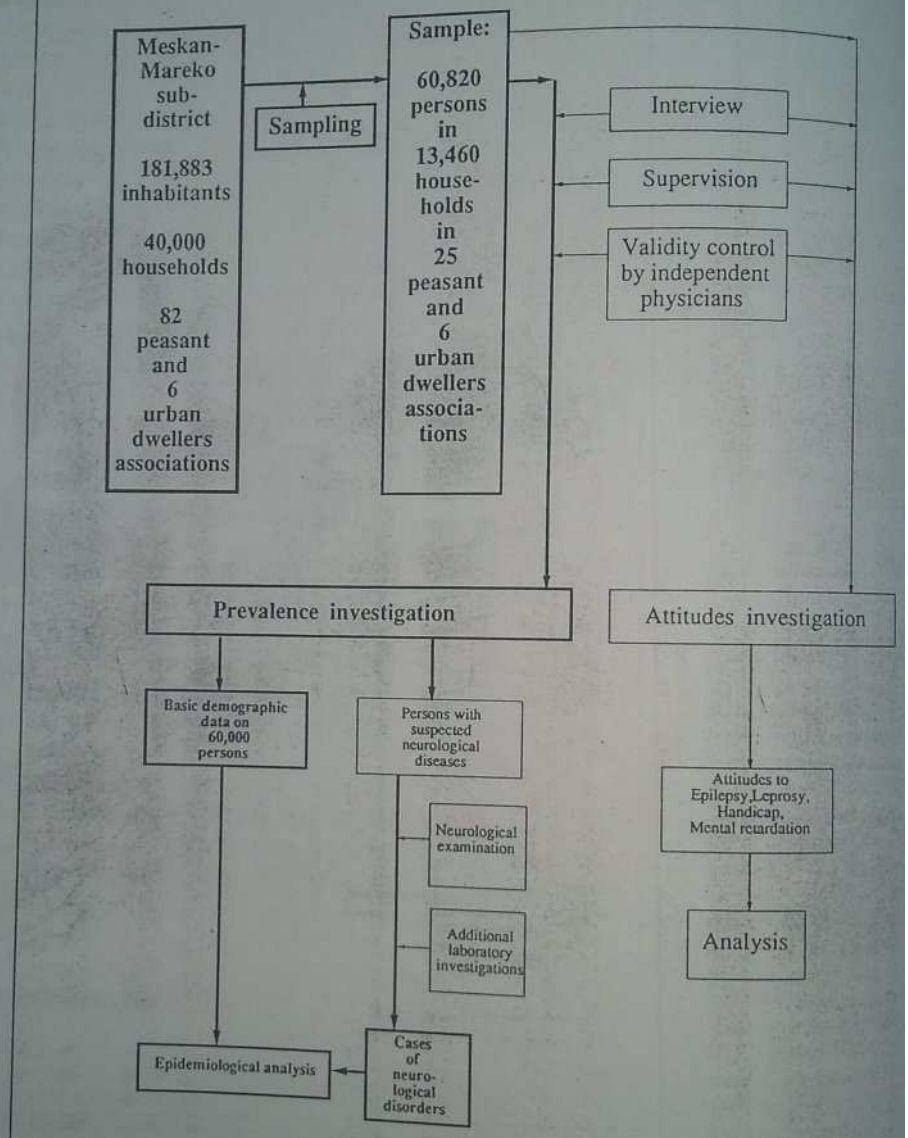


Fig. 2. Scheme of the neuroepidemiological survey.

not withhold information during the door-to-door interviews and clinical examinations. Secondary school graduates from the community were recruited and employed as lay health workers (enumerators). Recruitment criteria included sound knowledge of the local customs, culture and dialects, as well as previous experience in similar field survey. The lay health workers were then trained by epidemiologists and clinicians on the questionnaires, and instructed on simple observations and examinations of persons with neurological problems. Experts from the Ethiopian Mapping Institute instructed them on the art of simple mapping of a village. The field workers travelled on foot or horseback in the villages and lived with the villagers, who in many instances provided their meals. They were thus very well accepted by the population.

A health officer was recruited as a supervisor and trained in the Neurology Unit of the Department of Internal Medicine of the teaching hospital in Addis Ababa. His practical instruction in the recognition of neurological symptoms and signs was given by neurologists.

In each village, two enumerators with a supervisor mapped and numbered with chalk every house except centers of worship, schools, administrative offices, and other public facilities such as shops and mill houses. Then the lay health workers gave door-to-door interviews and aministered questionnaires to screen those with neurological disorders.

The head of the household or his wife gave information on each member of the family. All those with medical problems and physical and mental disabilities were further scrutinized through another questionnaire, in order to screen those with symptoms and signs of the neurological disorders of mental retardation, speech disturbance, epilepsy, blindness, deafness, movement disorder, walking difficulty and sensory disturbance, including problems caused by leprosy. A detailed neurological questionnaire was subsequently administered to all persons identified as having neurological disorders. Those with seizures were further interviewed for details of their symptoms by means of a special questionnaire.

The enumerators with the supervisor saw the affected individuals and performed simple examinations according to the training they had received from neurologists. Neurologists regularly visited the villages to examine and validate symptoms and diagnosis. The enumerators also administered questionnaires designed to find the attitudes of the community towards the common neurological disorders of epilepsy, physical handicap, leprosy and mental retardation. The survey is still in progress, and will be reported later.

From the Faculty of Medicine in Addis Ababa, medical officers were regularly recruited to administer the same questionnaires in the households already visited by enumerators. The reliability of the enumerators in the interview process and completion of the forms was evaluated, and appropriate action was taken. Enumerators who were found to be slow in mastering the art and techniques of field survey were dismissed.

During the study period, the research team provided services to the community. Those diagnosed as having epilepsy were started on phenobarbital, an inexpensive and easily available anticonvulsant. The physically handicapped identified in the survey, particularly those with residual poliomyelitis, were brought to the attention of the Cheshire Home for the Disabled, a non-profit organization based in Addis Ababa. The team from the home provided appliances locally produced in its workshop. Free tetracycline eye ointments were also dispensed to those suffering from trachoma, a very common eye infection in the community.

Results

With the assistance of the executive committees of the peasant and urban dwellers' associations, and through repeated visits, the enumerators succeeded in interviewing nearly all households. A participation ranging from 95 to 100% was achieved in the different villages surveyed.

The age and sex distribution of the population surveyed is shown in figure 3. It forms a pyramid with a broad base, where 59% of the inhabitants are below the age of 20 years. The median age was 14.5 years. The pattern is very similar to the national age and sex distribution [5]. The male-to-female ratio was 1:1.04.

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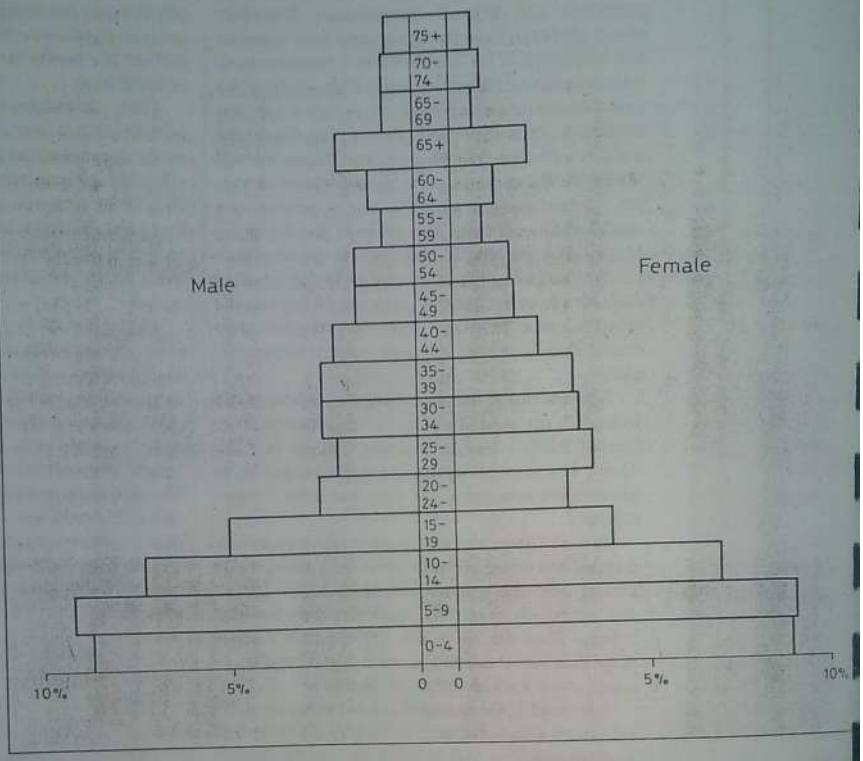


Fig. 3. Age and sex distribution of the population in Meskan and Mareko subdistrict, Shoa administrat region Ethiopia, central Ethiopia (60,820 inhabitants).

Fifty-four percent of the inhabitants, mainly the lowlanders, were Muslims, and the rest belonged to the Christian faith. The predominant ethnic group was the Gurage tribe (88.6%). Eighty percent of the population was found to be illiterate (unable to read and write), a rate much higher than the national figure of 40% quoted in a previous report [9] but similar to the rate found in a recent survey in north-western Ethiopia [10]. The average household size for the survey area was 4–5 persons.

There were persons identified as hav neurological deficits in the project areas. shown in table 1, the most common neu logical disorders in the rural commun were epilepsy, speech disturbance, polio elitis, mental retardation, peripheral neur athy (in particular, leprosy) and hemipare in that order.

Table 1. Neurological disorders in rural Ethiopians

Diagnosis	Sex		Total	Prevalence cases/100,000
	M	F		
Epilepsy	173	143	316	519
Speech disturbance	90	66	156	256
Deaf-mutism	38	38	76	125
Others	52	28	80	131
Poliomyelitis	82	65	147	241
Mental retardation	71	32	103	169
Peripheral neuropathy	58	36	94	154
Leprosy	40	23	63	103
Traumatic	11	4	15	24
Bell's palsy	2	6	8	13
Hereditary	4	2	6	10
Others	1	1	2	3
Hemiparesis	21	17	38	62
Early childhood onset	10	8	18	29
Cerebrovascular	4	5	9	15
Post-traumatic	1	1	2	3
Unknown etiology	6	3	9	15
Cerebral palsy	7	5	12	20
Optic atrophy	6	4	10	16
Perceptive deafness	4	3	7	12
Paraparesis	4	2	6	10
Parkinson's disease	4	0	4	7
Motor neuron disease	2	1	3	5
Ataxia	2	1	3	5
Chorea/athetosis	1	2	3	5
Tremors	1	2	3	5
Torticollis	1	0	1	2
Myopathy	0	1	1	2
Hemifacial spasm	1	0	1	2
Total	528	380	908	
Percent	58.1	41.9	100	

The overall prevalence rate of epilepsy (recurrent non-provoked seizures) in the rural community was 520/100,000 (table 2). The rate was high in Butajira town (790/100,000) as compared to the farming villages (460/100,000). The age-specific prevalence was highest in the age group of 5–14 years. Males were slightly more affected than females (1:0.8). A family history of epilepsy was obtained in 31.8%. Febrile convulsions in childhood were reported to have been present in 18.5% of the affected.

Speech disturbance was the second commonest neurological symptom (256/100,000)

found in the rural area studied. While most of the disabilities in speech were minor in nature, the more serious deficit of deaf-mutism, distributed equally in both sexes, formed 48.6% of the speech disturbances. It was found to have followed deafness due to otitis media or meningitis at a very early age.

Sequels of poliomyelitis (table 3) were found to be a very important problem in the community, with a prevalence rate o 241/100,000. Next to traumatic etiologies poliomyelitis was a common cause of loco motor disabilities encountered in the com munity (table 4). Sixty-two percent of th 147 affected with residual poliomyelitis wer below the age of 15 years at the time of th survey. In 69% of 144 patients who wer specifically studied, the paralytic disease wa found to have had its onset before the age o 2 years, and in 80% before 4 years (fig. 4) The lower limbs were affected in 98%. Th majority of the patients had been delivere at home and had not received vaccinatior The distribution in the highlands, lowland villages and towns was similar.

The age and sex distribution of those wit severe mental retardation is shown in ta ble 5. The prevalence was 169/100,00(Eighty percent of the cases were below th age of 19 years. Twice as many males a females were affected. Epilepsy, microcephal ly, macrocephaly and cerebral palsy wer important associated conditions. Down syndrome was found in 5%. One person ha neurofibromatosis.

Table 2. Prevalence of epilepsy in the rural subdistrict of Meskan and Mareko, central Ethiopia

Survey area	Number with epilepsy	Population surveyed	Prevalence per 100,000
Butajira town	78	9,843	790
Koshe/Enseno towns	7	1,421	490
Peasant association	231	49,556	470
Total	316	60,820	520

Table 3. Age-specific prevalence of residual poliomyelitis in Meskan and Mareko subdistrict: prevalen expressed as cases/100,000

Age group years	Survey area					
	Butajira town			peasant associations		
	number of polio cases	population	prevalence	number of polio cases	population	prevalen
0–4	4	1,435	280	28	9,017	310
5–19	23	4,449	520	51	20,238	250
20–45	7	2,318	300	22	13,521	160
45+	2	1,641	120	7	7,680	100
Total	36	9,843	370	108	49,556	220

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Table 4. Non-neurological disorders

Diagnosis	n	%	Prevalence per 100,000
Blindness	876		1,440
Both eyes	652	74.4	1,072
One eye	224	25.6	368
Post-infectious	219	25.0	360
Cataract	175	20.0	288
Post-traumatic	158	18.0	259
Others	324	37.0	533
Motor disability	684		1,124
Upper limb	216	44.6	355
Lower limb	468	55.4	769
Post-traumatic	301	44.0	495
Post-infectious/ inflammatory	116	17.0	191
Clubfoot	8	1.2	13
Tb spondylitis	7	1.0	12
Others	115	16.8	189
Deafness	224		368
Both ears	180	80.4	296
One ear	44	19.4	72
Post-infectious	135	60.0	22
Familial	11	5.0	18
Others	78	35.0	128

Table 5. Age and sex distribution and age-specific prevalence in 103 severely mentally retarded

Age group years	Sex		Total	Prevalence per 100,000
	male	female		
0–4	12	6	18	170
5–9	13	7	20	180
10–14	19	8	27	310
15–19	13	3	16	280
20–24	5	2	7	210
25–29	4	3	7	200
30 +	5	3	8	50
Total	71	32	103	169
Percent	68.9	31.1	100	

Leprosy was the commonest cause of peripheral neuropathy encountered, with a prevalence rate of 103/100,000. The majority of the patients (74.6%) were above 40 years of age. Most had advanced disease, and 80% were or had been on dapsone monotherapy. In 15% of the patients diagnosis was established for the first time. The male to female ratio was 1.6:1.

Traumatic neuropathy, mainly involving the brachial plexus (70%), was found in 15 cases (24/100,000). There were 8 persons with peripheral facial paralysis (Bell's palsy; 13/100,000), and 6 with neuropathy of the type of Charcot-Marie-Tooth's disease (10/100,000). Two had peripheral neuropathy of undetermined etiology.

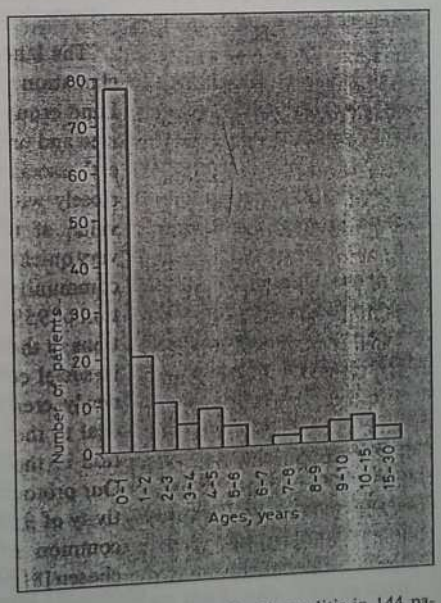


Fig. 4. Ages at onset of poliomyelitis in 144 patients in Meskan and Mareko subdistrict, Shoa administrative region Ethiopia, central Ethiopia.

Hemiparesis was found in 38 cases (62/100,000). Fifty percent were reported to have occurred before the age of 15 years. Cerebrovascular accidents were recorded in 9 persons (15/100,000) of whom 5 were males and 4 females. The ages of the patients ranged from 28 to 85 years. One, the youngest, had embolic stroke associated with rheumatic heart disease. The prevalence of cerebral palsy was 20/100,000. Seven of the 12 identified had mental retardation and 2 had epilepsy. Ten persons were found to have bilateral optic atrophy (16/100,000). The prevalences of the other less common neurological disorders are shown in table 1.

Discussion

The land reform policy of the 1975 Proclamation of Public Ownership of Rural Land brought scattered villages into centralized and organized peasant and urban dwellers' associations. Our research team worked closely with the associations, in which the value of the community-based study was very quickly accepted and appreciated by the community. This resulted in the participation of 95% or more of the different populations in the survey. In addition, the increase in social contact and interaction within the newly created villages contributed a great deal to the successful gathering of information in the interviews by our investigators. Our protocol/questionnaires yielded a sensitivity of 91% and specificity of 85% for the common neurological disorders that were chosen [8], thus confirming a fairly good reliability.

A wide range of prevalence rates for epilepsy has been reported from different studies in Africa. We may account for part of these variations by the different definitio classifications and methodologies used the study of epilepsies in African countri sometimes even in the same country. In dition, hospital-based studies, on which number of the prevalence figures were bas were open to selection bias and were oft unrepresentative of the community at lar Hence, caution should be exercised wh comparing prevalence rates.

Osuntokun [11], in his 1978 review epilepsy in Africa, based on existing comm nity-based studies from eastern, western a southern Africa, found the prevalence of disease to range from 4 to 8/1,000. This w excluding the high incidence (2,00 100,000) of epilepsy among the Wapogo tribe in Tanzania [12], which is proba genetically determined, and endemic f discovered in Liberia with rates as high 2,900/100,000 [13] and 4,000/100,000 [1

As has been the experience of other wo ers in different parts of Africa, epile proved to be the most common neurologi disorder in Ethiopia. The rates found comparable to the rates obtained in a rece community-based epidemiological sur carried out in Nigeria [15]. It is also in acc dance with a previous epidemiological su vey by Giel [16], performed in 1970 o small population base in western Ethiopi

Among our patients with epilepsy, the at onset was below 30 years in 74%, an history of febrile convulsions during chi hood was elicited in 18.5%. In persons w otherwise had nonprovoked seizures, feb episodes were also the most common pr pitating factor for seizures, as found 22.4% of our patients. These findings w very similar to the observations made Nigerian studies [17, 18]. A detailed clini and electroencephalographic description

epilepsy in the surveyed area will be reported in another paper.

Of the serious speech disorders, deaf-mutism was the most prominent, present in 48.7%. In the majority, it followed early hearing loss as a result of infectious diseases, mainly suppurative otitis media and meningitis. In this study, there was a family history in only 14% of those with deaf-mutism, in contrast to the 44% reported by Singh et al. [19] in their Indian series. The disorder was found to be common among Muslims, where consanguineous marriages are common [19]. This observation has also been confirmed in the study of the Indian population of Natal, South Africa [20]. Genetic or hereditary factors appears to play a very minor role in deafness and deaf-mutism in the community we studied.

In the absence of facilities for audiogram examination, the evaluation and diagnosis of perceptive deafness is difficult. In the villages, the inhabitants often interpret decreased hearing as complete deafness. It was difficult for the neurologist to make a definitive diagnosis of deafness at the field level with the facilities available. However, it is quite obvious from the results gathered that deafness secondary to suppurative otitis media and meningitis is common.

Holborow et al. [21] in Nigeria identified measles, meningitis and rubella as the main causes of deafness in West Africa. Viljoen et al. [22] also found that infections or infectious processes were responsible for the hearing loss among Zimbabwean children. Our findings are consistent with theirs.

Britton et al. [23], in their comparative study of hearing disabilities in Ethiopian and Swedish children, found a high prevalence among Ethiopians: 57% as opposed to 13%. Otitis media was found to be the most common etiological factor. Deafness associated with neuropathy and optic atrophy due to cassava consumption was described in Tanzania [24] and Nigeria [25]. This cause of deafness does not exist in Ethiopia, because cassava as a food item is unknown in the country. The high prevalence of deafness and deaf-mutism in the Ethiopian rural community calls for early diagnosis and treatment of otitis media and meningitis at the primary health care level.

Comprehensive immunization has been non-existent in the rural villages we studied. Over all, 97% of those with residual poliomyelitis had not received vaccination. There are different prevalence rates reported for residual poliomyelitis in developing countries. A community-based survey from Nigeria found a crude point prevalence of only 10/100,000 [26], which is much lower than what was obtained in this study. When we consider the rate among school-age children, our prevalence figure of 241/100,000 is similar to those of Harry and Munube [27] in Nigeria (240–260/100,000) and that in a previous study from Ethiopia [28]. However, these rates are much lower than the rates of 700/100,000 in Niger [29] and 460/100,000 in Ghana [30]. The vulnerable young age group for the attack of poliomyelitis in our population is similar to figures in the survey from Niger [29], and the findings of the Kenyan epidemic of 1956/57 [31].

The economic liability to the family and the society of those affected by residual poliomyelitis, particularly in a developing country, is obvious. For instance, in our study, 23% of those with residual paralytic poliomyelitis were unable to walk, hence totally dependent on the family. This is most unfortunate when poliomyelitis is a preventable disease through early immunization.

In Africa, prevalence studies for mental retardation are very scanty. Thus the problem has received very little attention. In his study of severe mental retardation among African children in an urban South African community, Power [32] found a prevalence rate between 264 and 336/100,000 children of school age (6–17 years). This is higher than the rate of 100/100,000 found in our survey among children of a similar age group. It is interesting to observe that there were very few adults with overt mental retardation or dementia.

Axton and Levy [33], who investigated 212 cases of Rhodesian mentally handicapped, reported primary (present at birth) causes in 23%, and acquired causes in 27%. On the other hand, Jitta [34] discovered abnormalities at birth to be the etiological factor in 44% of the 98 mentally retarded Kenyan African children he studied. In our situation, in just under half of the 103 mentally retarded who were identified, the disorder had its onset at birth. Thus, pre- and/or perinatal factors seem to be important causes of mental retardation in Ethiopia.

In the African context, the extended family has to bear the burden and heavy demand of caring for the mentally disabled who live protected and cared for. Older members of households look after them. Depending on the degree of their disability, the mentally handicapped are usefully engaged in looking after cattle, collecting firewood and running errands. Due to social stigma, the severe mentally retarded are often concealed by their families, a situation we frequently encountered during our survey.

In Ethiopia, even those children with minimal learning problems are not given the benefit of special educational facilities. In our study, none of the 103 mentally retarded had received or was receiving any type of schooling or vocational training.

It is to be noted, however, that our screening instrument was designed to detect those persons with overt (severe to profound) mental retardation. Even within this definition, the prevalence rate of 169/100,000 was quite alarming, as there may be more cases with mild to moderate degrees of retardation not discovered during our investigations. Thus, mental retardation at the rural level was an important medicosocial problem requiring further in-depth study and etiological analysis to define its magnitude, in order to plan for medical and social services for the affected and to develop strategies for primary prevention.

The majority of authors agree that the first priority in the prevention of mental retardation is improved obstetric care. In the population we studied, almost all deliveries at the village level took place at home in the traditional manner, unattended by medically qualified personnel. This situation will require dramatic changes and improvements. Expansion of mother/child health services and a compelling approach to the extended immunization program are urgently required.

The prevalence rate of peripheral neuropathy in our study is low compared with those in Nigeria [26]. Leprosy emerged as the most important cause, with its prevalence in the community surveyed similar to the rate of 100/100,000 for Shoa Administrative Region [35]. The discovery of 3 cases of Charcot-Marie-Tooth disease was surprising. This hereditary neuropathy seems not to have been reported before in Ethiopia.

Cerebrovascular accident is the most common neurological condition seen in pa-

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tients admitted to general hospitals in Ethiopia [36, 37]. Almost all studies on cerebrovascular accidents have been hospital-based. The prevalence of this condition, as determined from our community-based study, is lower than the findings by Osuntokun et al. [26] from Nigeria. We tend to subscribe to their view that the low prevalence rate for stroke may be due to the high mortality rate related to it. Further studies are required to determine the risk factors in Ethiopia.

There were only 12 children with cerebral palsy in this survey, with a prevalence of 40/100,000 children under 14 years. This is much lower than the figures from Britain (140/100,000) [38]. As discussed under epilepsy, this might give the false impression that cerebral palsy is rare in rural Ethiopia. The explanation for the low prevalence rates may be due to the possible inclusion of some of the cerebral palsy cases under the diagnoses of 'mental retardation' and 'hemiparesis of early childhood onset' (table 1) as well as the high mortality among the children affected by the condition.

Similar to findings in a previous study from Ethiopia [39] and in surveys among black populations elsewhere [40, 41], the prevalence rate of Parkinson's disease in our community was rather low compared to rates ranging from 66 to 187/100,000 in the white races [42]. The different prevalences of Parkinson's disease are also largely caused by the different sizes of the age populations in different countries.

Motor neuron disease was found in 3 persons among 60,820 inhabitants of the Meskan and Mareko subdistrict. They had onset of their disease at ages of 28, 38, and 42 years, respectively. All were advanced cases with overt symptoms and signs. It is therefore quite possible that early and mild cases might have been missed. As observed in our hospital-based experience and those of Osuntokun [43] in Nigeria, motor neuron disease in Africa affects the young predominantly, and tends to run a more benign course in comparison with the form of the disease found in Caucasians.

Blindness, caused mainly by cataract, infections and trauma, was very common, with a prevalence rate of 1440/100,000. The distribution of etiological factors for blindness is similar to that in previous reports from Ethiopia [44, 45]. However, optic atrophy was rare. A detailed investigation in collaboration with an ophthalmologist is under way to determine more accurately the etiological factors responsible for blindness in the rural community.

Unlike previously employed protocols [26, 46], our screening instrument did not include migraine headaches, low back pain and sciatica, because these conditions would have required the close participation of neurologists for interview and verification of diagnosis, as was the experience in Nigeria [47] and China [48]. Our research team could not easily afford this; hence we decided to concentrate on the other neurological conditions already discussed.

On the whole, however, our results are similar to those of Osuntokun et al. [26], thus giving credit to the reliability of the recently introduced neuroepidemiological methodologies. We believe that the results obtained will be useful for health care policy makers in planning for the better management and prevention of common neurological disorders such as epilepsy, poliomyelitis, mental retardation and deaf-mutism, all carrying significant medical and social implications.

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Clinical and electroencephalographic characteristics of epilepsy in rural Ethiopia: a community-based study

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A community-based epidemiological study of neurological disorders was performed in a rural area in Ethiopia. The most prevalent neurological disorder identified was epilepsy, found in 316 persons. The prevalence of epilepsy was 5.2/1000 inhabitants at risk, 5.8 for males, 4.6 for females. The highest age-specific prevalence was found for ages 10–19 years. Generalized tonic-clonic seizures were the most common seizure type and occurred in 81%. On clinical grounds, partial seizures occurred in 20% and in 29% of these secondary generalization followed. During seizures, 8.5% had been injured by burns and 5.7% by trauma. Eighty-four percent had seizures at least monthly. Seizures occurred in 4.8% of siblings. Traditional treatment with local herbs, holy water and amulets was the most common. Only 1.6% had been treated with recognized antiepileptic drugs. Mental retardation was the most common associated disorder, found in 7.9% of the persons with epilepsy. During a period of 2 years, 8 persons died of status epilepticus and 1 from severe burns as a result of falling into a domestic fire during a seizure. EEG was recorded in 73%. Epileptiform activity occurred in 18%.

INTRODUCTION

Epilepsy is a common disorder all over the world, affecting about 0.4–2.0% of populations surveyed[32]. In the developing countries epilepsy is a major neurological problem where in many cases treatment is possible but often not available. Many previous epidemiological studies of epilepsy in Africa have been urban- and hospital-based[2,5,10–12,25,28,33,34,37] or carried out in subgroups of the population[3], often where the disorder has been particularly common[17,22,38]. Because of selection bias, the results from these studies may not reflect the situation of epilepsy in the general population.

Epilepsy among rural populations in Africa has only been investigated in a few studies[14,25–28]. The only epidemiological study of epilepsy from Africa where the problem of selection bias has been largely avoided was carried out in Nigeria by Osuntokun et al.[30], using a screening instrument for neuroepidemiological survey that was developed within the Neurosciences Programme of the World Health Organization[29].

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A community-based rural epidemiological study of neurological disorders was performed in Ethiopia during 1986–1988. This paper is a clinical and electroencephalographic presentation of the persons with epilepsy identified in that study[35].

MATERIALS AND METHODS

The study was performed in the rural sub-district (woreda) of Meskan and Mareko in the district (awraja) of Haykoch and Butajira, 130 km south of the Ethiopian capital Addis Ababa. The population of Meskan and Mareko sub-district at the time of the study was 181,883 (ref. 6), organized into peasant and urban dweller's associations. The area consists of 3 small towns and 82 peasant associations. The survey was carried out in the 3 towns and 25 randomly selected peasant associations, including all households in the selected area. The population was found to be fairly stable during the investigation period, although there was a continuous increase of the population due to the birth rate exceeding the death rate. Migration in and out of the villages was limited. In order to get reliable information on the denominator, a census of the sampled area was performed simultaneously with the identification of cases. The population of the selected area was 60,820.

Secondary-school graduates from the community with a sound knowledge of the local customs, cultures and language were recruited and employed as lay health-workers (enumerators). They were trained in interview methodology for field surveys and instructed on simple observations and examinations of persons with neurological problems. Their supervision was undertaken by a Public Health Officer and neurologists.

In the study area, after informed consents had been obtained, the lay health-workers made door-to-door interviews and administered questionnaires to screen those with neurological disorders. The head of the household or his wife gave information on each member of the family. A special epilepsy form was administered for additional information from persons in the household with unconsciousness fits with or without frothing, or biting of the tongue or incontinence of urine, and from persons who had sudden jerky movements in part of the body. These persons were later examined close to their villages by neurologists who, on the basis of the previous information and their own interview with the affected person and relatives, made the final diagnosis. Attitudinal studies on epilepsy were also performed on sampled adults. An overview of the study is shown in Fig. 1.

The sensitivity and specificity of the screening instrument were pretested and found to be 91% and 85% respectively for detection of epilepsy[35].

Since large-scale surveys, such as the present one, take several months to complete, and the survey was performed in a society where calenders and knowledge of exact dates were lacking, the use of a specific prevalence day was not feasible. The whole survey was performed during 20 months, from October 1986 to May 1988. The collection of demographic data (number, sex, age) and screening for identification of cases took place during approximately 2 months in each town and peasant association. This information, later supplemented with a medical interview and examination, was used for the calculation of rates. Only persons found to be permanent residents for over 6 months in the selected towns and peasant associations at the time of the collection of demographic and medical data were included in the study. With the method used, a point prevalence on one specific day during the investigation period was established for a household in the survey area. The point prevalences of the 13,460 households surveyed during any one day of the investigation period of 20 months were the constituents of the prevalence rates provided for the whole investigation period. The latter prevalence should be regarded as a *point prevalence* rate with multiple point prevalence components and not as a *period prevalence*, the sum of point prevalence and incidence. Persons who had moved from other towns or peasant associations that belonged to the study sample were not included if they had been registered by field workers in their former residence. When calenders and knowledge of exact dates were lacking in a household, ages and dates given by respondents were counterchecked in relation to the 'local event calender,' i.e., important past social events (e.g., local battles, coronation of the Emperor, the Italian invasion, the 1974 Ethiopian

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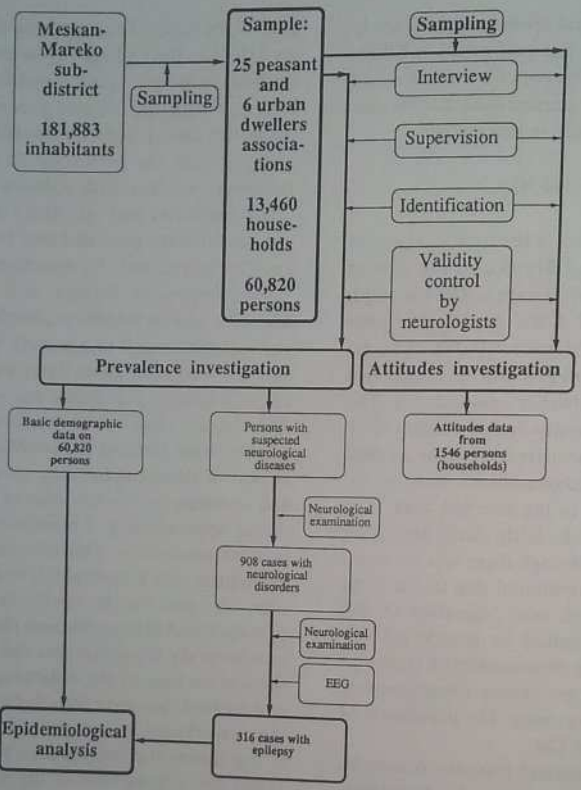


Fig. 1. Scheme of the survey.

revolution, etc.) or other events (e.g., rainy seasons, epidemics, etc.) well known to the inhabitants. Frequencies of seizures were counterchecked with two or more members of the family.

The criteria to be included in the study were for all persons of all ages that they should have active epilepsy, i.e., they should have had at least 2 unprovoked[21] seizures of which at least one should have occurred during the last 5 years, and/or they should be on antiepileptic treatment because of seizures at the time of the investigation. Persons who only had seizures in association with fever, alcohol abuse or which only occurred during acute diseases were excluded. Seizures were classified according to the International Classification of Epileptic Seizures, ICES[7]. Since the subclassification of partial seizures as simple and complex partial seizures is difficult to use in epidemiological studies of epilepsy, no subclassification of partial seizures was made except for the occurrence of secondary generalization.

Electroencephalographic (EEG) recordings were only performed on persons who fulfilled the criteria for active epilepsy. The reason for the examination and how it was to be carried out was carefully explained beforehand. For the purpose of this study the EEG machine was transported from Addis Ababa to the Health Center in the town of Butajira, the administrative center of the sub-district, and installed in a building of 18 m^2,

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made out of a transport container. Transport was provided for the persons with epilepsy who did not live nearby.

Some problem was faced during preparation for the EEG recording. Females in the villages traditionally wear their hair in the form of braids, often with oil and butter applied on it. In order to ensure proper application of electrodes, shaving the hair and washing of the scalp was proposed for all patients. This was accepted by the males but strongly opposed by the females. A compromise was worked out in which the females agreed to have their hair washed and the braids restyled in accordance with the pattern of electrode application. A local girl with braiding experience was employed for the purpose.

The EEG recording was carried out using a Nihon-Kohden Neurofax 7314F machine, with the standard array of electrodes used in the 10–20 international system. The patients were awake and provoked by photostimulation and hyperventilation. EEGs were classified as normal, paroxysmal abnormalities, unspecific abnormal (slowing) or epileptiform (spikes, sharp waves or spike-wave activity). According to localization, the pathological findings were designated as bilateral, unilateral or focal (restricted to one or two electrodes).

All patients with recurrent partial seizures (with or without secondary generalization) or recurrent primary generalized tonic-clonic seizures were started on the cheapest and most (at times the only) available anticonvulsant, phenobarbital.

Testing instruments for intelligence assessment for field work using native speakers did not exist. A diagnosis of severe mental retardation was made clinically. Such diagnosed persons relied heavily on their family members for help with the primary activities of daily life such as hygiene, dressing, feeding, etc., and they had no or only very limited communication capabilities.

RESULTS

Epilepsy was the most common neurological disorder identified in the general epidemiological study and was found in 316 persons, 173 males (54.7%) and 143 females (45.3%). Children 0–9 years old constituted 23.1%, and 36.7% were in the age group 10–19 years. The remaining 40.2% were 20 years or older with 5.7% being 55 years or older. Age- and sex-specific rates are shown in Table I and age-specific rates for the sexes combined are shown in Fig. 2. The crude prevalence rate for the sexes combined was 5.2/1000 inhabitants at risk. The highest rate for males was found between ages 10 and 14 years, and for females between ages 15 and 19 years. All households participated in the study and none of the persons suspected to have neurological disease during the screening phase refused interview and examination. Repeated visits to households by the lay health-workers resulted in a participation rate ranging from 95 to 100% in the different towns/villages surveyed.

TABLE I

Age- and sex-specific prevalence (cases/1000) of epilepsy in a rural Ethiopian community

Actual number of persons in parentheses.

Age group (years)	*Males*	*Females*
0–4	3.7 (20)	1.3 (7)
5–9	4.1 (23)	4.2 (23)
10–14	9.7 (43)	5.5 (23)
15–19	8.6 (26)	9.3 (24)
20–24	8.9 (14)	5.8 (10)
25–29	7.8 (10)	5.1 (11)
30–34	7.3 (11)	7.7 (15)
35–39	5.4 (8)	4.3 (8)
40–44	5.3 (7)	3.7 (5)
45–59	3.2 (3)	6.0 (6)
⩾50	2.4 (8)	3.3 (11)
Total	5.8 (173)	4.6 (143)

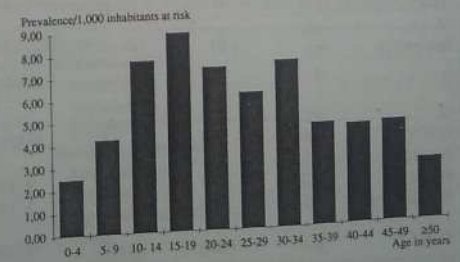


Fig. 2. Age-specific prevalence (cases/1000) of 316 persons with epilepsy in a rural Ethiopian community.

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TABLE II

Age at first seizure in 314 persons with epilepsy in rural Ethiopia

Age at first seizure	%
0–1 months	1.9
2–11 months	2.9
1–4 years	27.1
5–9 years	18.5
10–14 years	20.1
15–19 years	9.6
20–29 years	10.8
30–39 years	3.8
40–49 years	2.9
≥50 years	2.5

TABLE III

Duration of epilepsy in 314 persons in rural Ethiopia

Duration	%
<1 year	5.4
1–2 years	19.4
3–5 years	24.5
6–10 years	26.8
11–20 years	17.8
>20 years	2.9

Age at first seizure and duration of epilepsy

Age at first seizure was known for 314 cases and is shown in Table II. The first seizure occurred before ages 5 and 15 years, in 31.9% and 70.5%, respectively. The interval from the first seizure to the identification of a person with epilepsy in the study is shown in Table III. The duration in the majority was between 3 and 10 years.

Seizure types

Seizures consistent with generalized tonic-clonic seizures (GTCS) were described in 256 persons (81.0%). They were associated with frothing and tongue biting in 99.2% and with incontinence of urine in 45.7%. The GTCS seizures were, on clinical grounds, judged to be primary in 238 persons (75.3%). There was one person with absence seizures. This person had no other type of seizure.

Partial seizures occurred in 62 persons (19.6%). Most of these, 44 persons (13.9%), had seizures that were only partial, while 18 persons (5.7%) had partial seizures that sometimes or always evolved into secondarily generalized seizures. Since the state of consciousness could not systematically be observed during seizures, the proportion of partial seizures that were simple or complex cannot be presented. Seizures of unclassified type occurred in 15 persons (4.7%). During seizures, 8.5% had been injured by burns and 5.7% by trauma.

Seizure frequency and occurrence

The seizure frequency for different seizure types is shown in Table IV. Information on seizure frequency was available in 288 (91%). Eighty-six of 313 persons (27.5%) reported that seizures were sometimes associated with fever. Seizures had been noted to occur only during sleep in 11.2%, at awakening in 3.8%, only when awake in 53.8% and both during sleep and when awake in 31.2%.

Familial occurrence

The history for occurrence of seizures in rel-

TABLE IV

Seizure frequency by clinical type of seizure in 316 persons with epilepsy

Seizure type	*n*	*(%)*	*Seizure frequency n (%)*					
			Daily	*Weekly*	*Monthly*	*Every 4th month*	*Yearly*	*Unknown*
GTCS[a]	238	(75)	21 (7)	66 (21)	101 (32)	5 (2)	33 (10)	12 (4)
Absence	1	(0.3)						1 (0.3)
Partial	62	(20)	5 (2)	9 (3)	27 (9)	1 (0.3)	5 (2)	15 (5)
Unclassified	15	(5)	4 (1)	3 (1)	7 (2)		1 (0.3)	
Total	316	(100)	30 (10)	78 (25)	135 (43)	6 (2)	39 (12)	28 (9)

[a] GTCS: generalized tonic–clonic seizures.

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atives was obtained for 314 cases and is shown in Table V. One-third (31.9%) had relatives who had had one or several seizures. Seizures occurred in 9 of the 628 parents (1.4%), in 27 of the 558 siblings (4.8%) and in 5 of 296 children (1.7%). The proportion of siblings with seizures should be regarded as a minimum figure since seizures in siblings were only known for 189 cases (many adults with epilepsy were not willing to give information about the presence of seizures in siblings). One case had 2 first-degree relatives, 2 siblings, with seizures. Altogether, 41 first-degree relatives (parents, siblings and children) had experienced seizures, which constitutes 2.8% of all first-degree relatives.

Treatment of and beliefs about epilepsy

Information about treatment was obtained from 306 persons. Neither traditional nor conventional treatments had been given in 23.5% of the persons with epilepsy. Local herbs was the most common treatment used and had been tried by 36.0%. Holy water had been tried by 12.4%. Kitab, a protective amulet, was used by 7.5% and 2 persons (0.7%) had sacrificed animals. Some type of medication was used by 19.3% but only 8.5% used it as the only treatment, while 10.8% combined it with some type of traditional treatment. What these medications were is unclear since recognized antiepileptic drugs were not available in the area. Addis Ababa is the only close place for supply of antiepileptic drugs which were obtained by only 5 patients. Of the persons with epilepsy, 74.4% did not have any idea what caused the seizures, 17.4% thought they were due to evil spirits, 6.2% to tension state, 1.7% to head trauma and 0.3% to poison.

TABLE V

Familial occurrence of seizures in 314 persons with epilepsy

Relation to person with seizures	*Number*	*%*
No relatives with seizures	214	68.2
Parent(s)	9	2.9
Siblings	23	7.3
Grandparents	3	0.9
Children	5	1.6
Cousins	53	16.9
Other relatives	7	2.2

Other diseases

The most prevalent disease/impairments combined with the epilepsy were severe mental retardation and hemiparesis, found in 7.9% and 2.5%, respectively.

Mortality

During the last 2 years, 20 of the 316 persons with epilepsy died (6.3%). Death was related to epilepsy in 9 of the 20 persons, of whom 8 died in status epilepticus and 1 from severe burns from falling into a domestic fire during a seizure. The seizure frequency was high in these 9 persons. Four had daily seizures, 1 had weekly seizures and 4 had monthly seizures. In 7 persons, deaths were related to infections (malaria 1, epidemic meningitis 3, gastroenteritis 2, pneumonia 1) and 1 person died following trauma unrelated to seizure. Cause of death was unknown in the remaining 3 cases.

Electroencephalography (EEG)

EEG was performed on 230 persons (72.8%) and the findings are shown in Table VI. Abnormalities were demonstrated in 42.6%. Unspecific slow wave abnormalities were detected in 16.5%, paroxysmal disturbances in 7.8% and epileptiform discharges in 18.3%. Twenty-six persons had focal

TABLE VI

Electroencephalographic findings in 230 persons with epilepsy, in rural Ethiopia

Finding	*No. of persons*	*%*
Normal	132	57.4
Epileptiform[a], total	42	18.3
Focal	9	3.9
Unilateral	4	1.7
Bilateral	29	12.6
Paroxysmal[b] rhythms	18	7.8
Focal/unilateral	6	2.6
Bilateral	12	5.2
Unspecific abnormality, total	38	16.5
Focal	4	1.7
Unilateral	3	1.3
Bilateral	31	13.5

[a] 2 and [b] 3 persons also had unspecific abnormalities.

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unilateral or non-focal unilateral abnormalities on the EEG, of whom 13 had epileptiform activity, 6 paroxysmal activity and 7 an unspecific abnormality. Of these 26 persons, 21 had a clinical diagnosis of generalized tonic-clonic seizures without focal seizure manifestations. The results of the EEG investigation indicate that these 21 persons probably had a focal lesion (partial epilepsy) and the seizures were secondarily generalized. Thus, altogether 83 persons (26.3%) had clinically partial seizures or EEG findings which made a diagnosis of epilepsy of focal origin probable. This leaves 217 persons with primarily GTCS (68.7%).

DISCUSSION

The vast majority of populations in developing countries live in rural areas. In Ethiopia this is the case for over 90% of the population[6]. Epilepsy is a common neurological disorder which can be effectively treated in the majority of patients. It was therefore important to study persons with epilepsy who had been identified in a community-based rural study in order to gain information for future health education and planning of therapeutic programmes. This is, to the best of our knowledge, the first major community-based study of epilepsy in a rural African community.

Despite the social stigma associated with epilepsy[36], there was no refusal of interview or examination. Possible explanations for this may be that because of the villagization programme (creation of large nucleated villages) and newly established strict social orders, there was a certain degree of regimentation within the communities surveyed. All the officials, community leaders and village elders cooperated and helped us to reach the people. Another factor, which probably contributed significantly to the positive attitude of the study population towards the investigators, was the anticonvulsant treatment offered to all cases actually at the time of diagnosis in accordance with the WHO motto 'no survey without service.' Repeated house calls were made if an adult person was not available at the first visits.

There was a slight excess of males, which was most pronounced in the youngest age group. This was also found in the study of Cowan et al.[8] but not by Osuntokun et al.[31]. In both of these studies, rates of epilepsy in the age group 0–4 years were higher than in the present study. A possible explanation for this may be the very high infant and childhood mortality in Ethiopia[13], which probably makes vulnerable children, such as those with epilepsy, less likely to survive. In the study of Osuntokun et al.[31], prevalence rates also tended to be higher for males than females in the older age groups while the opposite was found in the present study. Due to the low number of persons in the older age groups in both studies, these differences may have occurred by chance.

In this study, the age-specific prevalence rates decreased in the adult age ranges. Previous studies show fairly stable prevalence rates in different adult age groups with a drop in rates after age 60 years[4,18]. Studies considered to have a more complete ascertainment of cases among the elderly found the highest rates in the older age groups[21,39]. Although cases might have been missed in older age groups in the present study, other plausible explanations are either that people remit from their epilepsy or that they die because of epileptic seizures or factors related to epilepsy, e.g., trauma and tumours. However, the prognosis is not always bad. Over one-fifth of cases in the present study had a duration of epilepsy exceeding 10 years even without medical treatment.

The crude prevalence rate for active epilepsy was 5.2/1000, which is comparable with the community-based study of Osuntokun et al.[30] who found a prevalence of 5.3/1000. The African studies that have found a prevalence of epilepsy exceeding 1% of the population[10,17,22,29] are based on investigations on either specially selected and/or small populations. The results of our study and that of Osuntokun et al.[30] may indicate that the prevalence of active epilepsy in the general African population is comparable to that which has been found in European and U.S. populations, 3.4–7.8/1000 (see refs. 8, 16, 19, 20, 21, 22, 39). However, due to a possible high mortality caused by untreated epilepsy in African populations, the prevalence rate of epilepsy found may underestimate the magnitude of the medical and social problem created by epilepsy. High prevalence rates (12.7–19.5/1000) have been reported from

outh America with a high proportion of primary eneralized seizures[9,15].

Precautions were taken to minimize the number f unidentified cases. Provision of free anticonvulant treatment with the readily available drug phenobarbital created a positive impression in the community, which probably made families with he disease more willing to volunteer the necessary information. In a few cases, heads of households withheld information because of the social stigma commonly associated with epilepsy. In the few instances where this occurred, mainly with young girls, community leaders came up with the required information. Considering the relatively low proportion of partial seizures found, it is likely that there are, nevertheless, cases that were not identified. This may partly be an effect of informants and community members not recognizing partial seizures as epileptic phenomena and possibly due to the relative insensitivity of the questionnaire to identify partial seizures. Moreover, many persons became scared when seeing a person with a generalized tonic-clonic seizure (e.g., fear of contagion by evil spritis). Therefore, partial seizure signs may not have been observed and only the secondary generalized phase has been reported.

The first seizure occurred during childhood in the majority of cases. Due to the retrospective character of this information, it is not known for how many of the children with a first seizure before age 5 years this may have been a febrile convulsion. For the vast majority of those with the first seizure after this age, the initial seizure was probably the first unprovoked seizure, being the first manifestation of the epilepsy disorder.

Most studies[19,21,24,30,39] have defined active epilepsy as the occurrence of unprovoked seizures during the last 2–5 years and/or treatment with antiepileptic drugs (AED). Thus, cases with >5 years since the last seizure are included because continuous AED treatment and factors related to the decision on when to stop AED treatment (e.g., EEG findings, type of vocation, pharmacological tradition, knowledge of prognosis) influence prevalence rates. In the present study, 98.4% were not treated with AED and as no persons with many years of freedom from seizure on AED treatment were included, the prevalence rates presented were largely unaffected by factors related to the use of AED.

Primary generalized tonic-clonic seizures were found to be the most common type of seizure. The distribution of different types of seizures depends, among other factors, on the age distribution of the population from which cases were collected. Primary generalized seizures dominated in children/adolescents[8]. The relatively high proportion of primarily generalized seizures as compared to other studies[21,23] may depend on the large proportion of children/adolescents in the present study in which 59.1% were in the age group 0–19 years. Osuntokun et al.[30] found that 55.4% had partial epilepsy in a population in Nigeria where the proportion of children/adolescents was similar to the present study but where the proportion of persons in ages 40 years and older was higher. In other previous epidemiological studies of epilepsy from Africa, primary generalized epilepsies dominate[2,5,10,22,25–28,33,34,37] with the exception of the studies of Danesi[12] and Van der Waals et al.[38] where partial epilepsies were most common. It is to be noted that Danesi studied a group of persons with epilepsy attending a specialized neurological clinic.

Important information from rural African studies where the majority of the epileptic population were not treated is data on the seizure frequency in persons in whom the disease has not been affected by medical treatment. Such basic background data may be of importance in evaluating the practical management of rural persons with epilepsy within the limited resources of a poor country. Levy et al.[25] found in a group of untreated persons, where over 90% had generalized seizures, that seizures occurred daily in 11%, monthly in 27%, several per year in 45% and once a year or less in 14% (3% unknown). In the study of Van der Waals et al.[38] only 3.3% were treated by antiepileptic drugs. They found the mean seizure frequency of primarily GTCS to be 0.99 seizures/week, while it was 1.08/week for simple partial seizures with secondary generalization and 2.69/week for complex partial seizures (of which 64% became generalized). Severe epilepsy was common in the present study, as 84% of persons with known seizure frequency had seizures at least monthly and the seizure frequency was higher

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han in the study of Levy et al.[25]. However, information on seizure frequency was not available for 8.9% in the present study, and it is likely that information was missing because of low seizure frequency in that group.

Osuntokun et al.[30] found seizures or 'similar illness' in 5% of first- or second-degree relatives while 24% had relatives who had experienced childhood febrile convulsions. This is close to the 31% in the present study who had a relative with experience of at least 1 seizure. The risk for epilepsy in siblings of persons with epilepsy has been estimated to be 5–15% if the proband had a generalized epilepsy, and 3–15% if the proband had a partial epilepsy, while the sibling risk is 1–2% in the general population[1]. In the present study, the proportion of siblings affected was 4.8%. This may be an underestimate considering the lack of information from many siblings of adult cases. One has also to consider the effect of the low age of many siblings, with a consequent low number of person years at risk. A follow-up at higher ages would probably yield a higher proportion of epilepsy in siblings.

Mental retardation has been reported in 20–22% of European epilepsy populations[20,39]. The lower proportion found in the present study is probably an effect of including only cases with severe mental retardation. A higher mortality during early childhood due to lack of medical facilities and low priority for nutritional supply to the mentally retarded in times of inadequate availability of food for the family may also have contributed.

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Lathyrism in Rural Northwestern Ethiopia: A Highly Prevalent Neurotoxic Disorder

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Lathyrism is a disorder of the central motor system, induced by heavy consumption of the grass-pea, *Lathyrus sativus* an environmentally tolerant legume containing the neurotoxic excitatory amino acid beta-N-oxalylamino-L-alanine (BOAA). A complete door-to-door resurvey of the Dembia and Fogera regions of northwestern Ethiopia, areas endemic for lathyrism, revealed an estimated mean disease prevalence of 0.6%–2.9%. Most patients developed the disease in the epidemic of 1976/77, although new cases appear to have occurred with an estimated mean annual incidence of 1.7: 10 000. Production and consumption of grass-pea is increasing in Ethiopia, making attempts to develop low-BOAA strains to prevent lathyrism increasingly important.

Lathyrism has been known since the time of Hippocrates (460–377 BC). Although this neurological disorder has in the past occurred in epidemics in North Africa, the Middle East, Asia and the Indian subcontinent, it is now only endemic in Ethiopia, India and Bangladesh.[1,2] The earliest accurate descriptions of the disease come from India, from Sleeman in 1844,[3] and Acton in 1922.[4] The toxic properties of Lathyrus flour were recognized in Europe as early as 1671 by the Duke of Wurthemberg, but it was only in the 1960s that investigators in India[5,6] firmly established the direct causative relationship of excessive consumption of grass-pea or chickling pea (*Lathyrus sativus*) and neurolathyrism. There is experimental evidence from primate studies that beta-(N)-oxalylamino-L-alanine acid (BOAA) is the neurotoxic amino acid involved in the aetiology and pathogenesis of lathyrism. However, well-nourished primates fed either *Lathyrus sativus* or BOAA develop only the early reversible clinical features of human lathyrism (eg muscle cramping) and other factors, such as malnutrition, may be required to trigger the cortical neuronal and pyramidal tract degeneration associated with the permanent spasticity of the human disease.[2,7]

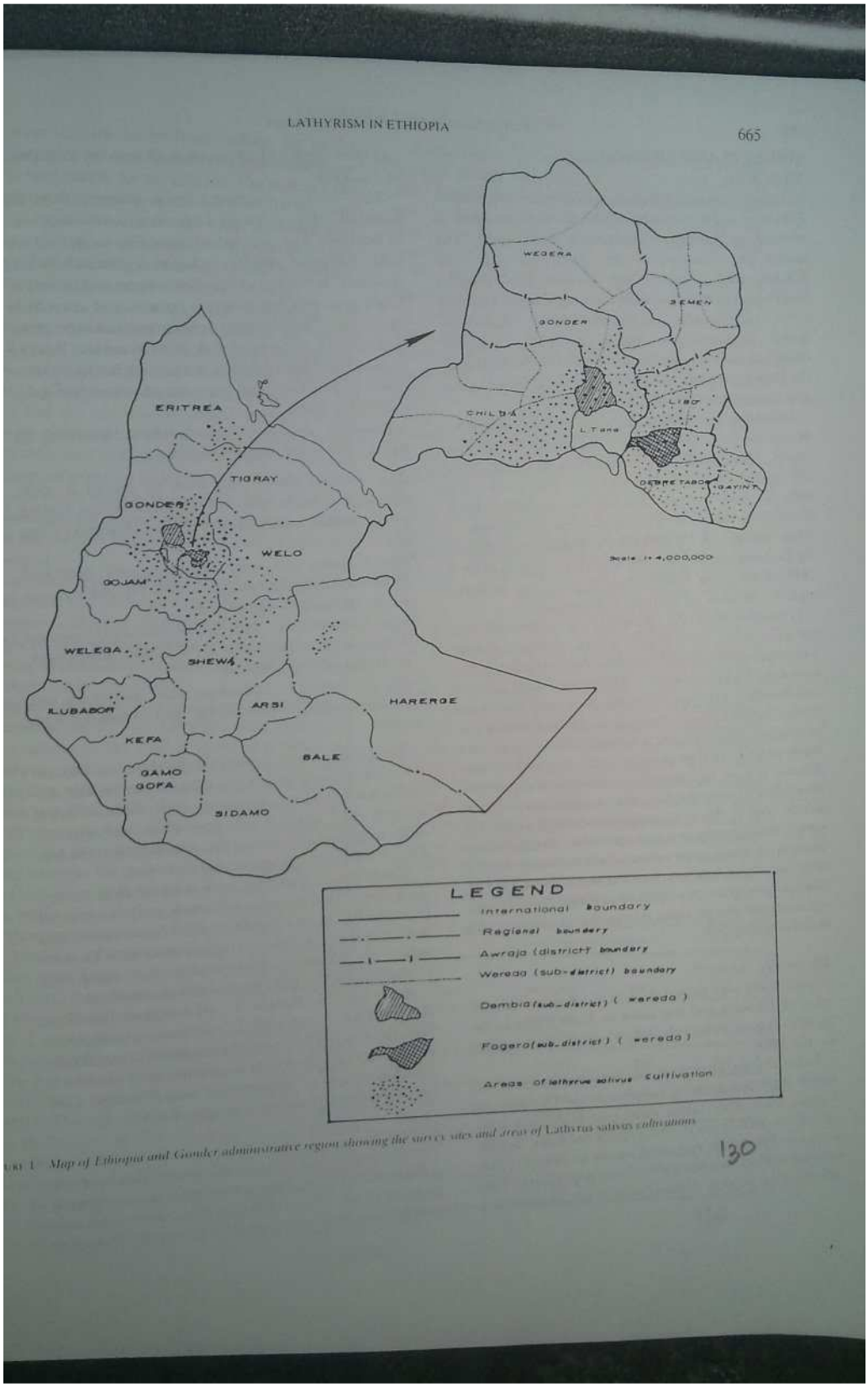
The disease has been known for many years in Ethiopia, where it has been given descriptive local names like 'sebere' and 'ye guaya beshita', 'guaya', all with the implications of a 'leg-breaking' (paralytic) nature. Ferro-Luzzi in 1947[8] gave the first scientific description of lathyrism in Ethiopia as observed in patients from the Serae area of Eritrea, north Ethiopia, where a locust-caused famine had occurred in 1946. Subsequently, Rizzotti in 1952[9] reported lathyrism in patients from northern and western Ethiopia. The disease received renewed attention in 1976/77 because of a famine-caused epidemic of lathyrism that occurred in the Dembia and Fogera sub-districts of Gondar in the northwestern part of the country (Figure 1).

The present study was carried out between July 1988 and January 1989 as part of a multidisciplinary collaborative project for the eradication of lathyrism[10] and improvement of *Lathyrus sativus*. It was designed to resurvey the same area to estimate the prevalence and incidence of the disease and to clarify the predisposing factors. It was also intended as a follow-up of subjects affected by lathyrism in the 1976/77 epidemic.

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Map of Ethiopia and Gonder administrative region showing the survey sites and areas of Lathyrus sativus *cultivation*

SUBJECTS AND METHODS

Study Area

In Figure 1 the stippled areas indicate the main parts of Ethiopia under grass-pea cultivation. Grass-pea is planted in September, harvested in February, and stored for consumption throughout the year. The hatched areas represent the sub-districts of Dembia and Fogera, where the study was undertaken. This part of the Lake Tana basin has succumbed to repeated epidemics, pestilence and climatic disasters.[11] The basin, though fertile, is periodically stricken by floods during the Ethiopian rainy season of July to September: it has also experienced periods of drought.

Following the Ethiopian Agrarian Reform Proclamation of 1975, farmers were organized into Associations. The sub-districts of Dembia and Fogera have 105 such Peasant Associations, and five towns each with its own Urban Dweller Associations. Each Peasant Association has an average population of 3000–5000 people. With a total population of 290 000, the Dembia and Fogera sub-districts occupy an area of 2445 sq km. The major occupation of the predominantly Christian inhabitants is agriculture.

In normal times, the farmers of the region cultivate teff (*Eragrostis teff*), maize, wheat, barley, sorghum and finger-millet, as well as pulses (mainly chick-peas) including *Lathyrus sativus*. When faced with drought and flooding, grass-pea becomes the staple diet of the poorer inhabitants of the region. Its cultivation and production have increased considerably because, as a hardy crop, *L. sativus* grows in a wide range of soil conditions, is easy to cultivate, is drought-resistant and also tolerates waterlogging. It can withstand pests and weeds, and at the same time gives a high yield. The people traditionally practice a primitive method of cultivation, in which oxen and manual labour are used for most aspects of land preparation and harvesting. One advantage of grass-pea cultivation is that farmers without oxen can also produce it in sufficient quantities for home consumption.

The Survey

A pilot study was undertaken in the Peasant Association of Gebeba and the town of Kola Duba in the Dembia region, before the major survey was launched in July 1988.

Door-to-door interviews of the inhabitants of the major grass-pea growing sub-districts of Dembia and Fogera were undertaken using questionnaires completed by well-trained and experienced lay health-workers. They were recruited locally to assure collaboration and acceptance by the local population. They obtained a complete census for each village surveyed, and then registered all people with walking difficulties of any kind.

They were all examined by an internist from the Gondar College of Medical Sciences, and the diagnosis of lathyrism was established according to specific criteria. Inclusion criteria included leg weakness and spasticity; sub-acute or insidious onset; and history of heavy grass-pea consumption prior to and at onset of the disease. The following were considered to be exclusion criteria: sensory deficit in extremities; marked asymmetrical leg weakness; continuing bladder and/or bowel dysfunction; and presence of peripheral gangrene in the limbs.

Resulting disability was classified according to Acton[1] with some modifications:

Stage 1: mild spastic gait with no use of a stick; increased stiffness and exaggerated deep tendon reflexes (DTR); ankle clonus present, Babinski's sign absent.
Stage 2: spastic gait, with use of one stick; increased stiffness; mild rigidity; exaggerated DTR; ankle clonus present, Babinski's sign present.
Stage 3: spastic gait, with use of two sticks; crossed adductor gait; exaggerated DTR; ankle clonus present; Babinski's sign present.
Stage 4: crawling or bedridden state; loss of leg use, with contractures; arms strong; and pyramidal signs present.

Village elders and leaders of the different Peasant Associations were interviewed to determine the dietary behaviour of the community, with emphasis on the amount and manner of grass-pea consumption. Knowledge and attitudes of the community to the toxicity of the pulse crop were also recorded.

Simultaneous with this medico-social field survey, agricultural investigators collected seed samples of grass-pea for chemical analysis of BOAA content. This was carried out at Addis Ababa University's Department of Chemistry calorimetrically, using the O-phthaldehyde (OPT) fluorescent dye method.[12]

Antibodies for human T cell lymphotropic virus (HTLV Type I and HIV-2, and human immunodeficiency virus (HIV), from 113 randomly selected lathyrism cases and 85 matched controls were assayed in the Department of Bacteriology and Virology, Limoges University Hospital, Limoges, France.

RESULTS

The interviews with village elders and heads of the communities revealed that lathyrism was a recognized problem in the region, although there were some misconceptions about its relation to *L. sativus*. Common

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eliefs were that the steam from boiling, the smoke om roasting or the dust from harvesting of the grass-ea were responsible for the disease. The pancake and w forms of the pulse were considered to be the most oisonous when consumed with milk. Although they ere aware of the toxic properties of grass-pea, com-unity elders stated that consumption of it was prefer-ble to starvation at times of severe shortage.

The grass-pea is an inexpensive, nourishing and asty legume. In markets located within the survey reas, the seed sold for 20 US dollars per 100 kg during arvest, and for 40 dollars at other times. Thirty per ent of a family's production was brought to the narket, and the rest was consumed at home. It was ommonly consumed in the roasted (kolo) or boiled nifro) forms, and its flour (shiro) was used to prepare the Ethiopian gravy or sauce (watt). The bread form kitta) was rarely prepared except at times of extreme ood shortage. Grass-pea was also used as a fodder rop by the farmers to fatten malnourished cattle and pack animals.

A wide range (111–860 mg/100 g of seed) of BOAA concentration was obtained from chemical analysis of the samples collected. Susceptibility to lathyrism is probably related to dose and duration of exposure to *L. sativus*. BOAA levels below 500 mg/100 g of seed are believed to be less toxic.[15]

In the surveyed sub-districts of Dembia and Fogera, 1792 patients affected by lathyrism were discovered. The prevalence of the disease in the community was therefore six per thousand (Table 1). The sensitivity of the screening procedure in the detection of those with lathyrism was 95%, with a specificity of 90%. Ninety-eight per cent were Christians, reflecting the dominant religion of the area. Eighty per cent were found to be illiterate whereas the national illiteracy rate is 25%.[14] In the Dembia area the disease was spread fairly uniformly, whilst in the Fogera area prevalences of 29 and 22 per thousand were found respectively for Shina and Shaga localities. These two villages are situated at fairly low altitudes in the middle of the Fogera plains thus suffering from recurrent flooding and poor harvest of crops other than grass-pea.

Table 2 shows the age and sex distribution of the patients affected by lathyrism (range 3–80 years). Fifty-five per cent of the patients were under 30 years and more males were affected than females (2.5:1) ($p \leq 0.001$). The age of onset was below 10 years in 26.4%, 10–20 years in 27%, 21–40 years in 31%, and 15.6% in the group above 40 years of age. In males, the 3–40 year age groups were evenly affected, whereas in females the majority were under 20 years of age at onset of the disease.

According to the majority of patients, the disease became evident from May to July, predominantly in July. The period of exclusive grass-pea consumption and incidence of paralysis showed the following pattern: 3–6 months (60%), 2–3 months (54%), up to one month (12%).

The majority of patients (60%) developed the disease during the epidemics of 1976 and 1977 (Figure 2). Thirty-one per cent of the patients were found to have contracted the disease after the epidemics, between 1978 and 1988. Thus, an average of 50 cases occur every year in the study area giving an estimated incidence rate in the region of 1.7:10 000. Affected families usually had a single case (85%); in some instances, two family members (10%) were affected and they were invariably younger males. The presence of three or more affected members in one family was rare.

Twenty of those with the disease reported that the paralysis was precipitated by manual work. Some reported a preceding febrile episode (15%) and diarrhoea (5%). However, obvious predisposing factors were not identified in the majority (60%) of the cases.

In the door-to-door survey, interviews of those who had contracted the disease ten or more years earlier showed that the majority had only vague recollections of their symptoms at onset. Thus, a history of the typical prodromal and painful muscle cramps in the legs was elicited in only 35%. However, stiffness and heaviness in the legs with associated numbness and burning sensations were the most common symptoms experienced by the majority of the patients before and around the onset of the paralysis, which was invariably accompanied by trembling and weakness of the legs. Generalized rheumatic pain and tightness at the waist were also registered as common initial complaints. Bladder fullness, urgency and, rarely, incontinence were reported in 4%. Onset was stated to be sub-acute (68%), acute (20%) or insidious (12%).

TABLE 1 *Prevalence of lathyrism in Dembia and Fogera sub-districts of northwestern Ethiopia*

Sub-district	Total population	No. of cases	Prevalence %
Dembia	160 000	999	0.6
Fogera	130 000	793	0.6
Total	290 000	1792	0.6
Peasant Associations	**Total population**	**No. of cases**	**Prevalence %**
Shina	7884	232	2.9
Shaga	4021	89	2.2
Total	11 905	321	

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TABLE 2 *Age and sex distribution of 1792 lathyrism cases from Dembia and Fogera regions*

Age group (years)	Male (%)	Female (%)	Total (%)	Age at onset: Male (%)	Female (%)	Total (%)	Population Ethiopia* 1986 (%)
0–10	49 (3.8)	32 (6.3)	81 (4.5)	154 (22.0)	103 (37.3)	257 (26.4)	33.9
11–20	341 (26.6)	166 (32.7)	507 (28.3)	175 (25.1)	88 (31.9)	263 (27.0)	20.7
21–30	267 (20.8)	139 (27.4)	406 (22.7)	120 (17.2)	33 (12.0)	153 (15.7)	14.6
31–40	168 (13.1)	64 (12.6)	232 (12.9)	117 (16.8)	32 (11.6)	149 (15.3)	12.2
41–50	183 (14.2)	50 (9.8)	233 (13.0)	65 (9.3)	12 (4.3)	77 (7.9)	8.2
51–60	152 (11.8)	31 (6.1)	183 (10.2)	67 (9.6)	8 (2.9)	75 (7.7)	6.0
61≥	124 (9.7)	26 (5.1)	150 (8.4)	— —	— —	— —	4.4
Total	1284 (100)	508 (100)	1792 (100)	698 (100)	276 (100)	974 (100)	(100)

* Central Statistical Office, Addis Ababa, 1987

Scoring the degree of disability was as follows: Stage 1 contained 52.4% of cases, Stage 2—41.6%, Stage 3—36%, and Stage 4—2.4%. The majority of females had milder disabilities (Stages 1 and 2). The latent cases as described by Dwivedi and Prasad[5] were included within Stage 1, the 'no-stick' stage.

Affected patients were farmers by occupation both before and after onset of paralysis, although many of the victims were subsequently engaged in lighter duties like weeding and looking after cattle. In addition to these jobs, women also took up weaving. In poor farming communities, as in Dembia and Fogera areas, where few job opportunities exist, people with lathyrism were more likely to be unemployed and/or become beggars.

Mental status, speech and cranial nerve function of all those with lathyrism were intact. Cerebellar signs were not detected. Spastic paraparesis of different degrees was associated with adductor spasm in the worse-affected cases, as well as with exaggerated deep tendon reflexes (84%), extensor plantar response (60%) and ankle clonus (64%). Brisk deep tendon reflexes in the upper limbs were found in only 4%, usually in the severely compromised patients. There was an asymmetrical atrophy of the left leg in a significant number of those with Stage 2 disability. We believe that this was caused by disuse of the left leg, resulting from holding the walking stick with the right arm and exerting weight on the right leg. Fasciculation was not encountered in any of the patients.

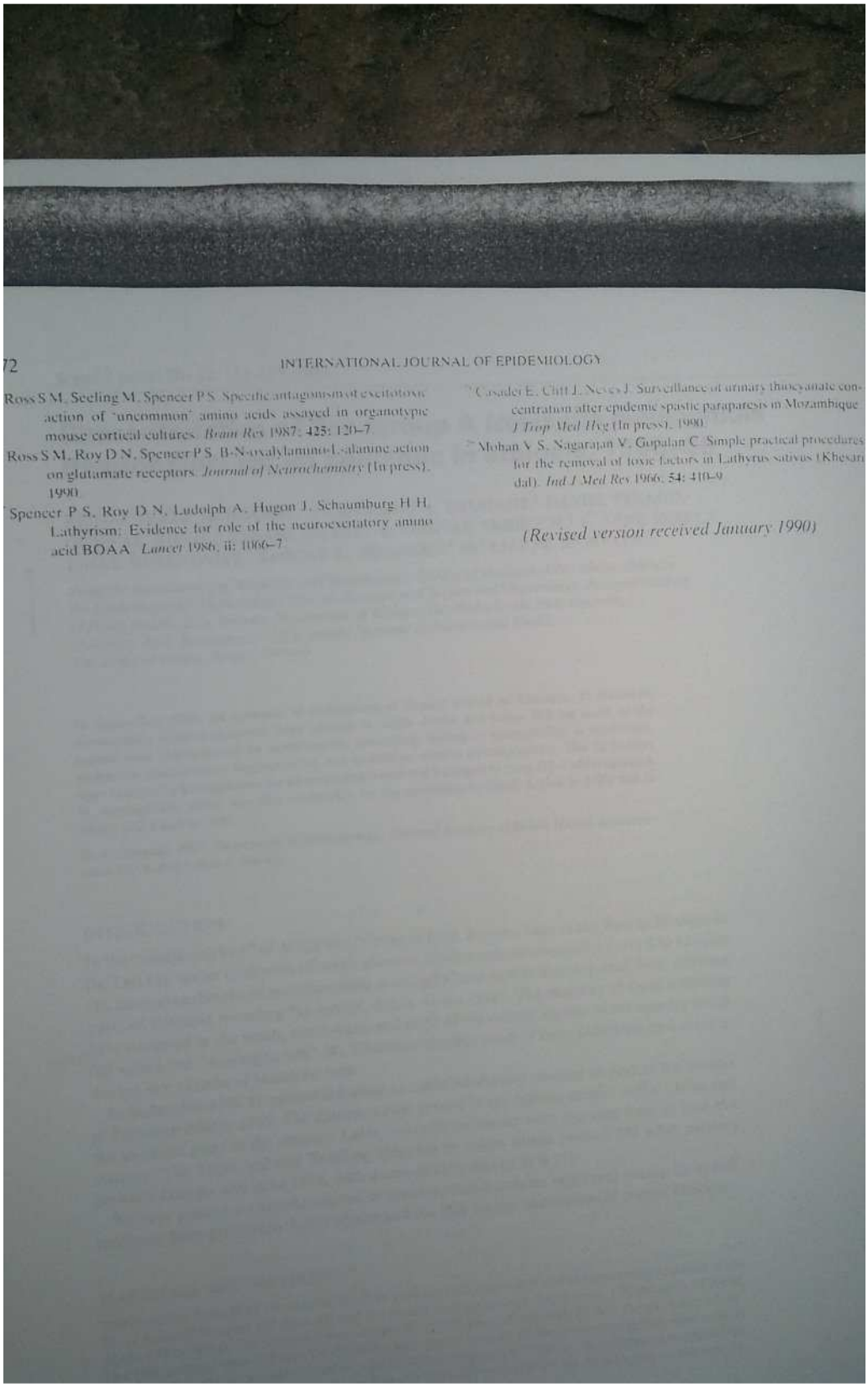
Objective sensory deficits to pin-prick and light touch in distal legs were uncommon (5%). Impotence was reported in only 1% of the patients, and mainly in those above the age of 60 years.

Patients sought traditional treatment (38%) in the form of holy waters and massage with different oils and lubricants. Twenty-eight per cent received contemporary treatment (mainly vitamins) from local health

TABLE 3 *Degree of disability by age and sex*

Stage	Male No	Male %	Female No	Female %	Total No	Total %
1 No stick	609	47.4	330	65.0	939	52.4
2 One stick	590	46.0	155	30.5	745	41.6
3 Two sticks	51	4.0	13	2.5	64	3.6
4 Crawler	34	2.6	10	2.0	44	2.4
Total	1284	100.0	508	100.0	1792	100.0

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Characteristics of Serogroup A Neisseria meningitidis Responsible for an Epidemic in Ethiopia, 1988–89

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In September 1988, an epidemic of meningococcal disease started in Ethiopia. 21 Neisseria meningitidis isolates recovered from patients in Addis Ababa and towns 200 km south of the capital were characterized by serogrouping, serotyping, testing of susceptibility to antibiotics, restriction endonuclease fingerprinting, and multilocus enzyme electrophoresis. The 21 isolates were essentially homogeneous for all properties tested and belonged to clone III–1 of serogroup A N. meningitidis, which was also responsible for the epidemics in Saudi Arabia in 1987 and in Sudan and Chad in 1988.

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INTRODUCTION

In the "meningitis belt" of Africa which extends from Burkina Faso in the West to Ethiopia in the East (1), major epidemics of meningococcal disease occur periodically, every 8 to 12 years (2). Several outbreaks of meningococcal meningitis have earlier been reported from different parts of Ethiopia including the capital, Addis Ababa (3–6). The majority of these outbreaks have occurred in the north, north-west, and parts of the central regions of the country which fall within the "meningitis belt" (4). Characteristically, most of these outbreaks took place in the hot dry months of March to June.

In September 1988 an epidemic started in Addis Ababa and reached its peak in the months of February–March 1989. The epidemic first spread in the regions around Addis Ababa and the southern parts of the country. Later, sporadic outbreaks were reported from all over the country. The Tikur Anbessa Teaching Hospital in Addis Ababa treated 278 adult patients between January and June 1989, with a case-fatality rate of 21 % (7).

We here present a characterization of meningococcal isolates recovered during the recent epidemic from patients in Addis Ababa and the Rift Valley lake regions of central Ethiopia.

MATERIALS AND METHODS

Cerebrospinal fluids (CSF) were collected from patients with meningitis and/or septicaemia admitted at the Tikur Anbessa Hospital (30 patients) and the Health Centers around Zewai town, 170 km south of Addis Ababa (20 patients). The patients were between 14 and 50 years of age, with 40 % in the age group 14–19. The CSF samples were cultured on chocolate agar plates. Isolates of Neisseria meningitidis were subcultured and the selected samples stored at −20°C. Before shipment to Norway, the isolates were cultured on chocolate agar plates and inoculated into Stuart's transport medium. Of 40 cultures sent to Norway, N. meningitidis was successfully recovered from 21.

Serogrouping was performed by slide agglutination with commercial antisera (Wellcome Reagents Ltd., Beckenham, UK) specific for the A, B, C, W135, X, Y, and Z polysaccharides, and by whole-cell ELISA with a monoclonal antibody against serogroup A (14-1-A) provided by Dr W. D. Zollinger.

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Serotyping was performed by the whole-cell ELISA procedure (8) with monoclonal antibodies against serotypes 4 (15-1-P4), 21 (14-1-P21), serosubtypes P1.1 (9-1-P1.1), P1.2 (3-1-P1.2), P1.3 (12-1-P1.3), P1.15 (2-1-P1.15), and P1.16 (3-1-P1.16) provided by Dr Zollinger; with monoclonal antibodies against serotype 4 (MN14G21.17) and serosubtype P1.9 (MN5 A10F), provided by Dr J. T. Poolman; and with monoclonal antibodies against serotype 4 (2303 C5) from Dr C. E. Frasch.

Antibiotic sensitivity testing for sulfadiazine, benzylpenicillin, chloramphenicol, rifampicin, minocycline and ceftriaxone were determined by the agar dilution method. Relative penicillin resistance was also tested with disc diffusion (9). Beta-lactamase activity was looked for applying the acidometric and chromogenic cephalosporin tests (10).

Electrophoresis of enzymes was performed as described by Selander et al. (11). Multilocus enzyme genotype of the isolates was compared to those of reference serogroup A strains (12) provided by Dr M. Achtman.

Restriction endonuclease fingerprinting of chromosomal DNA (RE) was performed as described by Bjorvatn et al. (13), using restriction endonucleases *Eco*RI and *Hin*dIII. All strains were tested at least twice. RE patterns were reproducible except for occasional doubling of bands that previously had appeared single, or weakening or strengthening of bands in a few particular locations.

RESULTS

The characteristics of the 21 isolates are given in Table I. All strains were serogroup A, serotype 21/4: P1.9. Three isolates reacted weakly or not at all with one (15-1-P4) of the 3 monoclonal antibodies against serotype 4, but all strongly bound the 2 other serotype 4 monoclonal antibodies and the serotype 21 monoclonal antibody.

All the isolates were resistant to sulfadiazine: 19 isolates had a MIC of sulfadiazine of 200 μg/ml and the remaining 2 differed by only one dilution step (100 μg/ml and 400 μg/ml, respectively). No beta-lactamase activity was detected and all the isolates proved fully sensitive to benzylpenicillin, chloramphenicol and ceftriaxone. No resistance against minocycline or rifampicin was detected by screening the isolates at drug concentrations of 1.0 and 0.25 μg/ml, respectively.

The 21 isolates belonged to the same clone as demonstrated by their identical multilocus genotypes. The electromorphs at all 14 enzyme assayed were similar to those of isolates assigned to clone III-1 by Olyhoek et al. (12).

Following *Eco*RI or *Hin*dIII digestion, the electrophoresed fragments of chromosomal DNA formed patterns consisting of approximately 45 typically located bands. For 6 strains, *Eco*RI digestion produced only a limited number of bands which prompted retesting with *Hin*dIII.

Table I. *Characteristics of 21 isolates of N. meningitidis from Ethiopia*

Property tested	Laboratory findings
Serogroup	A
Serotype : serosubtype	21/4[a] : P1.9
MIC sulfonamide	200 μg/ml[b]
Electrophoretic type[c]	1 4 5 6 4 1 3 2 1 8 2 3 2 2
Restriction endonuclease fingerprinting	Identical patterns[d]

[a] 3/21 isolates bound weakly or not at all monoclonal antibody 15-1-P4. All bound 14-1-P21, MN14G21.17, and 2303 C5.
[b] MIC of sulfadiazine for 2 isolates were 100 and 400 μg/ml, respectively.
[c] Electromorphs at the following enzymes in given sequence: malic enzyme, glucose 6-phosphate dehydrogenase, peptidase, isocitrate dehydrogenase, aconitase, 2 glutamate dehydrogenases, alcohol dehydrogenase, fumarase, alkaline phosphatase, 2 indophenol oxidases, adenylate kinase, and an unknown dehydrogenase.
[d] 19/21 proven, 2/21 likely identity.

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Complete clarification was thereby obtained in 4 of these cases, whereas the remaining 2 strains showed a small number of bands, albeit at typical locations. Hence, 19 strains had similar patterns indicating genetic identity or close clonal relationships. Identity of the remaining 2 strains is highly likely although not proven with this method.

DISCUSSION

The recent epidemic of meningitis in Ethiopia has 2 distinct characteristics that distinguishes it from previous outbreaks. Firstly, previously unaffected regions in the southern and eastern parts of the country have now been involved. Thus, the borders of the "meningitis belt" within Ethiopia are changing and extending. Secondly, whereas epidemics in the past appeared in the hot, dry months of March to June, the recent outbreak started in September and continued with peaks in the months of February and March. Scattered cases were still seen in August, the rainy month of the year.

As expected during an epidemic, the 21 N. meningitidis isolates exhibited very similar traits and represented a single clone, namely III-1. No difference was seen between strains from Addis Ababa and the Zewai area.

Clone III-1 had been responsible for epidemics in Finland and Brazil in the mid 1970s (12). Recently, meningococci of clone III-1 reached Saudi Arabia where they caused an outbreak among Haj pilgrims in Mecca in 1987 (2). Subsequently, clone III-1 caused severe epidemics in Sudan and Chad in 1988 (2, 14, 15). We show here that the recent outbreaks of meningitis in Ethiopia were also caused by clone III-1. Surveillance of the spread of this virulent clone to other African countries in the "meningitis belt" is warranted. In fact, preliminary results indicate that clone III-1 already has reached the Gambia (Bjorvatn & Caugant; unpublished data).

The isolates were resistant to sulfadiazine confirming that sulfonamides no longer have a place in the treatment or prophylaxis of meningococcal meningitis. The demonstration that the strains were sensitive to penicillin and chloramphenicol is essential to management of cases in developing countries (16).

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THE MANAGEMENT OF DIABETIC KETOACIDOSIS BY CONTINUOUS INFUSION OF LOW-DOSE INSULIN USING THE ORDINARY INTRAVENOUS PLASTIC BAG AND TUBING[1]

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ABSTRACT: Although the hourly intramuscular insulin regimen has been used in the management of diabetic ketoacidosis (DKA) in Ethiopia for over 7 years, continuous intravenous (IV) insulin infusion has never been previously used. In Tikur Anbessa Hospital, Addis Abeba, in 198788, we used the ordinary IV plastic bag and tubings alone to concurrently infuse the low-dose insulin and hydration solution in the management of 15 episodes of DKA in 13 patients, 5 males and 8 females. Initial blood glucose was over 400 mg/dl and urine ketones 4+ in all, and the level of consciousness ranged from drowsy to coma. Initially, 5 to 10 units of crystalline zinc insulin (CZI) was given IV directly to all but 2 patients. Then CZI was added to the normal saline IV bag and the dose of insulin was adjusted according to fluid requirements while at the same time maintaining the insulin rate at 5 to 10 units/hour until the blood glucose dropped to 250 mg/dl or lower. At this point the IV fluid was changed to 5% dextrose and the insulin infusion was reduced to 2 to 4 units/hour. The mean insulin requirement until the dextrose infusion was initiated was 33.2 ± 7.3 units, IV fluid requirement was 3.5 ± 0.8 litres and mean duration of treatment 4.4 ± 1.6 hours. There was one death which was not due to insulin resistance, while all other patients fully recovered. The study demonstrates that insulin infusion using the ordinary IV plastic bag and tubings is safe, simple, and convenient in the management of DKA and hence should be used whenever indicated and feasible.

INTRODUCTION

Although much advance has been made in the treatment of DKA, the mortality rate still remains high, ranging between 6% and 10% even in the best centres (1,2). Successful treatment of this condition requires, besides other supportive care of crucial importance, the administration of fluid, electrolytes, insulin and perhaps alkali under close observation.

The low-dose insulin regimen, given as continuous infusion or intermittent intramuscular injection, is nowadays well accepted (3-6). Insulin infusion is particularly preferred in those patients with severe dehydration and acidosis (7) as the absorption of intramuscularly injected insulin may be erratic. However, continuous insulin infusion has not been used in areas with suboptimal facilities because of lack of infusion pumps and because of the fear that insulin will be adsorbed to plastic containers and infusion tubings (8), thus reducing the dose delivered. It has been previously suggested that a small amount of albumin should be added to the infused solution to prevent insulin loss by adsorption (9).

In Ethiopia, patients with DKA have been treated with intermittent intramuscular low-dose insulin (10). As an alternative to this mode of insulin administration, we have used ordinary intravenous fluid plastic bag and tubing, containing no serum or albumin, to infuse low-dose insulin in the management of DKA. The end point of the trial was the time

[1]The paper was partly presented at the 24th annual medical conference of the Ethiopian Medical Association in May 1988.

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when patients were changed to dextrose infusion and maintenance insulin. The result of this study is described in this paper.

MATERIALS AND METHODS

A total of 15 consecutive episodes of DKA in 5 males and 8 females who were admitted to the Tikur Anbessa Teaching Hospital in Addis Abeba in 1987 and 1988 were studied using a prepared protocol. The mean age was 24.8 years (range 13-39 years). There were 3 new patients; the precipitating factors for the DKA in the remaining patients included omission of insulin in 8 episodes and infection in 4 others.

The diagnosis of DKA was made clinically in any patient presenting with hyperglycaemia over 300 mg/dl (>16.7 mmol/L), urine glucose of 3+ or more, ketonuria of 2+ or more, altered state of consciousness ranging from drowsiness to coma, evidence of metabolic acidosis as manifested by Kussmaul breathing with a respiratory rate of over 24/minute and acetone smell on the breath, and dehydration as evidenced by diminished skin turgor, soft or sunken eye balls and dry tongue.

The blood glucose was measured with Dextrostix (Ames) and a Glucometer (Ames) which gives reasonably accurate values up to 400 mg/dl. Spectrophotometric glucose determinations were available during working hours. Urine glucose was measured with Clinitest (Ames) and urine ketones with Acetest (Ames) tablets.

Management: Except for 2 episodes in males who were admitted to the general ward, the rest were managed in the medical intensive care unit (MICU) under close observation. An IV infusion was initially started with a litre of normal saline and the rate of infusion was adjusted according to the degree of dehydration, even though the first litre was invariably run in the first ½ to 1 hour. A loading dose of 5 to 10 units of crystalline zinc insulin (CZI) was given IV directly after taking blood for glucose determination. CZI was then added to the plastic bag containing IV fluid and the infusion was adjusted to give insulin at the rate of 5 to 10 units per hour the blood glucose dropped to ab 250 mg/dl and the dehydration w corrected, thus circumventing th use of a separate insulin infusion administered by a separate vein or by "piggyback" into the IV line carrying the replacement solution. As an example, if a patient requires 5 units of CZI and 500 ml. of fluid per hour, 10 units of CZI is added to a plastic bag containing 1 litre of solution and run over 2 hours. Similarly, other insulin doses and IV fluid requirements can be calculated and given.

The decision on the dose of insulin to be administered was arbitrarily based on the estimated weight of the patient as there was no means of weighing critically ill patients. Accordingly, CZI 5 units per hour was given to those patients judged to weigh 50 kg. or less, and 10 units per hour to those judged to weigh over 50 kg.

Blood pressure, pulse, respiration, level of consciousness, state of hydration, urine output and amount of fluid administered were recorded every hour. Blood glucose, urine glucose and urine ketones were also checked hourly. Other tests done included haemogram, urinalysis and blood urea nitrogen. An electrocardiogram (ECG) was done before the initiation of insulin therapy in almost all cases. Blood pH, PCO_2, PO_2, and serum insulin determinations were not possible and serum electrolytes were infrequently done.

When the blood glucose level reached 250 mg/dl or less, the IV fluid was changed to 5% dextrose in water or saline and the rate of insulin infusion was reduced to 2 to 4 units per hour. Once the patient was able to take food by mouth, the insulin infusion was stopped and intermediate acting insulin (Lente), at a dose of 0.6 to 0.8 units per kg together with 5 to 10 units of CZI was given subcutaneously; the latter was needed to keep a reasonable serum insulin level during the first few hours of the maintenance insulin therapy. The dose of insulin was then adjusted every 3 to 4 days according to the blood glucose level. In 3 episodes, however, a sliding scale was used until infection was controlled

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Potassium chloride was added to the IV bag in a dose of 20 m Eq per litre after the urine output reached 30 ml per hour or more and was continued until the patient was able to take food by mouth. Patients who had infections were treated with appropriate antibiotics. None of the patients received bicarbonate.

RESULTS

The initial clinical findings are found in Table 1. The systolic blood pressure ranged from 0 to 120 mmHg; in 10 of the 15 episodes it was less than 100 mmHg and 3 patients had no recordable blood pressure. Pulse rate ranged between 100 and 168/minute and the respiratory rate was over 30/min. in 10 episodes. Five patients were comatose and 6 had severe dehydration. The blood glucose was over 400 mg/dl and ketonuria was 4+ in all episodes. The ECG showed no flattening of the T-wave. The outcome of treatment is summarized in Table 2. The mean insulin requirement until the end point in those who survived was 33.2 ± 7.3 IU (range 20-60 IU). The mean duration of treatment in survivors was 4.4 ± 1.6 hours (± and IV fluid requirement 3.5 ± 0.8 litres).

There was 1 death in the 15 episodes of DKA. This was in a 30 year old newly diagnosed male diabetic who had been in coma for 18 hours at the time of admission. Initially, he had an abscess on the right upper thigh. Subsequently, he developed symptoms of diabetes for which he unsuccessfully tried local herbs. His condition deteriorated until finally he lapsed into unconsciousness. On arrival in the MICU, he was in deep coma and had no blood pressure. The rectal temperature was 36.5°C and he was moderatly dehydrated. The neck was rigid but the fundi were clear. The chest was full of rhonchi. There was an infected wound in the right upper thigh. The blood glucose was over 400mg/dl, urine glucose 4+ and ketonuria 4+. He was managed for his ketoacidosis and was adequately covered with antibiotics for his skin infection. Subsequently, he showed improvement and was able to recognize his relatives. His blood glucose came down to 250 mg/dl within 6 hours and he was switched to 5% dextrose infusion. The insulin infusion was reduced to 2-4 units per hour and KCl 20 mEg/L was added. The chest cleared completely and the neck became supple. However, about 23 hours after admission he had a sudden cardiorespiratory arrest and died. The cerebrospinal fluid analysis was normal and his blood glucose just prior to his death was 180 mg/dl.

DISCUSSION

Many physicians still have doubts about the safety and effectiveness of continuous infusion of low-dose insulin through ordinary IV bags and tubings containing no albumin or serum, even though the method is being used widely in the management of diabetes during surgical procedures. Thus, the objective of this study was to find out if this mode of insulin administration was as effective as the intermittent intramuscular route of insulin administration in the management of DKA. The results of the clinical trial clearly showed that continuous insulin infusion through the ordinary IV plastic bags and tubing containing no albumin or serum was as effective as the intermittent intramuscular route (10).

The method is advantageous in many ways, although it has some shortcomings as well. Firstly, it is the preferred route by which to administer insulin in those DKA cases who are severely acidotic and dehydrated with imminent or existing shock. Initial insulin absorption, which is prognostically crucial, is erratic in such patients if the intermittent intramuscular mode of insulin therapy is used (6-7). Secondly, it is simple, as it does not involve the use of other systems or methods (3,9,11-13), although vigilance is needed to ensure that the infusion is running properly in order to avoid rebound hyperglycaemia or worsening of the DKA. In addition,

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it is relatively safe since stopping or reducing the infusion will result in an almost immediate reduction of effect. Thirdly, it is convenient for patients as it avoids the intermittent discomfort of intramuscular insulin administration, although that has the advantage of delivering the required hourly insulin immediately. Certainly, the patients should be closely observed during treatment and no single mode of therapy replaces this requirement. Weinsenfeld et al (8) found that the magnitude of insulin loss by adsorption ranged from 20%-75%, depending on various factors including the concentration of insulin and the duration of IV infusion. Sonsken et al (9) suggested the addition of albumin to the infusion solution to prevent loss of insulin by adsorption. Our patients received 5 to 10 units of CZI per hour. If we consider the 20% to 75% loss of insulin by adsorption (8), then the net insulin amount which reached the vein would be expected to be in the range of 4.0 to 1.25 units per hour to 8.0 to 2.5 units per hour respectively. This rate of insulin infusion can result in a serum insulin concentration which ranges from 20 to 200 µU/ml (14), a level which is believed to be adequate to treat DKA. The serum insulin level was not determined in our cases as there was no facility at the time, but the rate of fall of blood glucose per hour in those patients with initial accurate blood glucose determinations was similar to findings in other studies (15-17, Table 3). This suggests that the serum insulin level must have been within a safe therapeutic range. Thus, although some of the insulin must presumably have been adsorbed into the plastic bag and tubing, the fear that the serum insulin level would be less than the level required for therapeutic effect is unfounded.

There was one death, resulting in a DKA mortality rate of 6.7%. The blood glucose in this case dropped steadily and reached 250 mg/dl in 6 hours. His mental status was improving. However, he suddenly developed cardiorespiratory arrest 23 hours after admission and expired. His death could not have been due to inadequate insulin as his blood glucose 30 minutes before was 180 mg/dl. The cause of death was not ascertained as autopsy was not possible, but cerebral oedema is one possible cause to be considered.

The mortality of 6.7% is similar to the 9.6% reported by Lester (18) and the 7.1% reported by Abdulkadir et al (10), two studies which used the intramuscular route for insulin administration. Furthermore, the duration of treatment as well as the fluid and insulin requirement is similar to the hourly intramuscular low-dose insulin regimen previously reported (10). This emphasises that continuous infusion of low-dose insulin through the ordinary plastic bag and tubings is as effective as intermittent intramuscular low-dose insulin administration, and hence can be used as an alternative to the latter, particularly in those patients with imminent or existing shock and severe acidosis. In this series, 2 patients were managed in the general medical ward while the rest were treated in the MICU. As vigilance is required to ensure that the infusion is running properly, the method should be used in places where there is adequate staff, although it may sometimes be possible even in the general ward.

The same IV bag and tubings were used to administer both the insulin and fluid simultaneously. The method is quite flexible in so far as the amount of insulin to be added to the bag is concerned. In other words, the amount of insulin to be added is determined entirely by how much fluid has to be given during a defined period of time. This obviates the need for a separate saline bag for insulin infusion which would be "piggybacked" into the IV line carrying the replacement solution, although the latter method is an alternative to consider.

The use of a loading dose of insulin is still a controversial issue. It has been suggested by some in order to rapidly saturate serum insulin binding antibodies and also initiate saturation of tissue insulin receptors (19), while others recommend it in patients with imminent or existing shock (20), but there are still others who do not favour loading doses at all (3, 21,22). In this study 2 patients did not receive a loading dose and they both recovered.

In conclusion, continuous CZI infusion using the ordinary IV plastic bag and tubing containing no albumin is an effective, simple, safe and convenient method which can be used in areas of suboptimal clinical facilities whenever indicated and feasible as an alternative to the intermittent intramuscular mode of therapy.

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TABLE 1. Initial clinical data in 15 episodes of DKA.

Case No.	Age (yrs.)	Sex	Duration of DKA (hrs.)	Blood Pressure (mmHg)	Pulse rate per minute	Respiratory rate per minute	Mental state	Degree of dehydration	Blood sugar (mg/dl)	Urine sugar	Urine ketones
1	39	M	9	80/60	120	26	Coma	Severe	>400	4+	4+
2	14	F	12	0	128	32	Stuporous	Severe	>400	4+	4+
3	30	M	18	40/0	100	26	Coma	Moderate	>400	4+	4+
4	20	M	24	80/0	110	34	Drowsy	Moderate	>400	3+	4+
5	31	M	12	70/0	104	36	Coma	Severe	>400	4+	4+
6	15	M	24	100/60	100	26	Coma	Severe	600	4+	4+
7	38	F	12	120/70	120	32	Drowsy	Mild	480	3+	4+
8	32	F	14	70/50	120	40	Stuporous	Moderate	630	4+	4+
9	18	F	?	0	158	52	Coma	Severe	710	4+	4+
10	32	F	8	90/60	108	30	Drowsy	Mild	450	3+	4+
11	39	F	24	90/60	120	28	Stuporous	Moderate	530	4+	4+
12	20	F	12	110/70	126	52	Drowsy	Moderate	>400	4+	4+
13	14	F	12	100/60	120	56	Drowsy	Moderate	>400	3+	4+
14	13	F	8	100/70	100	40	Drowsy	Moderate	>400	4+	4+
15	20	F	9	0	146	36	Stuporous	Severe	650	4+	4+

TABLE 2. Results of treatment in 15 episodes of DKA

Case No.	Total dose of insulin (I.U.)	Condition at the time of change to maintenance dose: Blood pressure (mmHg)	Pulse rate per min	Respiratory rate per minute	Mental state	Degree of dehydration	Time needed for full recovery (hr)
1	60	100/60	92	20	Drowsy	Normal	13.0
2	30	100/60	84	16	Alert	Normal	7.5
+3	60	80/40	86	20	Drowsy	Slight	-
4	30	90/60	80	18	Alert	Normal	6.5
5	30	110/70	80	20	Alert	Normal	6.0
6	40	120/80	88	20	Alert	Normal	6.5
7	40	130/90	88	24	Drowsy	Slight	8.0
8	25	90/60	92	26	Alert	Normal	4.5
9	45	100/70	110	32	Drowsy	Normal	5.5
10	30	100/60	86	24	Alert	Normal	7.0
11	35	100/70	90	22	Alert	Normal	23.5
12	28	90/50	86	26	Drowsy	Slight	5.0
13	30	100/60	94	22	Alert	Slight	11.5
14	40	100/60	84	28	Alert	Normal	12.0
15	30	90/60	100	22	Alert	Normal	4.0

TABLE 3. Summary of the results of studies of different routes of insulin administration in the management of DKA

Reference	Alberti et al (15)	Piters et al (16)	Page et al (17)	Kitabchi et al (4)	Present study
Number of patients	14	7	38	24	13
Insulin regimen	IM	IV	IV	IM	IV
Route	10-20	0	0	0.22/kg	5-10
Initial dose, I.U.	5-10	0.5 to 1.0	7.2 (3-24	0.22/kg @ 1st hr,; then 5	5-10/hr
Subsequent dose, I.U./hr					
Glucose	637	650	809	723	>400
Initial value, mg/dl	92	NC*	100	70	88
Rate of decrease, mg/dl/hr					
Time to reach target glucose, hr	4	13.7	NC	6.7	4.4
Initial pH value, mean	7.22	7.13	NC	7.13	NC
Bicarbonate					
Initial Value, mEq/L	10	5.7	NC	7.7	NC
Time to reach target bicarbonate, hr	NC	20.3	NC	11.1	NC
Ketones					
Initial value, mM	12	NC	11.3 (2.7 to 18.6)	15	NC
Time to reach target ketone concentration, hr	5	NC	4	7	NC
Development of hypokalemia (<3.4 mEq/L, no. of patients)	1	NC	1	0	NC
Plasma insulin, micro μ/ml	64-92	33 (0 to 90)	50-100	82	NC

NC = Not checked

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ACQUIRED PRIMARY ENDOCRINE FAILURE IN ADULT ETHIOPIAN PATIENTS

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ABSTRACT: Over a 4 year period, February 1986 to January 1990, 18 patients with acquired primary endocrine failure were seen in the weekly endocrine clinic of Tikur Anbessa teaching and referral hospital in Addis Abeba. Eight patients had hypothyroidism and 4 Addison's disease; 3 of the 5 hypothyroid and 2 of the 3 Addison's cases on whom autoantibodies were determined were positive. One patient had polyglandular failure, involving the adrenal and thyroid glands and the gonads. In one patient tuberculosis was the cause of Addison's disease and 2 patients each had hypothyroidism and hypoparathyroidism, respectively, following surgery. All the patients had clinical, hormonal and/or biochemical evidence of endocrine failure and all but the hypoparathyroid patients responded to the replacement therapy. There was one patient who had an unusual but confusing discordant hypothyroxinaemia and hypertriiodothyroninaemia who developed hypothyroidism during treatment for his Graves' disease; the hypothyroidism resolved when the medication was stopped. The results of this study indicate that autoimmune endocrine failure is probably not as rare as it was previously thought and hence further studies are recommended to find out if the incidence among Ethiopians is, indeed, similar to or different from the results in other African patients.

INTRODUCTION

Acquired primary endocrine failure, isolated or polyglandular, may result from various causes among which iatrogenic and autoimmune causes are important. Although endemic goitre, diabetes mellitus and hyperthyroidism are known to be fairly common in Ethiopia, so far there have been very limited reports on acquired primary endocrine failure in adult Ethiopians (1-2). The purpose of this paper is, therefore, to document 18 patients with endocrine failure resulting from various causes and also to create awareness of the existence of autoimmune endocrine failure among Ethiopians.

MATERIALS AND METHODS

During the study period from February 1986 to January 1990, a total of 372 consecutive endocrine patients were documented prospectively in the weekly endocrine clinic of Tikur Anbessa teaching and referral hospital in Addis Abeba of whom 21(5.6%) were clinically suspected to have endocrine failure. Of the 21 patients, 2 female Asians with hypothyroidism and an Ethiopian female who was suspected to have hypothyroidism but did not return for laboratory test were excluded, thus leaving 18(4.8%) patients who were included in the study. The pertinent clinical and biochemical data were recorded on each patient both initially and during subsequent follow-up visits.

The serum thyroxine (T_4) and triiodothyronine (T_3) were determined by the radio-immunoassay (RIA) technique and thyrotropin (TSH), follicle stimulating (FSH) and luteinizing (LH) hormones by the immunoradiometric assay (IRMA) method using, respectively, RIA-T_4, RIA-T_3, IRMA-TSH, IRMA-FSH and IRMA-LH diagno-

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stic kits obtained from the North East Thames Region Immunoassay (NETRIA) unit. The assays were run in duplicate, and radioactivity was measured by the gamma counter and automatic sample changing system (UK) and NE 1612 Turbo gamma counter (UK). The normal reference ranges were as follows: T_4, 58-160 n moles/L; T_3, 1.1-3.2 n moles/L; TSH, 0.38-4.8 mu/L; FSH, 1-25 mu/L and LH, 1-70 mu/L. Other investigations which were done whenever available and/or indicated included serum calcium, magnesium, phosphorus, sodium, potassium, chloride, urinary 17-ketosteroids, and blood glucose, haemoglobin, red blood cell morphology, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, erythrocyte sedimentation rate, I-131 thyroid scan and uptake and chest x-ray. Autoantibodies against the specific organ antigens were determined by the Department of Clinical Immunology, Karolinska and Roslagstulls hospitals, Sweden.

RESULTS

All but 5 patients came from Addis Abeba and its surrounding towns. The age, sex and aetiology of endocrine failure are given in Tables 1 and 2. There were 2 male and 16 female patients, for a male to female ratio 1:8.

Twelve patients had either a definite or probable autoimmune cause for the endocrine failure. The mean age at onset of the endocrine failure was 33.1 years (range, 22-56 years) and the mean duration of illness was 5.6 years (range, 1-25 years). There were 8 patients with primary hypothyroidism of a definite or probable autoimmune aetiology. The commonest presenting symptoms in these patients included excess sleep, cold intolerance, fatigue, dry skin and change of voice, while hoarseness of voice, puffy face, dry skin, coarse and sparse hair, and slow reflexes were frequent signs (Table 3). The mean TSH level was 61.2 mu/L with a range of 17.2 to 107.3 mu/L. The mean T_4 was 11.3 n moles/L and the range 4.7 to 49.68 n moles/L. The mean T_3 level was 0.51 n moles/L with a range of 0.13 to 1.02 n moles/L. In five of these patients autoantibodies to microsomal and antithyroglobulin antigens were determined and one was positive for both antimicrosomal and antithyroglobulin antibodies, another was positive only for antimicrosomal antibodies while one other patient was positive only for antithyroglobulin antibodies (Table 1).

Four patients had Addison's disease due to a definite or probable autoimmune cause (Table 2). They all presented with dark skin, fatigue, weight loss, and postural symptoms. All had hyperpigmentation of the skin and buccal mucosa and postural hypotension (Table 3). The mean urinary ketosteroids was 4.7 mg% (range, 1.3 to 6.0 mg%; normal, 6-15 mg%) but the blood glucose was normal. In three patients adrenal antibodies were determined and 2 of these were positive.

The only patient with polyglandular failure initially presented with symptoms and signs of Addison's disease and amenorrhoea and subsequently developed hypothyroidism as well. The urinary ketosteroids was 3.3 mg%; TSH, 10.9 mu/L; T_4 56.09 n moles/L; T_3, 0.5 n moles/L; FSH, 52.89 mu/L and LH, 86.86 mu/L.

None of the patients with definite or probable autoimmune endocrine failure had megaloblastic anaemia, and endoscopy was normal in 3 patients in whom the procedure was done. The serum potassium was high in 3 of the Addison's cases while the serum calcium, checked in 3 of the Addison's and 3 of the hypothyroid cases, was normal. The serum

chloride was normal in the Addison's cases but the serum sodium was low normal in 3 of the patients. The chest x-ray showed a small heart in 2 of the Addison's cases. The thyroid scan on the patient with goiterous hypothyroidism showed no uptake of the isotope in the right upper lobe and entire left lobe but uptake of isotope was present in the right lower lobe; uptake was 3.9% (normal, 4.8%) after 2 hours and 5.4% (normal, 30-40%) after 24 hours.

Four patients had thyroid surgery, 1 for Graves' disease and 3 for goitre, of whom 2 developed hypothyroidism and the other 2 hypoparathyroidism. In one of the hypothyroid patients, the TSH was 22.75 mu/L; T_4, 8.12 n moles/L and T_3, 0.13 n moles/L while in the other the TSH was 55 mu/L; T_4, 7.8 n moles/L and T_3, 0.2 n moles/L. The 2 patients with hypoparathyroidism had deterioration of vision in both eyes 3 to 5 years after surgery and at presentation they had positive Chvostek's and Trousseau's signs and bilateral cataract (Table 2). The serum calcium levels were 7.9 mg% and 6.4 mg% (normal, 9-11 mg%), respectively, but the serum magnesium was normal.

One patient with tuberculosis had secondarily developed Addison's disease and presented with signs and symptoms of the disease. The chest x-ray showed small heart and the urinary ketosteroid was 4 mg% but the serum calcium, sodium, potassium and chloride were normal. Of interest is a patient who had discordant hypothyroxinaemia and hypertriiodothyroninaemia while on propylthiouracil (PTU) treatment for Graves' hyperthyroidism. He developed cold intolerance, fatigue and sleepiness and later on developed goitre. The TSH was 52.67 mu/L; T_3, 66.37 n moles/L and T_4 46.4 n moles/L.

All the patients with hypothyroidism and Addison's disease were put on permanent specific replacement therapy and they improved subsequently. In the case of the patient with discordant hypothyroxinaemia and hypertriiodothyroninaemia, the PTU was first reduced to 50 mg, thrice daily, but as his hypothyroidism became worse and, indeed developed goitre, the medication was stopped and later on became euthyroid. The 2 patients with hypoparathyroidism received only calcium as there was no Vitamin D and hence the improvement was not satisfactory.

DISCUSSION

The clinical features and the laboratory data indicate that all the patients had endocrine failure due to autoimmunity, surgery, tuberculosis or PTU administration.

In this study, autoimmune endocrine failure was definite in 5 of the 8 patients (Tables 1 and 2) on whom autoantibody determination against the specific organ antigens was possible. The 3 patients who were negative for autoantibodies and the 4 others on whom antibody determination was not possible had no other causes known to induce endocrine failure in adults, and all responded both clinically and biochemically to the specific replacement therapy. Among the 8 hypothyroid patients, 7 had no palpable gland at all while the other had a tender goitre; this might indicate an end stage of Hashimoto's thyroiditis in the former and probably active Hashimoto's thyroiditis in the latter. Thus, although autoantibodies were not detected in the 2 cases (Table 1) and such determination was not possible in the other 3 cases, it is most likely that the hypothyroidism was of autoimmune origin.

The report on primary hypothyroidism in general and due to autoimmune cause in particular appears to be extremely rare or nonexistent among indigenous African patients (1, 4-7). Among 1,494 thyroid patients seen at the Kenyatta National Hospi-

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tal between 1968-1973, Gitau (4) came across 2 cases with primary myxoedema who were both Asians. In Uganda, Kajubi (5) found only 2 patients with primary hypothyroidism among 923 thyroid patients. In Ethiopia, Lester and Tsega (1) reported 2 cases with primary myxoedema but the aetiology was not defined although autoimmunity was the likely cause.

The reason for the rarity of primary endocrine failure among Africans was believed to be the reduced tendency to form autoantibodies as demonstrated among thyrotoxic patients (8-10). Indeed, McGill (10) found circulating thyroid antibodies in only 16% of Kenyan African thyrotoxic patients compared to 40% to 70% in their Caucasian counterpart. The rarity of autoantibodies among Ethiopians was also reported by Tsega et al (11). Thus, although previous studies seem to indicate the rarity of primary endocrine failure, it is difficult to accept the conclusions gleaned from such studies for a number of reasons. Firstly, some of these studies were retrospective and such studies are well known to have their own inherent problems. Secondly, Graves' hyperthyroidism and ketosis prone insulin dependent diabetes mellitus, which are both thought to be autoimmune mediated diseases, are fairly common in Ethiopia. Thirdly, the timing of autoantibody determination, in relation to the duration of the disease, also matters as the rate of positivity is expected to decline and become negative with time (12). Fourthly, the possibilities of blocking antibodies to the specific stimulating hormone should be considered. Lastly, in Africa communicable diseases and malnutrition are rampant and thus it is most probable that other noncommunicable diseases like autoimmune endocrine failure are likely to be overlooked. Thus, on the basis of the above considerations, one seriously questions the statement made with regards to the rarity of autoimmune endocrine diseases in African patients in general and Ethiopian patients in particular and thus further studies are required. The finding of 12 Ethiopian patients with primary endocrine failure due to definite or probable autoimmune causes (Tables 1 and 2) during a 4 year period may suggest that the condition is probably not as rare as it was previously thought. Of the 8 patients on whom autoantibodies were checked 5 were positive. Although this number is small, the rate of positivity is in clear disagreement with the rate of positivity reported by McGill (10) in thyrotoxic Kenyan Africans.

The patient with polyglandular failure had no antibodies checked but the presence of adrenal, thyroid and gonadal failure with high FSH and LH values and vitiligo strongly suggest an autoimmune aetiology.

Subtotal thyroidectomy for Graves' disease and nodular goitres is associated with hypothyroidism and hypoparathyroidism. Mekuria (2) reported 2 cases of myxoedema among 567 patients who had thyroid surgery. Of 39 Graves' hyperthyroid patients who were seen in the author's endocrine referral clinic between August 1986 and July 1989, 5 patients had subtotal thyroidectomy after they were controlled with antithyroid drugs of whom 1 developed hypothyroidism 1 year later while 3 remained euthyroid 2½ years after surgery; the other patient did not return subsequently and hence the state of thyroid function is unknown. Although hypothyroidism develops during the first year after surgery, a rising incidence with time to about 30% or more is expected (12) and hence the state of thyroid function in our 4 patients remains to be seen.

The 2 patients with hypoparathyroidism developed tetany within a week after subtotal thyroidectomy for goitre. There is no data on the

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incidence of hypoparathyroidism after thyroid surgery among Ethiopian patients who had the procedure. Mekuria (2) reported only postoperative transient tetany in 8.8% of 567 patients who underwent thyroid surgery. In other studies surgical hypoparathyroidism occurs in 0.5 to 1.0% (14) in experienced hands; however, the incidence increases alarmingly with surgical inexperience. Of equal importance is the development of cataract in the 2 patients. Thus, while subtotal thyroidectomy is an aesthetic or therapeutic necessity to be employed, the long term management of postoperative hypoparathyroidism is far from satisfactory under local circumstances where 1,25 $(OH)_2$ D_3 is not available. This state of affair certainly poses a serious concern as to whether or not one should trade-off hypoparathyroidism and its consequences for subtotal thyroidectomy, either for aesthetic or therapeutic reasons. Nevertheless, as complications from thyroid surgery are minimal in experienced hands, it is justified to suggest that such procedure are better done by those surgeons. Furthermore, surgical specimens should be carefully examined for inadvertently removed parathyroid glands as autotransplantation may possibly prevent hypoparathyroidism.

Among the inflammatory diseases, tuberculosis has traditionally been the most common cause of adrenal insufficiency. Indeed, autopsy series before the mid-1950s showed the presence of caseous necrosis of the adrenals in up to 80% of the cases (15). Although tuberculosis is no longer the main cause of Addison's disease in developed countries, it should still remain an important cause of adrenal insufficiency in areas like Ethiopia where the disease is rampant. In this study, there was only one patient who developed Addison's disease due to tuberculosis. However, one certainly cannot draw any conclusion from this as the study was conducted in an endocrine clinic. It would be more appropriate to conduct a study in a hospital or clinic setting where tuberculosis patients are treated in order to know the prevalence of Addison's disease.

Antithyroid drugs can obviously result in hypothyroidism if continued inadvertently. The patient with drug induced hypothyroidism is included in this study because of the rare but interesting and rather confusing discordant hypothyroxinaemia and hypertriiodothyroninaemia which developed during the course of treatment for his Graves' hyperthyroidism. Although he was clinically euthyroid, PTU was continued at a reduced dose (50 mg, thrice a day) because of the high T_3 level. Later on, however, the patient developed symptoms and signs of hypothyroidism while the T_3 still remained high. The drug was discontinued and the TSH was then found to be high. He remained clinically and biochemically euthyroid when last seen 10 months after the discontinuation of the PTU. Such discordant hypothyroxinaemia and hypertriiodothyroninaemia, occurring in 10% of treated hyperthyroid Graves' cases, was recently reported by Chen and Ladenson (3). In such patients, the hypothyroninaemia should make one suspicious of an impending or established hypothyroidism even in the presence of hypertriiodothyroninaemia. Thus, these patients should be carefully evaluated clinically, and TSH should be determined to understand the status of thyroid function. If the TSH is found to be elevated, antithyroid medication should be discontinued or reduced and the patient must be followed up subsequently.

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TABLE 1. Age and Sex distribution and aetiology of hypothyroidism in adult Ethiopian patients

Case No.	Age (yrs.)	Sex	CAUSE Definite	CAUSE Probable	Duration (yrs.)	Comment
1	26	F	Surgery	-	2.0	subtotal thyroidectomy for Graves' disease
2	50	F	Surgery	-	3.0	subtotal thyroidectomy for nodular goitre
3	33	F	AI*	-	10.0	positive for antimicrosomal and antithyroglobulin antibodies
4	54	F	AI	-	25.0	positive for antithyroglobulin antibody; myxoedematous at presentation
5	40	F	AI	-	5.0	positive for antimicrosomal antibody; myxoedematous at presentation
6	28	M	-	AI	6.0	negative for thyroid antibodies
7	60	F	-	AI	4.0	---
8	28	F	-	AI	2.0	Negative for thyroid antibodies; myxoedematous at presentation
9	40	F	-	AI	1.5	---
10	40	F	-	AI	1.0	enlarged and tender thyroid
11	52	M	PTU**	-	1.0	graves' hyperthyroidism with discordant T_4 and T_3 and hypothyroidism during treatment

*Autoimmunity
**Propylthiouracil

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TABLE 2. Age and sex distribution and aetiology of polyglandular, adrenal and parathyroid failure in adult Ethiopian patients

Case No.	Age	Sex	Gland Affected	CAUSE Definite	CAUSE Probable	Duration (yrs)	Comment
12	34	F	Polyglandular	—	AI*	3	adrenal, thyroid and gonadal failure
13	24	F	Adrenal	AI	--	3	positive for adrenal antibody but negative for thyroid antibodies
14	54	M	Adrenal	Tb**	--	½	---
15	28	F	Adrenal	AI	--	2	positive for adrenal antibody
16	29	F	Adrenal	--	AI	2½	negative for adrenal antibody
17	36	F	Parathyroid	Surgery	--	3	subtotal thyroidectomy for goitre; developed cataract after the hypoparathyroidism
18	39	F	Parathyroid	Surgery	--	5	subtotal thyroidectomy for goitre; developed cataract after the hypoparathyroidism

*Autoimmunity. **Tuberculosis

TABLE 3. Signs and symptoms in adult Ethiopian patients with endocrine hypofunction

Disease	Symptom	No. present	Sign	No. present
Hypothyroidism (n=11)	Sleepiness	9	Slow reflexes	9
	Cold intolerance	9	Dry skin	9
	Fatigue	8	Hoarse voice	6
	Dry skin	8	Puffy face	6
	Change of voice	7	Dry, sparce hair	6
	Dry hair	5	Slowness	5
	Weight gain	5	Odema	5
	Swelling of face	5	Pallor	3
	Muscle pain	3	Big tongue	2
	Neck swelling	3	Galactorrhoea	2
	Constipation	2	Goitre	1
	Swelling of legs	2	Yellow skin	1
Addison's disease (n=5)	Dark skin	5	Hyperpigmentation	5
	Fatigue	5	Hypotension	5
	Weight loss	5	Vitiligo	2
	Postural symptoms	5		
	Anorexia, vomiting	4		
	Salt craving	3		
	Amenorrhea	2		

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NATIONAL BLOOD REQUIREMENT, SERUM ALT AND HEPATITIS IN ETHIOPIAN BLOOD DONORS

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ABSTRACT: To appraise the national blood requirement and supply, and to determine the impact of alanine aminotransferase (ALT) and hepatitis B surface antigen (HBsAg) screening on the blood supply, 407 random blood donor sera were tested for HBsAg, human immunodefficiency virus (HIV), and ALT activity. HBsAg and anti-HIV antibody were determined by the enzyme linked immunosorbent assay (ELISA) technique using Hepanostica and Welcozyme kits, respectively. The Western Blot test was performed to confirm anti-HIV positive sera by the ELISA technique. ALT was determined by an automated photometer using ALAT kits and serologic testing for syphilis was done by the rapid plasma reagin (RPR) test. The amount of blood required in Ethiopia and the actual supply was calculated on the basis of the number and type of hospital beds in Addis Abeba and the amount of blood transfusions in units per hospital bed. The results showed that the combined donor and unit rejection rate was 34.6%. The annual blood requirement was 7 units for emergency and 4 units for nonemergency beds. The national blood requirement in 1989 was 64,350-80,000 units, but the supply met only a third of the requirement. The mean and 2SD cut off ALT levels were 28 and 69 IU/L, respectively. ALT was elevated in 9.1% of HBsAg positive but apparently healthy donors, while HBsAg screening eliminated 25% of those with elevated ALT activity. This data suggests that there is a serious blood shortage in Ethiopia and that the currently supplied blood is relatively unsafe in terms of hepatitis. Thus, HBsAg screening should be done together with the implementation of a blood policy that ensures the procurement of sufficient blood for haemotherapy in Ethiopia.

INTRODUCTION

The two main causes of post transfusion hepatitis are hepatitis B virus (HBV) and Non-A, Non-B (NANB) viruses. In the USA and Japan, where HBsAg screening is a routine procedure, the proportion of post-transfusion hepatitis that could be attributed to NANB viruses ranges from 71-100% in the populations studied (1-5).

The determination and occurrence incidence of NANB hepatitis is dependent on the level of ALT elevation and the presence of anti-hepatitis B-core (anti-HBc) antibody in donor blood. Thus, a combined screening for both reduces the incidence of post-transfusion NANB hepatitis by up to 60% (1,6). ALT and anti-HBc screening have been advocated as surrogate tests for NANB hepatitis by Alter et al (6). The authors predicted that exclusion of blood donors with abnormally increased ALT activity alone would result in the reduction of transfusion associated NANB hepatitis by 30%.

In a present Ethiopian study it was found that 79% of the blood donors had markers for HBV infection of whom 11% were positive for HBsAg, 66% for anti-hepatitis B-surface (anti-HBs) and 2% for anti-HBc antibodies (7). As the prevalence of hepatitis Be antigen (HBeAg) among HBsAg carriers was only 4% (7), and as there was a high prevalence of anti-HBs antibody in the general

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population, presumably protective against HBV infection (8-10), and considering the limited blood supply, HBsAg screening has been limited to blood units transfused to children, expatriates and immunocompromised patients whose serostatus is known.

Various studies have now established hepatitis C-vrus (HCV), with modes of transmission partially similar to that of HBV (11), accounts for the majority of post-transfusion NANB hepatitis (6). Moreover, / screening for anti-HCV antibody has become part of the standard blood screening practice in the USA and Europe (H.W. Reesink, Personal communication).

In view of the scarcity of blood and the current partial screening practice for HBV, the need to appraise the possible existence of HCV and the usefulness of surrogate ALT screening for its detection is appropriate. Moreover, due to the limited resources, the substantial expense incurred in running blood transfusion services, and the cost of introducing a new screening test, it is necessary to assess the safety of blood in terms of known hepatitis viruses and other transfusion associated infections in relation to the blood supply and demand in Ethiopia.

The objectives of this study are to assess the blood demand in relation to the present supply and screening practices, and to appraise the current HBV screening practice in view of the emergence of HCV as an agent transmissible through blood transfusions. Furthermore, an attempt will be made to establish reference values for ALT activity and evaluate the usefulness of ALT screening as a surrogate test for NANB hepatitis in Ethiopian blood donors.

MATERIALS AND METHODS

Assessment of demand and supply of blood: Ninety percent of blood in Ethiopia is collected by the five Ethiopian Red Cross Society (ERCS) blood transfusion centres located in Addis Abeba, Asmera, Harer, Yirgalem and Jima (12). In all centres there was a uniform blood screening practice i.e. anti-HIV and RPR screening of all units, discarding anti-HIV positive units and utilizing RPR reactive units after refrigeration for 5 days. HBsAg screening was done for blood units transfused to children, pregnant females, expatriates and immunocompromised patients whose serostatus was known. Thus, blood donation records for 1989 were analysed for the above centres in terms of current donor attendance, donor referral and unit rejection rates. The number of blood units that would be rejected if screening for HIV, HBsAg and ALT elevation was uniformly assessed for on all.

The number of hospital beds per department in Addis Abeba and eight other administrative regions was obtained directly by a supervisory team. In the remaining seven regions, hospital bed number per department was obtained through regional offices of health and/or personal contact. The annual number of hospital admissions in Ethiopia was obtained from the Ministry of Health registry.

Hospital beds for surgery, gynaecology/obstetrics, intensive care and outpatient departments were considered emergency beds and those for medicine, paediatrics, leprosy, ophthalmology, tuberculosis, psychiatry and ear, nose and throat (ENT) were considered non-emergency.

Blood utilization data for various departments was obtained for Tikur Anbessa teaching hospital from the hospital blood bank, while data for the remaining general and specialized hospitals were obtained from the main transfusion centre register. Blood utilization per emergency and non-emergency bed per annum was computed for the teaching hospital and specialized hospitals in Addis Abeba. It was assumed that the blood supply for Addis Abeba hospitals

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was fair, and that hospital beds were used relatively optimally. Thus, blood utilization data for Addis Abeba, taken as a national standard, in conjunction with findings of Leikola's study on world blood need (14) was used to estimate the national blood requirement.

Blood donors: A total of 407 random blood samples were collected from healthy adult volunteer blood donors in November 1989 in the Addis Abeba Blood Transfusion Centre. Enrolled blood donors were apparently healthy, first time donors, who underwent a standard blood bank health screening. This included filling out a questionnaire, interview and physical examination to determine the donors fitness to donate blood and ensure that the latter is safe for the recipient. Donors with a past history of jaundice, liver disease or those with abnormal physical findings were excluded from blood donation.

Serological and biochemical assays: Sera were stored at 4-8°C, and laboratory investigation was done within 6-12 hours of blood collection (15). ALT was determined using an automated photometer and ALAT kits (Boehringer diagnostica). The presence of HBsAg and anti-HIV antibody was determined by the ELISA technique using Hepanostica (organon Teknika) and Welcozyme kits, respectively. Sera which were repeatedly positive by ELISA were confirmed using the Western Blot (Biorad Strips). A serological marker for syphilis was checked by the RPR test of Becton Dickinson.

Mean ALT activity and two standard deviation (2SD) ALT cut off levels were calculated using log transformations as recommended by the American Association of Blood Banks (AABB) (16) in three categories of blood donors i.e. donors who were positive for anti-HIV antibody or HBsAg or those negative for both markers. Among those who were negative for anti-HIV antibody and HBsAg ALT activity and 2SD cut off values were calculated for both sexes.

RESULTS

A total of 11,700 hospital beds were estimated, of which 5,944 (50.8%) were considered acute beds. The total number of hospital admission in Ethiopia was estimated to be 200,000 for 1989. In Addis Abeba, a mean of 7.8 (range, 3.89.8 units) and 1.9 (range, 0.2-3.9 units) units of blood were respectively used per acute and non-acute bed per annum (Table 1).

Considering the relative ease of obtaining blood for emergency as opposed to non-emergency beds, the annual blood requirement per acute and non-acute bed was set at 7 and 4 units, respectively, for Addis Abeba hospitals. On this basis, the national annual requirement was found to be 64,350 units. However, according to Leikola's finding on world blood supplies and requirement (14) the estimated needs in Ethiopia 80,000 and 55,000 units, respectively, when hospital admissions and population size (Table 2) are considered as denominators.

The actual donor and unit rejection rate (Table 3) shows that 30% of the donors were referred for health reasons, mainly because of loss of weight (<50 kg.) and 34.6% of all attending donors and units bled were rejected on the basis of the current practice of partial screening for HBV. The introduction of ALT and HBsAg for screening all units together with referral of donors with syphilis seroreactivity, a marker of risk behaviour for the transmission of HIV, would raise the potential donor and unit rejection rate to 46.9%.

The mean ALT activity and 2SD ALT cut off levels of blood donors negative for both HBsAg and anti-HIV were 28 and 69 IU/L, respectively. ABO and RH blood groups had no influence on mean and cut off ALT

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values. As shown in Table 4, 9.1% of the donors who were positive for HBsAg had elevated Alt activity; this was 2.7 times the rate found in HBsAg negative donors. Similarly the ALT activity was raised in 8.4% of the donors who were positive for HIV; this was 2.5 times the rate found in HIV negative donors.

The prevalence of HBsAg positivity was 10.8%, and a combination of HBsAg and ALT for screening would result in a unit rejection rate of 13.8% (56/407) due to hepatitis.

DISCUSSION

Leikola's study on world blood supply and requirement (14) has shown that the index of donation per 1000 population was on the average 9.5 in middle income and 1.1 in low income countries. The study also concluded that roughly 10 annual donations per emergency hospital bed or 0.4 donations per patient admission to these hospitals would provide adequate blood and blood products for modern haemotherapy. In comparison to the world data, the current blood supply in Ethiopia of 23,381 units per annum amounts to only about a third of the estimated requirement, the index of donation being 0.51 per 1000 population.

Our estimation of the national blood requirement assumes that all hospitals in Ethiopia have access to modern blood services, are adequately staffed, and hospital bed utilization is similar to that of hospitals in Addis Abeba. Considering situations in 1989, where 60% of all hospital beds in Ethiopia had access to modern blood services (12), a realistic estimate of 38,610-48,000 would be obtained, which is roughly twice the current supply, indicating the need for an exceptional blood procurement effort.

Of the total donors, 3.9% (16/407) had raised ALT activity. Alter (17) recommends that the mean ALT levels should be determined by random analysis at each blood centre and that the value which is 2.25 SD above the log mean be used as a cut off value in deciding whether or not to use blood for transfusion. The current AABB criteria for deferring donors are: (1) two different serum levels of ALT above the 2SD cut off level determined by the particular laboratory and (2) a single ALT value that is more than 2 times the upper limit of normal (16). In our laboratory the two ALT cut off values were found to be 69 and 138 IU/L, respectively. There were only 2 donors who had a single ALT reading greater than 138 IU/L.

Raised ALT levels in apparently healthy individuals have been statistically correlated to at least one of the following: male sex (18-20), middle age (18-20), overweight (18-21), alcohol drinking habits (20-21), ongoing gastrointestinal symptoms (22) and drug induced liver injury (23). Shulman (24) has also reported that ALT levels in Hispanics are much higher than in White and Black donors.

The 2SD cut off ALT levels calculated separately for the two sexes were 71 IU/L for males and 69 IU/L for females. This is similar to the findings of previous studies (22-24). When age and sex were taken together, however, we found a similar pattern of activity in both sexes; ALT activity peaks in the 30s in males and in the 20s in females but declining thereafter in both sexes as age progresses (Table 5).

Even though a thorough history of alcohol intake wasn't taken and anti-HBc was not determined, the finding of elevated ALT activity in 3.4% of HBsAg negative apparently healthy donors may be a possible indicator of a risk for NANB hepatitis agents in such donor groups. This calls for further study on the prevalence of HCV in blood donors.

The elevated ALT activity observed in 9.1% of HBsAg positive donors indicates the activity of HBV; hence, the questionable partial screening practice, and the safety of the blood supply. Similarly, 8.4% of HIV positive donors have shown elevated ALT activity, reflecting the partial similarity of the epidemiology of both

agents.

When we use both of our cut off values and the AABB criteria in our donors, only 9.1% (4/44) of HBsAg positive donors would be deferred if ALT screening alone is introduced. HBsAg screening of all blood units would eliminate 25% (4/16) of donors with raised ALT activity (Fig. 1).

Alter's recent randomized prospective study has demonstrated that surrogate assays, i.e. anti-HBc and ALT screening for NANB agents, could detect approximately half of the blood donors who would transmit hepatitis C virus (6). Moreover, there seems to be little overlap between donors identified by anti-HBc and those identified by ALT testing. This has been shown by the findings of a study on HBsAg negative donors where only 15% of donors with elevated ALT had anti-HBc and only 8% of donors with anti-HBc had elevated ALT (25).

In conclusion, there is a serious blood shortage in Ethiopia, requiring an exceptional blood procurement effort and a more rational utilization of blood to avoid its wastage. Moreover, currently supplied blood units are relatively unsafe in terms of hepatitis transmission; hence, an improved policy for HBV screening is necessary. This will require substantial resources within the health sector for blood screening will need to allow for blood shortage resulting from discarded units. As there is an indication for the possible existence of NANB agents in currently supplied blood units, a study to assess the prevalence and post-transfusion sequelae of HCV in Ethiopia is recommended.

ACKNOWLEDGEMENT

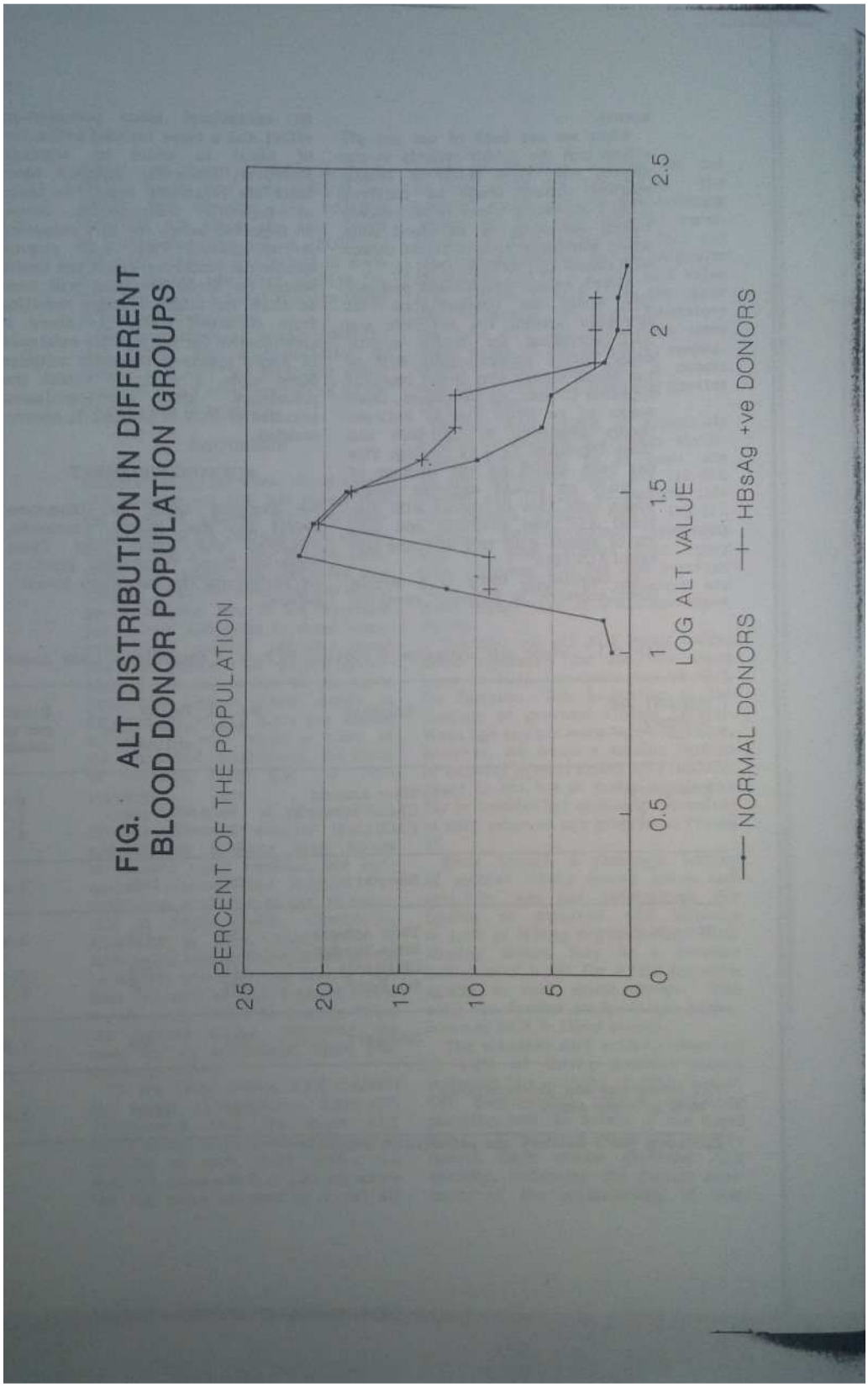
We sincerely thank Mr. Gizachew Teferi and Mrs. Helena Nousianen, Ethiopian and Finish Red Cross Societies blood transfusion services for performing the laboratory investigations.

TABLE 1. Blood unit utilization in relation to type of hospitals in Addis Abeba*

Hospital Bed Category	Hospitals	No. of beds	No. of blood units utilized	Blood units per bed per annum
Emergency	Tikur Anbessa	329	3211	9.8
	Ghandi Memorial	80	304	3.8
	Fistula	100	430	4.3
	Subtotal	509	3945	7.8
Non-emergency	Tikur Anbessa	134	523	3.9
	Ethio-Swedish	147	326	2.2
	Children's	187	37	0.2
	St. Peter			
	Subtotal	468	886	1.9
All emergency and non-emergency beds in Addis Abeba		3120	12247	3.9

*Excluding the 3 military and paramilitary hospitals

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TABLE 2. Estimation of blood requirements in Ethiopia

Source	Item	Number	Blood units per item	Requirement
Present study	Emergency beds	5944	7/bed	41608
	Non-emergency beds	5756	4/bed	23024
	All hospital beds	11700	5.5/bed	64350
World data*	Hospital admission	200000	0.4/admission	80000
	Acute beds only	5944	10/bed	59440
	Ethiopian population (in million)	48.7**	1.1 donation/ 1000 population	53570

*Ref. 18
**Ref. 25

TABLE 3. Actual and potential donor referral and unit rejection for 1989

Category	Item	Number	Percent
Blood collection	Donors attending	35761	100
	Units bled	25033	70
	Donors referred	10728	30
Laboratory rejection	Incomplete units	501	2
	HIV Positive	**	4
	HBsAg positive (of 2000 units tested)	**	10.8
	Sub-total	1652	6.6
Actual donor referral and unit rejection*			
Potential unit rejection	Incomplete units	**	2
	HIV-Positive	**	4
	HBsAg positive and/or	**	13.8
	elevated ALT	**	4.1
	RPR reactive		
	Sub-total	<5983	<23.9
Potential donor deferral and unit rejection		<16700	<46.9

*Laboratory rejection of blood units if screening of all blood units and discarding of positive samples for the above tests is instituted.
**As a unit of blood may be positive for more than one test, figures are not given.

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TABLE 4. ALT activity (IU/L) of various blood donor groups

Blood donors	Number tested	Mean ALT	Cut off ALT	Raised ALT No.	Raised ALT Percent
HIV positive	12	34	-	1	8.4
HBsAg positive	44	35	-	4	9.1
HBsAg and HIV negative	352	28	69	12	3.4
Total	408	-	-	16*	3.9

*One donor was positive for HBsAg, HIV and had raised ALT activity

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IMMUNOGENICITY, REACTOGENICITY AND COMPARISON OF TWO DOSES OF RECOMBINANT DNA YEAST-DERIVED HEPATITIS B VACCINE IN ETHIOPIAN CHILDREN

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Abstract. Hepatitis B virus infection and its sequelae, chronic hepatitis, cirrhosis of t liver and primary hepatocellular carcinoma (PHC), are important medical problems Ethiopia. There is a possibility to prevent these by mass immunization of neonates a children. To achieve this, the cost of the hepatitis B vaccine must be possible within t limited health budget of the country. This study, therefore, was conducted to find o comparative safety and immunogenicity of two doses, 10 mcg and 20 mcg, recombinant DNA yeast-derived hepatitis B vaccine in children, 2-14 years old. Thr hundred and fourteen non-immune children, from an initial sample of 380 children, we grouped into those below and those above 8 years of age. Each group was furth subdivided into boys and girls and each group was given either 10 mcg or 20 m hepatitis B vaccine, alternately, using the 0-1-6 months schedule. Anti-HBs titres we determined at one, two and seven months. Side effects were recorded by parents for thr days following each injection. Comparison of seroconversion rates (97-100%) and an HBs geometric mean titres (3421-6336) of boosted vaccinees in the different sex, age a dose groups showed no significant differences. There were minor side effects record in 76 children. Therefore, the 10 mcg and 20 mcg doses of recombinant DNA yea derived hepatitis B vaccine are equally safe and highly immunogenic in children 3- years of age.

Key words: Hepatitis B vaccine; Ethiopia

Introduction

The prevalence of hepatitis B virus (HBV) infection, viral hepatitis, cirrhosis of the liv and primary hepatocellular carcinoma is high in Ethiopia [1-4]. Perinatal or vertic transmission of HBV infection is uncommon in this population but horizontal transm sion occurs early in life and the prevalence gradually rises without a tendency to plateau [3-5]. Thus, the need for active mass immunization of all neonates a seronegative children against HBV in this hyperendemic area, fortunately withc requiring the additional use of the expensive hepatitis B immunoglobulin (HBIG), obvious, timely and cost-effective [6, 7].

Extensive vaccination trials have shown that plasma-derived and recombinant DN yeast-derived hepatitis B vaccines are equally safe and highly immunogenic in neonat children and adults [8]. However, vaccine safety and immunogenicity studies have n

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been conducted in this part of Africa. Furthermore, while plasma-derived hepatitis B vaccine remains very expensive because of limited human plasma sources and high cost of production, recombinant DNA yeast-derived hepatitis B vaccine can be produced in unlimited quantities at a low cost in the near future. To implement mass immunization programmes in developing countries like Ethiopia, it is essential to consider ways of further reducing the cost of hepatitis B vaccine. One way of achieving this would be by using a lower dose of the recombinant DNA yeast-derived hepatitis B vaccine if there was no compromise insafety and immune response. The purpose of this study, therefore, was to investigate the immunogenicity and safety of a recombinant DNA yeast-derived hepatitis B vaccine (Engerix B; Smith Kline Biologicals, Belgium) and to compare the immune responses of 10 mcg and 20 mcg doses of the vaccine in Ethiopian children, 3-14 years of age.

Subjects and Methods

Vaccinees

Children of hospital employees were recruited for this study to achieve maximum compliance with the seven months study. A detailed explanation, stating the objectives of the study, the advantages and possible side effects of the vaccine, was circulated to the employees of Tikur Anbessa Hospital and Yekatit 12 Hospital, both located in Addis Ababa. Consenting parents were asked to register their children aged 2-14 years and were provided with a list of local signs (induration, redness, swelling and pain) and general symptoms (fever, headache, gastrointestinal symptoms, dizziness, fatigue and others) to be recorded as absent, mild, moderate or severe 3 consecutive days following the administration of each vaccine dose. In addtion, nurses, experienced in maternal and child health care delivery, were instructed to explain what was expected from the parents of the vaccinees during the conduct of the vaccination programme. This was carried out in the presence of all parents every morning before commencing vaccination.

Study desing

The population was stratified initially according to age (< 8 years and > 8 years) and these groups were further stratified according to sex. In each of the four groups, doses of 10 mcg (Dose A) or 20 mcg (Dose B) were assigned to alternate subjects.

Then, for logistic reasons, all vaccinees were given their appropriate dose of hepatitis B vaccine immediately following venesection (4-8 cc) for baseline hepatitis B virus marker determination. In marker positive subjects, further doses were not given.

Inclusion criteria

All children between the ages of 2 and 14 years, without previous hepatitis B vaccination, negative for HBsAg, anti-HBc and anti-HBs and without acute or chronic disease or a history of allergy to any vaccine preparation were included in the study.

Withdrawal

Subjects who requested discontinuation of the vaccination, those who failed to comply with protocol specifications and those who manifested serious adverse reactions in whom the continuation of the vaccination at any level may pose a serious risk to the subject must withdraw.

Vaccination

Yeast-derived recombinant DNA hepatitis B vaccine (Engerix B; Smith Kline Biologicals, Rixensart, Belgium; Lots 129A4, 127A4 and 174A4 in glass vials containing 20 mcg (1 ml)) was administered intramuscularly according to the randomization at zero, one and six months. Group A subjects received 0.5 ml (10 mcg) and grup B received 1 ml (20 mcg) of the vaccine. Anti-HBs titres were determined at one, two and seven months. Inititally seronegative subjects who developed detectable anti-HBs (> 1 mIU/ml) after receiving 1-3 doses of the vaccine were regarded as seroconverters. Anti-HBs levels of 10 mIU/ml or higher, as measured by

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radioimmunoassay (RIA), are generally considered protective and the duration of protection against hepatitis B virus infection is directly correlated with the height of anti-HBs titres achieved by immunization [9-11].

Laboratory methods

Screening for hepatitis B virus markers (HBsAg, anti-HBc and anti-HBs) was performed using commercial RIA kits (Abbott Laboratories) by the Department of Medical Microbiology, Section of Clinical Virology, University of Lund, Malmo, Sweden, and by Smith Kline Biologicals, Rixensart, Belgium. Anti-HBs titres were determined by Smith Kline Biologicals, Rixensart, Belgium, and by the Nuclear Medicine Unit of Black Lion Hospital, Faculty of Medicine, Addis Ababa University, using commercial RIA kits (Abbott Laboratories), the results being expressed in International Units (mIU/ml).

Statistical evaluation

Differences in age, age range, sex and anti-HBs geometric mean titres (GMT's) between the two vaccine doses and age groups were evaluated using the Student's t test.

Results

From a total of 380 children (191 boys and 189 girls) screened, 314 (156 boys and 158 girls) were seronegative for hepatitis B virus markers and hence eligible for inclusion. Sixty subjects (16%) were excluded because of HBV marker positivity while the remaining six subjects were excluded for other reasons such as failure to obtain adequate blood samples. As shown in *table 1*, there was no significant difference between age, range of age, dose and sex, except for sex difference between subjects under 96 months of age.

Seventy-six vaccinees, 38 (24%) from the 10 mcg dose group and 38 (25%) from the 20 mcg dose group, reported mild to moderate symptoms and signs: fever (32), headache (32), gastrointestinal symptoms (26), dizziness (22), fatigue (24), redness (24), pain (21), swelling (11) and induration (11) at the site of vaccine inoculation. Thus, among the general constitutional symptoms, fever (often a subjective report by parents) and headache were the commonest complaints. Neither the general nor the local signs and symptoms were severe enough to warrant discontinuation of immunization in any subject. Side effects were more commonly observed following the administration of the first dose of vaccine but became progressively less with subsequent injection.

Seroconversion rates one month after the first 10 or 20 mcg dose of hepatitis B vaccine were 62% and 73%, respectively ($p > 0.05$). One month after the administration of the second dose, the seroconversion rate was 94% in each dose group and almost the same in those below and above 8 years of age. One month after the third dose, the seroconversion rates reached 97-100% in both age and dose groups. The anti-HBs geometric mean titres (GMT's) between the two vaccine doses and age groups showed no significant differences except between the two dose groups following the second dose of hepatitis B vaccine (see *table 2*; Student's t tests: $p = 0.016$). These results, summarized in *table 2* and *figure 1*, indicate that the 10 mcg and 20 mcg recombinant DNA yeast derived hepatitis B vaccine are highly and equally immunogenic in Ethiopian children between 2 and 14 years of age. Also, when seroconversion rates and GMT's of anti-HBs were analyzed at one, two and seven months in each dose and age group according to sex, there was no statistical difference except between the doses for all the females at month 2 (Student's t test: $p = 0.033$) (*table 3*).

The distribution of protective anti-HBs levels in initially seronegative and in seroconverted subjects at one, two and seven months as well as in each age and dose group showed a progressive rise, being more marked after the second dose. Both booster

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Table 1. Sex and age (months) distribution of subjects

Age	Vaccine dose	Total population				Seronegative subjects							
		Male	Mean ±S.E.	Female	Mean ±S.E.	Total		Male ±S.E.	Mean	Female	Mean ±S.E.	Total	
all subjects	10 mcg	98	96.1 ±8.8	92	89.6 ±7.4	190	93.0 ±5.8	85	92.6 ±9.4	75	91.1 ±8.2	160	92.3 ±6.3
< 96 months (24-96 months)		45	54.4 ±5.8	49	61.1 ±5.7	94	57.9 ±4.1	42	53.9* ±5.7	39	62.5* ±6.1	81	58.0 ±4.3
> 96 months (97-168 months)		53	131.5 ±6.5	43	122.2 ±5.7	96	127.3 ±4.5	43	130.4 ±7.2	36	123.7 ±6.5	79	127.3 ±4.9
all subjects	20 mcg	93	98.0 ±8.9	97	91.3 ±8.2	190	94.6 ±6.0	71	95.1 ±10.4	83	91.2 ±9.1	154	93.0 ±6.8
< 96 months		42	58.2 ±7.1	51	57.8 ±5.5	93	58.0 ±4.4	35	57.4 ±8.0	44	57.1 ±6.1	79	57.2 ±4.9
> 96 months		51	130.7 ±6.8	46	128.4 ±6.4	97	129.6 ±4.7	36	131.7 ±8.0	39	129.6 ±7.1	75	130.6 ±5.3
	Total	191	97.0 ±6.2	189	90.5 ±5.5	380	93.8 ±4.2	156	93.7 ±6.9	158	91.5 ±6.2	314	92.6 ±4.5

*Student's t tests were performed between age, range of age (< 96 months or > 96 months), dose and sex. There is only one significant difference between sexes for seronegative subjects aged under 96 months (*p = 0.042).

Table 2. Seroconversion rates (SC) and geometric mean titres (GMTS) of anti-HBs according to vaccine dose and age group at indicated time

Dose (mcg)	*Age (years)*		*Month 1*	*Month 2*	*Month 7*
10		SC	44/81	77/81	80/81
	< 8	%	54.3	95.1	98.8
		GMT	5.4	17.3	3421.4
		SC	55/79	74/79	79/79
	> 8	%	69.6	93.7	100
		GMT	7.6	24.4	3667.8
		SC	99/160	151/160	159/160
	Total	%	61.9	94.4	99.4
		GMT	6.5	20.4*	3541.6
20		SC	58/78	74/78	78/78
	< 8	%	74.4	94.9	100
		GMT	7.7	31.5	6836.0
		SC	53/75	70/75	73/75
	> 8	%	70.7	93.3	97.3
		GMT	5.8	30.8	3681.3
		SC	111/153	144/153	151/153
	Total	%	72.5	94.1	98.7
		GMT	6.7	31.2*	5067.6

*Student's t test (p = 0.016)

Statistical analysis of the GMTs between the two vaccine doses and age groups showed no significant differences except as noted above.

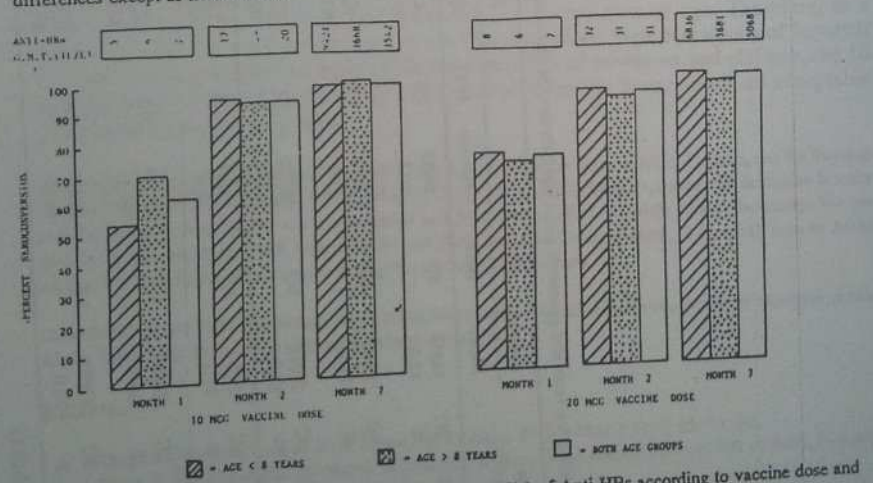


Figure. Seroconversion rates and geometric mean titres (GMT's) of Anti-HBs according to vaccine dose and age group at month one, two and seven.

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Table 3. Seroconversion rates and geometric mean anti-HBs titres in seroconverters at month one, two and seven in each group according to sex

Dose (mcg)	Age (years)		Month 1		Month 2			Month 7			
			Males	GMT	Females	GMT	Males	GMT	Females	GMT	Males	GMT	Females	GMT
10	< 8	SC	18/42	5.3	26/39	5.4	41/42	20.0	36/39	14.6	41/42	4182.2	39/39	2769.5
		%	42.9		66.7		97.6		92.3		97.6		100	
	> 8	SC	32/43	6.4	23/36	9.8	42/43	24.7	32/36	24.0	43/43	4463.8	36/36	2901.3
		%	74.4		63.9		97.7		88.9		100		100	
	Total	SC	50/85	6.0	49/75	7.1	83/85	22.2	68/75	18.5*	84/85	4324.1	75/75	2832.0
		%	58.8		65.3		97.6		90.7		98.8		100	
20	< 8	SC	25/34	6.5	33/44	8.8	33/34	34.4	41/44	29.4	34/34	9425.4	44/44	5333.3
		%	73.5		75.0		97.1		93.2		100		100	
	> 8	SC	24/36	5.1	29/39	6.5	32/36	29.2	38/39	32.3	34/36	3115.3	39/39	4257.9
		%	66.7		74.4		88.9		97.4		94.4		100	
	Total	SC	49/70	5.8	62/83	7.6	65/70	31.7	79/83	30.7*	68/70	5418.8	83/83	4797.3
		%	70.0		74.7		92.9		95.2		97.1		100	

*Student's t test (p = 0.033)
All the comparisons were performed between group (dose, age) and sex. There is only one significant difference: Between doses for all the females at month 2.

doses of the vaccine induced anti-HBs values > 10 in 97-100%, > 100 in 95-99% and > 1000 in 69-84% of the boosted subjects.

Discussion

The mild local and systemic reactions observed in this study after the 10 mcg and 20 mcg Smith Kline Biologicals recombinant DNA yeast-derived hepatitis B vaccine are not different from those reported elsewhere [12, 13]. The total absence of apparent hypersensitivity reactions after repeated injections of each dose of the vaccine is in support of earlier studies that revealed that the minute amount of yeast (*Saccharomyces cerevisiae*) protein present in the vaccine is very unlikely to cause a serious IgE-type allergic reaction [13, 14].

Following the third (6 month) dose of yeast-derived recombinant DNA vaccine, using either 10 mcg or 20 mcg, almost 100% protection (10 mIU/ml or higher anti-HBs titre being the protective level) was achieved while between 69% and 84% of the subjects acquired anti-HBs levels greater than 1000 mIU/ml. Since duration of protection is directly correlated with the level of anti-HBs, it is safe to assume that vaccinees in both dose groups would probably be protected for at least 3-5 years beyond which time they may require a further booster injection [11]. Though hypothetical at the present time, repeated exposure to hepatitis B virus in highly endemic areas, such as in Ethiopia, may induce a 'natural booster' effect and thus the need for further booster injection may not arise.

Recent studies comparing the protective efficacy of 10 mcg and 20 mcg of the Smith Kline Biologicals yeast-derived recombinant DNA hepatitis B vaccine in neonates and a limited number of children have concluded that a dose of 10 mcg is not significantly less immunogenic, seroconversion rates and GMT's of anti-HBs being comparable [15]. On the other hand, Hollinger [16] has cautioned that 'more may be better' and the production of recombinant vaccine containing a dose less than 20 mcg may be ill-advised. This study, however, compared the reactogenicity and immunogenicity of these two doses of yeast-derived hepatitis B vaccine in 314 children, between 2 and 14 years of age, and found both to be equally safe and immunogenic irrespective of age. Therefore, in a country, where the economic resources are limited and the high prevalence of hepatitis B virus infection demands a nationwide immunization of newborns and children, the 10 mcg dose of the recombinant DNA yeast-derived hepatitis B vaccine is an acceptable alternative to the 20 mcg dose.

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CHRONIC IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP) IN ADULT ETHIOPIANS: CLINICAL FINDINGS AND RESPONSE TO THERAPY

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ABSTRACT: Between January 1982 and December 1989, thirty four cases of chronic idiopathic thrombocytopenic purpura (ITP) were seen in adult Ethiopians in the Department of Internal Medicine in-patient and haematology referral clinic, of Tikur Anbessa teaching hospital. Twenty three were females and eleven males; female to male ratio of 2.1:1. The age range was 13-57 years, with a mean of 24.9 years. The commonest manifestations were: purpura, epistaxis, gum-bleeding and menorrhagia. The duration of symptoms ranged from one month to over ten years (median 4.5 months). The platelet counts ranged from 4000/mm^3 to 77,000/mm^3 (mean - 19,200/mm^3), haemoglobin 3.01 to 15.4 gm/dl (mean - 8.2 gm/dl). Four (11.8%) patients were not treated; of these, one went into spontaneous remission. Thirty patients (88.2%) were treated with prednisolone 1.0 to 1.5 mg/kg/day orally. Of these, 7(23.3%) had excellent, 2(6.7%) good, 6(20%) fair, and 15 (50%) had poor responses. Ten patients had splenectomy with 5(50%) excellent 2(20%) good, 2(20%) fair and 1(10%) poor response. One patient with refractory ITP was treated with immunosuppressive drugs and had an excellent response. Fifteen patients are alive and on followup 3-122 months (median 33 months) after diagnosis, fifteen are lost after followup of 1-66 months (median 9 months) and four have died 1-18 months (median 2 months) after diagnosis. Chronic ITP is frequently seen in adult Ethiopians, its clinical features and response to therapy are similar to those reported in the literature.

INTRODUCTION

Chronic idiopathic thrombocytopenic purpura (ITP) is said to have been first described by Werlof in 1735 after whom it was named, Werlof's disease. Full description of the disorder came from subsequent investigators; Krauss, Frank and Minot (1). The cause of chronic ITP had remained unknown until the early 1950's when Harrington demonstrated the cause to be an antiplatelet factor present in over 60% of patients with ITP (2). The antiplatelet factor was further characterized and found to be an immunoglobulin G (3). Based on these findings, it is felt that the prefix "idiopathic" is inappropriate and must be replaced by "immune" or "autoimmune" and defined as: a syndrome characterized by persistent thrombocytopenia caused by a circulating antiplatelet factor that results in platelet destruction by the reticuloendothelial system (4). Baldini divided ITP into acute and chronic forms (5). The acute form occurs more frequently in children, affecting both sexes equally, usually follows a viral illness, is transient, and recovery occurs spontaneously in the majority of the cases. Only about 10% progress into the chronic form. The chronic form occurs mainly in adults, females are affected two to four times more commonly than males. It is characterized by persistence and perpetuation with very few spontaneous remissions.

Chronic ITP is said to be rare among American Negroes (6), the explanation being that subcutaneous bleedings

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were difficult to detect because of the deep pigmentation of the Negro skin. The literature from Africa is also deficient in reports on ITP in Africans. There are a few reports from South Africa (8,9) and Kenya (10). There were very few cases of ITP reported from hospitals in Ethiopia in the 1960's and 1970's (11,12). Sixteen cases of ITP were reported among haematological admissions over a five year period but without detailed description on their clinical and laboratory features or response to therapy (13). The present study includes the reported sixteen cases and analyses the clinical and laboratory presentations and response to different modalities of therapy and compares the findings with similar studies elsewhere.

PATIENTS AND METHODS

This study is based on the analysis of thirty-four newly diagnosed cases of adult chronic idiopathic thrombocytopenic purpura (ITP) seen in the Department of Internal Medicine in-patients and the haematology referral clinic of the Tikur Anbessa Hospital between January 1982 and December 1989. All patients included, had symptoms for at least three months (with and without therapy) including symptoms of bleeding and documented thrombocytopenia. One patient who was diagnosed in 1979 but was in relapse and another patient who had splenectomy for autoimmune haemolytic anaemia (AIHA) six years before presentation with bleeding were included.

The diagnostic and inclusion criteria for chronic ITP were as those used by Difino et al (7) with some modification. These were:

1. Age 13 years or older
2. Documented thrombocytopenia with at least two platelet counts of 80,000/mm^3 or less
3. Normal to increased numbers of megakaryocytes on bone marrow aspirates

Patients were excluded from the study if they had:

1. Recently ingested a drug known to be associated with thrombocytopenia
2. Evidence of sepsis, disseminated intravascular coagulation or presence of severe microangiopathy on peripheral blood smear
3. An established diagnosis associated with destructive thrombocytopenia (e.g. - systemic lupus erythematosus (SLE), infectious mononucleosis or chronic lymphocytic leukaemia)
4. Evidence for a known cause of platelet sequestration (e.g. large spleen, vascular tumour)
5. Leukaemia, lymphoma or aplastic anaemia

The diagnosis was established in all patients by performing complete blood counts by manual methods. Peripheral blood smears and bone marrow aspirates were stained by Wright's stains, bleeding time, prothrombin and partial thromboplastin times were done by standard methods (14). In addition, direct and indirect antiglobulin (Coomb's) test, antinuclear antibody (A.N.A.) test, lupus erythematosus (L.E.) preparation, rheumatoid factor (R.F.), liver and renal function tests were done to exclude other causes of thrombocytopenia.

Initial therapy was with prednisolone 1.0-1.5 mg/kg body weight/day orally. In very few occasions it was raised to 2 mg/kg/day orally (15). Patients failing to respond to prednisolone or relapsing after its discontinuation were advised to undergo splenectomy. Splenectomies were performed in the Department of Surgery by one of us (O.J). Hydrocortisone 100 mg intravenously four hourly was given intra-operatively and up to forty-eight hours after surgery and then tapered off and switched to oral prednisolone if therapy with corticosteroids was deemed necessary. Immunosuppressive drugs used were: Vincristine 1.4 mg/m^2 intravenously weekly (16), cyclophosphamide 150 mg orally daily (17) and danazol 200 mg orally three times daily (18). Low doses (10-20 mg) of prednisolone were continued to maintain platelet

counts at about 50,000/mm^3 in patients with poor response to initial prednisolone or splenectomy (19).

The response to therapy was classed into four categories according to Bouroncle and Doan (20).

1. Excellent: complete clinical and haematological remission (platelet count $\geq$150,000/mm^3) maintained after discontinuation of prednisolone or splenectomy.
2. Good: Initial complete clinical and haematological remission but relapsing after discontinuation of therapy.
3. Fair: partial clinical and haematological remission, platelets increase to at least 50,000/mm^3 while on or after discontinuation of therapy.
4. Poor: no clinical or haematological improvement on or after discontinuation of therapy.

The age, sex, clinical findings, haematological, immunological, biochemical, bone marrow aspiration results as well as the responses to therapy were recorded prospectively and analysed. The Student 't' test was used to calculate the statistical significance of different variables related to response to therapy.

RESULTS

During the eight-year study period, thirty four cases of chronic ITP were seen. Twenty three were females and eleven were males, giving a female to male ratio of 2.1:1. The overall age range was 13-57 years with a mean of 24.9 years. The age range for females, 14-57 (mean 24.8) years was similar to that of males, range 13-54 (mean 25.1) years.

The clinical manifestations at presentation are shown in Table 1. In 25 (73.5%) patients easy bruising with or without bleeding at other sites was the presenting symptom. Three (8.8%) had only skin bleeding as the only symptom. The commonest signs were petechiae and ecchymoses in 31 (91.2%) and pallor in 25 (73.5%) cases. Twenty three (67.4%) required blood transfusion during the course of their illness. One (2.9%) patient had splenomegaly of 12 cm below the left costal margin. A 30 year old lady was pregnant at the time of presentation and subsequently delivered a live female baby weighing 3100 grams. The platelet count of the mother prior to labour was 210,000/mm^3. Six hours after delivery it was 110,000/mm^3 while the neonate's was 105,000/mm^3. After three days post-partum mother and child had platelet counts of 185,000/mm^3 and 175,000/mm^3 respectively. The mother was treated with prednisolone 15 mg/day to keep her platelet count at or above 50,000/mm^3. This was gradually tapered and discontinued.

A 20 year old young lady first presented with post-partum haemorrhage and skin bleeding. She had severe thrombocytopenia while the neonate had only mild thrombocytopenia which corrected spontaneously eventually. The mother was initiated on prednisolone therapy but failed to respond and subsequently had an excellent response to splenectomy.

Two teen-age girls first presented to gynaecologists with a history of menorrhagia for which they were treated with oral contraceptive pills with the diagnosis of dysfunctional uterine bleeding. Subsequently, they were diagnosed as ITP and were treated with prednisolone to which they responded well; their menstrual cycles and amounts of bleeding became normal.

The platelet counts at presentation ranged 4,00077,000/mm^3, (mean 19,200/mm^3). Thirty-two patients (94.1%) had platelet counts less than 50,000/mm^3. Fourteen (41.2%) had platelet counts less than 20,000/mm^3, while 9 (26.5%) and 7 (20.6%) had platelet counts 10,000-20,000/mm^3 and 20,000 -30,000/mm^3, respectively. Only two (5.9%) patients had platelet counts above 50,000/mm^3. The haemoglobin ranged from 3.0-15.4 gm/dl (mean 8.2 gm/dl). Twenty five (73.5%) had haemoglobin less than 11.0 gm/dl. The white blood

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cell count ranged from 3100-14,800/-mm^3 (mean 6865/mm^3), all with a normal differential count.

The peripheral blood smears showed "giant" platelets in the majority (88.2%) of the cases. The bone marrow aspirates showed normal erythropoiesis and myelopoiesis. In three cases (8.8%), there was eosinophilia without peripheral eosinophilia. In 25(73.5%) cases, the megakaryocyte number was increased with decreased platelet budding. In the remaining 9(26.5%), the megakaryocyte number was normal.

The Coomb's test, A.N.A, R.F., L.E. preparations, renal and liver function tests were negative or normal at presentation. A 26 year old lady became A.N.A. and L.E. preparation positive after three years of diagnosis of ITP while she was in complete remission on no treatment. She presented with puffiness of the face, leg swelling and scanty urine. She had high blood pressure, pericardial friction rub and anasarca. She had high blood urea nitrogen and creatinine. She was treated with antihypertensive drugs and prednisolone for systemic lupus erythematosus. Her platelet counts have remained normal.

Thirty patients were initially treated with prednisolone, four were not treated as they had minimal symptoms, and two had platelet counts above 50,000/mm^3. The response to therapy is shown in Table 2. One of the untreated patients went into spontaneous complete remission after five months of diagnosis. Subsequently, she became pregnant and gave birth to a live healthy baby in hospital. There was no recurrence of her ITP during pregnancy nor was there bleeding tendency in her offspring.

Of the thirty patients treated with prednisolone, 9(30%) had initial complete remission with 7(23.3%) continuing in complete remission, 6(20%) had a fair response while 15(50%) had poor response. Ten patients including poor responders and those who relapsed after prednisolone discontinuation underwent splenectomy. Seven were females and three were males. A 16 year old male who had splenectomy for prednisolone resistant AIHA at the age of 10 years is not included in the splenectomy group. Seven (70%) of patients who underwent splenectomy had an initial good response with five (50%) remaining in complete remission.

The patient who had splenectomy as a child for AIHA was unresponsive to high doses of prednisolone, i.e. 2 mg/kg/day. He was treated with Vincristine and cyclophosphamide. Danazol was subsequently added. He had an increase in platelet count to 50,000/mm^3 in the first week and to more than 150,000/mm^3 in the second week of therapy. He received three doses of Vincristine, cyclophosphamide was given for three months and danazol for four months. While on these drugs, the prednisolone was being tapered off and subsequently discontinued. Now he is still in complete remission four and a half years after the diagnosis of ITP.

The responses were analysed for different variables, i.e., age, sex and duration of symptoms at presentation. There was no significant difference between responders and non-responders for prednisolone in the above mentioned variables, ($p>0.35$). However, there was significant difference in response to splenectomy in young and older patients, ie, the mean age for responders was 19 years compared to mean age of 35 years for nonresponders and partial responders ($p<0.0005$).

As of December 1989, fifteen patients are alive and on follow-up, 3-122 (median 33) months after diagnosis. Nine are in continuous complete remission; four after prednisolone and five after splenectomy. Four are in partial remission on prednisolone 10-20 mg daily; two after prednisolone and two after splenectomy. Two are in relaspe; both were initially not treated. Fifteen patients are lost to follow up 1-66 months (median 9 months) after diagnosis. Five were

in continuous complete remission, eight partial remission and two in relapse.

Four patients died in hospital 118 months (median 2 months) after diagnosis. One patient was in continuous complete remission after prednisolone therapy for 16 months. She developed an acute febrile illness of undetermined cause and died due to septic shock four days after admission. A 26 year old male, a poor responder to prednisolone awaiting splenectomy, suddenly developed intracranial haemorrahge and died. A 20 year old male had splenectomy with good response, developed hospital - acquired pneumonia and died from it six weeks after surgery. A 47 year old female had undergone splenectomy, failed to respond and died of continuous bleeding irrespective of high doses of prednisolone and transfusions.

There were no surgery associated deaths (ie, deaths within 24 hours of surgery). There was no significant bleeding intraoperatively, only a few patients were transfused with platelet concentrates. No infection with *Streptococcus pneumoniae* was encountered in our post-splenectomy patients, although we did not use pneumococcal vaccine due to its unavailability.

DISCUSSION

Chronic ITP is diagnosed by excluding other disorder that may be associated with thrombocytopenia; drugs, SLE, infections, mainly viral, leukaemia, lymphoma, evidence of disseminated intravascular coagulation and hypersplenism (5,7,19,22). The clinical features, response to therapy and course of this disorder are fully described in large series in Caucasians (7,19,22,23,24). There are ony a few cases of chronic ITP reported from Africa in African populations (8,9,10). In Ethiopia also, very few cases were reported before the 1980's (11,12) without any detailed description. The current communication included the sixteen cases reported previously (13) and has attempted to present details of clinical and haematological features as well as the response to therapy and outcome of follow-up.

The clinical and haematological presentations of our patients are similar to those reported in the Caucasians (7,19,22-24) and Kenyans (10). The mean age of our patients (24.9 years) is lower compared to those of the Caucasians (by over 10 years), but similar to those of the Kenyans (28.7 years). The lower mean age in our patients compared to that of the Caucasians may be the reflection of the age strata of the respective populations. The sex ratio of female to male of 2.1:1 is similar to those reported in other series (7,10,19,22-24). The commonest presenting symptom was subcutaneous bleeding with or without bleeding from other sites in 25(73.5%) cases, while 31(91.2%) cases had petechiae and ecchymoses on examination. These findings are similar to those found in Caucasians but higher than that found in Kenyans (10). In the American series, ITP is said to be uncommon in American Negroes and the reason given was that it was difficult to detect subcutaneous bleeding due to the deep pigmentation of the Negro skin (6,7); and the same was said to possibly be the reason for paucity of ITP cases in Kenyans (10). Anaemia is said to be rare in ITP patients in western literature (3,4,7,19,22), but was a common finding, at presentation, in our series as was the case with the Kenyan series where anaemia was present in 90.5% of the cases (10). Splenomegaly is a rare finding at presentation. Doan et al (21) found splenomegaly in 2.6% while Jiji et al (19) found it in 1.1%, and Thompson et al (23) found it in 4.5%, which are comparable to our finding of one case (2.9%).

The mean platelet count at presentation was 19,200/mm^3; this was lower compared to 32,800/mm^3 from Kenya, (10), similar to the 18,500/mm^3 by Thompson et al (23) but higher than 5,700/mm^3 reported by Difino et al (7). In our series, 32 (94.1%) had platelet counts of less than 50,000/mm^3 while only 2 (5.9%) had greater than 50,000/mm^3 but less than 80,000/mm^3. Platelet counts

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less than 50,000/mm^3 are said to be insufficient to support challenged haemostasis (3,7). The bone marrow findings of normal to increased number of megakaryocytes with abscence of platelet budding, lack of segmentation of the nucleus and lack of granularity of the cytoplasm are said to be a reflection of an increase in megakaryocyte turnover due to peripheral platelet destruction (1).

Thirty patients in this series were initially treated with prednisolone while four were observed without treatment. The indications were platelet counts of less than 50,000/mm^3 and bleeding from mucous membranes. Of the untreated patients, a 14 year old girl went into spontaneous complete remission after five months of follow-up. She subsequently became pregnant and delivered a normal female baby. Spontaneous remissions are known to occur in ITP. Thompson et al (23) found a 4.5% spontaneous complete remission among 66 patients. Patients are known to relapse in pregnancy (7), but our patient did not relapse during or after pregnancy.

Of the thirty patients initially treated with prednisolone, 2(6.7%) had a good response and 7(23.3%) had an excellent response. These results are comparable to those of other studies (7,19,22,23) (Table 3). The response to prednisolone was analysed for age, sex and duration of symptoms before initiation of therapy. There was no significant difference ($p>0.35$) in responses with above variables. Difino et al (7) had observed that patients who present within two weeks of onset of symptoms had a favourable response to prednisolone compared to those who presented after two weeks, other investigators did not find such an association (19,2,23).

Ten patietns underwent splenectomy. Two (20%) had a good response, 5(50%) had an excellent response. Again, this response rate is similar to those of other reports (Table 3). Response to splenectomy was associated with the age of the patients at presentation. The mean age of the responders (19 years) was significantly lower than the mean age of the partial and non-responders (35 years) ($p<0.0005$). This was also the observation of Difino et al (7). Patients who failed to respond or relapsed after splenectomy were treated with low dose (10-20 mg) of prednisolone indefinitely (19).

A 16 year old male who had splenectomy at the age of 10 years for prednisolone resistant autoimmune haemolytic anaemia had refractory ITP to high doses of prednisolone. He was treated with vincristine, cyclophosphamide and danazol in doses mentioned above. He responded starting in the first week of immunosuppressive therapy; we have ascribed the response to possibly vincristine which is said to induce remission early - within 7-10 days of initiation of therapy. vincristine is said to have both an immunosuppressive and thrombocytotic effects (16). Cyclophosphamide is also used and reported to have induced remissions in refractory ITP cases, but the effects were observed after two to four months of therapy (17). Danazol, an androgen with less virilizing effects, was reported to have induced remissions in 70-80% of patients with refractory ITP in small series of patients (18). Our patient is also interesting in that he might have had AIHA and immune thrombocytopenic purpura (Evan's syndrome) (24) as a child, which responded to splenectomy. The indications for splenectomy at that time were said to be for AIHA and hypersplenism, because he had splenomegaly of 10 cm below the left costal margin and thrombocytopenia.

SLE is said to develop in some patients with ITP two to three years after splenectomy (3). Early workers had claimed that splenectomy for ITP accelerated the expression of SLE or activated a "dormant" form of the disease (25). This claim has been challenged, however, and not accepted by most workers in the field (22). One of our patients deve-

loped SLE after three years while in remission without undergoing splenectomy.

The management of ITP in pregnancy is of some concern as it affects both the mother and the fetus. Neonates born to mothers with ITP, active or in remission, are said to develop thrombocytopenia in most instances (3). There is no good parameter to predict which neonate will develop thrombocytopenia. The risk of intracranial haemorrhage is increased if thrombocytopenic fetuses are delivered vaginally. Therefore, some authorities recommend an elective Cesarean section (26) while others recommend vaginal delivery unless there is some recognized obstetrical indication for section (27). In our series, the one patient who had ITP during pregnancy, delivered vaginally a normal female baby. Both mother and neonate had satisfactory platelet counts at delivery.

In conclusion, chronic ITP is frequently seen among adult Ethiopians; its clinical and haematological presentations and response to therapy are similar to other African and western patients.

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TABLE 1. Clinical findings at presentation in 34 chronic ITP patients

Symptoms	Frequency (out of 34)
Purpura	25
Epistaxis	22
Gum bleeding	15
Menorrhagia	11
Melena	3
Haematemesis	2
Haematuria	1
Post-partum haemorrhage	1
Signs	
Petechiae and ecchymoses	31
Pallor	25
Gum bleeding	9
Bullae	3
Subconjunctival haemorrhage	1
Splenomegaly	1

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TABLE 2. Response to therapy in 34 chronic ITP patients

Therapy	No. of patients	Response			
		Excellent	Good	Fair	Poor
None	4	1	-	2	1
*Prednisolone	30	7	2	6	15
Splenectomy	10	5	2	2	1
Prednisolone + Immunosuppressants	1	1	-	-	-
Total		14	4	10	17

*Initially treated with prednisolone

TABLE 3. Therapeutic response of ITP in previous and the current series

	Meyers(22)	Thompson(23)	Jiji(19)	Difino(7)	Current series
Year	1961	1972	1973	1979	1989
Age (yrs)	>13	>14	>10	>16	>13
Prednisolone therapy					
Number	71	57	92	59	30
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Good response	31 (44)	13 (23)	22 (24)	25 (42)	2 (6.7)
Excellent response	10 (14)	13 (23)	21 (23)	13 (23)	7 (23.3)
Reinduction excellent response	0 (0)	4 (7)	5 (6)	3 (5)	1 (3.3)
Total excellent rsponse	10 (14)	17 (30)	26 (29)	16 (28)	8 (26.7)
Splenectomy					
Number	54	31	51	37	10
Good rsponse	47 (67)	22 (71)	44 (86)	27 (63)	2 (20)
Excellent response	45 (83)	20 (65)	34 (67)	18 (49)	5 (50)
Postsplenectomy steroids excellent response	-	-	2 (?)	2 (25)	-
Prednisolone and Immunosuppressants	-	-	-	-	1 (3.3)
Accessory splenectomy	-	-	-	3 (60)	-
Total excellent response	55 (77.5)	37 (65)	62 (68)	39 (68)	14 (46.7)

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Low HTLV-1 seroprevalence in endemic tropical spastic paraparesis in Ethiopia

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Abstract

Tropical spastic paraparesis (TSP), a chronic progressive myelopathy, occurs in Ethiopia in epidemic form as neurolathyrism, while the endemic form has remained obscure. We describe the clinical features of 22 patients with TSP and the results of screening for HTLV-1 in these patients, 26 patients with other neurological disorders, 14 patients with leukaemia and 66 blood donors. The major manifestations in the patients with TSP were weakness and spasticity of the lower limbs with upper motor neurone signs and minimal sensory loss and bladder dysfunction. Two patients with TSP (9%), 2 patients with other neurological disorders (7·7%) and one patient with leukaemia and deafness were seropositive for HTLV-1. All the 66 blood donors were seronegative. Our results suggest that HTLV-1 may not play a major role in the pathogenesis of TSP in Ethiopia.

Introduction

Tropical spastic paraparesis (TSP) is a chronic condition of gradual onset manifesting as weakness and stiffness of legs, with clinical findings of spasticity, hyperactive tendon reflexes, bladder disturbance and minimal sensory loss. Tropical myeloneuropathies have been associated with nutritional deficiencies (CRUICKSHANK, 1976) and cyanide toxicity (OSUNTOKUN, 1981; CASEDI *et al.*, 1984), but obscure myelopathies have also been commonly encountered (MONTGOMERY *et al.*, 1964; MANI *et al.*, 1969; BADEMOSI & OSUNTOKUN, 1982; ROMAN *et al.*, 1985). Hospital experience and a clinical study (JENIK *et al.*, 1981) indicate that spastic paraparesis of undetermined cause is not uncommon in Ethiopia. Epidemic outbreaks of spastic paraparesis due to neurolathyrism have been reported from the north-western part of Ethiopia (GEBRE-AB *et al.*, 1978).

Recent studies from areas such as the Caribbean, Colombia, Seychelles, West African and southern Japan have linked the endemic form of TSP with human T-lymphotropic virus type 1 (HTLV-1) (GESSAIN *et al.*, 1985; RODGERS-JOHNSON *et al.*, 1985; ROMAN *et al.*, 1987; GESSAIN *et al.*, 1986; OSAME *et al.*, 1987). Myelopathy associated with HTLV-1 has also been reported from non-endemic areas such as the United Kingdom and France (CRUICKSHANK *et al.*, 1989; GOUT *et al.*, 1989). Except for a case report of TSP probably associated with HTLV-1 in an Ethiopian naturalized in Sweden (RYBERG *et al.*, 1987), there has not been a study to show the causative relationship in Ethiopia. We studied 22 Ethiopian patients with TSP investigated at the main referral hospital in Addis Ababa.

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Materials and Methods

Twenty-two patients with spastic paraparesis admitted to Tikur Anbesa teaching hospital in Addis Ababa from January 1985 to September 1988 were included in this study. Patients diagnosed as having TSP had the following characteristics: a history of gradual progression of weakness in the legs within 6 months of onset of illness, bladder dysfunction, numbness or burning pains in the legs, and absence of relapses. Clinical findings included spastic legs, hyperactive deep tendon reflexes, and absence of sensory level. All had normal myelographic studies.

Laboratory investigations included complete blood count, haemoglobin determination, erythrocyte sedimentation rate (ESR), venereal disease research laboratory test (VDRL), brucella titre, urine analysis, stool examination, tuberculin skin test, X-ray of chest and spine, cerebrospinal fluid (CSF) analysis, and serological testing for HTLV-1 and human immunodeficiency virus 1 (HIV-1).

Twenty-six patients with other neurological diseases, 14 patients with leukaemia seen at the hospital during the same period and 66 blood donors also underwent serological testing. Of those with neurological disorders, 8 had Guillain-Barré syndrome, 5 had peripheral neuropathies, 3 had motor neurone disease, 3 had primary optic atrophy, 2 had spastic paraparesis of acute onset, and one each had transverse myelitis, acute brachial plexitis, intracranial tuberculoma, neurofibroma and cauda equina lesion.

Serological studies

Sera collected from 46 patients and 30 control subjects (14 leukaemics and 16 blood donors) were frozen in dry ice and shipped to the Virology Department of Umea University, Sweden, where the analysis was made. Analysis of the sera of 2 patients with TSP and 50 blood donors was done at la Laboratoire de Bacteriologie-Virologie, Hôpital Universitaire Dupuytren, Limoges, France. Sera were first heat-inactivated by incubation at 56°C for 45 min. The sera studied in Sweden were tested for the presence of anti-HTLV-1 antibodies using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Dupont de Nemours, Wilmington, Delaware, USA). The sera were diluted 1:20 in dilution buffer and incubated in HTLV-1 coated microtitre plate wells for 60 min at 37°C. The wells were then washed and incubated with alkaline phosphatase-conjugated goat anti-human immunoglobulin G(IgG) antibodies for 30 min at 37°C, and the results

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visualized by incubation with substrate solution (p-nitrophenylphosphate). Sera repeatedly reactive in the ELISA were verified by immunoblotting, using a commercially available immunoblot assay (Dupont de Nemours). Briefly, sera were incubated overnight with nitrocellulose filter strips containing HTLV-1 peptides. The reactivity of sera with individual HTLV-1 peptides was demonstrated by the successive treatment of the strips with biotin-labelled rabbit anti-human IgG, avidin-conjugated horseradish peroxidase, and substrate.

The analysis in Limoges was performed as follows: the sera were screened comparatively by 2 techniques; indirect immunofluorescence assay (IF) using HUT 102 clone B2 (GESSAIN *et al.*, 1985) and enzyme immunoassay (HTLV-1 EIA, Abbott Laboratories, Chicago, USA). All positive sera and those doubtful by at least one of the 2 techniques were submitted to Western blotting using HUT 102 clone B2 cells. IF was done according to methods described by VERDIER *et al.* (1989).

Sera were considered to be reactive for HTLV-1 if they reacted with at least the P19 and the P24 antigens. Two sera which reacted with the P24 antigen only were considered to be cross-reactive with HIV-1 since they also expressed strong anti-HIV-1 activity. All samples were screened for antibodies against HIV-1 antigen by ELISA (Behringwerke, Marburg, Federal Republic of Germany) and positive serum samples were confirmed by immunoblotting (Dupont de Nemours).

Results

The clinical characteristics of the 22 patients (16 male and 6 female) with TSP are summarized in Table 1. Their mean age was 30·6 years (range 18–47 years). 15 patients came from different rural parts of the country, while 7 were from the city of Addis Ababa. Although most of the patients were from low socio-economic groups their nutritional status was fairly good. Three patients admitted consumption of chick-ling pea, the neurotoxic seed *Lathyrus sativus*. None of the patients had received a blood transfusion before the onset of their illness and there was no intravenous drug user among them. There was no history of similar illness in the families of the patients.

Only 2 patients with TSP (Table 1) and 3 patients with Guillain-Barré syndrome, neurofibroma of the thoracic spinal cord, and leukaemia with bilateral deafness (Table 2) showed a high titre of anti-HTLV-1 antibodies in their sera. Antibodies against HIV-1 were detected in 7 patients, 4 with Guillain-Barré syndrome, and one each with acute peripheral neuropathy, motor neurone disease, and acute myelopathy. None of the patients with TSP were seropositive for HIV-1.

Other laboratory tests on the patients with TSP did not show any consistent abnormality. ESR was elevated in 4; and parasites (*Ascaris lumbricoides*, *Entamoeba histolytica* and *Giardia lamblia*) were seen in the stools of 8 patients. Tuberculin skin tests were strongly positive in 16 patients (72·7%), which is similar to the rate found in the general population (TEKLU, 1988). None of the patients had positive serum VDRL. CSF cells, 5–50/mm^3, were found in 3 patients (13·6%) with mildly elevated protein levels

Table 1. Clinical characteristics of 22 patients with tropical spastic paraparesis

Sex ratio (male:female)	2·7:1	
Mean age at onset (years)	26·6	(15–42)*
Mean duration of disease (years)	3·5	(1–10)*
Pyramidal signs (legs)	22/22	
Sensory signs (legs)		
Touch and pain sensitivity impairment	4/22	
Vibration and position sense impairment	5/22	
Urinary disturbance		
Absent	7/22	
Frequency and urgency	12/12	
Incontinence or retention	3/22	
Cerebrospinal fluid pleocytosis	3/22	
HTLV-1 antibodies (positive)	2/22	
HIV-1 antibodies (positive)	0/22	

*Range.

Table 2. HTLV-1 and HIV-1 serological studies in neurological patients and controls

Clinical diagnosis	Seropositive HTLV-1	Seropositive HIV-1	No. of cases
Guillian-Barré Syndrome	1	4	8
Acute peripheral neuropathy	–	1	5
Motor neurone disease	–	1	3
Primary optic atrophy	–	–	3
Acute myelopathy (spastic paraparesis of acute onset)	–	1	2
Transverse myelitis	–	–	1
Acute brachial plexitis	–	–	1
Intracranial tuberculoma	–	–	1
Neurofibroma, thoracic spinal cord	1	–	1
Cauda equina lesion	–	–	1
Leukaemia	–	–	14
Blood donors	–	–	66
Total	3	7	106

(40–60 mg/dl); spinal X-rays and myelograms were normal in all of them.

Case report

L.G. was a 38-year-old Ethiopian male of middle socio-economic status, who was healthy until 10 years before the onset of a slowly increasing weakness in the legs. This was followed 6 months later by numbness in his feet and urinary urgency. He developed impotence over the last 5 years. On admission to the hospital in May 1985 he was found to have weakness of the legs with spasticity but no sensory deficit. His laboratory studies were normal except for *E. histolytica* trophozoites in his stool. CSF studies showed 5 mononuclear cells/mm^3, protein level of 45 mg/dl and glucose of 90 mg/dl. Serological tests for *Brucella melitensis* and syphilis were negative. Nerve conduction studies were within normal limits. Myelogram showed no abnormality. HTLV-1 antibodies were detected in the serum (titre 1/5000) and CSF (titre 1/80). On Western blot analysis the serum showed specific bands against the HTLV-1 specific polypeptides P19, P24 and P26. The IgG index (the index for intrathecal synthesis of IgG) was normal according to the formula of LINK & TIBLING (1977). The serum of the patient's wife showed a high titre of antibodies to HTLV-1 (1/2500). The sera of the patient and his wife were negative for HIV-1 anti-

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bodies. Lymphocyte study of the patient's peripheral blood smear showed irregularities of the nuclei and chromatin pattern in some cells. The patient showed no improvement on high dose corticosteroid therapy.

Discussion

An epidemic form of spastic paraparesis has been reported from Ethiopia (GEBRE-AB *et al.*, 1978), due to consumption of chickling pea (*L. sativus*), a hardy crop cultivated during drought. The neurotoxin from this seed, β-N-oxalylamino-L-alanine (BOAA), is considered to be the causative agent of neurolathyrism (SPENCER *et al.*, 1986).

Endemic forms of TSP are commonly seen in hospital practice, and in most cases the cause is unclear. Patients with TSP also come from areas of the country where *L. sativus* is not cultivated and malnutrition is not a serious problem. In the 3 patients in this series who had consumed chickling pea, the amount was small and over a short period. It was therefore not very likely to have been responsible for the paraparesis.

An investigation (JENIK *et al.*, 1981) of Ethiopian patients with spinal cord syndromes (non-traumatic adhesive arachnoiditis) did not reveal a major aetiological agent. Diagnosis of post-inflammatory arachnoiditis was made on myelography in some of these patients. A therapeutic trial made on suspicion of tuberculosis and syphilis as possible causes had unsatisfactory results.

The characteristic features of TSP in Ethiopia appear to be similar to those described from other tropical areas (ROMAN, 1988; MORGAN *et al.*, 1988). The male preponderance (2.7:1) in our series may not be a true picture because, in our experience, male patients are more likely to come from rural areas to major hospitals in the cities. Other reports suggest that women tend to seek medical attention more often than men (ROMAN *et al.*, 1985).

A serological survey in Israel showed a high prevalence of HTLV-1 antibodies (37%) in Falashas, Ethiopian Jews who had recently immigrated to Israel from the rural highlands of northern Ethiopia (BEN-ISHAI *et al.*, 1985). This was a higher prevalence of seropositivity than that reported from different parts of Africa (SAXINGER *et al.*, 1984). However, two other studies on 10 sera (KARPAS *et al.*, 1986) and 259 sera (WEISS *et al.*, 1986) from Falasha immigrants to Israel did not reveal any HTLV-1 reactivity.

The present study showed a low prevalence of HTLV-1 antibodies in patients with TSP (9%) and other neurological disorders (7·7%), and in the control group of blood donors and leukaemic patients (1·3%). The mean prevalence of HTLV-1 antibodies in sera of patients with TSP from Jamaica, Tumaco, Martinique and Seychelles was 80% (ROMAN *et al.*, 1987). The seropositivity in the 5 Ethiopian patients is unlikely to be a mere chance association as more patients with neurological diseases had positive results than the control group. Two of the 5 HTLV-1 positive patients had classical TSP. Another patient had chronic myelogenous leukaemia with unexplained bilateral deafness of recent onset. The fourth patient presented with clinical findings, CSF analysis and electrophysiological studies diagnostic of Guillain-Barré syndrome. The last patient had neurofibroma of the thoracic spinal cord and made a remarkable improvement after surgery; this could well have been a chance association. A number of studies have evaluated the association between HTLV-1 and various degenerative and inflammatory disorders of the nervous and muscular systems. According to some of these studies, HTLV-1 does not seem to be related to chronic neurological disorders other than TSP (LOLLI *et al.*, 1987; MORA *et al.*, 1988). However, it has also been shown that in some patients chronic myeloneuropathy diagnosed as chronic progressive multiple sclerosis, chronic progressive myelopathy, or chronic inflammatory polyradiculoneuropathy may be associated with HTLV-1 or related retroviruses (KAWANISHI *et al.*, 1989).

Seven of the patients in our series with neurological disorders had HIV-1 infection (26·9%), 4 of whom had Guillain-Barré syndrome. One patient had acute myelopathy, and another had acute peripheral neuropathy. The last patient presented with a typical clinical and electromyographical picture of motor neurone disease of recent onset. In our hospital experience the frequent neurological complications of HIV-1 infection are acute neuropathies, particularly Guillain-Barré syndrome, and acute myelopathies rather than subacute encephalitis, which is considered to be the most frequent cause of neurological dysfunction (GABUZDA & HIRSCH, 1987).

Although several studies have demonstrated the neurotropism of HTLV-1 and a clear association with TSP by demonstrating intrathecal synthesis of IgG antibodies to HTLV-1 and detection of HTLV-1 deoxyribonucleic acid (DNA) sequences in patients with TSP and through viral isolation (CERRONI *et al.*, 1988; BHAGAVATI *et al.*, 1988; JACOBSON *et al.*, 1988), this study indicates that a single aetiological agent may not be responsible for TSP in Ethiopia. As suggested by others, the search for HTLV-1 clues may not have to be restricted to assay for HTLV-1 antibodies in patients with chronic neurological diseases, as negative serology in retrovirus infection is not unusual (KAPROWSKI & DE FREITAS, 1988). With the new genetic method of the polymerase chain reaction some HTLV-1 negative sera, such as those in this study, may be shown to contain fragments of HTLV-1 DNA (EISENSTEIN, 1990).

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ATTITUDES OF RURAL PEOPLE IN CENTRAL ETHIOPIA TOWARD EPILEPSY

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Abstract—In the farming community of the sub-district of Meskan and Mareko in central Ethiopia, where the prevalence of epilepsy is known to be 5.2/1000, a door-to-door survey was undertaken in 1546 sampled households to find out public attitudes to epilepsy. Nearly 64% of the respondents were in the age group of 14–50 years, and 58.6% were women. The majority (86%) were illiterate, and 94% had incomes of a subsistence level; 89% had heard or witnessed seizures. Traditional views on the association of evil spirits and superstition was prevalent. By 45% of the interviewees, the disease was believed to be contagious through physical contacts during an attack. Although there was sympathetic concern in the community for the person suffering from epilepsy, negative attitudes were strong on matrimonial associations, sharing of accommodation and physical contacts with affected persons, particularly when there were obvious signs and frequent attacks by seizures. The study demonstrates that the rural community has very poor knowledge of the causes and nature of epilepsy, and this has resulted in social deprivations and at times, rejection of the sufferers.

Key words—epilepsy, knowledge, attitudes, 'evil spirit', Africa

INTRODUCTION

In African communities there are widespread beliefs that epilepsy is due to possession or bewitchment by evil spirits or the devil, and in some of the cultures the spirit is believed to be those of ancestors [1–6]. There are also beliefs that the transmission of the disease is by physical contact, such as by saliva [7–9]. In central Uganda, epilepsy is attributed to the presence of a lizard in the brain, and epileptic falls occur whenever the lizard moves [10]. Therefore, attitudes toward epilepsy and the person with epilepsy in indigenous Africa are invariably unfavourable, because they reflect the mythical beliefs about the disease.

As in Africa at large, excluding infections of the central nervous system, epilepsy is the most common neurological disorder in Ethiopia [11]. Besides its high prevalence, epilepsy, like leprosy, carries a strong social stigma, and those afflicted by it can become ostracized by the society. While Giel has reported on the social consequences of the disease in Ethiopia [12], there has been no detailed study of public attitudes to it. This study addresses itself to this question.

MATERIALS AND METHODS

Between 1986 and 1988 an epidemiological study of neurological disorders was carried out in the rural sub-district of Meskan and Mareko (population 181,883) covering an area of 1500 km² in the Shoa Administrative Region of central Ethiopia. The town of Butajira is the administrative centre of the sub-district. At the time of the survey, the sub-district comprised 6 urban dwellers' associations and 82 peasant associations. There was a total of about 40,000 households in the sub-district, with an average family size of 4.5 members.

A 30% random sample of the peasant associations was taken and all the urban dwellers' associations were surveyed. The study thus included 25 of the 82 peasant associations and all the three towns within the sub-district, involving 60,820 inhabitants in 13,460 households. Eighty-nine per cent of the inhabitants were from the Gurage ethnic group, while the rest were from the Kembata, Oromo, Amhara and Tigre ethnic groups.

Following the Ethiopian Agrarian Reform Proclamation of 1975, farmers were organized into peasant associations while the inhabitants of the towns and cities were brought under the urban dwellers' associations. Thus, when the study was started, 17 of the 25 peasant associations selected for the survey were villagized into nucleated settlements and 4 more got villagized during the study period. The remaining 4 villages, all in the highlands, were still not villagized at the end of the survey because of their heavy dependence on the onset (Enset ventricosum) diet. The enset, is a false banana which takes about 5 years to mature for consumption. The staple diet of the Gurage people, kocho, is produced from the core of the underpart of the plant.

In the survey, trained lay health-workers were employed as enumerators to administer specially designed questionnaires to detect neurological symptoms and signs and used in a community-based study in the same area [11].

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Concomitant with this exercise, the lay health workers were also trained to interview adults, mainly heads of households, on their opinions of common neurological disorders that may carry significant negative and unfavourable attitudes in the community. These disorders were mental retardation, physical handicap, leprosy and epilepsy. In order to avoid confusion, every fourth household of all the randomly selected villages in the study area was interviewed on each of the disorders. This resulted in the inclusion of 1546 households for the epilepsy attitudinal survey.

The enumerators were secondary school graduates who came from the villages (8) and the town of Butajira (5). There were 11 males and 2 females with ages ranging from 26 to 31 years. Ten belonged to the Gurage and one each of the Amhara, Kembata and Oromo ethnic groups. All were able to speak at least one of the Gurage dialects.

The questionnaire used for the study is shown in the Appendix. The questions were made as simple and straightforward as possible and translated into Amharic, the Ethiopian official language. To avoid bias and get as much information as possible, the questions were constructed to encourage open answers. In order to ensure a uniformity of response during the door-to-door interviews, the enumerators were instructed how to translate the questions into the language of the respondent in a standardized manner. Before the administration of the questionnaire, the aims and purpose of the study was clearly explained to the respondents. There was a 94% participation in the interviews.

The chi-square test (with Yates' correction) was used for test of independence between two variables.

RESULTS

Different names were used for epilepsy in the community. The most common were azurit, zewur, tchot, eldoa and enquliyet in the different Gurage dialects. Gegebdo and tchote were used in the Kembata and Oromo languages respectively. All the terms refer to the 'spinning' effect and/or the accompanying fall of the disease, as perceived by the respondents. In the Tigre language it is called as heman baria (the slave's illness). Yemitil beshita (the falling sickness), as it is commonly known in the official language, Amharic, was used by only 10% of the respondents.

Table 1. Characteristics of respondents

Characteristics		No.	%
Age (yr)	14–25	206	14.2
	26–35	377	26.0
	36–45	338	23.3
	46 +	531	36.5
Sex	Male	606	41.6
	Female	850	58.4
Religion	Christian	674	46.3
	Moslem	781	53.7
Marital status	Married	1147	78.8
	Widow/widower	162	11.2
	Single	76	5.2
	Divorced	70	4.8
Level of education	Illiterate	1240	85.2
	Read and write	120	8.2
	Grade 2–8	75	5.2
	Grade 9 and above	21	1.4
Occupation	Farmer	1267	87.0
	Housewife	75	5.1
	Merchant	37	2.5
	Labourer	29	2.0
	Dependent	27	1.9
	Student	13	0.9
	Government employee	9	0.6

As summarized in Table 1, 63.5% of the respondents were in the age range of 14–45 years. Their major occupation was farming (86.7%), and the men were often in the fields when the lay heath-workers made their door-to-door visits. Thus, there were more females (58.4%) among the respondents. There were slightly more Muslims (53.7%) than Christians. The majority of the respondents (78.8%) were married, with children; 85% were illiterate (those who could not read or write), and those that were literate obtained their skill from church and regular schools as well as through participation in the literacy campaign. Only 1.4% had secondary school education. The vast majority, 94% had incomes at subsistence level (U.S. 120 dollar per annum) and only 1% could be classified as well-to-do.

As shown in Table 2, 89% of those interviewed stated that they had heard or read about epilepsy; 86% had witnessed a seizure attack during their lifetime; 14% admitted that they had a family member with epilepsy.

Table 2. Public response to attitudinal questions

Question	Response number	Answer: Yes (%)	No (%)	Don't know (%)
Have you heard or read about epilepsy?	1441	89.0	11.0	—
Have you seen someone with seizure attack?	1338	86.2	13.8	—
Do you have a family member with epilepsy?	1332	14.3	85.7	—
Is epilepsy hereditary?	1274	4.9	95.1	—
Is epilepsy contagious?	1269	44.6	53.4	2.0
Is epilepsy a form of insanity?	1265	1.9	98.1	—
Would you employ an epileptic?	1254	25.0	75.0	—
Are you willing to work with an epileptic?	1257	52.7	46.1	1.2
Would you house a person with epilepsy under pressure?	1260	67.2	32.2	0.6
Do you think a person with epilepsy should be hidden from public?	1262	1.8	98.2	—
Would you allow an epileptic to use public transport?	1262	90.1	9.1	0.8
Would you shake hands with an epileptic?	1262	90.8	9.2	—
Would you have a person with epilepsy as a friend?	1259	40.6	58.3	—
Do you object to your own child associating with persons with epilepsy?	1254	65.1	33.9	—

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Table 7. Attitudes toward epilepsy among urban and rural inhabitants

Question	Urban	Rural	P value
Causes of epilepsy:			
Don't know	85.7	79.9	
Evil spirit	12.4	17.6	0.11
Other	1.9	2.5	
Inheritance:			
Inherited	5.0	4.9	0.86
Not inherited	95.0	95.1	
Contagiousness:			
Yes	40.4	30.0	0.01
No	57.1	68.0	
Don't know	2.5	1.8	
Attitudes to marriage:			
Positive	25.0	26.0	0.94
Negative	71.2	72.9	
Don't know	3.8	1.1	
To work with epileptic:			
Positive	70.2	53.9	<0.001
Negative	25.5	45.5	
Don't know	4.3	0.6	
Allow own child to play with epileptic:			
Yes	50.9	67.7	0.001
No	45.4	32.7	
Don't know	3.7	0.6	
Employ epileptic:			
Yes	23.0	25.3	0.60
No	77.0	74.7	
Suggested treatment:			
Traditional	3.7	0.1	
Holy water	1.9	0.2	
Conventional	8.8	0.6	<0.001
Don't know	85.6	99.1	

play with persons with epilepsy. On the other hand they were more positively inclined to work with a person having the disease. As with educated respondents more of the urban inhabitants were willing to use modern medicine for the management of the disease.

DISCUSSION

People in rural communities in Africa perceive epilepsy as a feared and dreaded disease because of its alleged association with evil spirits and witchcraft. As a result of these traditional beliefs and superstitions, the person with epilepsy in Africa suffers from social deprivation and prejudice. In Ethiopia, as in other African countries, the person with epilepsy faces serious social stigmatization and may even be ostracized by society.

Many who have read the very descriptive reports of Giel on the epileptic outcast in Ethiopia [12] have been led to believe that all or most Ethiopians with epilepsy are outcast and banished to their fate in churchyards and cemeteries. This survey indicates that the attitude picture towards epilepsy in rural Ethiopia is not as pronouncedly negative as described. The special situation where rejection does occur is when an epileptic has uncontrolled seizures resulting in severe burn deformities and/or profound mental retardation [13]. In this respect, the situation in Ethiopia is not different from that in other African countries. For instance, writing about Tanganyika in 1959, Smart [4] has clearly identified the "demented and anti-social groups of epileptics" that constituted 12% of admissions to mental hospitals.

As evidenced by this study there is also a 'time-limited' form of rejection during seizure attacks. This is exemplified by the fact that 50% of the respondents in this study admitted that they would instruct their children to run away from playmates who develop seizure attacks which points to the belief of respondents on the contagious nature of the disorder.

The response of the interviewees from the rural community during our recent survey has succeeded in registering the prevalent beliefs on and attitudes toward epilepsy. Concerning the background of the community studied, it should be noted that the characteristics that were most relevant to our attitudinal study were the high illiteracy rate of 85%, and the prevalence of epilepsy in the community (5.2/1000), where the majority of those suffering from epilepsy were not receiving anticonvulsant treatment. Because of the close social contacts and interactions within the community, the majority of the respondents to the door-to-door interviews had witnessed seizure attacks, but were not aware of the causes of the disease.

Although epilepsy was still feared and dreaded in the rural community studied, we were impressed by the fact that the respondents showed reasonable understanding and tolerance to the person with epilepsy, particularly if the sufferer did not exhibit aggressive tendencies and did not have other signs of affection by the disease. There was a particular sympathy for children with the disease, both from parents and the general public. It is interesting that more people (65%) were willing to allow their children to play with peers having epilepsy, compared to the experience of Dada and Odeku [14] in Nigeria, where 84–93% of respondents in two studies opposed such an association.

In addition, 98% of the respondents in this study did not believe that the person with epilepsy should be concealed from the public, and only 2% thought the disease to be a form of insanity. The great majority of the respondents stated that they would allow the person with epilepsy to use public transport, and were also willing to shake hands with those known to have epilepsy. About half were also willing to work with such a person.

On the other hand, the lack of knowledge about epilepsy in the population studied came out clearly in this study. The majority did not know what to do for a person with epilepsy during a convulsive attack. Some of those who had opinions suggested indigenous approaches aimed at neutralizing or appeasing supernatural causes based on mythical views of evil spirits and bewitchments.

Inasmuch as obviously negative attitudes were concerned, almost half of the respondents thought epilepsy to be contagious. This would explain why many Ethiopians with epilepsy present with severe burns, because onlookers are afraid to pull them out of domestic fires. Similar views on the transmittability of epilepsy by direct physical contact with the person with epilepsy or his secretions have been reported from Tanzania [7], Uganda[8] and Nigeria [9].

There was also a strong stand on matrimonial association with a person having the disease: 74% disapproved of it. Respondents gave accounts of cases where husbands divorced their wives, or wives

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Table 3. Question: would you allow someone from your family to marry a person with epilepsy?

Result (1257 responses)	%
Yes	26.0
Will not tolerate (reason not specified)	33.6
No, the epileptic is unable to earn a living	23.3
No, contagious	11.8
No, genetically unadvisable	3.9
Don't know	1.4

Only 5% considered epilepsy hereditary, and a very small number of the interviewed (2%) thought it to be a form of insanity. When asked if epilepsy was contagious, 45% of those that responded answered in the affirmative. Of these, 98% considered contact during a convulsive attack to be the most important method of transmission. Any type of contact with a person having epilepsy without a convulsive attack played only a minor role in the transmission of the disease to a healthy person, according to the respondents.

When asked if they would employ a person with epilepsy, 75% responded that they would not. However, 52.7% were willing to work with a person suffering from epilepsy. Sixty-seven per cent stated that they would give residential accommodation only if they were under pressure to do so.

Agreement to the use of public transport by a person with epilepsy was given by 90%, and a nearly equal percentage were willing to shake hands with someone having the disease; 41% were willing to be friends with persons with epilepsy, although only 4.6% of the respondents had a person with epilepsy as a friend at the time of the survey. When asked if they would allow their own children to play with another child having epilepsy, 65% responded that they would not object. However, we were told by about 50% of the respondents that they would instruct their children to run away from their playmate if he/she was to develop a convulsive attack.

Only 26% were willing to allow someone with epilepsy to marry a member of their family. Belief that the person with epilepsy was incapable of being gainfully employed and generating an income to support a family was stated by 17%, while 11.8% gave the contagious nature of the disease as a reason for disallowing marriage with an epileptic (Table 3).

Nearly 52% of the response regarding knowledge on the cause of epilepsy belonged to the category 'don't know'. Of the affirmative answers, the favoured opinion was evil spirits (30%). Eight per cent believe that epilepsy was a curse or punishment from God. Very few of those interviewed thought of natural causes such as accidents and infections (Table 4).

Table 4. Question: do you think you know the cause of epilepsy?

Result (1270 responses)	%
Don't know	51.6
Evil spirit	30.0
Punishment/curse from God	8.0
Physical contact with a convulsing person	5.0
Born with it	5.0
Febrile disease	0.2
Accident	0.1
Lightening	0.1

Table 5. Question: do you know what to do for someone having a convulsive attack/fit?

Result (1265 responses)	%
Don't know	88.5
Protect/guard patient	5.7
Give herbal medicine	2.7
Give holy water	0.9
Hanged man's rope	0.9
Conventional medicine	0.9
Strike match near nose	0.4

Among the respondents, 89% did not know what care to give to a person with epilepsy during a seizure attack. About 6% stated that they would guard and protect the person having the convulsion from hurting himself. Interestingly, 12 persons (0.9%) gave the information that tying a hanged man's rope which had been used for suicide had a therapeutic effect during an attack. Herbal medicines and wearing religious charms on the body were also mentioned as possible treatment by 2.7%. Modern drugs were the least favoured form of treatment (Table 5).

When asked if they would consider a person with epileptic fits well controlled cured from his illness, 66.7% answered in the affirmative, while 28.8% stated that the disorder was incurable.

Regarding the question of how society should care for the epileptic, only 54.4% had opinions. About 34% responded that society should give alms to the sufferers; 16.4% thought that medicines should be provided. Very few people saw the role of government in caring for the persons with epilepsy. Two respondents believed that animal sacrifice to evil spirits was necessary (Table 6).

The attitudinal findings in this study were similar between men and women, and between followers of either the Christian or Muslim faith. Older respondents (above the age of 50 years) had significantly more negative attitudes to epilepsy and person with epilepsy than the respondents under 40 years of age. Surprisingly, those respondents who had family members with epilepsy did not significantly differ in their attitudes to the majority who did not have affected family members.

When the effects of education was analysed, it was found that there were no statistically significant differences. However, the number of those with secondary education was too small to draw reasonable conclusions.

Analysis of the data comparing rural to urban respondents (Table 7) revealed that both groups had similar attitudes on inheritance of epilepsy and marriage to a person with epilepsy. What was surprising, though, was the significantly higher percentage of urban respondents who thought epilepsy to be contagious and were unwilling to allow their children to

Table 6. Question: how should society take care of persons with epilepsy?

Result (1214 responses)	%
Don't know	45.6
Give alms	34.2
Medicine to be provided	16.4
Let own family help	1.6
Government to take care	1.5
Pray for them	0.5
Give sacrifices to the spirits	0.2

ran away, on discovering that the other partner was suffering from epilepsy.

Respondents were found to be negatively inclined to giving residential accommodation to the person with epilepsy. Surprisingly, only 30% of those respondents having a relative with epilepsy expressed their willingness to accommodate a person with epilepsy. In addition, nearly 60% of the interviewees were reluctant to have a person with epilepsy as a friend.

As in other parts of Africa [2, 15], we knew that in Ethiopia native medicines in the form of herbal remedies, holy water or charms to wear, given by faith healers or spiritual healers, were commonly used in the community we studied for the alleged purposes of treatment, prevention and cure of epilepsy. However, this was not evidenced in this study. We think this may be due to a tendency of respondents to hide the information, least they are blamed as old-fashioned and superstitious.

The view of the rural respondents to society's responsibility to the care of the epileptic was interesting. They saw giving alms an important contribution, to the epileptic and very few expected the government to play an active role, although 16.4% thought the provision of medicine for the affected was required for the care of the person with epilepsy.

Dada in 1968 showed that attitudes varied considerably in different parts of Nigeria [16]. We may therefore question whether our attitudinal findings in the rural central region of Ethiopia are representative of views in the country as a whole. Although there may be some variations and deviations, we judge from our experience in other rural areas of Ethiopia that our findings are fairly representative of the predominant attitudes on the disease. This is further supported by the fact that, although the community we studied was predominantly of the Gurage ethnic group, other major ethnic sectors of the country were also represented in it.

Iivanainen *et al.* [17] have clearly shown in their study that respondents' acquaintance with an epileptic person, education level and age were important factors in acquiring and incorporating useful information about epilepsy. Caveness *et al.* [18] have also confirmed that the most favourable opinion about epilepsy was from the better educated, better employed, young and urban members of the population. Among the population we studied, urban people had more negative attitudes toward epilepsy than rural. The relative negative attitudes of the urban respondents may probably be due to their frequent exposure to the very unfortunate persons with uncontrolled seizures exhibiting unsightly burns and demented states. Such individuals are often seen in the streets of the towns and the compounds of worship places as beggars.

Epilepsy is a major public health problem in developing countries. Besides the disease itself, the problems of the epileptic anywhere in the world are compounded by the difficulties commonly encountered in schools and employments. These problems are particularly serious in Africa, as shown by the studies of Dada and Odeku [14] and Danesi [19] in Nigeria. In the context of the Ethiopian rural population, this study points to the need for intensive efforts to disseminate correct information about epilepsy through every means possible, together with an improved health care delivery system which would provide and guarantee adequate and continuous supply of cheap anticonvulsants within the existing basic health services.

It is thus fair to expect that the nation-wide literacy campaign which is vigorously being propagated in Ethiopia at the present time will contribute significantly to the future national health educational efforts, creating increased awareness and helping to eradicate beliefs and archaic traditional practices which typically predominate the attitudes of the rural population toward epilepsy in Ethiopia. In this respect, the present efforts on the part of those that care for persons with epilepsy in the production of health educational materials and programmes on the mass media to inform those that suffer from the disease and the general public should be sustained and developed. Needless to say, primary health care has to be developed in order to prevent the common causes of epilepsy, such as complicated obstetric conditions and central nervous system infections.

The curriculum of training of medical students, nurses and other health personnel responsible for primary health care is being modified to include special orientations on the diagnosis and close follow up of persons with epilepsy. As we observed in this study, the rural population is quite receptive and appreciative of the health education on epilepsy given by our enumerators. They also follow very carefully the instructions on the anticonvulsant therapy. These positive attitudes of the rural population should be exploited further in the efforts to change the wrong belief and practices pertaining to epilepsy.

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APPENDIX

Attitude Questionnaire

Date	Farmers/Urban Association	House No.	Interviewer

TO BE ANSWERED BY ONE MEMBER OF THE HOUSEHOLD, PREFERABLY BY THE HEAD OR WIFE.

—Name of informant _____ Age _____ Sex _____

—Marital status: Married ___ Single ___ Divorced ___ Widow ___

—Number of children: Male ___ Female ___ Total ___

—Occupation: _____ Income per month: _____

—Education: Illiterate ___ Read and write ___ Grade ___

—Religion: Christian ___ Moslem ___ Other ___

ATTITUDES TO EPILEPSY

—Have you ever heard or read about epilepsy? Yes ___ No ___

If yes, where? _____

—Is there in your language another name for a person who falls with jerking in arms and legs and does not respond when spoken to?

Yes ___ No ___ If yes, specify _____

After giving a full description of the different types of epilepsy (including partial and absence seizures) the enumerator tells the respondent: WE REFER TO ALL THESE MANIFESTATIONS AS EPILEPSY AND THAT IS THE TERM WE WILL USE IN THE QUESTIONS TO FOLLOW.

—Have you ever seen anyone who was having an epileptic seizure?

Yes ___ No ___

—Have you among your relatives anyone with epilepsy?

Yes ___ No ___

If yes, specify relation _____

—Do you know or did you know anyone else with epilepsy?

Yes ___ No ___

—Do you think you know the cause of epilepsy?

Yes ___ No ___

If yes, explain: _____

—Do you think that epilepsy is inherited?

Yes ___ No ___

If yes, in what way? _____

—Do you think that epilepsy is contagious?

Yes ___ No ___

If yes, how? _____

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—If yes, is epilepsy contagious:
during the epileptic attack only ___
at all times ___

—Do you think epilepsy is a form of insanity?
Yes ___ No ___

—Do you know what to do with a person having an epileptic attack?
Yes ___ No ___
If yes, what? _____

—If you have assisted a person with epilepsy during an attack and the attack continues, do you know what to do next?
Yes ___ No ___
If yes, what? _____

—Can a person who has had attacks be prevented from having further attacks or be made to have less attacks in the future?
Yes ___ No ___
If yes, how? _____

—If a person with epilepsy has been treated and his epileptic attacks have disappeared, will you consider him/her to be an ordinary healthy person?
Yes ___ No ___
If no, why? _____

—If you had the opportunity, would you employ someone with epilepsy?
Yes ___ No ___
If no, why? _____

—Are you willing to work with a person having epilepsy?
Yes ___ No ___
If no, why? _____

—Would you allow your own child to play with a child having epilepsy?
Yes ___ No ___
If no, why? _____

—What would you do if you are forced to accommodate a person with epilepsy?
_____

—Do you have a friend with epilepsy?
Yes ___ No ___

—Will you be a friend of someone that has epilepsy?
Yes ___ No ___
If no, why? _____

—May anyone in your family marry someone who has epilepsy?
Yes ___ No ___
If no, why? _____

—Are you afraid of someone who has epilepsy?
Yes ___ No ___
If yes, why? _____

—Should a family having a member with epilepsy hide him/her from outsiders?
Yes ___ No ___
If yes, why? _____

—Do you think a person with epilepsy should use public transportation?
Yes ___ No ___
If no, how should he/she travel? _____

—Would you shake hands with a person known to have epilepsy?
Yes ___ No ___

—How should the society take care of a person with epilepsy?
_____

At the end of the interview health education on epilepsy is given to the respondent and his/her family by the enumerator. 188

Recent studies have shown that there is a strong association between human T-cell lymphotropic virus (HTLV) and endemic tropical spastic paraparesis (TSP) as well as the non-tropical syndrome of HTLV-I-associated myelopathy (HAM) described in Japan [1,2]. In Africa, the distribution of HTLV-I infection has not yet been extensively investigated but there are reports to indicate that the prevalence of HTLV-I infection is high in West Africa [3–7] as well as in endemic foci of TSP, such as the Seychelles Islands [8]. A high rate of HTLV-I infection has also been observed in West African leprosy patients [5]. We therefore studied the HTLV-I and HIV status in Ethiopian leprosy patients.

Between October 1988 and September 1989, blood was taken, after informed consent, from leprous and non-leprous patients attending the clinic of the All Africa Leprosy and Rehabilitation Training Centre (ALERT), Addis Ababa. There were 74 patients with multibacillary leprosy (MB), 130 patients with paucibacillary leprosy (PB), and 46 with an indeterminate form of leprosy. Serum samples were obtained from 201 dermatological patients in whom clinical evaluation and skin histology had ruled out leprosy and also from 47 hospital personnel. Two hundred and twenty-five control blood samples were also collected from different areas of northern Ethiopia, including Addis Ababa, and 140 from the blood donors at the Ethiopia Red Cross Blood Transfusion Centre. There were no prostitutes among the groups under study as determined by interviews.

All sera were screened comparatively by two techniques in Limoges, France: an indirect immunofluorescence assay (IFA), using HUT 102 clone B2, and an enzyme immunoassay (HTLV-I EIA, Abbott Laboratories, Chicago, Illinois, USA). All positive sera, or sera doubtful by at least one of the two techniques, were submitted to Western blot analysis.

Sera were considered positive for antibody to HTLV-I if they reacted with at least one envelope protein (gp46) and one major *gag* protein or proteins (p24 and/or p19). Indeterminant samples by Western blot (only one gene product) were tested systematically by radioimmunoprecipitation assay (RIPA). We considered positive only sera reacting simultaneously with two gene products: *gag*, *env* or *tax* genes by Western blot and/or RIPA [6].

Sera were tested for HIV-1 and HIV-2 using a recombinant HIV-1 HIV-2 enzyme immunoassay EIA (Abbott GmbH, Diagnostika, Wiesbaden, FRG); those found positive by EIA were confirmed by Western blot HIV-1 and HIV-2 (new Lav Blot I and III, Diagnostics Pasteur, Garches, France). The criteria for positivity were as described previously [9].

Table 1. Prevalence of antibodies to HTLV-I and HIV-1 in Ethiopian leprous patients and controls.

	ALERT hospital																	
	Leprous patients						Non-leprous patients						Control					
Age (years)	M	F	Total	%	HTLV-I	HIV-1	M	F	Total	%	HTLV-I	HIV-1	M	F	Total	%	HTLV-I	HIV-1
0–9	1	0	1	0.4	0	0	2	2	4	1.6	0	0	3	0	3	0.8	0	0
10–19	17	28	45	18.0	0	1	19	28	47	19.0	0	0	37	23	60	16.4	0	0
20–29	33	28	61	24.4	0	3	34	43	77	31.0	1	4	78	39	117	32.1	0	6
30–39	42	18	60	24.0	1	2	38	27	65	26.2	1	3	58	25	83	22.7	0	3
40–49	28	13	41	16.4	0	2	18	6	24	9.7	0	0	32	24	56	15.4	0	0
50–59	22	5	27	10.8	0	0	13	7	20	8.1	0	0	21	9	30	8.2	0	0
>60	10	4	14	5.6	0	0	7	4	11	4.4	0	0	13	3	16	4.4	0	0
Unknown	0	1	1	0.4	0	0	0	0	0	0.0	0	0	0	0	0	0.0	0	0
Total	153	97	250	100.0	1	8	131	117	248	100.0	2	7	242	123	365	100.0	0	9
%	61.2	38.8	100.0		0.4	3.2	52.8	47.2	100.0		0.8	2.8	66.3	33.7	100.0		0	2.5

ALERT, All Africa Leprosy and Rehabilitation Training Centre; M, male; F, female.

The prevalence of antibodies for HTLV-I and HIV-1 in leprous patients and sex- and age-matched controls is shown in Table 1. Antibodies to HTLV-I were found in three women: one among the leprosy patients (0.4%), and two from the dermatological control patients (0.8%), one of whom was co-infected with HIV.

Antibodies to HIV-1 were found at higher prevalence in the three cohorts: eight of the leprous patients (3.2%); seven of the non-leprous control patients of the ALERT hospital, excluding hospital personnel (3.3%); and nine of the second group of controls (2.5%). Three of the seropositive leprosy patients were MB, three were PB, and two presented with an indeterminate form of leprosy. None were in reaction state. Of the men, four were unmarried or divorced labourers, one was a farmer and another a truck-driver. One woman was divorced and the other unemployed. Among the HIV-1 dermatological cases, five were women and two were man. Their conditions included actinomycosis, eczema, neurodermatitis, hyperkeratosis and unidentified mycosis. All the leprous patients and the controls were seronegative for HIV-2.

Absence of exposure to HTLV-I among the 140 blood donors and among 113 non-neurological outpatients from a teaching hospital in Addis Ababa was striking. The seropositivity for all three retroviruses among the 112 controls from the rural areas of northern and central Ethiopia was confirmed.

In community surveys of African countries, prevalences of antibody to HTLV-I ranging from 0.06 to 3.9% have been reported in Ghana, Gabon, Liberia, Senegal, Nigeria, Zaire, Kenya and Egypt [3,10,11]. Verdier *et al.* [5] demonstrated that the HTLV-I seropositivity was high among leprous patients in Congo and the Ivory Coast (5.6 and 5.7%, respectively, after adjustment). On the other hand, samples from leprous patients in Senegal and Yemen were seronegative [6]. Available results of HTLV-I serosurveys show that the infection rate is low in Ethiopia in both TSP and normal controls [12–14]. Our study confirms these observations. The low prevalence of HTLV-I infection among the leprous patients in Ethiopia probably reflects the low infection rate (0.0–0.8%) in the general population.

We propose that HTLV-I infection appears not yet to have significantly penetrated into the general Ethiopian population. Whether this low diffusion of the HTLV-I virus will be sustained or follow the trend with HIV that has progressively penetrated into Ethiopia, Sudan, Djibouti and Egypt [15] remains to be seen.

Seropositivity for HIV in Ethiopia was detected for the first time in two out of 167 specimens collected from patients with Bell's palsy in 1984–1985 [14]. Current epidemiological studies show that prevalence rates range from 2.4 to 2.9% [16,17]. As demonstrated to a lesser degree in this study, the prevalence of HIV infection in the three groups studied did not differ from those reported. Unlike the report of Meeran [18] in Zambia, and of Léonard *et al.* [9] in the Ivory Coast, we did not find a significantly higher HIV infection rate in leprous patients compared with controls.

The HIV infection in the leprous patients studied is likely to be too recent to modify, as in *M. tuberculosis* infection, the course and spread of the disease. However, the superimposition of HIV infection on *M. leprae* contagion, still widespread, is a matter of great concern [19].

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PREVALENCE OF ATHEROSCLESIS OF THE AORTA IN ETHIOPIANS: A POSTMORTEM STUDY
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PREVALENCE OF ATHEROSCLESIS OF THE AORTA IN ETHIOPIANS: A POSTMORTEM STUDY

M. MARU

SUMMARY

The study showed that some type of atherosclerotic lesions of the aorta were found in 58 (47%) of 124 autopsies examined. Fatty streak was found in 41 (32%), fibrous plaque in 28 (23%), calcified lesions in 7 (6%) and complicated lesions in 5 (4%) cases. Fatty streak was found only in 23% of the cases below the age of 20 years. It was the dominant lesion below the age of 60 years in both the thoracic and abdominal aorta. Fibrous plaque was not found below the age of 30 years but a rapid increase in prevalence occurred by the age group of 40-49, reaching peak level of 80% by the age of 70-79 years. Complicated and calcified lesions started to appear in the thoracic and abdominal aorta by the age of 40-49 years,with a rapid increase in prevalence after the age of 60 years. The study demonstrated clearly that atherosclerotic lesions of the aorta are definitely present in nearly half of the autopsied Ethiopians aged 10 years and upwards.

INTRODUCTION

Atherosclerosis is believed to be a rare disease in the Ethiopian population. There are no available data on the prevalence of atherosclerosis and its clinically important complications to date except a few isolated case reports(1,2,3).

In order to elucidate this problem a study was done of the aorta for atherosclerosis and the heart for scars of myocardial infarction and coronary atherosclerosis in autopsied persons from September 1982 to January 1986.

MATERIALS AND METHODS

Autopsy was performed well on all deaths whenever permission was granted by relatives. Consent for autopsy for patients who died of natural death was rare. The presence of four types of atherosclerotic lesions in the aorta from just above the aortic valve upto the bifurcation of the iliac arteries was investigated. The four lesions are fatty streaks, fibrous plaques, calcified and complicated lesions. Fatty streaks are slightly elevated yellow lipid deposits which stain dark red with Sudan IV. Fibrous plaques are firm elevated intimal lesions which are grey, glistening and translucent. Carlcified lesions are areas where calcium deposition is detectable either visually or by palpation, without overlying haemorrhage, ulceration or thrombosis. Complicated lesions are areas in which there is ulceration, haemorrhage or thrombosis, with or without calcium deposits. The aortic lesions were assessed visually during the time of the autopsy and after fixation by the chief pathologist of the Pathology Department. The findings were recorded under thoracic, abdominal and aorta complete. The thoracic aorta is that part of the aorta extending from a horizontal line drawn through the first two intercostal arteries to a horizontal line drawn through the upper edge of the orifice of the coeliac artery. The abdominal aorta is that part of the aorta extending from a horizontal line drawn through the upper edge of the orifice or the coeliac artery to a horizontal line drawn through the inner surface of the bifurcation of the aorta. The aorta complete is the aorta from just above the aortic valves to the bifurcation of the abdominal aorta.

The heart was also investigated for the presence of myocardial infarction and lesions of atherosclerosis in the main branches of the coronary arteries.

The average annual autopsy rate in the Gondar College Hospital was about 40. The majority were forensic cases who died of accidents homoicides, poisoning and destitutes who were found dead in their homes or on the streets. The medical history and the clinical diagnosis before death were in most of the cases unavailable. All the patients were indigenous Ethiopians from the low socio-economic class. Histories of hypertension, cigarette smoking, diabetes mellitus and elevated plasma cholesterol levels were unavailable. During the study period, 124 cases had postmortem examinations and the findings were recorded as recommended by Spain and Bradess(4).

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RESULTS

A total of 124 aortas from 106 (85%) men and 18 (15%) women aged 10-75 years were studied. The mean age was 37 ± 8 years. The material was divided into 10-year age groups. The main aspects considered in the study were: the time of onset, prevalence of various types of atherosclerotic lesions and the changes in their prevalence with age. Because of the small number of females, the results are presented together for both sexes.

The major causes of death in the Gondar Hospital for the years 1984 and 1985 and the study series are shown in Tables 1 and 2.

Table 1

Major causes of death of 602 patients in Gondar Hospital for the years 1984 and 1985

Causes of death	%
1. Pulmonary tuberculosis	16.2
2. Pulmonary infections	10.6
3. Gastro-enteritis and colitis	10.6
4. Heart disease (all types)	10.0
5. Cirrhosis and hepatitis	6.5
6. CNS (all types)	5.6
7. Bacterial meningitis	4.8
8. Accidents, homocides and poisoning	4.2
9. Diabetes mellitus	3.3
10. Intestinal obstruction	2.8
11. Others	23.4

Table 2

Major causes of death of the 124 patients after autopsy

1. Accidents, homocides and poisoning	27.0
2. Pulmonary infections	23.0
3. Pulmonary tuberculosis	16.0
4. Cardiac failure (all causes)	8.1
5. CNS (all types)	5.6
6. Cirrhosis	4.0
7. Peritonitis	4.0
8. Emphysema	4.0
9. Bacterial meningitis	2.4
10. Bacterial colitis (diarrhoea)	2.4
11. Pulmonary embolism	2.0
12. Others	1.5
Total	100

The prevalence of the four atherosclerotic lesions: Thoracic aorta: Out of 124 people aged 10 years upwards 58 (47%) had some lesions of atherosclerosis. Fatty streak was the only lesion present in 11-27% of the cases below 40 years of age. After the age of 40 years, the frequency decreased to 21% and remained at that level up to the age of 79 years.

Fibrous plaque did not occur below 40 years of age. After the age of 40 years the frequency increased rapidly from 33% at 40-49 years to 60% by the age group of 70-79 years. Complicated and calcified lesions did not occur below 40 years of age. By the age of 40-49 years 4% and by the the age of 60-69 years 42% of the cases had calcified lesions and for complicated lesions the frequency was between 4-17% (Table 3).

Table 3

Age distribution of different atherosclerotic lesions of the thoracic and abdominal aorta

Age (yrs)	Case No.	Fatty streak		Fibrous plaque		Calcified lesion		Complicated lesion	
		Thor* aorta	Abdo+ aorta	Thor* aorta	Abdo+ aorta	Thor* aorta	Abdo+ aorta	Thor* aorta	Abdo+ aorta
10-19	13	2 (15)	2 (15)	-	-	-	-	-	-
20-29	35	4 (11)	3 (9)	-	-	-	-	-	-
30-39	25	7 (27)	7 (27)	-	3 (11)	-	-	-	-
40-49	24	5 (21)	12 (50)	8 (33)	8 (33)	1 (4)	-	1 (4)	1 (4)
50-59	9	2 (22)	4 (44)	3 (33)	3 (33)	-	-	-	-
60-69	12	1 (8)	1 (8)	6 (50)	7 (58)	5 (42)	4 (33)	2 (17)	3 (25)
70-79	5	1 (20)	1 (20)	3 (60)	1 (20)	1 (20)	-	-	-
Total	124	2 (18)	30 (24)	20 (16)	22 (19)	7 (6)	5 (4)	3 (2)	4 (3) (14)

Numbers in brackets represent percentages
* Thoracic
\+ Abdominal

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Abdominal aorta: In the abdominal aorta similar features were observed in the prevalence of various atherosclerotic lesions. Fatty streak was found with the same frequency as in the thoracic aorta for the age groups of 30-39. For the age groups of 40-49 and 50-59 years the frequency was found to be 50% and 44% respectively. Thereafter the lesions decreased rapidly in both parts of the aorta.

Fibrous plaque was found with the same frequency as in the thoracic aorta but appeared 10 years earlier. The number of cases with complicated and calcified lesions was small. Both lesions were found after the age of 40 years with the same frequency in both parts of the aorta (Table 3).

Aorta complete: Out of the 124 aortas examined, 58 (47%) had atherosclerotic lesions. Fatty streak without any other lesion was found upto the age of 20 years. It was the most frequent form of lesion upto the age of 59 years. After the age of 60, the frequency of fatty streak decreased rapidly.

Fibrous plaque was not found under 30 years of age. Thereafter its frequency increased from 11% at age 30-39 years to 44% by the age of 60 years. After 60 years of age the frequency of fibrous plaque increased dramatically and by the age of 70 years 80% of the cases had this feature. The overall prevalence rates for fatty streak and fibrous plaque in the aorta were found to be 32% and 23% respectively. The frequency distribution of fatty streak and fibrous plaque by birth cohort is shown in Figure 1.

Figure 1

Frequency of atherosclerotic lesions by birth cohort

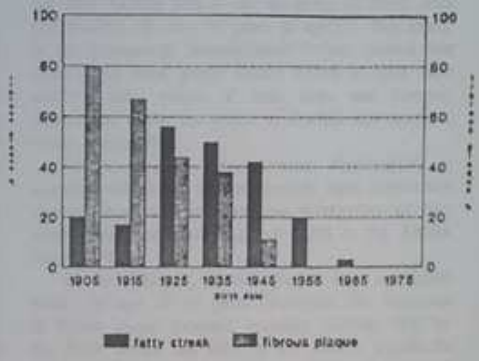


Table 4

Age distribution of atherosclerotic lesions of the aorta complete

Age (yrs)	No. cases	Fatty streak	Fibrous plaque	Calcified lesion	Complicated lesion
10-19	13	3 (3)	-	-	-
20-29	35	7 (20)	-	-	-
30-39	26	11 (42)	3 (11)	-	-
40-49	24	12 (50)	9 (38)	1 (4)	1 (4)
50-59	9	5 (56)	4 (44)	-	-
60-69	12	2 (17)	8 (67)	5 (42)	4 (33)
70-79	5	1 (20)	4 (80)	1 (20)	-
Total	124	41 (32)	28 (23)	7 (6)	5 (4)

Numbers in brackets represent percentages

development of fatty streaks. However, in order to establish a cohort effect it is essential to do several cross-sectional studies each one by age, using similar methods.

In the case of fibrous plaque, the increasing association with age could not be explained by a cohort effect. The cohort which had a high rate of fibrous plaque at birth or ten years of age could not survive to the age of 65 or 75 years. This is only possible if the disease was nonfatal. Therefore the development of fibrous plaque is associated with advancing age.

As urbanization increases, the diet becomes more westernized, the number of smokers becomes prevalent and the population becomes aged, the prevalence of atherosclerosis and its complications will increase. Therefore prevention of the atherosclerosis and its complications which is appropriate to the health and economic development of the country will be necessary.

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Relative Contribution of HLA-DQA and -DQB Alleles to Predisposition to Insulin-Dependent Diabetes Mellitus

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ABSTRACT: The presence of DQA and DQB alleles conferring protection or susceptibility was assessed in a panel of 39 insulin-dependent diabetes mellitus patients and 39 healthy control subjects from the central highland of Ethiopia. The results were grouped into three entities: a combination of alleles conferring susceptibility, a group conferring protection, and a group without any apparent HLA-DQ or -DR predisposition to insulin-dependent (type 1) diabetes mellitis (IDDM). Statistical analysis revealed that the relative risk of the first group is 64.1. If a similar approach is applied to the data on a study in caucasoid IDDM patients and controls of Kahlil and colleagues, the pattern is fully consistent with the data presented here, with an extraordinarily high relative risk (RR 258.2). It will be of interest to study whether this subdivision is reflected or supported by clinical or etiologic differences of the disease. The predictive value of susceptibility phenotypes appears to be more accurate by the proposed subdivision. Furthermore, in combination with islet-cell antibody analysis, assessment of genotype will permit more accurate identification of prediabetic individuals to be entered in clinical trials. *Human Immunology 34, 142–146 (1992).*

ABBREVIATIONS

ICA	islet-cell antibody
IDDM	insulin-dependent (type 1) diabetes mellitus
IHW	International Histocompatibility Workshop
PCR	polymerase chain reaction
RR	relative risk

INTRODUCTION

The risk to develop insulin-dependent (type 1) diabetes mellitus (IDDM) is genetically determined [1]. A strong association of alleles of class II genes of the human major histocompatibility complex (HLA) with IDDM has been described. The mechanism of this association is unknown, and no clues exist as to how the occurrence of IDDM in families without any history of the disease has to be explained. HLA-DR3 and -DR4 confer susceptibility to IDDM [2]. Recently, the HLA-DQ subregion of class II came into focus as a possible candidate for gene-conferring resistance [3]. Sequence comparison of DQA and DQB alleles associated with resistance or susceptibility to IDDM has revealed some interesting features [4, 5]. Arginine at position 52 of the DQα chain was associated with susceptibility (S), whereas nonarginine residues correlated with resistance (P). In the DQβ chain, the amino acid aspartic acid at position 57 was strongly associated with protection (P), whereas non-Asp correlated with susceptibility (S). A model based upon analysis of the presence of DQA-52-Arg/non-Arg and DQB-57-Asp/non-Asp led to a hierarchy of susceptibility phenotypes: the more "susceptible" alleles (of both DQA and B), the more patients, and conversely, the more protective alleles, the more healthy control subjects.

The relative contribution of DQA and DQB has

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never been assessed in a noncaucasoid North African population. To verify the value of the DQA and DQB susceptibility markers in the prediction of IDDM, we determined the alleles of HLA class II loci (HLA-DRB1, 3, 4, 5, DQA1, DQB1, and DPB1) in a population study of 39 healthy individuals and 39 IDDM patients of the Ethiopian central highland, a homogeneous African population. This was achieved by regular DNA amplification of the HLA class II loci by polymerase chain reaction (PCR) followed by oligonucleotide hybridization with allele-specific or allele-associated probes [6].

MATERIALS AND METHODS

DNA was extracted from peripheral blood mononuclear cells following standard procedures, according to the protocol of the 11th International Histocompatibility Workshop (IHW).

Polymerase chain reaction. Amplification of DNA was performed by the PCR using a programmable thermocycler (Perkin Elmer-Cetus) and a set of (specific) primers for the second exon of DRB, DPB, DQA, and DQB genes, provided by the 11th IHW. The amplification took place during 35 temperature cycles, allowing the DNA to denature (30 seconds 97°C), the primers to anneal, and the annealed primers to extend (30 seconds, 74°C). Finally, there was an additional 10-minute incubation at 74°C to complete DNA synthesis.

Each 100-μl PCR reaction mixture contained 0.1–0.5 μg genomic DNA, 50 mM KCl, 10 mM Tris–HCl, pH 8.4, 4 mM $MgCl_2$, 60 μg/ml bovine serum albumin, 20 pmol of each primer, 200 μM of each desoxy nucleotide triphosphate (dNTP) (Pharmacia Chemicals), and 2.5 U of Taq DNA polymerase (Perkin Elmer-Cetus).

To analyze the amplified product, 5 μl of the amplified DNA mixture was loaded on a 2% (wt/vol) agarose gel in Tris–borate buffer supplemented with 0.5 μg/ml ethidium bromide (TBE).

Oligonucleotide probes. The oligonucleotide probes identifying the known alleles at the DRB, DQA, DQB, and DPB loci were provided by the 11th IHW.

Dot-blot hybridization. Of each amplified DNA sample, 5 μl was denatured in 100 μl 0.4 N NaOH, 25 mM EDTA for 10 minutes, and applied to prewetted Highbond-N^+ membranes using a dot blot apparatus (BioRad). Wells were washed with 100 μl 5× SSPE (3 M NaCl, 0.2 M NaH_2PO_4, 20 mM EDTA, pH 7.4) and DNA was crosslinked to the membranes by ultraviolet irradiation using a Stratalinker 1800 (Stratagene) apparatus set at 25 mJ. The membranes were prehybridized in TMACl buffer (3 M tetramethyl ammonium chloride 50 mM Tris–HCl pH 7.5, 5 mM EDTA, 1% SDS) containing 0.1 mg/ml herring sperm, for 30 minutes at 50°C.

Oligonucleotide probes (10 pmol) were ^{32}P labeled at the 5'-end using T4-polynucleotide kinase (Pharmacia) and 40 μCi of ^{32}P γ-ATP (NEN, Du Pont, 6000 Ci/mmol) as according to the method of Maxam and Gilbert. Labeled probes were purified by Biospin-6 columns (Bio-Rad) according to the manufacturer's instructions.

To the hybridization mixture 2×10^5 cpm/ml labeled probes were added followed by 3- to 15-hour hybridization at 50°C. The membranes were rinsed in TMACl buffer for 5 minutes and then subjected to a critical wash step in the same buffer (fresh) for 15 minutes at 57°C and autoradiographed on Kodak XAR-5 film using an intensifying screen. Sometimes, additional washings in TMACl buffer were carried out with slightly increasing temperature steps to obtain a better discrimination.

RESULTS

The frequency of DR3, DR4, and DR3 + 4 in the patient population (87.2%) is higher than in controls (33.3%). A slight decrease of DPB1*1301 (3.8% of patients versus 12.5% of controls) was also noticeable. The typing results of the susceptibility- and resistance-related DQA-52 and DQB-57 amino acid residues are summarized in Table 1. In contrast to the situation in

TABLE 1a Typing results of HLA-DQA and -DQB of patients and controls

Genotype	Patients	Controls
DQA		
SS	21	3
SP	15	18
PP	3	18
DQB		
SS	33	21
SP	6	17
PP	0	1
DQA and DQB		
SSSS	17	0
SSSP	16	13
SSPP/SPPP/PPPP	5	26

Indicated are the numbers of individuals expressing susceptible (S) or protective (P) alleles of DQA and/or DQB.
DQA-52 Arg = S; DQB-57 non-Asp = S.
DQA-52 non-Arg = P; and DQB-57 Asp = P.
$\chi^2 = 29.8$; $p = 0.00001$ (Fisher).

TABLE 1b Woolf–Haldane analysis of Ethiopian individuals

Genotype	Patients		Controls		RR	P	95% CI
	+	−	+	−			
SS	17	22	0	39	61.4	10^{-4}	7.7–490
SP*	16	23	13	26	1.4	0.48	0.56–3.4
SPP SPPP PPPP*	6	33	26	13	0.10	10^{-5}	0.04–0.27

Indicated are numbers of individuals; RR, relative risk; and 95% CI, 95% confidence interval.

*Distribution of susceptibility and protection between DQA and DQB:

DQA/DQB	Patients	Controls
SP/SS	10	10
SS/SP	6	3
PP/SS	3	11
SP/SP	3	7
PP/PS	0	7
PS/PP	0	1

caucasoids, the number of DQB-57Asp positive (P) homozygotes in controls is very low. DQA-52Arg positive (S) homozygotes are much more frequent among patients compared to controls than DQB-57Asp negative (S) homozygotes, implying an important role of DQA in predisposition to IDDM. The results of the DQA and DQB genotype combined were grouped into three entities: a combination of alleles conferring susceptibility (group I), and a group conferring protection (group III: two or more protective DQA/B alleles). The remaining a group displayed no apparent HLA-DQ-associated predisposition to IDDM (group II: one protective allele of either DQA or DQB).

Reanalysis of the results published by Khalil and colleagues [5] on French caucasoids with respect to the same group distinction as in Table 1 revealed strikingly similar results (Table 2).

With regard to the distinction in three groups (Tables 1 and 2), we evaluated the genotypes of eight caucasoid subjects containing circulating islet-cell antibodies (ICAs, measured by indirect immunofluorescence on pancreas sections) selected from a 10-year follow-up study on the occurrence of ICAs in childhood diabetes (Table 3) [7]. The results indicate that three of four individuals with ICAs and a fully susceptible genotype (group I) have developed IDDM. No ICA-positive individuals were ranked in group II. Of four ICA-positive subjects ranked in group III (i.e., two or more protective alleles of DQA and/or DQB), three have not developed IDDM to date.

DISCUSSION

To our knowledge, this study represents the first analysis of genotypes in a homogeneous African population with regard to predisposition to IDDM. In Afro-Caribbean subjects, race-specific DR7 and DR9 haplotypes with a positive association with IDDM have been described [8]. The DQA1 of DR7 and DR9 haplotypes in this patient population was identical to the DQA1 found in caucasoid DR4 haplotypes associated with the disease. The DQB1 of the DR9-DQw2 haplotype in

TABLE 2 Genotype analysis of French Caucasoid IDDM patients and controls

Genotype	Patients		Controls		RR	P	95% CI
	+	−	+	−			
SSSS	32	18	0	73	258	10^{-6}	33.1–2010
SSSP	16	34	10	63	2.1	0.07	0.94–4.87
SSPP SPPP PPPP	2	48	71	2	0.01	10^{-5}	0.003–0.042

Indicated are numbers of individuals; RR, relative risk; and 95% CI, 95% confidence interval.

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TABLE 3 Predictive value of ICAs and DQA/B genotype

Subject	Genotype (DQA/DQB)	IDDM	Prediction on basis of ICA*	Prediction on basis of Genotype*
1	Group I (SS/SS)	+	−	+
2		+	+	+
3		+	+	+
4		−	+	+
5	Group III (SP/SP)	+	+	−
6	(PP/SS)	−	+	−
7	(PP/SS)	−	+	−
8	(PP/PP)	−	+	−

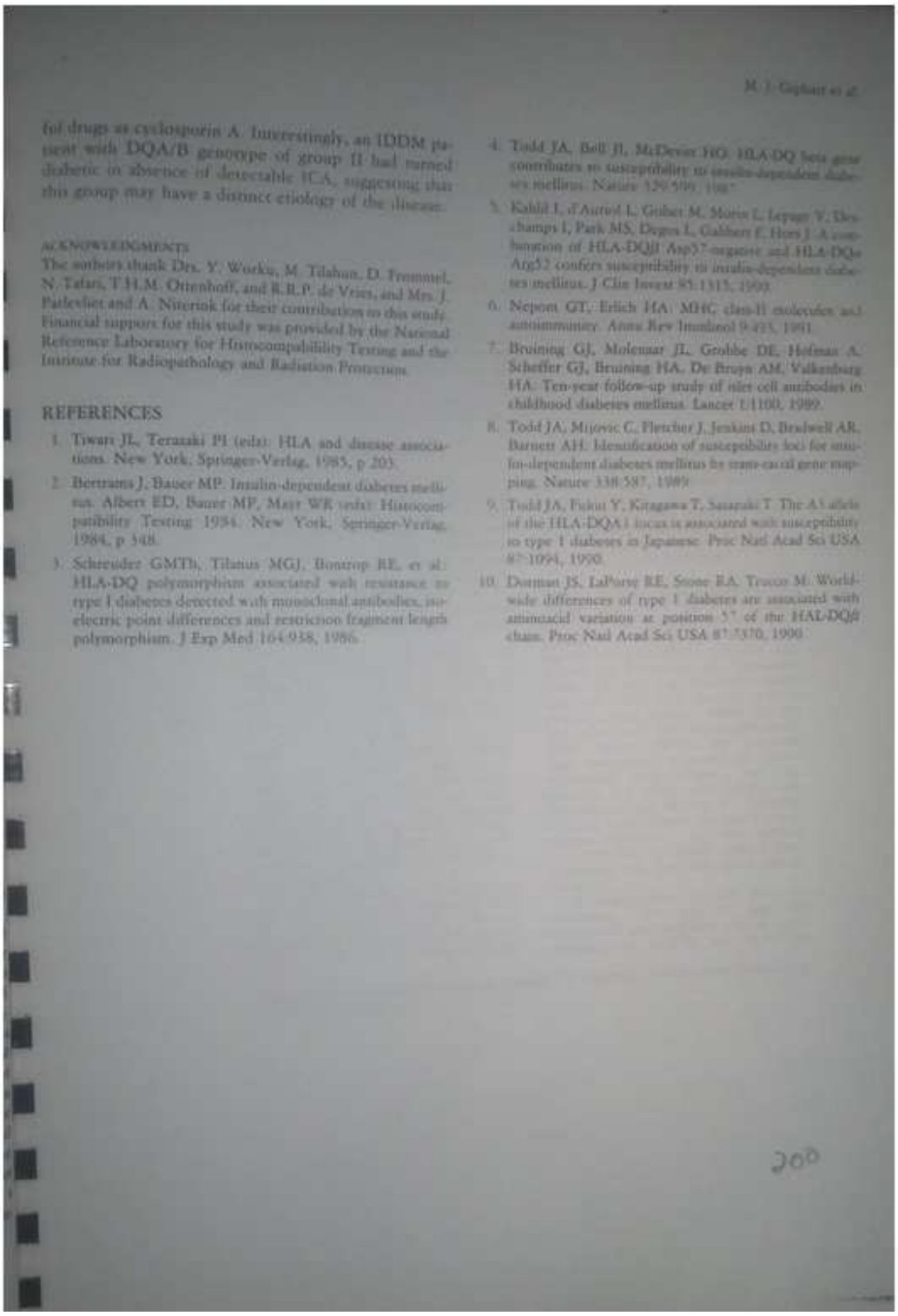
* Increased (ICA-positive or genetically susceptible, +) or decreased (ICA-negative or genetically protected, −) risk to develop IDDM.

blacks (without Asp on position 57) predisposed to IDDM, although the DQA1 in this haplotype is identical to the DQA1 in the nonpredisposing caucasoid DR9. As in blacks, DR9 is positively associated with IDDM in the Japanese population, but the DQB1 here is Asp57 positive [9]. The high frequency of Asp-57-encoding DQB1 alleles in this ethnic group may account for the rarity of IDDM in Japan. It is hypothesized that the 30-fold difference in IDDM incidence across racial groups and countries is related to variability in the frequency of Asp57-positive DQB1 alleles [10]. While comparing our results obtained in Ethiopians with similar studies in caucasoids, we can draw the same conclusions in both ethnically different populations. If all the alleles of both DQA and DQB are of the susceptible type a strong genetic predisposition to IDDM is observed (RR 64 in Ethiopians and 258 in caucasoids). In case of one protective allele of either DQA or DQB, no association between IDDM and HLA is seen. Apparently, the genetic association is reduced in this group, probably to a minor genetic risk factor. Two or more protective alleles is strongly associated with resistance (RR < 0.10). If a genetic component exists in the SSSP group, the predisposing gene remains obscure. A non-MHC (major histocompatibility complex) gene may be involved, or alternatively, the development of IDDM in this group is completely determined by environmental factors. The relative frequencies of patients in the SSSS group versus the SSSP group affects the outcome of the statistical analysis, i.e., there is an excess of the recessive type in caucasoids compared to Ethiopian central highlanders (frequency of SSSS versus SSSP nearly equal to 2 : 1 in caucasoids compared to nearly equal to 1 : 1 in Ethiopians). It will be of interest to assess whether the MHC-associated and the nonassociated appearance of IDDM represent distinct entities of the disease characterized by, e.g., familial IDDM, (co)existence of islet cell autoantibodies, insulin autoantibodies, 64kDa GAD autoantibodies, age of onset, and association with viral infection.

The present study reveals that the contribution of the DQA locus to the predisposition of IDDM may be critical. In case of DQB-asp57-negative homozygote individuals, a single protective DQA allele may balance the genetic predisposition to IDDM to a "neutral" state, whereas two protective DQA alleles seem to overrule susceptibility and confer protection. Therefore, it is important to take both the DQA and DQB genotype into consideration.

It is of interest that all individuals in group I (SSSS) and group II (SSSP) are HLA-DR3 and/or -DR4 positive (data not shown). Both DR alleles are found to be associated with susceptibility to IDDM. However, the results of this study demonstrate that the association of DR3/4 can be distinguished in a fraction with strong positive association with IDDM, and a fraction with a neutral association on basis of DQ genotyping. Therefore, HLA-DR typing is insufficient for the prediction of IDDM.

With regard to the predictive value of ICAs and DQ genotype, it is shown that a prediction on basis of either circulating ICAs or DQ genotypes alone only covers four of eight cases of ICAs and IDDM (Table 3). A prediction of development of IDDM in case of a combination of DQ genotype and circulating ICAs increases the accuracy of the prediction: development of IDDM would have been predicted correctly in seven out of eight individuals. This implies that genotype analysis in combination with ICAs serology is a more accurate measure to identify individuals with ongoing islet cell destruction. Because, at most, half of the ICA-positive children eventually will become diabetic, the detection of circulating ICAs itself is not sufficient to include a healthy child in therapeutic trials with potentially harm-



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ful drugs as cyclosporin A. Interestingly, an IDDM patient with DQA/B genotype of group II had turned diabetic in absence of detectable ICA, suggesting that this group may have a distinct etiology of the disease.

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CASE REPORT

CRYPTOCOCCAL MENINGITIS IN A YOUNG ETHIOPIAN WOMAN WITH AIDS

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ABSTRACT: The case of a 20 year old Ethiopian woman with cryptococcal meningitis and acquired immunodeficiency syndrome (AIDS) is presented. Though cryptococcal infections have been reported from many countries throughout the world, this is the first case reported from Ethiopia in a patient with the acquired immunodeficiency syndrome (AIDS). The clinical manifestations, diagnosis, and treatment are discussed, with a review of recent literature.

INTRODUCTION

Cryptococcus neoformans (C. neoformans) infections are life threatening opportunistic infections causing morbidity and mortality in individuals with defective cellular immunity, and are the initial presenting illnesses in 3% of, and the most common disseminated fungal infections in, patients with the acquired immunodeficiency syndrome (AIDS) (1).

Cryptococcosis will develop at some point during their illness in approximately 10% of patients with AIDS in the United States, and in as many as 33% of African AIDS patients (2-4). Among the infectious agents causing neurological disease in patients with AIDS, *C. neoformans* ranks third after human immunodeficiency virus (HIV) itself and *Toxoplasma gondii* (5). The diagnosis is simplified by a high index of suspicion and a low threshold for the performance of lumbar puncture in a high risk individual.

Therapy of this infection in patients with AIDS has been associated with high failure and relapse rates, as has been the therapy of other opportunistic infections in such severely immunocompromised individuals (5).

The purpose of this report is to alert physicians practising in Ethiopia to the need for early detection and treatment of this infection in the era of the HIV epidemic.

CASE REPORT

A.G., a 20 year old female from Addis Abeba, presented to the Medical OPD of Tikur Anbessa Hospital, Addis Abeba, in January 1990 with complaints of generalized pruritic skin lesions for 6 months, and headache, fever and poor appetite of 3 months duration. The skin changes started as flat, scaly lesions, which did not heal with local ointment applications. These were followed by headache and low-grade intermittent fever associated with nausea, vomiting, anorexia and progressive weight loss. She denied any history of diarrhoea and was bedridden in the last 2 weeks before admission. She had worked in a bar intermittently until a year previously and had had many sexual partners.

On examination at the time of admission, the patient appeared acutely ill and restless with a temperature of 39.5°C and extensive

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oral thrush. There was no lymphadenopathy. On the skin, pubic and perineal regions, widespread irregular erythematous and whitish macular patches with peripheral scaling and tiny vesicles were seen, from 3x5 to 8x10 cms in size. She had neck stiffness but was conscious and well oriented. Investigations showed a haemoglobin (Hb) of 10.5g%, white cell count (WBC) of 3400/mm^3, erythrocyte sedimentation rate (ESR): 92mm/1hr, platelet count 175,000/mm and blood films negative for haemoparasites. Urinalysis showed 3+ albumin, and many pus cells and red cells/HPF. Urine culture was negative. VDRL was non-reactive. Lumbar puncture done on arrival showed clear CSF, with normal protein and glucose levels and no cells. CSF culture showed yeast cells and an india ink preparation was positive for C. neoformans. Blood, taken for bacterial cultures, grew yeast cells. Renal and liver function tests were normal. Chest x-ray was normal. KOH preparation from a skin-snip showed rounded yeast cells. ELISA and Western blot tests for HIV infection, done at the National Research Institute of Health (NRIH), were both positive.

The patient was given supportive treatment and amphotericin B 0.6 mg/kg daily. The fever came down, but the general condition of the patient did not improve. She complained of headache, photophobia, nausea and vomiting. Lumbar puncture was repeated 8 days after treatment was commenced: CSF culture and India ink preparation were negative. Urea nitrogen (BUN) repeated 2 weeks later was normal. Four weeks after admission, she suddenly vomited fresh blood massively and died immediately before transfusion could be given.

DISCUSSION

C. neoformans is a yeast-like fungus ubiquitous in nature which reproduces by budding. Naturally acquired cryptococcosis occurs in animals as well as in man, but neither man to man nor animal to man transmission has been documented. Circumstantial evidence suggests that the disease occurs after the organism is aerosolized and inhaled into the lungs (6,7). The virulence of the organism probably plays little role in determining the outcome of infection. The crucial factor appears to be the immune status of the host and the most serious cryptococcal infections usually occur in individuals with defective cell-mediated immunity (7). An increased risk of infection with *Cryptococcus neoformans* is found in patients receiving therapeutic doses of corticosteroids, patients with lymphoreticular malignancies, sarcoidosis and organ transplantation, and recently in patients with HIV infection. The infection in these patients is usually disseminated, and they often have other concomitant opportunistic infections, such as the oral thrush seen in our patient (1,5).

The clinical manifestations may vary from a complete lack of symptoms to localized infections or overwhelming dissemination (3,7). Cryptococcal meningitis may present in an indolent manner or as an acute illness in patients with AIDS. Among 22 first-episode patients, the duration of symptoms before diagnosis ranged from one day to four months, with a mean of 31 days in one study (3). Headache and fever, the most common symptoms, are present in 80 to 90% of patients, stiff neck in 30%, photophobia in 20 to 30%, mental status changes in 20%, and non-specific symptoms including nausea, vomiting and malaise are seen in 40 to 50% of patients. Our patient had all these clinical manifestations. Symptoms like seizures indicating focal neurological involvement are uncommon (5).

Meningitis with or without systemic involvement is the commonest initial

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manifestation of cryptococcal infections. In two reported series of documented cryptococcal infections in patients with AIDS, meningitis was seen in 22 of 26 and 18 of 27 patients.

Extraneural involvement occurred in about 50% of the patients and the most frequent sites of dissemination have been the lungs, blood, lymph nodes, liver, spleen, kidney, bone marrow and skin, but virtually any organ may be involved.

The presence of persistent fever and headache in any individual at risk, as in individuals suspected or documented to have HIV infection, should indicate a search for cryptococcal disease of the CNS (5). The diagnosis of cryptococcal meningitis is sufficient by itself for the diagnosis of AIDS in a high risk individual (8). Although multiple infections or non-infectious diseases may mimic CNS cryptococcosis, the primary diagnostic considerations include neurological diseases caused by HIV, toxoplasmosis, lymphoma (either primary CNS or metastatic disease) and tuberculous meningitis in endemic areas (5).

The diagnosis involves the collection of appropriate body fluids (CSF, blood, urine, sputum) and tissue specimens for culture, India ink stain, cryptococcal antigen detection and histopathological evaluation with special stains.

Of particular note is the observation by many clinicians that the CSF cell count, and protein and glucose levels, may be normal or only slightly abnormal in patients with AIDS and cryptococcal meningitis.

The CSF indices in patients with cryptococcal meningitis but without AIDS are, however, almost always abnormal. However, in patients both with and without AIDS, organism specific studies on CSF, including India ink preparation, culture and cryptococcal antigen determination, are usually positive (5). Blood and CSF cultures were positive in our patient. Cryptococcal antigen studies were not done, as they are not currently available at Tikur Anbessa Hospital.

In one study involving 18 patients with AIDS and cryptococcal meningitis, the WBC count was < 5 cells/mm^3 in 11 of 17 patients tested, the protein level was < 45 mg/dL in 5 of 16 and the glucose level was > 40 mg/dL in 11 of 16 patients. In 3 patients these CSF indices were normal, as they were in our patient. By contrast, the CSF culture was positive in all 18 patients, India ink preparation was positive in 14 of 17 and the cryptococcal antigen titre was 1:8 (range 1:2048) in all 16 patients tested (2). Thus, the clinician should not be misled by normal or only slightly abnormal CSF WBC count, protein and glucose levels in patients with AIDS and suspected cryptococcal meningitis. Greater diagnostic reliance should be placed on the more specific tests, such as fungal cultures, India ink preparation and cryptococcal antigen determinations. Blood culture, if positive, is characteristic of disseminated cryptococcosis and should be taken from all patients. The organism can be isolated from blood in the standard media used for bacteriologic cultures, but usually Sabouraud's or other suitable media should be used (5,7).

Several studies have indicated that amphotericin B with or without flucytosine is the preferred method of treatment for patients with acute or first episode cryptococcal infections (9-11). The dose of amphotericin B when used alone ranges from 0.5 to 0.8 mg/kg per day. When combined with flucytosine, its average dose is 0.3 mg/kg, the dose of flucytosine being 150 mg/kg per day. This mode of treatment resulted in an initial response in only 58% of patients in 2 recently published studies (2,3). Many patients, especially those with AIDS, do not tolerate flucytosine because of unacceptable toxicity, primarily manifested as bone marrow depression. Furthermore, no increase

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in the rate of response and no decrease in the rate of relapse have been seen with combination therapy (11,12). The optimal dosage and duration of therapy for primary cryptococcal diseases in AIDS patients are uncertain. Most clinicians aim for 1.5 to 2.0 gm total dose of amphotericin B, usually given in 6 weeks' time in AIDS patients (10,11). Patients should be followed with lumbar punctures done weekly for culture, India ink preparation and antigen titre determination, if possible.

Although conventional amphotericin B therapy with or without flucytosine is often successful for acute infections, current data suggest that approximately 50% of AIDS patients with previously treated cryptococcal infections will experience a relapse within 6 months. Therefore a maintenance regimen of at least weekly amphotericin B (100 mg per week) is now incorporated into the management of patients with AIDS to reduce the likelihood of relapse (2-5).

Alternative drugs for the treatment of acute cryptococcal infections and for maintenance therapy include the triazole derivatives. Preliminary studies done with fluconazole and itraconazole are promising (13-15).

It should be noted that our patient sought medical treatment late and had far advanced and disseminated cryptococcal infection. Prognostic factors associated with a high risk of relapse or early death remain largely undefined and are reviewed elsewhere (16,17).

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EPIDEMIC MENINGOCOCCAL MENINGITIS IN ADULT ETHIOPIANS IN ADDIS ABEBA, ETHIOPIA, 1988

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ABSTRACT: 278 patients with pyogenic meningitis admitted to the Tikur Anbessa Teaching Hospital in Addis Abeba, Ethiopia, between January and December 1988 were studied prospectively to describe the epidemiology, microbiology, clinical features and outcome of infection. Fifty-nine per cent of the patients were admitted in the hot dry season between January and the end of June. About half of the patients (57%) were in the age group 15 to 19 years; the male to female ratio was 1.8:1. Two hundred sixty-two specimens (94%) were examined by Gram stain/or culture. N. Meningitidis was cultured from 161 of 243 CSF specimens (65%) and the Gram stain was diagnostic in 108 of 140 CSF specimens (77%). Both Gram stain and culture were negative in 90 of 262 specimens (34%). Thirty-five of the isolates were serogrouped and all were found to belong to serogroup A. All 30 isolates tested for drug sensitivity were resistant to sulfadiazine but sensitive to penicillin. Forty-three of 204 patients died of their infection, a case fatality rate of 21%: 60% of the deaths occurred in the first 24 hours after admission. Eleven of 13 patients with meningococcaemia expired. The case fatality rates for meningitis and meningococcaemia were 16% and 85% respectively. Nine patients (4%) developed neurologic sequalae: 4 hemiplegia, 3 nerve deafness, 2 cranial nerve palsies. This high morbidity and mortality from meningococcal infection demonstrates the need for a national surveillance programme for the prevention and control of meningococcal disease in the country.

INTRODUCTION

Epidemic meningococcal meningitis is a serious public health problem in many countries in Africa, including Ethiopia, which lie within the "African Meningitis Belt" (1-5). Several epidemics have occurred in the country in the past decade, the most serious in 1981 affecting nearly 40,000 people (6). Epidemics occur in cycles of 5-10 years and tend to occur during the hot dry season between January and the end of June.

During 1988-89 an outbreak of meningococcal meningitis occurred in Ethiopia, including within the capital city, Addis Abeba. Fifty thousand cases were reported to the Epidemiology Division of the Ministry of Health (7). The present report describes the epidemiology, bacteriology, clinical features and outcome of infection in patients admitted during this time to the Tikur Anbessa Teaching Hospital in Addis Abeba.

PATIENTS AND METHODS

Adult patients age > 15 years with pyogenic meningitis admitted to the medical outpatient department of the Tikur Anbessa Teaching Hospital between January and December 1988 were studied prospectively. Demographic data and symptoms and signs on admission were reviewed and entered into a prepared protocol. All patients had lumbar puncture on admission and the cerebrospinal fluid (CSF) specimens were studied for cells, protein and glucose. The

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diagnosis of meningococcal meningitis was confirmed by positive culture of CSF and/or demonstration of the organism by Gram stain. Diagnosis was also accepted in patients with clinically proven pyogenic meningitis in whom the organism was not demonstrated by culture or Gram stain. A clinical diagnosis of acute meningococcaemia was made in patients who presented with fever, purpuric rash and normal CSF; most of these patients also had hypotension. *N. meningitidis* isolated from CSF were serogrouped using antisera from Difco Laboratories by the Bacteriology Department of he Addis Abeba University. Drug sensitivity was tested by the Kirby Bauer disc diffusion method on Muller Hinton agar. Climatic records were obtained from the National Meteorological Services.

RESULTS

DEMOGRAPHY AND CLIMATE: Two hundred seventy-eight patients with pyogenic meningitis were admitted to the medical outpatient department of the Tikur Anbessa Hospital between January and December 1988 1988; of these 74 patients were transferred to other hospitals in town because of shortage of beds. The majority of the patients (85%) were from Addis Abeba while the rest were from nearby towns. Figure 1 shows the age and sex distribution of the patients. About half of the patients (57%) were in the age group 15 to 19 years, the male to female ratio being 1.8:1.

Fifty-nine percent of the patients were admitted in the hot dry season between January and the end of June.

CEREBROSPINAL FLUID (CSF) ANALYSIS

Two hundred sixty-five of 278 CSF specimens (95.3%) had changes compatible with pyogenic meningitis, i.e. polymorphonuclear pleocytosis, low glucose and elevated protein levels. Thirteen patients had normal CSF findings. These were clinically diagnosed as meningococcaemia without meningitis on the basis of the presence of purpuric rash/or hypotension.

BACTERIOLOGY: Of 278 patients who had lumbar puncture, 262 CSF samples (94%) were examined by Gram stain and or culture. Both Gram stain and culture were performed on 121 specimens. One hundred twenty-two specimens were studied by culture alone while 19 specimens were examined by Gram stain alone. *N. meningitidis* was cultured from 161 of 243 specimens (66%). The Gram stain was diagnostic in 108 of 140 specimens (77%). Both gram stain and culture were negative in 90 of 262 specimens (34%). Thirty-five of the isolates were serogrouped and all were found to belong to serogroup A. Thirty isolates tested for drug sensitivity were resistant to sulfadiazine but sensitive to penicillin. The clinical presentation of the patients is summarised in Figure 2. Of the 204 patients admitted to Tikur Anbessa Hospital, 43 died of their infection, a case fatality rate of 21%. Sixty percent of the deaths occurred in the first 24 hours after admission. Eleven of 13 patients with meningococcoemia expired. The case fatality rates for meningitis and meningococcaemia were 16% and 85% respectively.

Nine patients (4%) had neurologic sequalae at the time of discharge: 4 patients hemiplegia, 3 nerve deafness and 3 cranial nerve palsies. Twenty percent of the patients were treated with a combination of penicillin and chloramphenicol while the rest were treated with penicillin alone. The duration of treatment was 7 to 10 days, depending on the judgement of the attending physician. Hydrocortisone in addition to specific

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antimicrobial treatment was used in eight of the eleven patients who presented with a clinical picture compatible with fulminant meningococcaemia.

DISCUSSION

Ethiopia forms the eastern boundary of the African Meningitis Belt. Several epidemics have occurred in the country in the past 15 years (4-9). However, most of the available studies are based on reports to the Ministry of Health or on retrospective analysis. The inadequacy of the reporting system and the difficulty of establishing definite diagnosis in rural health stations limit the usefulness of these earlier studies. In 1988-89 an epidemic of meningococcal meningitis occurred in the country affecting nearly 50,000 people (7). The patients reported here in detail are those cases seen at the Tikur Anbessa Hospital in Addis Abeba, the capital, during this time. Although in one third of the cases of pyogenic meningitis in this series an aetiologic diagnosis was not made, it is reasonable to assume that many of these cases were caused by *N. meningitidis*. Prior antibiotic treatment and inadequacy of bacteriological services contribute to the aetiologically unconfirmed cases. Fifty-seven percent of the patients were in the age group 15 to 19 years and the male to female ratio was 1.8:1. The general epidemiologic features, and the age and sex distribution, were similar to recent epidemics reported from other African countries (10-13). The reason for male preponderance in most epidemics is not fully understood. Differences in the social and behavioural characteristics of the sexes may be responsible for the increased frequency of meningococcal infection in young adult males. Meningococcal infections tend to occur in the hot dry season when the mean maximum temperature is high and absolute humidity low. The seasonality and cyclic nature of these epidemics is not completely understood. Earlier studies emphasize change in meningococcal carriage to be the most important factor determining the frequency of disease transmission (1). However, recent studies on the meningococcal carrier state do not support this view (11,12). Greenwood (12) has suggested that low absolute humidity coupled with a high incidence of upper respiratory infections damage the upper respiratory mucosa and alter the proportion of subclinical to clinical cases.

Little work has been done on the bacteriology of meningococcal infection in this country. However, the available reports have shown that group A meningococci are responsible for many of the epidemics (13,14). Group A, and to a lesser extent group C, meningococci have caused many of the recent epidemics in Africa (12,13,15,16). During an epidemic of meningococcal meningitis among military recruits near Addis Abeba, two of the isolates were shown to belong to serogroup C (13). During the present epidemic all the 35 isolates typed belonged to group A.

Resistance of meningococci to sulfa drugs has become widespread in many countries in Africa; resistance rates of 5-70% have been reported (13, 17). In Ethiopia, the few isolates tested were shown to be resistant to sulfadiazine with MIC between 5 and 10 mg/dl (1,8). Although minimum inhibitory concentrations were not studied, all the 30 isolates tested were found to be resistant to sulfadiazine and sensitive to penicillin by disc diffusion. Continuous bacteriologic surveillance to monitor shifts in serogroup and drug sensitivity pattern is important to formulate preventive and management strategies during epidemics.

The reported mortality rates from meningococcal meningitis have varied between 3 and 30% (1). On average, many recent epidemics in Africa have reported mortality rates between 5 and 10% (2,16,19-21) (Table 1). The case fatality rate of 21% during this epidemic is twice as much as

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reported in most epidemics but similar to the case fatality of 26% reported in a recent epidemic in Gambia (21).

Mortality of meningococcal meningitis, as well as other types of meningitis, varies greatly between different studies. Several factors play a role, some of which are: availability of proper medical care (urban/rural), under reporting to central registries, the fact that most of the deaths occur during the first 24 hours after admission suggesting that many patients too sick to travel the long distances to the health services die at home, the age of patients studied, the number of cases with septicaemia, and strain associated differences (of which little is known).

The major neurologic sequalae found in this study were obvious. However, neurologic sequalae were probably much commoner if less obvious and more difficult to recognise sequalae had been included.

The high morbidity and mortality from meningococcal infection during this epidemic demonstrates the need for a national surveillance programme for the prevention and control of meningococcal infection in the country.

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TABLE 1. Reported mortality rates: epidemic meningococcal meningitis

Year	Place	Authors	Reference	Case fatality rate
1977	Ghana	Belcher et al.	19	11%
1979	Nigeria	Greenwood et al.	2	8%
1982	Mali	Binin et al.	20	11%
1983	Burkina-Faso	Broome et al.	16	10%
1987	Gambia	Greenwood et al.	21	26%

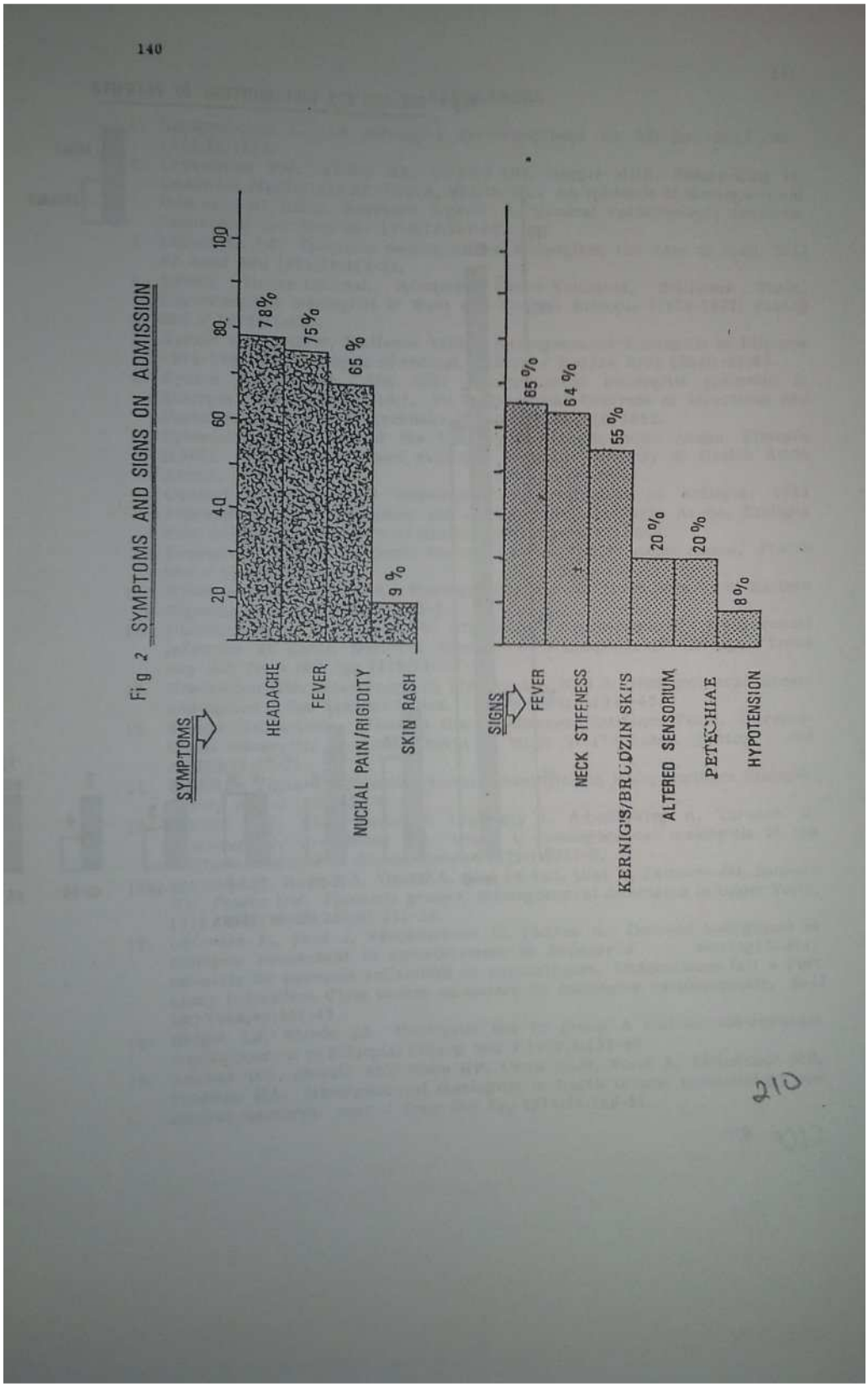
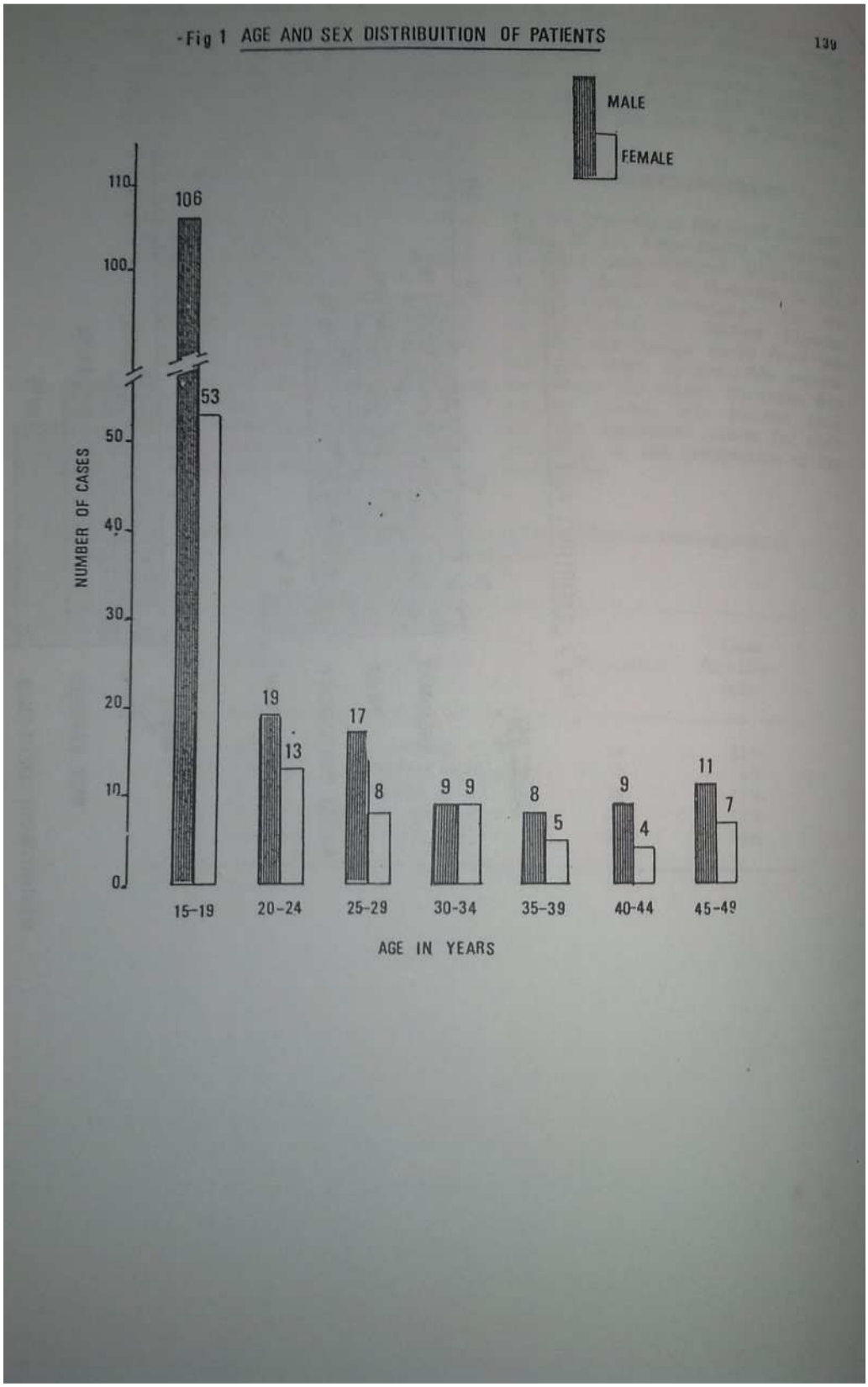


Fig 2 SYMPTOMS AND SIGNS ON ADMISSION

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DNA Fingerprinting in the Epidemiology of African Serogroup A Neisseria meningitidis

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The restriction endonuclease (RE) technique was used to compare 172 meningococcal group A strains collected between 1969 and 1990, mainly from countries of the so-called African Meningitis Belt, the Gambia and Ethiopia. The 64 strains from various African countries (Niger, Chad, Burkina Faso, Cameroon, Morocco, Djibouti) were distributed within 3 main restriction enzyme patterns (REPs); the 77 Gambian strains fell into 5 REPs and the 24 Ethiopian strains into 2 such patterns. Several of the main REPs were formed by clusters of closely related clones. Clones, very similar to dominating REPs of the 1960s in Niger, Burkina Faso and Cameroon, were in the 1980s found to be strongly represented in the Gambia to the extreme west of the Meningitis Belt. One of the Gambian clones from 1983–86 was identical to an Indian clone recovered in New Delhi 1986–87. Another clone was detected in 1983 in the Gambia, in 1589 again in the Gambia as well as in Ethiopia, and in 1990 in Tanzania. Our results are largely in line with those of previous studies based on modern techniques of protein and isoenzyme electrophoresis. The RE method is useful mainly for the exact genotypic differentiation of closely related clones, and seems to be a valuable complement to phenotypic tools for epidemiological mapping of Group A meningococcal infection.

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INTRODUCTION

At intervals of 8–12 years, meningococcal epidemics reaching prevalence rates of up to 500–1 000/100 000 inhabitants have caused major public health problems in several countries of Sahelian Africa. Typically, the epidemics start well into the dry season and spread in the population with dramatic speed until ending abruptly with the onset of the rainy season (1–3). Apart from the fact that most epidemics of the so-called African Meningitis Belt seem to be caused by group A meningococci, little is known about the mechanisms triggering this particular epidemiological pattern. In fact, until recently it was quite unclear whether each epidemic wave is caused by a new and antigenically different bacterial clone, or represents outbreaks by the same virulent clone at intervals that are regulated mainly by the level of herd immunity. Over the last few years, accumulating evidence (3–6) suggests that a limited number of clonal populations, each consisting of one or several closely related clones, may circulate for decades between countries and even continents. Under favourable conditions such as international mass migration caused by the annual pilgrimage to Mecca, local outbreaks may within weeks spread to other countries and continents. According to Olyhoek et al. (6), at least 7 predominant clones have caused major epidemic waves since 1915. Insight into the epidemiology of group A meningococcal infection has recently been dramatically improved by the introduction of a number of modern research tools such as panels of monoclonal antibodies for serological testing (7), starch gel electrophoresis of cytoplasmic enzymes (5, 6, 8), and sodium dodecyl sulphate-polyacrylamide gel electrophoresis of bacterial outer membrane proteins (6). In addition to such phenotypic technologies, a

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Table 1. *DNA restriction enzyme patterns of 64 meningococcal isolates from various African countries (1961–86)*

Clone designation	Type representative	No. ofisolates	Similarity (%) to standard		Origin and year of isolation
			004	250	
Afr I.1	004	16	100		Niger 61 Burkina F. 61–62,65
Afr I.2	006	23	96		Niger 63–64 Cameroon 66
Afr I.3	256	1	98		Burkina F. 66
Afr I.4	86088	2	96		Niger 86
Afr II.1	250	5	<50	100	Djibouti, Morocco 67
Afr II.2	023	7	<50	80	Niger, Chad 63
Afr III	295	10	50	50	Morocco 67

genotypic approach, using so-called restriction endonuclease (RE) techniques, has been applied (5,9–13). It was the purpose of this study to explore further the potential of the RE technique for epidemiological mapping of group A meningococcal strains from Africa.

MATERIAL and METHODS

Bacterial strains

Strains from different African countries. 64 strains, representing Niger ($n = 39$), Burkina Faso (7), Chad (2), Cameroon (1), Morocco (11) and Djibouti (4), were obtained from the collection of the meningococcal reference centre at Institut de Médecine Tropicale du Service de Santé des Armées in Marseille, France; of these 64 strains, 36 had previously been thoroughly investigated for their clonal population structure by Olyhoek et al. (6). Except for 2 carrier strains from 1986, all isolates were obtained from the cerebrospinal fluid (CSF) of clinical cases of meningitis. The distribution of these strains by location and time is shown in Table 1.

Gambian strains. We investigated 77 strains collected during the period 1983–89. Of these, 25 originated from the CSF or blood of clinical cases; 13 from the Farafenni epidemic in 1983, and the others from different parts of the country during the years 1984 ($n = 5$), 1985 (3), 1986 (2) and 1987 (2). Of the remaining 52 strains 40 were recovered from carriers and 12 from persons of unknown clinical status. The carrier strains from 1984 included 4 isolates from non-vaccinated Senegalese citizens from across the border from Farafenni, and 6 carrier strains from vaccinated Gambians. The 1985 material included 5 carrier strains from schoolchildren at Bakau, an urban area near the capital Banjul. Also included are 26 carrier strains obtained in 1988 and 1989, during screening surveys of about 600 inhabitants in the Farafenni area at a time of low transmission.

Ethiopian strains. 24 strains were obtained from clinical cases hospitalised at Tikur Anbessa University Hospital of Addis Ababa or at the Health Centre in Zway, 200 km south of the capital. The strains represented all age groups, although with a dominance of young adults, and were all collected during the major epidemic of 1988–89.

Tanzanian strain. 1 strain was isolated in Moshi, in August 1990, from one of the several hundred patients involved in an outbreak of meningococcal disease then occurring in the Kilimanjaro and Arusha regions. (The strain was obtained by courtesy of the Department of Laboratory Services, Kilimanjaro Christian Medical Centre, Moshi.)

Indian strains. For comparison with the African strains 6 group A strains from clinical cases in New Delhi in 1985/86 were included in the study. (These were provided by courtesy of Professor Shriniwas, Department of Microbiology, All India Institute of Medical Sciences, New Delhi.)

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were kindly provided by Dr Dominique Caugant, National Institute of Public Health (SIFF), Oslo, Norway.

Bacteriological technique.

All strains were isolated on chocolate agar. Subcultures of suspected Neisseria meningitidis were serogrouped by slide agglutination using commercial antisera (Wellcome Reagents Ltd., Beckenham, UK). Only group A isolates are included in the material. The African strains obtained from Marseille had been lyophilized for up to 25 years; the Gambian, Ethiopian and Indian strains had been kept at −20°C for a maximum of 5 years, prior to reculture and restriction endonuclease typing in Norway.

Restriction endonuclease analysis

The RE analysis of chromosomal DNA was performed as described by Bjorvatn et al. (9), using the endonuclease EcoRI. If EcoRI produced incomplete patterns, HindIII was used. Previous experience (9) shows that these 2 enzymes are equally efficient, and that nothing is gained by combining them, except in cases where the bacterial DNA turns out to be refractory to one of them. All strains were tested at least twice. Following enzyme digestion, electrophoresis and staining of the resulting DNA fragments, 2 persons, independent of each other, visually compared the RE patterns (REPs) with selected reference strains. The degree (%) of similarity between test strain and reference was defined as the number of identical bands divided by the total number of bands in both REPs. This grading of similarity is fairly exact only with closely related strains.

In this work a clone is defined as bacterial isolates with an identical REP. Closely related patterns (80% homology or more) will be referred to as clonal clusters within one main pattern, whereas isolates differing from each other by more than 20% will be assigned to different main patterns.

In order to avoid confusion with other nomenclatures our main patterns are given the prefix Afr, Gam, Eth, etc. plus Roman numerals (I, II, etc) for the main groups, and in addition Arab numerals for each of the representatives of clonal clusters within a group, e.g. Afr. II. 1, Afr. II. 2, etc.

RESULTS

EcoRI produced satisfactory REPs in 143 cases, whereas additional Hind III digestion was required with 29 of the strains. Among the 172 strains under study, a total of 19 different clones distributed within 9 main REPs were identified. The 166 African strains represented 17 clones and 8 main patterns. The results will first be presented separately for each of the 5 strain collections.

Various African strains

The 64 isolates belonged to 3 main genetic patterns, here designated Afr I-III (Table I). The Afr I differed from the Afr II pattern by more than 50%. The Afr I cluster (cluster reference strain no. 004, Niger 1961) consisted of 42 isolates and was distributed within 4 closely related REPs, Afr I.1 – Afr I.4 (clone reference strains no. 004, 006, 256 and 86088, respectively). The REPs within the Afr I cluster differed from each other by 1–4 bands, i.e. < 10%. The isolates belonging to this cluster were recovered in Niger, Burkina Faso and Cameroon during the period 1961–86.

The second main pattern, the Afr II cluster (cluster reference strain no. 250) was represented by 12 isolates, and distributed within the two REPs Afr II.1 (5 isolates) and Afr II.2 (7 isolates), which were about 80% related. The representatives of this cluster originated from Djibouti and Morocco 1965–67 (Afr II.1) and Niger and Chad 1963 (Afr II.2).

The third main pattern, Afr III (clone reference strain no. 295, Morocco 1967) was represented by 10 completely homologous isolates originating from Fez in Morocco 1967.

The REPs obtained with the strains from various African countries are shown in Fig. 1.

Of the 64 isolates included in our collection from various African countries, 36 had previously been studied by Olyhoek et al. (6), using SDS-PAGE and multilocus enzyme

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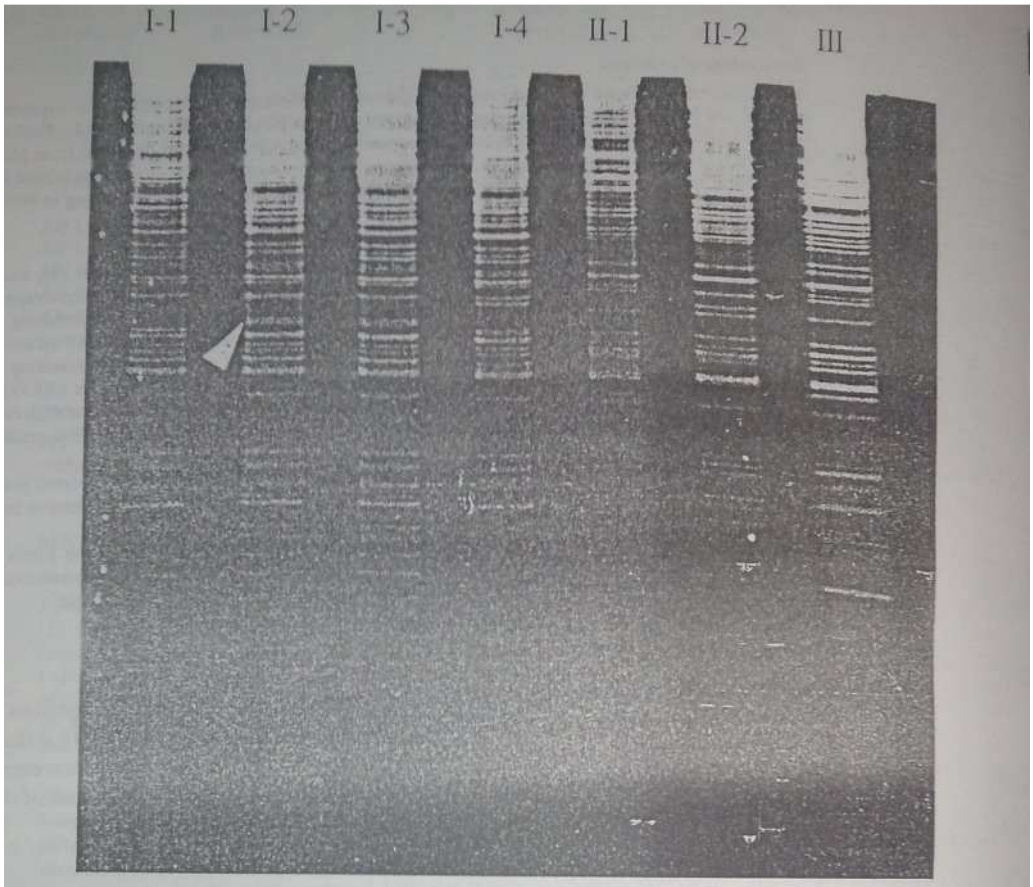


Fig. 1. Restriction enzyme patterns (REP) obtained with meningococcal isolates from various African (Afr) countries. Lanes 1–4: The representatives of the closely related Afr I cluster (Afr I. 1–4). Lanes 5 and 6: The Afr II cluster. Lane 7: The Afr III clone. The individual representatives of the main clonal patterns (cluster) e.g. Afr I. 1–4, do not differ from the REP of the type strain by more than 20% (difference in < 10 out of about 50 comparable band locations). Persistent discrepancy in a single location is considered sufficient to differentiate between the members of a cluster, e.g. the I. 1 and I. 2 clones of the Afr I cluster (arrow).

electrophoresis. This permitted a direct strain-by-strain comparison between RE analysis and the 2 other systems for strain differentiation. The results of this comparison are summarised in Table III. Most representatives of our clones Afr I.1 and I.2 were classified by Olyhock et al. (6) as clone IV-1 ET 42, but 3 out of our 11 Afr I.1 isolates were assigned to ETs 43, 44 and 45. The RE-detected difference between the clones Afr I.2 and Afr I.3 was reflected by ET but not by clonal differentiation whereas the RE difference between Afr II.1 and Afr II.2 was detected by both other systems. However, one of the 3 Afr II.1 strains was assigned to ET 29 rather than ET 30.

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Table II. *Restriction enzyme patterns of 77 meningococcal isolates from the Gambia 1983–88*

Clone designation	Type representative	No. of isolates	Year of isolation	Similarity (%) to standards		Similarity (%) to other RE patterns	
				944	1181		
Gam I.1	944	41	83–86	100		Ind I	100
Gam I.2	549	15	83–84	99		Afr I.1	98
						Ind I	97
						Afr I.1	95
Gam II.1	1181	1	83	<50	100	Unknown	
Gam II.2	B57	1	85	<50	91	Unknown	
Gam II.3	c1987	1	87	<50	90	Unknown	
Gam III	1344	16	83,88	<50	<50	Eth I.1	100
						Tan I	100
Gam IV	872	1	83	<50	<50	Unknown	
Gam V	8871	1	83	<50	<50	Unknown	

Gambian strains

The 77 isolates belonged to 5 main genetic patterns, designated Gam I – Gam V (Table II), and showed only remote mutual similarity. The Gam I cluster (cluster reference strain no. 944) consisted of 2 closely related clones, Gam I.1 (41 isolates, clone reference no. 944) and Gam I.2 (15 isolates, clone reference strain no. 549), differing from each other by 1 band only. The Gam II cluster contained 3 different REPs, differing from each other by < 10%, and all represented by 1 isolate only. 16 isolates belonged to the Gam III pattern (clone representative strain no. 1344), whereas both Gam IV and Gam V were represented by single isolates. The REPs that were obtained with the Gambian isolates are shown in Fig. 2.

Ethiopian strains

Of the 24 strains analysed, 17 were proven to be identical, and 2 more were probably identical (REP referred to as Eth I.1, clone reference strain no. 30), whereas another 4

Table III. *A comparison of clonal relationships using restriction enzyme technique and a combination of SDS-PAGE of 2 outer membrane proteins and multilocus enzyme electrophoresis*

Our results		No. compared	No. differed	Olyhoek et al.	
Clone	Type representative			Clone	ET
Afr I.1	004	11	3[a]	IV-1	42
Afr I.2	006	14	0	IV-1	42
Afr I.3	256	1	0	IV-1	44
Afr II.1	250[b]	3	1[c]	II-1	30
Afr II.2	023	7	0	I-3	15

[a]Three strains (018, 037 and 178) were assigned as ET 45, 44 and 43, respectively.
[b]Olyhoek's results based on strain 252, which we lost, but found identical to our type representative 250.
[c]One strain (223) was assigned as ET 29.

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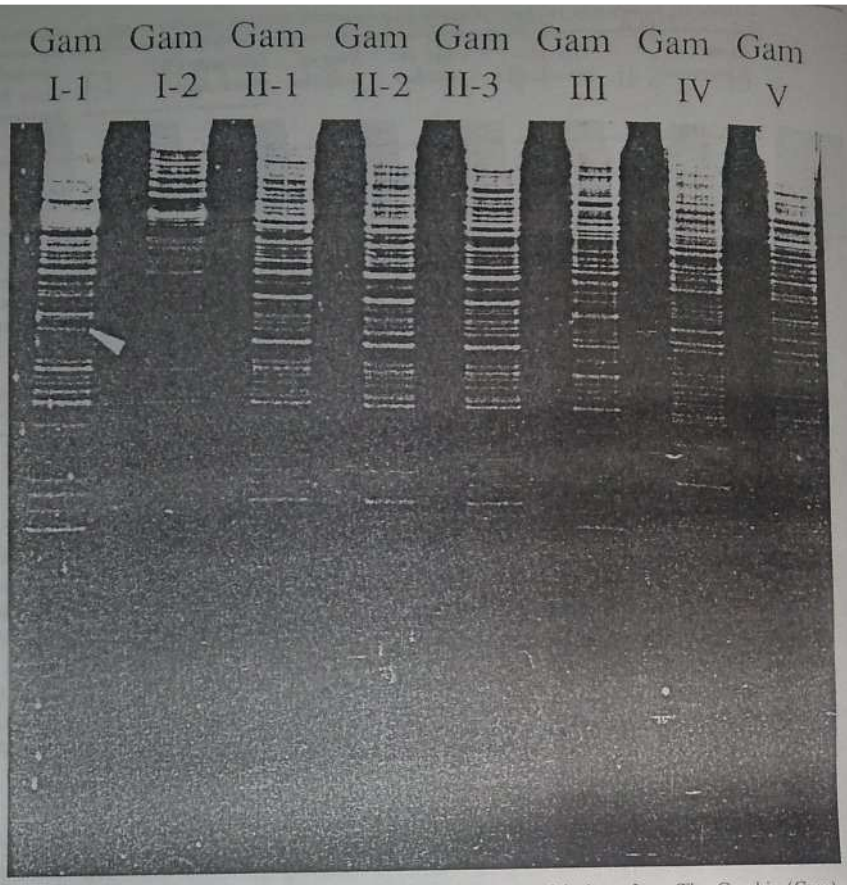


Fig. 2. Restriction enzyme patterns obtained with meningococcal isolates from The Gambia (Gam). Lanes 1 and 2: The closely related clones Gam I-1 and Gam I-2 (one line difference only, arrow). Lanes 3–5: The Gam II cluster. Lane 6: The Gam III clone. Lanes 7 and 8 represent single isolates of apparently uncommon group A clones.

isolates differed from this pattern by 1 particular band only (Eth I.2, clone reference strain no. 32). One isolate, Eth II, differed significantly (i.e. by > 10 bands) from the Eth I cluster. On 6 occasions the EcoRI endonuclease produced an insufficient number of bands for reliable comparison. In 4 of those cases, subsequent digestion by Hind III solved this problem beyond doubt; in the 2 remaining cases identity with the Eth I.1 pattern was likely, but not proven with this technique. The REPs of the Eth I cluster are depicted in Fig. 3.

Indian (New Delhi) strains

The 6 strains studied were equally distributed within 2 REPs, Ind I (clone reference strain

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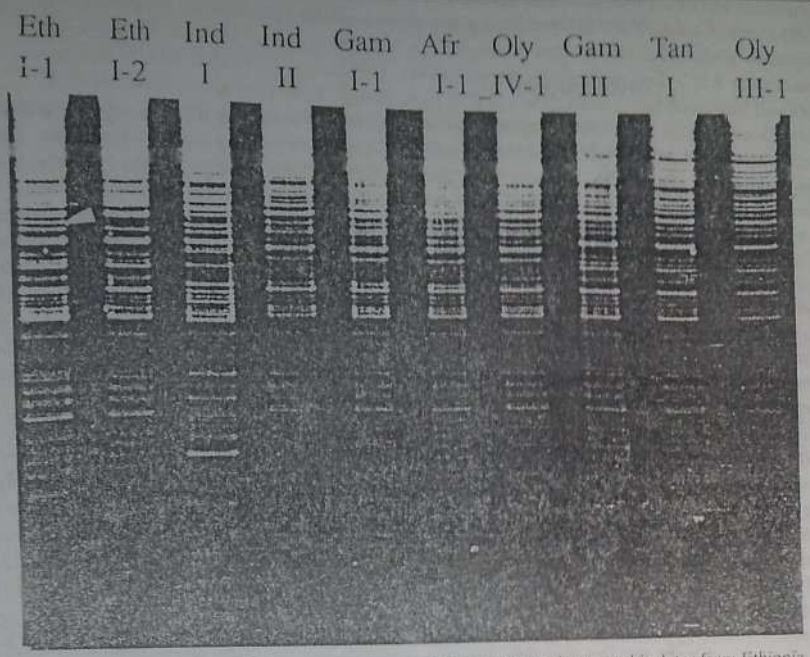


Fig. 3. Comparison of restriction enzyme patterns obtained with meningococcal isolates from Ethiopia (Eth), India (Ind), Gambia (Gam), Tanzania (Tan) and other African countries. Type representatives of clones III-1 and IV-1 (Olyhoek et al., ref. 6) are also included. The 2 Ethiopian clones I-1 and I-2 (Lanes 1 and 2) are very closely related (one line difference only, arrow), whereas the Indian clones I and II (Lanes 3 and 4) are clearly different. Note that the Gam I-1 (Lane 5) and Afr I-1 (Lane 6) clones are quite similar, but not identical. Complete identity is found between the Gam III (Lane 8), Eth I-1 (Lane 1), Tan I (Lane 9) and the Olyhoek (Oly) III-1 reference clone (Lane 10). Similarly, the Ind I clone (Lane 3) and the Gam I-1 (Lane 5) are identical, and differ by 1 line only from the reference clone Oly IV-1 (Lane 7).

no. 1680) and Ind II (clone reference strain no. 1213), which differed from each other > 50%. The Ind I and II REPs are shown in Fig. 3.

Relationship between REPs from different geographical areas

The clones of the Gam I cluster were found to be closely related to, but not completely identical with the 4 clones of the Afr I cluster. However, the Gam III proved identical to the dominant REP of the recent Ethiopian epidemic, Eth I, as well as to the recent isolate from Tanzania (Fig. 3). Furthermore, complete identity was found between Gam III, Eth I, Tan I and the III-1 reference strain according to Olyhoek et al. (6), obtained from SIFF. The clone reference strain of Gam III (No. 1344) was recovered from a Gambian case in 1983, but we have no further isolates of this clone until our screening in 1989 of school children in Korojolakunda, near Basse in the easternmost part of The Gambia, where a fatal case of

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meningococcal disease had occurred a few days previously. 15 isolates of REP type Gam III were obtained among the contacts of this case.

DISCUSSION

Our results support previous observations indicating that meningococcal disease in countries of the African Meningitis Belt is caused by a small group of clones, some of which are closely related. Thus, over the past 30 years bacteria belonging to the complex of almost identical clones Afr I and Gam I were widely spread within the Belt. On the other hand strains of markedly different REPs seem regularly to have contributed to meningococcal morbidity inside (Afr II.2, Gam II. 1–3) as well as outside (Afr II.1, Afr III) the traditional Belt countries. The dominance of a particular clone at the time of major epidemics has been emphasized by the recent introduction of the highly virulent III-1 clone (6), which in the present paper is represented by Gam III/Eth I.1 and Tan I. According to Salih et al. (12) the large 1988 epidemic in the Sudan was completely dominated by strains of clone ET3/III-1. As shown here, clone III-1 also dominated the 1988 epidemic in Ethiopia, although we found 2 closely related versions, Eth I.1 and Eth I.2.

Moore et al. (3) suggest that the wave of clone III-1 infection that in 1987–89 swept over Saudi Arabia, Ethiopia, Sudan and Chad, originated in Nepal, and followed the pilgrim routes to and from Mecca. It is highly probable that the mass migration of pilgrims plays an important role in the spread of the meningococcal epidemics in these parts of the world. However, the direction and pattern of the epidemic flow seem to be quite complex, probably in part because of interactions between prevailing meningococcal clones. Thus, the Ind I clone that was isolated in New Delhi in 1986 is identical to the clone Gam I.1 that existed in the Gambia at least during 1983–86, possibly indicating a flow from west to east. Similarly, the suggestion of a flow of clone III-1 from Nepal via Saudi Arabia to Africa is contradicted by the fact that this clone too, was found in The Gambia already in 1983. Unfortunately, further spread of the highly virulent III-1 clone was easily predictable. In 1989 and 1990 Tanzania has had outbursts of meningococcal disease both in the Dar es Salaam area and more recently also in the Northern Zone. That the III-1 (Tan I) was involved at least in the latter is proven here.

A total of 17 different clones distributed within 8 main REPs were found among the 165 African strains represented in the present material. In their extensive review article on the clonal population structure of N. meningitidis serogroup A, Olyhoek et al. (6) identified 15 electrophoretic types (ETs) and 6 clones among 256 African strains recovered during the period 1960–1983. Our material included 36 of these strains, which allowed direct comparison between the different techniques employed. Applying our strict definition of a clone, the RE technique apparently has a power of resolution similar to that of ET, whereas our definition of main REPs appears roughly to cover the relatively wide clonal concept of Olyhoek et al. Although in general there is a fair agreement between the results, on occasion the ET revealed subtle differences not seen by the RE technique, and vice versa.

Crowe et al. (5) report that all of their 226 group A strains that were collected in The Gambia during the period 1982–88 were of clone IV-1, ET 42, although the isolates varied to some extent in the expression of certain surface components. Our survey of Gambian strains covers largely the same period and geographical areas. Although we confirm that the majority of isolates from this period are closely related (Gam I.1 and Gam I.2 representing 66/77 isolates), the extreme uniformity of the epidemiological picture as reflected by clonal analysis becomes less striking when viewed by RE classification. Admittedly, the difference between the dominating Gam I.1 and Gam I.2 was represented by 1 band only, and appears subtle. However, this difference was remarkably consistent, and was observed in a relatively

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large number of strains. Interestingly, our finding that 5 different clones were represented among the 77 Gambian isolates comes very close to the results obtained with this technique by Crowe et al. (5). Among the 63 serogroup A strains isolated in The Gambia between 1982 and 1984, 59 showed a similar REP (L-1) whereas 4 isolates showed slightly different patterns (L2-L5). Olyhoek et al. (11), comparing clonal analysis with DNA restriction analysis, found a total of 13 REPs among their 34 ETs and 21 clones, and concluded that the discriminating ability of the RE technique was less than that of the other techniques. On the other hand, as shown by Crowe et al. (5) and now supported by our results, RE analysis may sometimes permit further discrimination when applied to strain populations, which by clonal analysis and ET mapping are found completely homogeneous. Obviously, these techniques are only partly congruent, and are likely to have somewhat different fields of application.

The RE method is exact and highly reproducible, but labour intensive and technically demanding. Also, electrophoretic enzyme typing and analysis of outer membrane proteins are techniques that are normally restricted to highly specialised research laboratories. The level of resolution depends upon choice of restriction endonuclease, or the number of enzymes or protein components that are included in the test battery. Thus, using another series of enzymes, Moore et al. (3) on several occasions arrived at clonal assignments different from those reported by Olyhoek et al. (6). Similarly, another choice of restriction endonucleases in this study might have changed some of our conclusions regarding clonal relationships. It should be emphasised, however, that the principal agreement between the results obtained with these very different epidemiological tools is quite striking, and seems to confirm the relevance of their respective contributions. For the screening of large numbers, the RE technique seems less suitable, at least without automated reading and interpretation of the often complicated band patterns. (In our experience, scanning of band patterns by densitometer cannot replace careful visual examination.) Also, except for closely related isolates, it is quite difficult to assess numerically the degree of relatedness between strains. On the other hand, for the exact differentiation of small numbers of closely related clones, this method has proven very efficient (5, 10, 12).

Crowe et al. (5) recently reported reduced sensitivity to complement-mediated killing in a small proportion of Gambian group A isolates. This potentially important observation is a timely reminder of the need for simple epidemiological tools that will identify more specifically the phenotypic or genotypic characteristics of particularly virulent bacterial clones.

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MULTIPLE MYELOMA IN ETHIOPIANS: ANALYSIS OF 22 CASES

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ABSTRACT: Twenty-two cases of multiple myeloma were seen in the Department of Internal Medicine, Tikur Anbessa (Black Lion) Hospital, a teaching and referral hospital in Addis Ababa, Ethiopia, from January 1983 to December 1990. The age range was 38 to 76 (mean ± SD = 51.5±12.2) years; a third were in the fifth decade. The male: female ratio was 1.75:1. The common clinical findings were bone pain in 20 (91%), bone tenderness in 15(68%), anaemia in 14 (64%) and spinal cord compression in 8 (36%). The erythrocyte sedimentation rate (ESR) was raised in 21. Serum protein was raised in 17(77%) and hyperglobulinaemia was seen in 20 (91%). Serum uric acid, blood urea nitrogen (BUN) and calcium were elevated in 10, 8 and 5 patients respectively, Bence-Jones proteinuria and albuminuria were each found in 9 patients. All patients had radiological abnormalities; 9 had a combination of lytic lesions, osteoporosis and pathological fractures (41%). Ten patients presented in clinical stage III. Four patients are being followed after 3-84 (median 40.5) months; eight were lost to follow-up 1-8 (median 2.0) months after diagnosis. Ten patients have died after 1-55 (median 11) months. Multiple myeloma is not uncommon in Ethiopians. Except for a lower age at presentation, the clinical, haematological, biochemical, and radiological findings, and the response to therapy, are similar to those reported elsewhere.

INTRODUCTION

Multiple myeloma is a neoplasm of mature and immature plasma cells. The clinical manifestations result from uncontrolled, progressive proliferation of these cells, marrow replacement by them, and their overproduction of certain proteins and/or polypeptide chains (1). Multiple myeloma accounts for about 1% of malignant diseases and slightly more than 20% of haematological malignancies in the United States of America (USA) (2), its incidence there being about 2.0-4.0 cases/100,000/years in blacks and 1.0-2.0 in whites (3), while in England and Sweden the rates were about 3.0/100,000/year without any racial differences (4). Earlier reports suggested that multiple myeloma was uncommon in Africans (5), the reasons being underdiagnosis due to lack of medical facilities. Subsequently, however, this disorder has been reported in indigenous Africans and people of African descent (6-9). In Ethiopia, only seven cases of multiple myeloma were reported in the 1970's (10-13). In a more recent analysis of haematological admissions, eleven cases of multiple myeloma were mentioned without detailed description (14). The aim of this prospective study is to describe the clinical, haematological, biochemical, radiological and follow-up findings and compare them to those seen elsewhere.

PATIENTS AND METHODS

Twenty-two consecutive new cases of multiple myeloma, including one transferred from the Orthopaedic Department, admitted to the medical

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wards of the Tikur Anbessa (Black Lion) Hospital, Addis Abeba University's teaching and referral hospital, during the period January 1983 through December 1990 were included in this study. No patients were referred from the Surgical or Gynaecology Departments during the study period. All patients with the diagnosis of multiple myeloma were hospitalised for investigation and management.

The age, sex, date of diagnosis and type of multiple myeloma as well as the clinical, haematological, biochemical, urinalysis (including Bence-Jones protein), radiological, bone marrow aspiration, and other tissue biopsy results were recorded prospectively. Peripheral blood films and bone marrow aspirates were stained by Wright's stain (15). For inclusion in the study, at least two of the following diagnostic critria had to be fulfilled (16):

1. increased numbers (>10%) abnormal plasma cells in the bone marrow aspirate
2. biopsy proven plasmacytoma, either in bone or soft tissue
3. the presence of a monoclonal protein in plasma and/or urine
4. osteolytic lesions, or osteoporosis if bone marrow plasma cells are >30%
5. myeloma cells (abnormal plasma cells) in the peripheral blood.

Clinical staging was according to Durie and Salmon (17). The chemotherapeutic agents used were melphalan 0.25mg/kg/day and prednisolone 40mg/day given for four days every four to six weeks (18), or cyclophosphamide 250 mg/m^2/d and prednisolone 40mg/day given for four days every three to four weeks (19). Both regimens were given for up to two years and stopped; then patients were followed every 3-6 months until relapse occurred.

Response to therapy was rated according to Alexanian *et al.* (20):

Good - improvemnt of >50% of the parameters initially abnormal

Partial - improvement of <50% of the parameters initially abnormal

No response - no change in any of the parameters initially abnormal.

Progression - progression of the disease

RESULTS

During the study period, twenty-two cases of multiple myeloma were seen in the medical wards of the Tikur Anbessa Hospital. Fourteen were males and eight females (M:F 1.75:1). The age range was 38-76 years (mean $\pm$SD = 51.5$\pm$12.2). One-third were in the fifth decade. The age and sex distribution is shown in Table 1.

The clinical features at diagnosis are shown in Table 2. The commonest findings were bone pain and tenderness, pallor and/or difficulty walking. Three of the patients with weakness had severe anaemia. Kidney biopsy to look for *amyesidosis* was not done in any of the patients. The patient with nausea and vomiting had high serum calcium and BUN levels.

The haematological parameters are shown in Table 3. Anemia was present at the time of diagnosis in 14, leucopenia in 3 and thrombocytopenia in 4. No patients had haemorrhagic manifestations. The ESR was raised in 21 patients, being above 50mm/hr in 20 and above 100mm/hr in 11. Intense rouleaux formation was seen in 10 cases (46%). Bone marrow aspiration showed plasmacytosis in excess of 10% in 20(91%) of the cases, in one the sample was poor and in the other the diagnosis was confirmed by bone biopsy.

The biochemical data are shown in Table 4. The total serum protein was $\geq$ 10.0gm/dl in 11 patients. The serum electrophoresis showed a sharp peak in the gamma-region in 13, beta-region in 5 and alpha-region in two, and was normal in two. Hypoalbuminaemia of $\leq$ 3.0gm/dl was seen in four patients.

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finding was the combination of lytic lesions, osteoporosis and pathological fractures in 41%, comparable to Western, Kenyan and Jamaican series (2,8,9).

As all patients were symptomatic at the time of presentation, supportive treatment was given as indicated. In addition, nineteen patients were treated with chemotherapeutic agents, with responses comparable to those reported elsewhere (18-20), although the number of patients in this series is small. The follow-up of these patients has been erratic and poor; 8 were lost to follow-up 1-8 (median 2) months after diagnosis. This problem was seen in Kenyans as well (8). Ten patients have died 1-55 (median 11) months after diagnosis, less than the median survival of 20 months in the North American series (2) but better than the Jamaican of 2.2 months (9).

In conclusion, multiple myeloma is not uncommon in Ethiopians and, apart from its presentation at a relatively younger age, the clinical, biochemical, radiological findings and response to therapy are similar to those in Caucasian and other African populations.

TABLE 1. Age and sex distribution at diagnosis

Age group (Years)	Male	Female	Total
31-40	5	1	6
41-50	4	3	7
51-60	3	1	4
61-70	1	3	4
71-80	1	-	1
Total	14	8	22

TABLE 2. Clinical features at presentation in 22 patients

Symptoms	No.	Signs	No.
Bone pain	20	Bone tenderness	15
Difficulty/inability in ambulation	8	Pallor	14
Weight loss	8	Spinal cord compression	8
Generalized weakness	7	Soft tissue mass	3
Fever and sweating	3	Gibbous	3
Swelling externally	3		
Nausea and vomiting	1	Lymphadenopathy	2
Generalized body swelling	1	Anasarca	1
Decrease in urine volume	1		

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Immunoelectrophoresis was done in only five patients: 2 had IgG, 2 IgA, and 1 light chain disease. The corrected serum calcium was above 12.0mg/dl in five patients. Blood urea nitrogen (BUN) was above 80mg/dl in 5 patients. Significant albuminuria (>1.0 gram/24 hours) and Bence-Jones proteinuria occurred in nine (40.9%) patients each.

All patients had abnormal radiological findings at presentation (Table 5). The clinical stage at diagnosis is given in Table 6.

Nineteen patients were treated with chemotherapeutic agents, one had excision of L 3 vertebral plasmacytoma (proved by histology after surgery) and radiotherapy, while two patients were not given specific therapy as they had terminal disease (Table 7). Of the 20 treated, four were inevaluable as they either died or were lost to follow-up within one month of initiation of therapy. Of the evaluable 16 patients, seven had good, 8 partial and one no response. Currently, four patients continue to be followed 3-84 (median 40.5) months and 8 are lost to followup 1-8 (median 2) months after diagnosis. Ten patients have died 1-55 (median 11) months after diagnosis. Three died of renal failure and 3 of infection, one of auto accident ten months after diagnosis while in remission of his primary disease, and one of congestive heart failure due to anaemia. Two patients died at home, the causes of death were not known. Autopsies were not done in any.

DISCUSSION

Multiple myeloma occurs in all parts of the world (1). Its incidence in USA is said to be more in blacks than in whites (3) although this is not confirmed elsewhere (2,4). In Ethiopia, very few cases were reported in the 1970's (10-13) without detailed description. The current communication includes the eleven cases reported previously (14) and has attempted to present clinical, haematological, biochemical, and radiological details as well as the response to therapy.

In most Caucasian series (2-5) the peak incidence has been in the sixth or seventh decade with very few patients below the age of 40 years. In the present series, 7 of the 22 patients were in the fifth decade, and 6 less than 40 years of age, a pattern which has been found in previous studies from Africa (6-8). This may mean that the disease is seen at a younger age in Africans than in Caucasians. The male to female ratio of 1.75:1 observed in this series is similar to previous Western (2) and African series (7,8). Bone pain, mainly low back pain, occurred in 20 patients, slightly higher than in previous reports (2-9), possibly due to the fact that most patients sought medical advice at an advanced stage of the disease. Pathological fractures occurred in 10 (46%), more commonly in the vertebral axis with spinal cord compression. This figure is comparable to the 33% seen in Rhodesia (now Zimbabwe) and Kenya (6,8).

Anaemia was present at the time of diagnosis in 14. This figure is comparable to that found in a large Caucasian series (2), and in Kenya and Jamaica (8,9). The anaemia was severe (Hgb < 8 gm%) in 8 of 22, in contrast to 8% of Caucasians (2) but similar to the finding in Jamaicans (9). The erythrocyte sedimentation rate was raised in 21 (96%), comparable with previous series (2-9). It was above 100 mm/hr in half the patients as was the case in the Jamaican series (9).

The biochemical results were similar to those reported from North America, England, Kenya and Jamaica (2,4,8,9). Particularly, the serum electrophoretic pattern was similar to that in North America and Jamaica (2,9). We do not have any explanation for the high alpha and beta peaks. Serum alkaline phosphatase was raised in only 3 of our patients, similar to the Jamaican series (9) but at variance with the Kenyan (8) which found a rise in 33.3%.

All patients in this series had abnormal radiological findings at the time of presentation. The commonest

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TABLE 5. Radiographic findings at presentation

Findings	No.
Lytic lesion only	2
Osteoporosis only	3
Lytic lesion and osteoporosis	6
Osteoporosis and pathological fractures	2
Lytic lesions, osteoporosis and pathological fractures	9
Total	22

TABLE 6. Clinical stage of 22 myeloma patients

Stage	No.	Renal function
I	6	A - 6 B - 0
II	6	A - 6 B - 0
III	10	A - 2 B - 8
Total	22	22

A = BUN < 30 mg/dl
B = BUN ≥ 30 mg/dl

TABLE 7. Response to therapy in multiple myeloma patients

Therapy	Total	Response				
		Good	Partial	No response	Progression	Inevaluable
Melphalan + prednisolone	5	3	2	-	-	-
Cyclophosphamide + prednisolone	14	3	6	1	-	4
Surgery + radiotherapy	1	1	-	-	-	-
None	2	-	-	-	-	2
Total	22	7	8	1	-	6

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TABLE 3. Initial haematological parameters in 22 patients

Parameter	Range	Mean	S.D.	Abnormal in	No. abnormal
Hgb (gm/dl)	4.2-18.5	9.4	4.1	<11.5	14
WBC (per mm^3)	2,300-12,800	6370	2542	<4000	3
Platelets (per mm^3)	45,000-215,000	146,500	55,296	<100000	4
ESR (mm/hr)	10-170	101	40	>20	21
Rouleaux formation				present	17

Note: Hgb = Haemoglobin; WBC = White blood cell
ESR = Erythrocyte sedimentation rate
SD = Standard deviation

TABLE 4. Biochemical data at diagnosis in 22 patients

Parameter (normal value)	Range	mean	S.D.	Abnormal if	No. abnormal
Total serum protein (6.5-8.5 gm/dl)	5.8-13.8	9.9	1.9	>8.5	17
Serum albumin (3.5-4.5 gm/dl)	2.4-5.5	3.6	0.8	<3.5	14
Serum globulins (1.5-3.5 gm/dl	0.5-9.3	4.7	2.0	>3.5	20
Serum calcium (9.0-11.0 mg/dl)	8.1-22.0	11.2	3.1	>11.0	5
Alkaline phosphatase (80-220 iu/L)	78-254	154.9	54.5	>220	3
Serum uric acid (3.0-7.0 mg/dl)	3.4-18.0	9.1	4.2	>8.0	10
Serum BUN* (10-25 mg/dl)	6.9-130	38.2	37.1	>30	8
Bence-Jones Proteinuria				present	9
Urine albumin				≥1gm/24hrs	9

* BUN = Blood urea nitrogen

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6. NEUROPSYCHOLOGICAL ASPECTS OF EPILEPSY IN AFRICAN COUNTRIES *

Introduction

Psychosocial problems and psychological testing in epilepsy

The occurrence of psychosocial problems related to epilepsy is well recognized and documented [Dodrill et al., 1984; Dowds et al., 1985]. In certain situations these problems may be more troublesome than the seizure disorders themselves [Livingston, 1981]. What makes these associated psychological and social problems very crucial in the management of the epileptic is the universally recognized negative public attitude toward epilepsy.

Review of the literature on neuropsychological study of persons with epilepsy reveals a number of problems encountered in reaching sound judgements and conclusions from the tests.

Epilepsy encompasses a heterogenous group of seizure disorders with their own aetiologies, clinical characteristics and psychological consequences. For instance, partial complex seizures are commonly associated with psychosocial problems. The ways they manifest also differ with the laterality of the temporal lobe involved. Therefore, the nature and degree of cognitive impairment and personality deviations in persons with epilepsy will be influenced by a number of diseased-related and non-related variables which make psychological testing difficult to interpret. The disease-related factors include type of seizure, age of onset, frequency, duration of ictus, occurrence of status, electroencephalographical characteristics, aetiology of the seizure and behavioural effects of anticonvulsant drugs. The educational standard of the person with epilepsy has been shown to be a very important non-disease related factor in the tests [Brittain, 1980]. This aspect will have a great deal of relevance when we discuss the patients with epilepsy in Africa.

Single psychological tests, such as those commonly employed to measure general intelligence, are insufficient to assess intellectual functions and deficit in persons with epilepsy. Such tests of intelligence applied to people with epilepsy have come under criticism because they may be unreliable in the detailed examination of the relationship between cerebral function and behaviour.

There is also the factor of intellectual deterioration during the course of the epilepsy which needs to be evaluated in cases where this is suspected. In this respect serial assessment appears to offer the best hope of elucidating factors responsible for cognitive deterioration [Thompson and Huppet, 1980]. Here again, the African situation where the majority of people with epilepsy have never been treated with anticonvulsants will need to be borne in mind.

Methodologies of psychological testing

On the methodological considerations of psychological testing of persons with

* Contributed by R. Tekle-Haimanot.

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epilepsy, Reitan [1976], based on extensive review of the literature, concluded that methods should be developed to achieve a reasonable representation of psychological correlates of epilepsy. This will be best achieved through a battery of psychological tests designed to measure brain-behavior relationships. This approach has been accepted and extensively used in recent years. The construction and development of the Washington Psychosocial Seizure Inventory (WPSI) has further contributed to the objective assessment of psychosocial problems in epilepsy. This inventory has proved to be useful in both clinical and research context. From a practical aspect it shows itself useful in determining the vocational and social adjustment of an individual with epilepsy [Dodrill, 1980].

What do experts in the field think of the functions of psychological testing in epilepsy? At the conclusion of the first Workshop of Persons with Epilepsy [WOPSASSEPY1, 1980], expert opinions were divided on the issue. The majority of experts believed that such tests were important to elucidate the psychological functioning of the person with epilepsy and that the results of these tests might be used to modify the influence of seizure phenomena, anticonvulsant drugs and social reactions due to the attached stigma. These experts felt that specific tests tailored for epilepsy would be required, and that this will serve a useful purpose to help the epileptic adjust to and achieve a normal life. On the other hand, there were some that questioned the need for specialized tests for epilepsy and also cast doubts on the eventual practical value of these tests to the patient.

In the light of these controversies it would be of interest to examine epilepsy in Africa, and the place of psychological testing of African people with epilepsy.

Problems of epilepsy in Africa

Prevalence

Besides infections of the central nervous system (CNS), epilepsy is the most prevalent non-traumatic neurological disorder in Africa. The prevalence rates generally vary from 4 to 7/1,000 [Tekle-Haimanot, 1990], except for exceptionally high frequencies reported from Tanzania [Jilek-Aall et al., 1979] and Liberia [van der Waals et al., 1983], where genetic and other factors have been implicated. The prevalence rates from African studies, including more recent ones undertaken on large population bases [Osuntokun et al., 1987; Tekle-Haimanot et al., 1990], fall within the range of rates (5–6/1,000) obtained in the United States [Hauser and Kurland, 1975] and England [Brewis, 1966]. These epidemiological comparisons may give the wrong impression that epilepsy is not generally a very common problem in Africa. This is certainly not the case. Due to possible high mortality caused by untreated epilepsy in African populations, the prevalence rate of epilepsy may be underestimated.

There appear to be differences of opinion on the clinical patterns of epilepsy in Africa. Many studies [Levy, 1970; Dada, 1970; Billinghurst et al., 1973; Tekle-Haimanot, 1985] suggest that grand mal seizures are very common. However, more recent hospital-based studies from neurological and epilepsy clinics, using carefully monitored criteria and sophisticated investigations, have shown that partial complex seizures are more common [Danesi, 1983],

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and have very strong associations with febrile convulsions [Danesi, 1985].

Aetiological considerations

While previous investigations [Osuntokun, 1985] have suggested birth traumas and central nervous system infections as the main aetiological factors for epilepsy in Africa, Ogunniyi et al. [1987] in their hospital-based case-referent study have shown previous febrile seizures and head trauma to be risk factors for epilepsy, while immunization during childhood decreased the risk of epilepsy. The role of febrile convulsions in partial complex seizures has also been emphasized. Based on available experiences, it is fair to conclude that childhood febrile convulsions, birth injury, CNS infections and head injury are the main factors associated with epilepsy in Africa [Danesi, 1983].

Public attitudes toward the disease

In African communities there are widespread beliefs that epilepsy is due to possession or bewitchment by evil spirits or the devil, and in some of the cultures the spirit is believed to be those of ancestors [Smartt, 1959; Levy et al., 1964; Billington, 1968; Cardozo, 1976]. There are also beliefs that the transmission of the disease is by physical contact, such as by saliva [Jilek-Aall et al., 1979; Billinghurst et al., 1973; Osuntokun and Odeku, 1970; Tekle-Haimanot et al., 1991]. Hereditary factors have also been incriminated in some cultures [Tekle-Haimanot et al., 1991]. In central Uganda, epilepsy is attributed to the presence of a lizard in the brain, and epileptic falls occur whenever the lizard moves [Bennett, 1963]. Thus, attitudes toward epilepsy and the person with epilepsy in indigenous Africa are invariably unfavourable, because they generally reflect the mythical beliefs about the disease. Like leprosy, epilepsy carries a strong social stigma, and those afflicted by it can become ostracized by the society.

Management of seizure disorders

In developing countries, where basic health services are inadequate and in many areas non-existent, the majority of persons with epilepsy continue to suffer from their seizures without their disease being recognized and diagnosed. The management of epilepsy in developing countries and particularly in Africa is far from satisfactory. There are estimates that suggest that between 80%–94% of patients with active epilepsy in developing countries are not receiving anticonvulsant therapy [Shorvon, 1988]. This would mean that an alarmingly high number of African epileptics live and suffer with their disease. A high mortality rate has also been reported among epileptics, as in Ethiopia [Tekle-Haimanot, 1990]. This would inevitably mean that a significant proportion of those destitute epileptics that do not succumb to the disease end up with mental deterioration and mental subnormality.

Izurova and Iloege [1989] reported that 18% of 580 epileptic children that they studied in Nigeria were mentally retarded, a prevalence rate higher than in the general population. The authors explained that the high prevalence rate was due to episodes of status epilepticus, early age at onset of the seizures and long delay before presentation to hospital for treatment.

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Priorities in the care of African epileptics

Certainly the first and foremost priority in the care of the African epileptic would be the identification of the sufferers and the provision of anticonvulsant therapy. Since financial difficulties are the main cause of defaulting among African epileptics on treatment, it has been suggested that anti-epileptic drugs should be provided at little or no cost [Danesi, 1987]. This very big task has not yet been achieved in many of the African countries, because of the poorly developed health delivery services and shortages of trained manpower and medicines. In view of the meagre resources and financial constraints of the majority of the African countries, health planners have been forced to provide care for epileptics within the framework of the basic health delivery system, using low cost drugs such as phenobarbitone [Osuntokun, 1979]. This may not be the ideal, but is the best that African countries could provide for their patients with epilepsy.

While diagnosis and anticonvulsant therapy is the most important aspect in the management of the epilepsy in Africa, such activities would be ineffective unless accompanied by intense health educational programmes aimed at informing people with epilepsy and the general public at large, about the causes of the disorder and the values of anti-epileptic medications. Such specialized educational programmes should be aimed at counteracting the negative public attitudes toward people with epilepsy. The programmes need to focus on schools, health institutions and mass organization, because of the high illiteracy rate in many African countries [Danesi, 1987; Tekle-Haimanot et al., 1991].

Psychological evaluation of patients with epilepsy in Africa

Psychology in Africa

Before we analyze the question of psychological testing in epilepsy, we must examine the position of psychology as a discipline in the African context. Most psychological research in Africa has used Western frames of reference to examine African problems. In addition, the lack of knowledge of the indigenous problems and sometimes the biased views of the non-African researchers have been responsible for the shortcomings of much of the published work. At the same time very little has been done in the development of psychology in Africa by African scholars themselves. For instance, modern universities have not encouraged the introduction and propagation of teaching in psychology in their curricula. The African preoccupation with the pressing problems of the economical backwardness, food shortages and malnutrition, as well as disease and ignorance, might perhaps explain why a discipline like psychology has not received due attention [Yusuf Omar Abdi, 1975].

The importance of psychological investigations cannot be underestimated. If we take epilepsy in Africa, there are very strong reasons and indications for study of its psychosocial effects on the patient and the general public. As has been mentioned earlier, the African public has the wrong and superstitious perception that the causes of epilepsy are heredity, witchcraft and possession by evil spirits. These negative attitudes will reflect strongly in the difficulties encountered by African people with epilepsy concerning adjustment to social and

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dardized African-oriented tools for assessing these psychosocial problems.

I believe that there is a strong need for teams consisting of psychologists, sociologists, epidemiologists and neurologists interested and knowledgeable in the problems of epilepsy in Africa to come together and examine the relevance of psychological tests pertaining to epilepsy.

Such a team of experts could set about organizing a general framework and guidelines for the use of psychological testing in cases of brain damage and neurological disorders in general, and in epilepsy in particular. This will have to be tailored for the African situation, with due consideration of the special problems and needs of those that would require practical help.

On the other hand, there is a strong need in developing countries to encourage the establishment of epilepsy associations or leagues. These associations, with an effective and active participation of patients, would foster the development of information programmes on epilepsy, individuals with epilepsy employment associations and other rehabilitation facilities to provide people with epilepsy with opportunities to lead a normal life, with less fear of rejection by the society they live in.

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BRIEF COMMUNICATION

THE EFFICACY OF HYDROCHLOROTHIAZIDE, TIMOLOL AND ENALAPRIL IN ETHIOPIANS WITH ESSENTIAL HYPERTENSION

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ABSTRACT: A double-blind trial of hydrochlorothiazide, timolol and enalapril was carried out in Ethiopians with essential hypertension at the Tikur Anbessa Hospital, Addis Abeba, between 1987 and 1990. Patients with a supine diastolic blood pleasure of 95-120 mmHg after a washout period of 2 weeks were randomized to receive hydrochlorothiazide 25 mg daily, timolol 10 mg daily or enalapril 10 mg daily. Doses were doubled at 4 weeks if the diastolic blood pressure remained above 95 mmHg. At the end of 8 weeks of treatment, there were 9 patients taking hydrochlorothiazide, 10 patients taking timolol and 7 patients taking enalapril. Hydrochlorothiazide significantly lowered both systolic and diastolic blood pressure at 4 and 8 weeks compared with pre-treatment levels. Timolol and enalapril did not significantly lower the systolic blood pressure, but each lowered the diastolic blood pressure at 4 weeks and 8 weeks respectively. More patients on hydrochlorothiaside attained a diastolic blood pressure of <90 mmHg while less patients required doubling of dosage compared to timolol and enalapril. It is concluded that Ethiopian hypertensives may respond better to diuretics than to beta-blockers or angiotensin converting enzyme inhibiters, as found in other black populations.

INTRODUCTION

Evidence that there are racial differences in the response to antihypertensive medication has been accumulating over the years. Black South Africans have been shown to be less responsive to beta-blockers than South African Indians or whites (1,2). In studies carried out in black Kenyans (3), black Zimbabweans (4), and Jamaicans (5), beta-blockers did not cause a significant reduction in blood pressure compared with placebo. Studies in black Americans have shown that diuretics are more effective than beta-blockers (6,7). A comparative study of enalapril and propranolol in black South Africans showed that neither was useful as monotherapy in that population (8).

There is no published information regarding the drug treatment of hypertension in Ethiopian patients. The racial background of the majority of Ethiopians is believed to be a mixture of African and Middle Eastern blood. It is therefore, difficult to predict whether Ethiopian hypertensives would respond to treatment in a similar manner to other homogenous black populations. At the Tikur Anbessa Hospital in Addis Abeba, physicians treat hypertensives according to their individual experience. The commonest drugs prescribed are thiazides, alpha methyldopa and beta blockers. This study was, therefore, undertaken as a preliminary step towards the evaluation of the efficacy of antihypertensive drugs in Ethiopian patients.

PATIENTS AND METHODS

Consecutive adult patients aged 18 years and over, with untreated supine diastolic blood pressure of 95-120 mmHg referred from the general medical out-patient clinics to the hypertension clinic of Tikur Anbessa

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Hospital were included in the study. The period of study was from September 1987 to November 1990. Physicians were requested to refer patients before initiating drug treatment. The few patients who came with treatment already started were instructed to discontinue all antihypertensive medication at the first visit. Patients with severe target organ damage manifested by grade III retinopathy, cardiac failure or renal failure were not included in the study. Patients with a known cause of hypertension and patients with asthma, diabetes mellitus or significant cardiac, hepatic, renal or neurologic diseases were excluded. Consent was obtained from each patient after adequate verbal explanation.

Blood pressures were recorded by specifically trained nurses using a random zero mercury sphygmomanometer. Recordings were made after patients had rested for at least half an hour, and two minutes after assuming the supine position. The Korotkoff phase V was taken as the diastolic blood pressure. A relevant history was taken and physical examination was done by the author. Baseline laboratory investigations consisted of urine analysis, urea, creatinine, transaminases, bilirubin, fasting blood glucose, uric acid, haemoglobin, white cell count, chest x-ray and E.C.G.

After a run-in period of at least 2 weeks on moderate sodium restriction and without any antihypertensive medication, patients who persisted with a diastolic blood pressure of 95-120 mmHg were randomized to receive hydrochlorothiazide 25 mg daily or timolol 10 mg daily or enalapril 10 mg daily. Both physician and patients did not know the type of drug taken. Drugs were given secret code numbers and the correct dose was dispensed in a prepacked envelope. Patients were evaluated every 2 to 4 weeks. The dose of each drug was doubled at the end of 4 weeks and quadrupled at the end of 8 weeks if the diastolic blood pressure remained above 95 mmHg. Patients with intolerable side effects were withdrawn from the study and shifted to some other form of treatment. Compliance to treatment was assessed by asking the patient carefully at each visit how regularly the drug was being taken.

Patients who completed 8 weeks of treatment and follow-up were included in the analysis. The baseline blood pressures and those at 4 and 8 weeks of follow-up were analysed for consistency. The unpaired t test was used to ascertain similarity of patients under the different treatment programmes, and the paired t test was used to assess the effect of treatment on the blood pressure in each group. A p value <0.05 was considered to be significant.

RESULTS

Sixty-seven patients were initially enrolled in the study. Treatment and follow-up was carried out as an out-patient in all cases. Thirty two patients showed up at 4 weeks, 26 attended up to 8 weeks and only 17 attended up to 12 weeks. Only patients that were followed for at least 8 weeks were included in the results. Table 1 gives baseline data on the patients in the different treatment groups. There are no major differences between the groups regarding age, sex, duration of hypertension and baseline blood pressure.

There was no overt evidence for target organ damage on physical examination in any patient. One patient from each of the three treatment groups had mild cardiomegaly on chest x-ray. One patient in the enalapril group had ECG evidence of left ventricular hypertrophy although his chest x-ray was normal. Liver and renal function studies were normal on all patients.

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Table 2 shows the main results of the study. Hydrochlorothiazide significantly lowered both systolic and diastolic pressures at 4 and 8 weeks compared with pretreatment levels. Timolol had no beneficial effect on the systolic blood pressure but produced a significant lowering of the diastolic blood pressure at 4 weeks. Enalapril also did not cause significant lowering of the systolic blood pressure; the diastolic blood pressure at 8 weeks was significantly lowered.

As shown in Table 3 more patients on hydrochlorothiazide attained a diastolic blood pressure of <90 mmHg while less patients required doubling of dosage compared to those on timolol and enalapril. Because of the small numbers in each category, these differences were not subjected to formal statistical testing. No patients on hydrochlorothiazide suffered significant side effects during the followup period. One patient each on timolol and enalapril had to be withdrawn from the study because of intolerable side effects.

DISCUSSION

The large number of drop-outs from the study is unfortunate. The likely explanation for this is the fact that many of the patients visited the hospital with complaints unrelated to hypertension and hypertension was detected incidentally. Such patients may not appreciate the need for antihypertensive treatment and followup once their original problem has settled.

The small number of patients in this study, therefore, does not allow strong conclusions to be drawn on the efficacy of the antihypertensive drugs tested. However, the trend observed is similar to findings in studies in other black populations. The efficacy of diuretics as monotherapy has been a fairly uniform observation (6,7,9). It has been speculated that the success of diuretic therapy in black hypertensives is due to the finding of larger proportions of low renin hypertensives compared with with whites (10-11). Actual studies, however, have not confirmed this speculation; no significant difference occurred between patients with low renin and normal renin in response to diuretics (9,12).

The relatively poor response of black hypertensives to beta-blockers has also been explained on the grounds of renin-volume status. The study by Holland (12), however, has failed to show influence of renin status on the response to beta-blockers. The present study has shown a mean rise in the systolic blood pressure in the group treated with timolol. It was only the diastolic blood pressure at 4 weeks which attained a barely significant reduction at $p<0.05$. The response to the angiotensin converting enzyme inhibitor enalapril was slightly better than that to timolol, though much inferior to hydrochlorothiazide in the present study. It has been documented that black hypertensives do not respond to converting enzyme inhibitors as well as whites (8,14).

It has been pointed out that using higher doses of beta-blockers (4,6) and converting enzyme inhibitors (13) in black hypertensives would result in equivalent levels of blood pressure reduction to those in whites taking relatively smaller doses. The present study has not been able to demonstrate the effect of maximal doses of timolol and enalapril as the follow-up period was not long enough.

In conclusion, this small study has indicated that Ethiopian hypertensives may respond to thiazide diuretics better than to beta-blockers or angiotensin converting enzyme inhibitors in a manner similar to other black populations in Africa and elsewhere. A larger scale study is obviously necessary to confirm these preliminary observations.

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TABLE 1. Patient characteristics

	Thiazide	Timolol	Enalapril
Number	9	10	7
Sex M/F	4/5	5/5	4/3
Mean age ± SD	43.6±13	48.3±10	36.7±10.8
Mean duration of hypertension (yr)	2.5	3.4	3.8

TABLE 2. Supine blood pressure response to hydrochlorothiazide, timolol and enalapril

		Supine Blood Pressures, x ± SD				
		Baseline	4 weeks	p	8 weeks	p
Thiazide	Systolic	163.7±20.8	145.8±15.2	<0.025	146.3±19.5	<0.01
	Diastolic	104.1±8.2	92.6±11.7	<0.02	94.7±8.4	<0.025
Timolol	Systolic	157.4±25.1	160.8±34.4	NS	161.6±3.5	NS
	Diastolic	103.2±5.3	97.4±10.9	<0.05	97.6±17	NS
Enalapril	Systolic	162.1±18.1	159.7±29.6	NS	150.4±22.1	NS
	Diastolic	104.4±6.2	96.3±16.8	NS	94.1±9	<0.01

X - mean
SD - standard deviation
NS - not significant

TABLE 3. Dosage, attainment of target blood pressure and side effects

	Number of patients			
	Total	Required doubling of dose	Diastolic BP < 90	Side effects
Thiazide	9	4	5	0
Timolol	10	6	4	3*
Enalapril	7	4	3	2**

*leach of severe fatigue (drug withdrawn); mild fatigue, palpitation.
**leach of severe dizziness (drug withdrawn), mild postural dizziness.

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MULTIPLE MYELOMA IN ETHIOPIANS: ANALYSIS OF 22 CASES

Milkias Shamebo, MD and Redda Tekle-Haimanot, MD

ABSTRACT: Twenty-two cases of multiple myeloma were seen in the Department of Internal Medicine, Tikur Anbessa (Black Lion) Hospital, a teaching and referral hospital in Addis Abeba, Ethiopia, from January 1983 to December 1990. The age range was 38 to 76 (mean ± SD = 51.5±12.2) years; a third were in the fifth decade. The male: female ratio was 1.75:1. The common clinical findings were bone pain in 20 (91%), bone tenderness in 15(68%), anaemia in 14 (64%) and spinal cord compression in 8 (36%). The erythrocyte sedimentation rate (ESR) was raised in 21. Serum protein was raised in 17(77%) and hyperglobulinaemia was seen in 20 (91%). Serum uric acid, blood urea nitrogen (BUN) and calcium were elevated in 10, 8 and 5 patients respectively, Bence-Jones proteinuria and albuminuria were each found in 9 patients. All patients had radiological abnormalities; 9 had a combination of lytic lesions, osteoporosis and pathological fractures (41%). Ten patients presented in clinical stage III. Four patients are being followed after 3-84 (median 40.5) months; eight were lost to follow-up 1-8 (median 2.0) months after diagnosis. Ten patients have died after 1-55 (median 11) months. Multiple myeloma is not uncommon in Ethiopians. Except for a lower age at presentation, the clinical, haematological, biochemical, and radiological findings, and the response to therapy, are similar to those reported elsewhere.

INTRODUCTION

Multiple myeloma is a neoplasm of mature and immature plasma cells. The clinical manifestations result from uncontrolled, progressive proliferation of these cells, marrow replacement by them, and their overproduction of certain proteins and/or polypeptide chains (1). Multiple myeloma accounts for about 1% of malignant diseases and slightly more than 20% of haematological malignancies in the United States of America (USA) (2), its incidence there being about 2.0-4.0 cases/100,000/years in blacks and 1.0-2.0 in whites (3), while in England and Sweden the rates were about 3.0/100,000/year without any racial differences (4). Earlier reports suggested that multiple myeloma was uncommon in Africans (5), the reasons being underdiagnosis due to lack of medical facilities. Subsequently, however, this disorder has been reported in indigenous Africans and people of African descent (6-9). In Ethiopia, only seven cases of multiple myeloma were reported in the 1970's (10-13). In a more recent analysis of haematological admissions, eleven cases of multiple myeloma were mentioned without detailed description (14). The aim of this prospective study is to describe the clinical, haematological, biochemical, radiological and follow-up findings and compare them to those seen elsewhere.

PATIENTS AND METHODS

Twenty-two consecutive new cases of multiple myeloma, including one transferred from the Orthopaedic Department, admitted to the medical

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wards of the Tikur Anbessa (Black Lion) Hospital, Addis Abeba University's teaching and referral hospital, during the period January 1983 through December 1990 were included in this study. No patients were referred from the Surgical or Gynaecology Departments during the study period. All patients with the diagnosis of multiple myeloma were hospitalised for investigation and management.

The age, sex, date of diagnosis and type of multiple myeloma as well as the clinical, haematological, biochemical, urinalysis (including Bence-Jones protein), radiological, bone marrow aspiration, and other tissue biopsy results were recorded prospectively. Peripheral blood films and bone marrow aspirates were stained by Wright's stain (15). For inclusion in the study, at least two of the following diagnostic critria had to be fulfilled (16):

1. increased numbers (>10%) abnormal plasma cells in the bone marrow aspirate
2. biopsy proven plasmacytoma, either in bone or soft tissue
3. the presence of a monoclonal protein in plasma and/or urine
4. osteolytic lesions, or osteoporosis if bone marrow plasma cells are >30%
5. myeloma cells (abnormal plasma cells) in the peripheral blood.

Clinical staging was according to Durie and Salmon (17). The chemotherapeutic agents used were melphalan 0.25mg/kg/day and prednisolone 40mg/day given for four days every four to six weeks (18), or cyclophosphamide 250 mg/m^2/d and prednisolone 40mg/day given for four days every three to four weeks (19). Both regimens were given for up to two years and stopped; then patients were followed every 3-6 months until relapse occurred.

Response to therapy was rated according to Alexanian *et al.* (20):

Good - improvemnt of >50% of the parameters initially abnormal

Partial - improvement of <50% of the parameters initially abnormal

No response - no change in any of the parameters initially abnormal.

Progression - progression of the disease

RESULTS

During the study period, twenty-two cases of multiple myeloma were seen in the medical wards of the Tikur Anbessa Hospital. Fourteen were males and eight females (M:F 1.75:1). The age range was 38-76 years (mean ±SD = 51.5±12.2). One-third were in the fifth decade. The age and sex distribution is shown in Table 1.

The clinical features at diagnosis are shown in Table 2. The commonest findings were bone pain and tenderness, pallor and/or difficulty walking. Three of the patients with weakness had severe anaemia. Kidney biopsy to look for *amyeidosis* was not done in any of the patients. The patient with nausea and vomiting had high serum calcium and BUN levels.

The haematological parameters are shown in Table 3. Anemia was present at the time of diagnosis in 14, leucopenia in 3 and thrombocytopenia in 4. No patients had haemorrhagic manifestations. The ESR was raised in 21 patients, being above 50mm/hr in 20 and above 100mm/hr in 11. Intense rouleaux formation was seen in 10 cases (46%). Bone marrow aspiration showed plasmacytosis in excess of 10% in 20(91%) of the cases, in one the sample was poor and in the other the diagnosis was confirmed by bone biopsy.

The biochemical data are shown in Table 4. The total serum protein was ≥ 10.0gm/dl in 11 patients. The serum electrophoresis showed a sharp peak in the gamma-region in 13, beta-region in 5 and alpha-region in two, and was normal in two. Hypoalbuminaemia of ≤ 3.0gm/dl was seen in four patients.

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Immunoelectrophoresis was done in only five patients: 2 had IgG, 2 IgA, and 1 light chain disease. The corrected serum calcium was above 12.0mg/dl in five patients. Blood urea nitrogen (BUN) was above 80mg/dl in 5 patients. Significant albuminuria (>1.0 gram/24 hours) and Bence-Jones proteinuria occurred in nine (40.9%) patients each.

All patients had abnormal radiological findings at presentation (Table 5). The clinical stage at diagnosis is given in Table 6.

Nineteen patients were treated with chemotherapeutic agents, one had excision of L 3 vertebral plasmacytoma (proved by histology after surgery) and radiotherapy, while two patients were not given specific therapy as they had terminal disease (Table 7). Of the 20 treated, four were inevaluable as they either died or were lost to follow-up within one month of initiation of therapy. Of the evaluable 16 patients, seven had good, 8 partial and one no response. Currently, four patients continue to be followed 3-84 (median 40.5) months and 8 are lost to followup 1-8 (median 2) months after diagnosis. Ten patients have died 1-55 (median 11) months after diagnosis. Three died of renal failure and 3 of infection, one of auto accident ten months after diagnosis while in remission of his primary disease, and one of congestive heart failure due to anaemia. Two patients died at home, the causes of death were not known. Autopsies were not done in any.

DISCUSSION

Multiple myeloma occurs in all parts of the world (1). Its incidence in USA is said to be more in blacks than in whites (3) although this is not confirmed elsewhere (2,4). In Ethiopia, very few cases were reported in the 1970's (10-13) without detailed description. The current communication includes the eleven cases reported previously (14) and has attempted to present clinical, haematological, biochemical, and radiological details as well as the response to therapy.

In most Caucasian series (2-5) the peak incidence has been in the sixth or seventh decade with very few patients below the age of 40 years. In the present series, 7 of the 22 patients were in the fifth decade, and 6 less than 40 years of age, a pattern which has been found in previous studies from Africa (6-8). This may mean that the disease is seen at a younger age in Africans than in Caucasians. The male to female ratio of 1.75:1 observed in this series is similar to previous Western (2) and African series (7,8). Bone pain, mainly low back pain, occurred in 20 patients, slightly higher than in previous reports (2-9), possibly due to the fact that most patients sought medical advice at an advanced stage of the disease. Pathological fractures occurred in 10 (46%), more commonly in the vertebral axis with spinal cord compression. This figure is comparable to the 33% seen in Rhodesia (now Zimbabwe) and Kenya (6,8).

Anaemia was present at the time of diagnosis in 14. This figure is comparable to that found in a large Caucasian series (2), and in Kenya and Jamaica (8,9). The anaemia was severe (Hgb < 8 gm%) in 8 of 22, in contrast to 8% of Caucasians (2) but similar to the finding in Jamaicans (9). The erythrocyte sedimentation rate was raised in 21 (96%), comparable with previous series (2-9). It was above 100 mm/hr in half the patients as was the case in the Jamaican series (9).

The biochemical results were similar to those reported from North America, England, Kenya and Jamaica (2,4,8,9). Particularly, the serum electrophoretic pattern was similar to that in North America and Jamaica (2,9). We do not have any explanation for the high alpha and beta peaks. Serum alkaline phosphatase was raised in only 3 of our patients, similar to the Jamaican series (9) but at variance with the Kenyan (8) which found a rise in 33.3%.

All patients in this series had abnormal radiological findings at the time of presentation. The commonest

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finding was the combination of lytic lesions, osteoporosis and pathological fractures in 41%, comparable to Western, Kenyan and Jamaican series (2,8,9).

As all patients were symptomatic at the time of presentation, supportive treatment was given as indicated. In addition, nineteen patients were treated with chemotherapeutic agents, with responses comparable to those reported elsewhere (18-20), although the number of patients in this series is small. The follow-up of these patients has been erratic and poor; 8 were lost to follow-up 1-8 (median 2) months after diagnosis. This problem was seen in Kenyans as well (8). Ten patients have died 1-55 (median 11) months after diagnosis, less than the median survival of 20 months in the North American series (2) but better than the Jamaican of 2.2 months (9).

In conclusion, multiple myeloma is not uncommon in Ethiopians and, apart from its presentation at a relatively younger age, the clinical, biochemical, radiological findings and response to therapy are similar to those in Caucasian and other African populations.

TABLE 1. Age and sex distribution at diagnosis

Age group (Years)	Male	Female	Total
31-40	5	1	6
41-50	4	3	7
51-60	3	1	4
61-70	1	3	4
71-80	1	-	1
Total	14	8	22

TABLE 2. Clinical features at presentation in 22 patients

Symptoms	No.	Signs	No.
Bone pain	20	Bone tenderness	15
Difficulty/inability in ambulation	8	Pallor	14
Weight loss	8	Spinal cord compression	8
Generalized weakness	7	Soft tissue mass	3
Fever and sweating	3	Gibbous	3
Swelling externally	3		
Nausea and vomiting	1	Lymphadenopathy	2
Generalized body swelling	1	Anasarca	1
Decrease in urine volume	1		

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TABLE 3. Initial haematological parameters in 22 patients

Parameter	Range	Mean	S.D.	Abnormal in	No. abnormal
Hgb (gm/dl)	4.2-18.5	9.4	4.1	<11.5	14
WBC (per mm^3)	2,300-12,800	6370	2542	<4000	3
Platelets (per mm^3)	45,000-215,000	146,500	55,296	<100000	4
ESR (mm/hr)	10-170	101	40	>20	21
Rouleaux formation				present	17

Note: Hgb = Haemoglobin; WBC = White blood cell
ESR = Erythrocyte sedimentation rate
SD = Standard deviation

TABLE 4. Biochemical data at diagnosis in 22 patients

Parameter (normal value)	Range	mean	S.D.	Abnormal if	No. abnormal
Total serum protein (6.5-8.5 gm/dl)	5.8-13.8	9.9	1.9	>8.5	17
Serum albumin (3.5-4.5 gm/dl)	2.4-5.5	3.6	0.8	<3.5	14
Serum globulins (1.5-3.5 gm/dl	0.5-9.3	4.7	2.0	>3.5	20
Serum calcium (9.0-11.0 mg/dl)	8.1-22.0	11.2	3.1	>11.0	5
Alkaline phosphatase (80-220 iu/L)	78-254	154.9	54.5	>220	3
Serum uric acid (3.0-7.0 mg/dl)	3.4-18.0	9.1	4.2	>8.0	10
Serum BUN* (10-25 mg/dl)	6.9-130	38.2	37.1	>30	8
Bence-Jones Proteinuria				present	9
Urine albumin				$\geq$1gm/24hrs	9

* BUN = Blood urea nitrogen

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TABLE 5. Radiographic findings at presentation

Findings	No.
Lytic lesion only	2
Osteoporosis only	3
Lytic lesion and osteoporosis	6
Osteoporosis and pathological fractures	2
Lytic lesions, osteoporosis and pathological fractures	9
Total	22

TABLE 6. Clinical stage of 22 myeloma patients

Stage	No.	Renal function
I	6	A - 6 B - 0
II	6	A - 6 B - 0
III	10	A - 2 B - 8
Total	22	22

A = BUN < 30 mg/dl
B = BUN ≥ 30 mg/dl

TABLE 7. Response to therapy in multiple myeloma patients

Therapy	Total	Response				
		Good	Partial	No response	Progression	Inevaluable
Melphalan + prednisolone	5	3	2	-	-	-
Cyclophosphamide + prednisolone	14	3	6	1	-	4
Surgery + radiotherapy	1	1	-	-	-	-
None	2	-	-	-	-	2
Total	22	7	8	1	-	6

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DNA Fingerprinting in the Epidemiology of African Serogroup A Neisseria meningitidis

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The restriction endonuclease (RE) technique was used to compare 172 meningococcal group A strains collected between 1969 and 1990, mainly from countries of the so-called African Meningitis Belt, the Gambia and Ethiopia. The 64 strains from various African countries (Niger, Chad, Burkina Faso, Cameroon, Morocco, Djibouti) were distributed within 3 main restriction enzyme patterns (REPs); the 77 Gambian strains fell into 5 REPs and the 24 Ethiopian strains into 2 such patterns. Several of the main REPs were formed by clusters of closely related clones. Clones, very similar to dominating REPs of the 1960s in Niger, Burkina Faso and Cameroon, were in the 1980s found to be strongly represented in the Gambia to the extreme west of the Meningitis Belt. One of the Gambian clones from 1983–86 was identical to an Indian clone recovered in New Delhi 1986–87. Another clone was detected in 1983 in the Gambia, in 1989 again in the Gambia as well as in Ethiopia, and in 1990 in Tanzania. Our results are largely in line with those of previous studies based on modern techniques of protein and isoenzyme electrophoresis. The RE method is useful mainly for the exact genotypic differentiation of closely related clones, and seems to be a valuable complement to phenotypic tools for epidemiological mapping of Group A meningococcal infection.

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INTRODUCTION

At intervals of 8–12 years, meningococcal epidemics reaching prevalence rates of up to 500–1 000/100 000 inhabitants have caused major public health problems in several countries of Sahelian Africa. Typically, the epidemics start well into the dry season and spread in the population with dramatic speed until ending abruptly with the onset of the rainy season (1–3). Apart from the fact that most epidemics of the so-called African Meningitis Belt seem to be caused by group A meningococci, little is known about the mechanisms triggering this particular epidemiological pattern. In fact, until recently it was quite unclear whether each epidemic wave is caused by a new and antigenically different bacterial clone, or represents outbreaks by the same virulent clone at intervals that are regulated mainly by the level of herd immunity. Over the last few years, accumulating evidence (3–6) suggests that a limited number of clonal populations, each consisting of one or several closely related clones, may circulate for decades between countries and even continents. Under favourable conditions such as international mass migration caused by the annual pilgrimage to Mecca, local outbreaks may within weeks spread to other countries and continents. According to Olyhoek et al. (6), at least 7 predominant clones have caused major epidemic waves since 1915. Insight into the epidemiology of group A meningococcal infection has recently been dramatically improved by the introduction of a number of modern research tools such as panels of monoclonal antibodies for serological testing (7), starch gel electrophoresis of cytoplasmic enzymes (5, 6, 8), and sodium dodecyl sulphate-polyacrylamide gel electrophoresis of bacterial outer membrane proteins (6). In addition to such phenotypic technologies, a

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Table I. *DNA restriction enzyme patterns of 64 meningococcal isolates from various African countries (1961–86)*

Clone designation	Type representative	No. ofisolates	Similarity (%) to standard		Origin and year of isolation
			004	250	
Afr I.1	004	16	100		Niger 61
Afr I.2	006	23	96		Burkina F. 61–62,65 Niger 63–64 Cameroon 66
Afr I.3	256	1	98		Burkina F. 66
Afr I.4	86088	2	96		Niger 86
Afr II.1	250	5	<50	100	Djibouti, Morocco 67
Afr II.2	023	7	<50	80	Niger, Chad 63
Afr III	295	10	50	50	Morocco 67

genotypic approach, using so-called restriction endonuclease (RE) techniques, has been applied (5,9–13). It was the purpose of this study to explore further the potential of the RE technique for epidemiological mapping of group A meningococcal strains from Africa.

MATERIAL and METHODS

Bacterial strains

Strains from different African countries. 64 strains, representing Niger ($n = 39$), Burkina Faso (7), Chad (2), Cameroon (1), Morocco (11) and Djibouti (4), were obtained from the collection of the meningococcal reference centre at Institut de Médecine Tropicale du Service de Santé des Armées in Marseille, France; of these 64 strains, 36 had previously been thoroughly investigated for their clonal population structure by Olyhoek et al. (6). Except for 2 carrier strains from 1986, all isolates were obtained from the cerebrospinal fluid (CSF) of clinical cases of meningitis. The distribution of these strains by location and time is shown in Table I.

Gambian strains. We investigated 77 strains collected during the period 1983–89. Of these, 25 originated from the CSF or blood of clinical cases; 13 from the Farafenni epidemic in 1983, and the others from different parts of the country during the years 1984 ($n = 5$), 1985 (3), 1986 (2) and 1987 (2). Of the remaining 52 strains 40 were recovered from carriers and 12 from persons of unknown clinical status. The carrier strains from 1984 included 4 isolates from non-vaccinated Senegalese citizens from across the border from Farafenni, and 6 carrier strains from vaccinated Gambians. The 1985 material included 5 carrier strains from schoolchildren at Bakau, an urban area near the capital Banjul. Also included are 26 carrier strains obtained in 1988 and 1989, during screening surveys of about 600 inhabitants in the Farafenni area at a time of low transmission.

Ethiopian strains. 24 strains were obtained from clinical cases hospitalised at Tikur Anbessa University Hospital of Addis Ababa or at the Health Centre in Zway, 200 km south of the capital. The strains represented all age groups, although with a dominance of young adults, and were all collected during the major epidemic of 1988–89.

Tanzanian strain. 1 strain was isolated in Moshi, in August 1990, from one of the several hundred patients involved in an outbreak of meningococcal disease then occurring in the Kilimanjaro and Arusha regions. (The strain was obtained by courtesy of the Department of Laboratory Services, Kilimanjaro Christian Medical Centre, Moshi.)

Indian strains. For comparison with the African strains 6 group A strains from clinical cases in New Delhi in 1985/86 were included in the study. (These were provided by courtesy of Professor Shriniwas, Department of Microbiology, All India Institute of Medical Sciences, New Delhi.)

Other strains. Reference strains for the III-1 and IV-1 clonal patterns described by Olyhoek et al. (6) were kindly provided by Dr Dominique Caugant, National Institute of Public Health (SIFF), Oslo, Norway.

Bacteriological technique.

All strains were isolated on chocolate agar. Subcultures of suspected Neisseria meningitidis were serogrouped by slide agglutination using commercial antisera (Wellcome Reagents Ltd., Beckenham, UK). Only group A isolates are included in the material. The African strains obtained from Marseille had been lyophilized for up to 25 years; the Gambian, Ethiopian and Indian strains had been kept at −20°C for a maximum of 5 years, prior to reculture and restriction endonuclease typing in Norway.

Restriction endonuclease analysis

The RE analysis of chromosomal DNA was performed as described by Bjorvatn et al. (9), using the endonuclease EcoRI. If EcoRI produced incomplete patterns, HindIII was used. Previous experience (9) shows that these 2 enzymes are equally efficient, and that nothing is gained by combining them, except in cases where the bacterial DNA turns out to be refractory to one of them. All strains were tested at least twice. Following enzyme digestion, electrophoresis and staining of the resulting DNA fragments, 2 persons, independent of each other, visually compared the RE patterns (REPs) with selected reference strains. The degree (%) of similarity between test strain and reference was defined as the number of identical bands divided by the total number of bands in both REPs. This grading of similarity is fairly exact only with closely related strains.

In this work a clone is defined as bacterial isolates with an identical REP. Closely related patterns (80% homology or more) will be referred to as clonal clusters within one main pattern, whereas isolates differing from each other by more than 20% will be assigned to different main patterns.

In order to avoid confusion with other nomenclatures our main patterns are given the prefix Afr, Gam, Eth, etc. plus Roman numerals (I, II, etc) for the main groups, and in addition Arab numerals for each of the representatives of clonal clusters within a group, e.g. Afr. II. 1, Afr. II. 2, etc.

RESULTS

EcoRI produced satisfactory REPs in 143 cases, whereas additional Hind III digestion was required with 29 of the strains. Among the 172 strains under study, a total of 19 different clones distributed within 9 main REPs were identified. The 166 African strains represented 17 clones and 8 main patterns. The results will first be presented separately for each of the 5 strain collections.

Various African strains

The 64 isolates belonged to 3 main genetic patterns, here designated Afr I-III (Table I). The Afr I differed from the Afr II pattern by more than 50%. The Afr I cluster (cluster reference strain no. 004, Niger 1961) consisted of 42 isolates and was distributed within 4 closely related REPs, Afr I.1 – Afr I.4 (clone reference strains no. 004, 006, 256 and 86088, respectively). The REPs within the Afr I cluster differed from each other by 1–4 bands, i.e. < 10%. The isolates belonging to this cluster were recovered in Niger, Burkina Faso and Cameroon during the period 1961–86.

The second main pattern, the Afr II cluster (cluster reference strain no. 250) was represented by 12 isolates, and distributed within the two REPs Afr II.1 (5 isolates) and Afr II.2 (7 isolates), which were about 80% related. The representatives of this cluster originated from Djibouti and Morocco 1965–67 (Afr II.1) and Niger and Chad 1963 (Afr II.2).

The third main pattern, Afr III (clone reference strain no. 295, Morocco 1967) was represented by 10 completely homologous isolates originating from Fez in Morocco 1967.

The REPs obtained with the strains from various African countries are shown in Fig. 1.

Of the 64 isolates included in our collection from various African countries, 36 had previously been studied by Olyhoek et al. (6), using SDS-PAGE and multilocus enzyme

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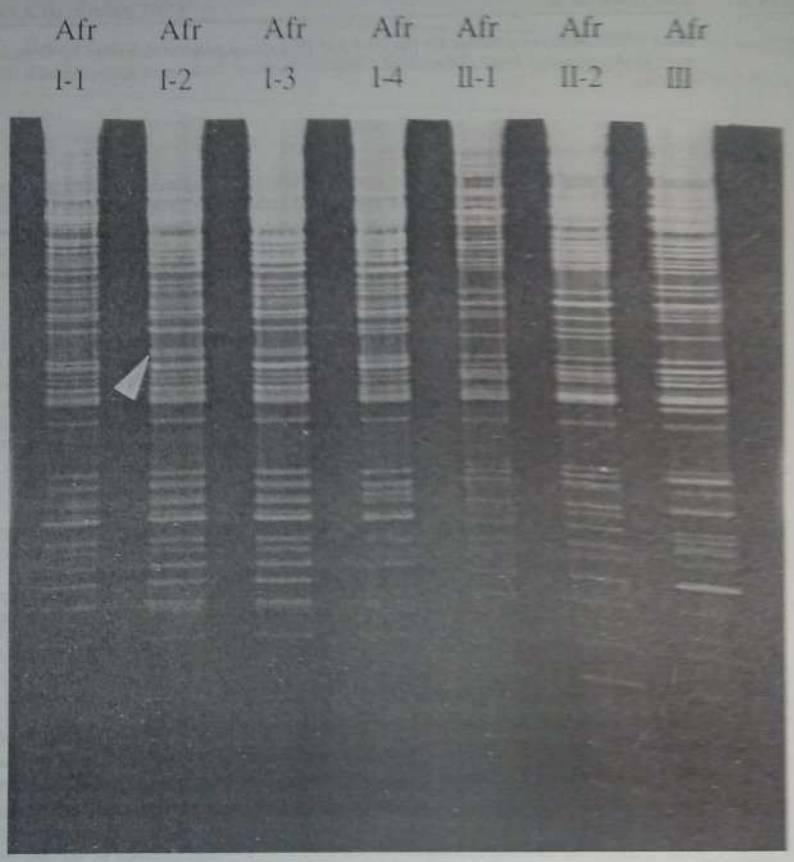


Fig. 1. Restriction enzyme patterns (REP) obtained with meningococcal isolates from various African (Afr) countries. Lanes 1–4: The representatives of the closely related Afr I cluster (Afr I. 1–4). Lanes 5 and 6: The Afr II cluster. Lane 7: The Afr III clone. The individual representatives of the main clonal patterns (cluster) e.g. Afr I. 1–4, do not differ from the REP of the type strain by more than 20% (difference in < 10 out of about 50 comparable band locations). Persistent discrepancy in a single location is considered sufficient to differentiate between the members of a cluster, e.g. the I. 1 and I. 2 clones of the Afr I cluster (arrow).

electrophoresis. This permitted a direct strain-by-strain comparison between RE analysis and the 2 other systems for strain differentiation. The results of this comparison are summarised in Table III. Most representatives of our clones Afr I.1 and I.2 were classified by Olyhoek et al. (6) as clone IV-1 ET 42, but 3 out of our 11 Afr I.1 isolates were assigned to ETs 43, 44 and 45. The RE-detected difference between the clones Afr I.2 and Afr I.3 was reflected by ET but not by clonal differentiation whereas the RE difference between Afr II.1 and Afr II.2 was detected by both other systems. However, one of the 3 Afr II.1 strains was assigned to ET 29 rather than ET 30.

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Table II. *Restriction enzyme patterns of 77 meningococcal isolates from the Gambia 1983–88*

Clone designation	Type representative	No. of isolates	Year of isolation	Similarity (%) to standards		Similarity (%) to other RE patterns	
				944	1181		
Gam I.1	944	41	83–86	100		Ind I	100
Gam I.2	549	15	83–84	99		Afr I.1	98
						Ind I	97
Gam II.1	1181	1	83	<50	100	Afr I.1	95
Gam II.2	B57	1	85	<50	91	Unknown	
Gam II.3	c1987	1	87	<50	90	Unknown	
Gam III	1344	16	83,88	<50	<50	Unknown	
Gam IV	872	1	83	<50	<50	Eth I.1	100
Gam V	8871	1	83	<50	<50	Tan I	100
						Unknown	
						Unknown	

Gambian strains

The 77 isolates belonged to 5 main genetic patterns, designated Gam I – Gam V (Table II), and showed only remote mutual similarity. The Gam I cluster (cluster reference strain no. 944) consisted of 2 closely related clones, Gam I.1 (41 isolates, clone reference no. 944) and Gam I.2 (15 isolates, clone reference strain no. 549), differing from each other by 1 band only. The Gam II cluster contained 3 different REPs, differing from each other by < 10%, and all represented by 1 isolate only. 16 isolates belonged to the Gam III pattern (clone representative strain no. 1344), whereas both Gam IV and Gam V were represented by single isolates. The REPs that were obtained with the Gambian isolates are shown in Fig. 2.

Ethiopian strains

Of the 24 strains analysed, 17 were proven to be identical, and 2 more were probably identical (REP referred to as Eth I.1, clone reference strain no. 30), whereas another 4

Table III. *A comparison of clonal relationships using restriction enzyme technique and a combination of SDS-PAGE of 2 outer membrane proteins and multilocus enzyme electrophoresis*

Our results		No. compared	No. differed	Olyhoek et al.	
Clone	Type representative			Clone	ET
Afr I.1	004	11	3[a]	IV-1	42
Afr I.2	006	14	0	IV-1	42
Afr I.3	256	1	0	IV-1	44
Afr II.1	250[b]	3	1[c]	II-1	30
Afr II.2	023	7	0	I-3	15

[a]Three strains (018, 037 and 178) were assigned as ET 45, 44 and 43, respectively.
[b]Olyhoek's results based on strain 252, which we lost, but found identical to our type representative 250.
[c]One strain (223) was assigned as ET 29.

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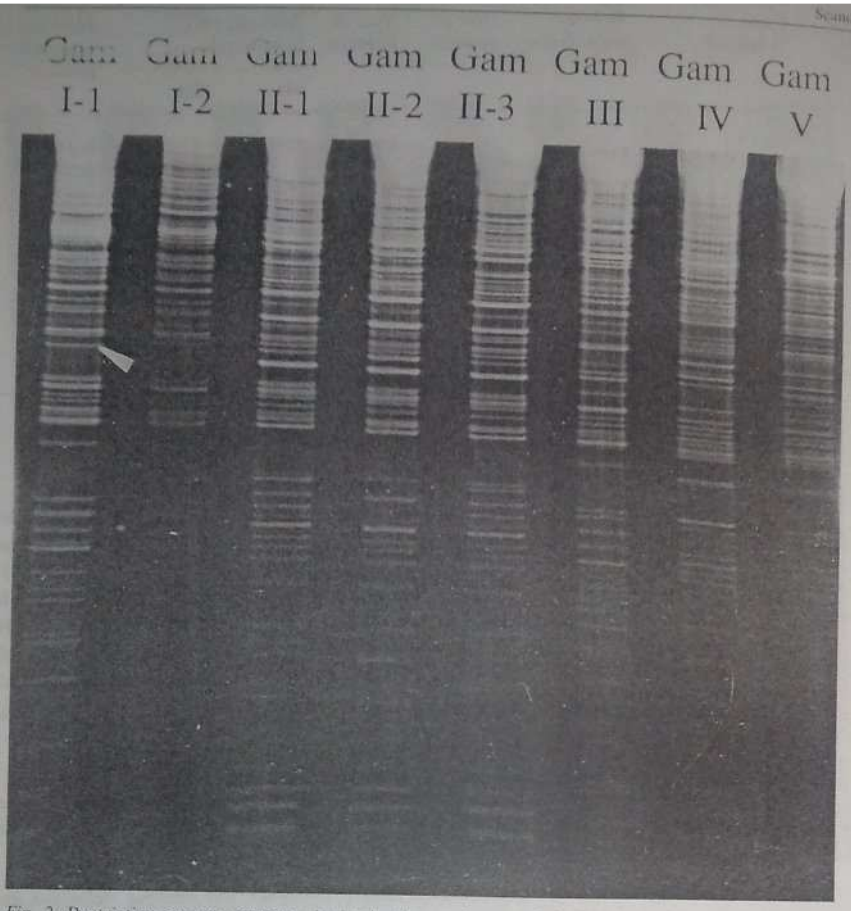


Fig. 2. Restriction enzyme patterns obtained with meningococcal isolates from The Gambia (Gam). Lanes 1 and 2: The closely related clones Gam I-1 and Gam I-2 (one line difference only, arrow). Lanes 3–5: The Gam II cluster. Lane 6: The Gam III clone. Lanes 7 and 8 represent single isolates of apparently uncommon group A clones.

isolates differed from this pattern by 1 particular band only (Eth I.2, clone reference strain no. 32). One isolate, Eth II, differed significantly (i.e. by > 10 bands) from the Eth I cluster. On 6 occasions the EcoRI endonuclease produced an insufficient number of bands for reliable comparison. In 4 of those cases, subsequent digestion by Hind III solved this problem beyond doubt; in the 2 remaining cases identity with the Eth I.1 pattern was likely, but not proven with this technique. The REPs of the Eth I cluster are depicted in Fig. 3.

Indian (New Delhi) strains

The 6 strains studied were equally distributed within 2 REPs, Ind I (clone reference strain

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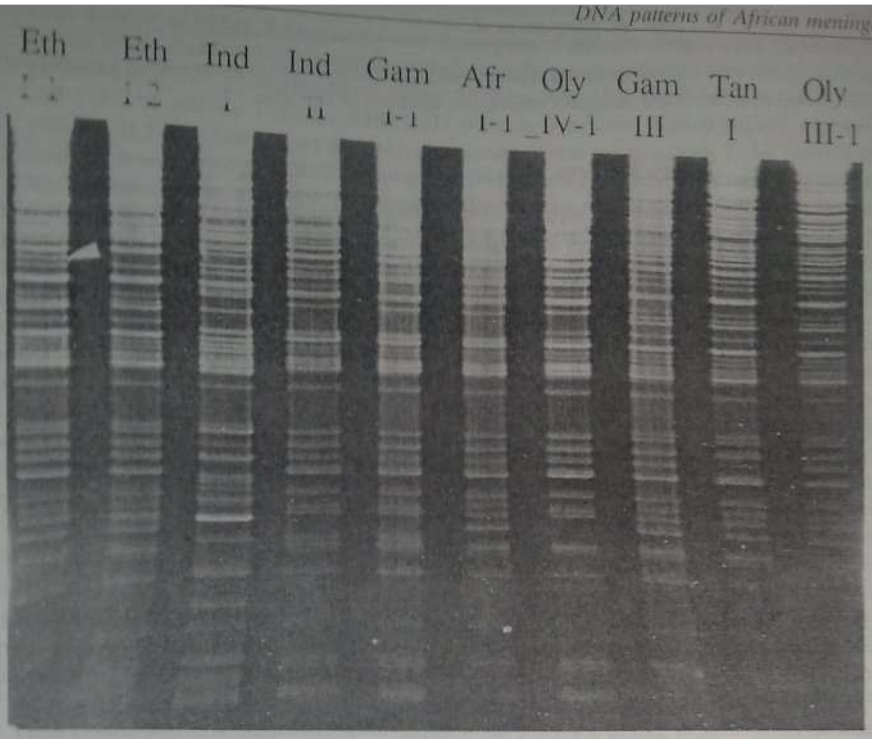


Fig. 3. Comparison of restriction enzyme patterns obtained with meningococcal isolates from Ethiopia (Eth), India (Ind), Gambia (Gam), Tanzania (Tan) and other African countries. Type representatives of clones III-1 and IV-1 (Olyhoek et al., ref. 6) are also included. The 2 Ethiopian clones I-1 and I-2 (Lanes 1 and 2) are very closely related (one line difference only, arrow), whereas the Indian clones I and II (Lanes 3 and 4) are clearly different. Note that the Gam I-1 (Lane 5) and Afr I-1 (Lane 6) clones are quite similar, but not identical. Complete identity is found between the Gam III (Lane 8), Eth I-1 (Lane 1), Tan I (Lane 9) and the Olyhoek (Oly) III-1 reference clone (Lane 10). Similarly, the Ind I clone (Lane 3) and the Gam I-1 (Lane 5) are identical, and differ by 1 line only from the reference clone Oly IV-1 (Lane 7).

no. 1680) and Ind II (clone reference strain no. 1213), which differed from each other > 50%. The Ind I and II REPs are shown in Fig. 3.

Relationship between REPs from different geographical areas

The clones of the Gam I cluster were found to be closely related to, but not completely identical with the 4 clones of the Afr I cluster. However, the Gam III proved identical to the dominant REP of the recent Ethiopian epidemic, Eth I, as well as to the recent isolate from Tanzania (Fig. 3). Furthermore, complete identity was found between Gam III, Eth I, Tan I and the III-1 reference strain according to Olyhoek et al. (6), obtained from SIFF. The clone reference strain of Gam III (No. 1344) was recovered from a Gambian case in 1983, but we have no further isolates of this clone until our screening in 1989 of school children in Korojolakunda, near Basse in the easternmost part of The Gambia, where a fatal case of

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meningococcal disease had occurred a few days previously. 15 isolates of REP type Gam III were obtained among the contacts of this case.

DISCUSSION

Our results support previous observations indicating that meningococcal disease in countries of the African Meningitis Belt is caused by a small group of clones, some of which are closely related. Thus, over the past 30 years bacteria belonging to the complex of almost identical clones Afr I and Gam I were widely spread within the Belt. On the other hand strains of markedly different REPs seem regularly to have contributed to meningococcal morbidity inside (Afr II.2, Gam II. 1–3) as well as outside (Afr II.1, Afr III) the traditional Belt countries. The dominance of a particular clone at the time of major epidemics has been emphasized by the recent introduction of the highly virulent III-1 clone (6), which in the present paper is represented by Gam III/Eth I.1 and Tan I. According to Salih et al. (12) the large 1988 epidemic in the Sudan was completely dominated by strains of clone ET3/III-1. As shown here, clone III-1 also dominated the 1988 epidemic in Ethiopia, although we found 2 closely related versions, Eth I.1 and Eth I.2.

Moore et al. (3) suggest that the wave of clone III-1 infection that in 1987–89 swept over Saudi Arabia, Ethiopia, Sudan and Chad, originated in Nepal, and followed the pilgrim routes to and from Mecca. It is highly probable that the mass migration of pilgrims plays an important role in the spread of the meningococcal epidemics in these parts of the world. However, the direction and pattern of the epidemic flow seem to be quite complex, probably in part because of interactions between prevailing meningococcal clones. Thus, the Ind I clone that was isolated in New Delhi in 1986 is identical to the clone Gam I.1 that existed in the Gambia at least during 1983–86, possibly indicating a flow from west to east. Similarly, the suggestion of a flow of clone III-1 from Nepal via Saudi Arabia to Africa is contradicted by the fact that this clone too, was found in The Gambia already in 1983. Unfortunately, further spread of the highly virulent III-1 clone was easily predictable. In 1989 and 1990 Tanzania has had outbursts of meningococcal disease both in the Dar es Salaam area and more recently also in the Northern Zone. That the III-1 (Tan I) was involved at least in the latter is proven here.

A total of 17 different clones distributed within 8 main REPs were found among the 165 African strains represented in the present material. In their extensive review article on the clonal population structure of N. meningitidis serogroup A, Olyhoek et al. (6) identified 15 electrophoretic types (ETs) and 6 clones among 256 African strains recovered during the period 1960–1983. Our material included 36 of these strains, which allowed direct comparison between the different techniques employed. Applying our strict definition of a clone, the RE technique apparently has a power of resolution similar to that of ET, whereas our definition of main REPs appears roughly to cover the relatively wide clonal concept of Olyhoek et al. Although in general there is a fair agreement between the results, on occasion the ET revealed subtle differences not seen by the RE technique, and vice versa.

Crowe et al. (5) report that all of their 226 group A strains that were collected in The Gambia during the period 1982–88 were of clone IV-1, ET 42, although the isolates varied to some extent in the expression of certain surface components. Our survey of Gambian strains covers largely the same period and geographical areas. Although we confirm that the majority of isolates from this period are closely related (Gam I.1 and Gam I.2 representing 66/77 isolates), the extreme uniformity of the epidemiological picture as reflected by clonal analysis becomes less striking when viewed by RE classification. Admittedly, the difference between the dominating Gam I.1 and Gam I.2 was represented by 1 band only, and appears subtle. However, this difference was remarkably consistent, and was observed in a relatively

large number of strains. Interestingly, our finding that 5 different clones were represented among the 77 Gambian isolates comes very close to the results obtained with this technique by Crowe et al. (5). Among the 63 serogroup A strains isolated in The Gambia between 1982 and 1984, 59 showed a similar REP (L-1) whereas 4 isolates showed slightly different patterns (L2-L5). Olyhoek et al. (11), comparing clonal analysis with DNA restriction analysis, found a total of 13 REPs among their 34 ETs and 21 clones, and concluded that the discriminating ability of the RE technique was less than that of the other techniques. On the other hand, as shown by Crowe et al. (5) and now supported by our results, RE analysis may sometimes permit further discrimination when applied to strain populations, which by clonal analysis and ET mapping are found completely homogeneous. Obviously, these techniques are only partly concruent, and are likely to have somewhat different fields of application.

The RE method is exact and highly reproducible, but labour intensive and technically demanding. Also, electrophoretic enzyme typing and analysis of outer membrane proteins are techniques that are normally restricted to highly specialised research laboratories. The level of resolution depends upon choice of restriction endonuclease, or the number of enzymes or protein components that are included in the test battery. Thus, using another series of enzymes, Moore et al. (3) on several occasions arrived at clonal assignments different from those reported by Olyhoek et al. (6). Similarly, another choice of restriction endonucleases in this study might have changed some of our conclusions regarding clonal relationships. It should be emphasised, however, that the principal agreement between the results obtained with these very different epidemiological tools is quite striking, and seems to confirm the relevance of their respective contributions. For the screening of large numbers, the RE technique seems less suitable, at least without automated reading and interpretation of the often complicated band patterns. (In our experience, scanning of band patterns by densitometer cannot replace careful visual examination.) Also, except for closely related isolates, it is quite difficult to assess numerically the degree of relatedness between strains. On the other hand, for the exact differentiation of small numbers of closely related clones, this method has proven very efficient (5, 10, 12).

Crowe et al. (5) recently reported reduced sensitivity to complement-mediated killing in a small proportion of Gambian group A isolates. This potentially important observation is a timely reminder of the need for simple epidemiological tools that will identify more specifically the phenotypic or genotypic characteristics of particularly virulent bacterial clones.

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Attitudes of rural people in central Ethiopia towards leprosy and a brief comparison with observations on epilepsy

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Summary To find out public attitudes toward leprosy a door-to-door survey was carried out in 1546 sampled households in the rural farming community of Meskan and Mareko in central Ethopia, where the prevalence of leprosy is estimated to be 1 : 1000. Attitudes toward leprosy were compared with attitudes to epilepsy, studied in a previously performed survey in the same community. Eighty-seven per cent of the respondents were above the age of 25, and 59·5% were females. There were slightly more Muslims (54%) than Christians. The majority of the interviewees (87%) were farmers, with an illiteracy rate of 84%. Ninety-five per cent and 83%, respectively, were not willing to employ or work with a person having the disease. Seventy-five per cent would not allow their children to associate with a playmate suffering from leprosy. Comparative analysis of attitudes in the same community showed that negative attitudes toward leprosy were stronger than those toward epilepsy, particularly with regard to matrimonial associations, sharing of accommodation, and physical contact with an affected person. The reasons for these differences appear to be the community's deeply entrenched belief that leprosy is both hereditary and contagious, expressed respectively by 48% and 53% of the respondents. In order to minimize the perpetuation of negative attitudes, there is a need to educate and impress on the population that leprosy is a treatable infectious disease which is not congenitally acquired, and that it is even curable if detected early. The study reinforces previously proposed suggestions that, in developing countries such as Ethiopia, leprosy care should be integrated into the general health services.

Introduction

About 10 million people in the world, mainly in developing countries, are infected by

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leprosy; 12% are found in Africa.[1] Situated in the north-eastern part of Africa, Ethiopia covers an area of 1·25 million sq km and has a population of 46,000,000.[2] It belongs to the leprosy-endemic regions of the African continent. A review of the leprosy control programmes in the country (1976–89) revealed that the cumulative national average prevalence rate was 2·6 per thousand.[3] Although a decline in the detection rate has been noticed since 1982, coinciding with the introduction of multiple drug therapy (MDT), leprosy remains a serious public health problem in the country.

Besides the physically disfiguring and disabling effects of the disease, its victims and their families suffer a great deal from social prejudices and isolation. The situation in Ethiopia is similar to that recorded from other developing countries. As Giel wrote in 1968, 'Among the outcasts of the society, concentrated around the churchyards and cemeteries of Ethiopia, lepromatous lepers are the most easily recognized'.[4]

The objective of the present study is to evaluate the knowledge and traditional beliefs and attitudes toward leprosy in a rural Ethiopian community. An attempt will also be made to compare the attitude toward leprosy with that previously recorded for epilepsy in the same community.[5]

Subjects and methods

Between 1986 and 1988 an epidemiological study of neurological disorders was carried out in the rural subdistrict of Meskan and Mareko (population 181,883) in the Shoa Administrative Region of central Ethopia. At the time of the survey, the subdistrict comprised 6 town-dwellers' associations and 82 peasant associations. There was a total of 40,000 households in the subdistrict, with an average family size of 4·5 members. The study was undertaken in a random selection of 30% of the associations, involving 60,820 inhabitants. The majority of the inhabitants (89%) were from the Gurage ethnic group, while the rest were from the Oromo, Amhara, Tigre and Kembata ethnic groups. In the survey, trained lay health workers were employed to administer specially designed questionnaires to detect neurological symptoms and signs;[6] the questionnaires were those used for a community-based study of neurological disorders in the same area.

Concomitant with this survey, the lay health workers were also trained to interview adults, mainly heads of households, on their opinions of common neurological disorders that may carry significant negative and unfavourable attitudes in the community. These disorders included mental retardation, physical handicap, leprosy and epilepsy. In order to avoid confusion, every fourth household of all the randomly selected villages in the study area was interviewed on each of the disorders. This resulted in the inclusion of 1546 households each for the attitudinal surveys of leprosy and epilepsy.

The questionnaire used for this study and shown in the Appendix was translated into Amharic, the 'official' Ethiopian language. Local dialects were used in the interviews whenever required. Before the administration of the questionnaire, the aims and purpose of the study were clearly explained to the respondents, and their consent was obtained. There was a 94% and 95% participation in the interviews on epilepsy and leprosy respectively.

The chi-square test (with Yates' correction) was used as a test of independence between two variables.

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Results

As summarized in Table 1, the characteristics of the respondents for the leprosy and epilepsy interviews were very similar. Taking those who responded to the questionnaire on leprosy, 85% were above the age of 25, and the majority (87%) were farmers. There were slightly more Muslims (54%) than Christians. Eighty-two per cent were married, and of those 89% had children. The rate of illiteracy were very high (84%). As the men in the community were often in the fields during the door-to-door visits of the lay health workers, there was a slight preponderance of females (59·6%) among the respondents to the interview on leprosy, similar to that experienced in the study of epilepsy.

Those who were literate obtained their skill from church and regular schools, as well as through participation in the literacy campaign. Less than 2% had received secondary school education. The vast majority in the community (94%) had incomes at subsistence level ($US 120 per annum), and only 1% could be classified as well-to-do.

Table 1. Characteristics of respondents

	Epilepsy		Leprosy	
Characteristics	No.	%	No.	%
Age (years)				
14–25	206	14·2	195	13·4
26–35	377	26·0	420	29·0
36–45	338	23·3	368	25·4
46+	531	36·5	468	32·2
Sex				
Male	606	41·6	586	40·3
Female	850	58·4	865	59·6
Religion				
Christian	674	46·3	666	45·9
Moslem	781	53·7	785	54·1
Marital status				
Married	1147	78·8	1183	81·5
Widow/Widower	162	11·2	125	8·6
Single	76	5·2	84	5·8
Divorced	70	4·8	59	4·1
Level of education				
Illiterate	1240	85·2	1223	84·3
Read and write	120	8·2	93	6·4
Grade 2–8	75	5·2	109	7·5
Grade 9 and above	21	1·4	26	1·8
Occupation				
Farmer	1267	87·0	1265	87·2
Housewife	75	5·1	85	5·9
Merchant	37	2·5	40	2·7
Labourer	29	2·0	15	1·0
Dependant	27	1·9	20	1·4
Student	13	0·9	12	0·8
Government employee	9	0·6	14	1·0

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In Ethiopia leprosy is commonly referred to as qumtina, an Amharic word denoting 'the state of amputation or mutilation'. Likewise, a person with leprosy is called qwomata. These terms were used by 70% of the respondents, in spite of the fact that only 7% of them were from the Amhara ethnic group. The preferred term for leprosy in Amharic is sega dewe, which literally translates as 'the disease of the flesh'; this term was used by only 0·3% of the respondents. Other less commonly-used terms for leprosy within the study population were buska, gegehu yelegode and yajamoy in the Mareko, Meskan and Silti dialects of the Gurage language, and shishera was used by the Hadiya language-speakers. All these terms have equivalent meanings and connotations similar to the Amharic word qumtina.

As shown in Table 2, the proportion of respondents that had heard of, or, in a few cases, read about leprosy and epilepsy was equal. However, a higher percentage of respondents had seen a sufferer from leprosy. Interestingly, a significantly higher proportion of respondents believed that leprosy is hereditary and contagious, as compared to epilepsy. The negative attitude towards leprosy is further demonstrated by the unwillingness or intolerance of the respondents to employ, work or live with a person

Table 2. Public response to attitudinal questions

Question	Response number	Answer (%) Yes	No	Don't know	*p* value
Have you heard or read about leprosy?	1365	90·3	9·7		
. . . . . epilepsy?	1441	89·0	11·0	—	>0·10
Have you seen someone with leprosy?	1351	95·9	4·1		
. . . . . epilepsy?	1338	86·2	13·8	—	<0·001
Do have a family member with leprosy?	1347	2·3	97·7		
. . . . . epilepsy?	1332	14·3	85·7	—	<0·001
Is leprosy hereditary?	1328	47·8	52·2		
Is epilepsy hereditary?	1274	4·9	95·1	—	<0·001
Is leprosy contagious?	1324	53·1	43·8	3·1	
Is epilepsy contagious?	1269	44·6	53·4	2·0	<0·001
Is leprosy a form of insanity?	1321	1·0	99·0		
. . . . . epilepsy?	1265	1·9	98·1	—	0·01<0·05
Would you employ a leper?	1316	3·8	95·1	1·1	
. . . . . an epileptic?	1254	25·0	75·0	—	<0·001
Are you willing to work with a leper?	1317	15·6	83·3	1·1	
. . . . . an epileptic?	1257	52·7	46·1	1·2	<0·001
Would you house a person with leprosy under pressure?	1314	0·4	98·9	0·7	
. . . . . epilepsy?	1260	67·2	32·2	0·6	<0·001
Do you think a person with leprosy should be hidden from public view?	1314	3·6	96·4		
. . . . . epilepsy?	1262	1·8	98·2	—	0·001<0·01
Would you allow a leper to use public transport?	1314	97·2	2·8		
. . . . . an epileptic?	1262	90·1	9·1	0·8	<0·001
Would you shake hands with a leper?	1314	22·5	77·5		
. . . . . an epileptic?	1262	90·8	9·2	—	<0·001
Would you have a person with leprosy as a friend?	1308	9·3	90·7		
. . . . . epilepsy?	1259	40·6	58·3	1·1	<0·001
Would you allow your child to play with a child having leprosy?	1311	25·2	74·8		
. . . . . epilepsy?	1254	65·1	33·9	1·0	<0·001

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Table 3. Question: Would you allow someone from your family to marry a person with epilepsy/leprosy?

Results	Respondents				
	Epilepsy 1257		Leprosy 1313		
	No.	%	No.	%	Value
				p	
Yes	327	26·0	39	3·0	<0·001
Would not tolerate (reason not specified)	422	33·6	213	16·2	<0·001
No, the sufferer is unable to earn a living	292	23·3	185	14·0	<0·001
No, contagious	148	11·8	302	23·0	<0·001
No, genetically inadvisable	49	3·9	563	42·9	<0·001
Don't know	18	1·4	11	0·8	

having the disease. Similarly, fewer respondents were willing to be friends with or allow their children to be associated with a person suffering from leprosy; 78% of the interviewees were unwilling to shake hands with a leprosy sufferer, compared with 9% that expressed the same attitudes to a patient with epilepsy.

When asked if they would accept a successfully treated and cured case of leprosy, nearly 42% of the interviewees responded with 'once a leper, always a leper'.

When the attitudes to marriage were evaluated (Table 3), only 3% expressed probable consent to a family member undertaking a matrimonial relationship with a person affected by leprosy. On the other hand, there was a 26% positive response on the same question concerning epilepsy. The main factors contributing to the strong reluctance concerning marriage with a leprosy sufferer were the fear of contagion and hereditary considerations, as well as the feeling that a person with leprosy is incapable of being gainfully employed. Whereas 38% of those interviewed on epilepsy thought that evil spirits and punishment from God were responsible for the disorder, only 13% of respondents implicated these reasons for leprosy. The respondents considered genetic

Table 4. Question: What do you think is the cause of epilepsy/leprosy?

Results	Respondents				
	Epilepsy 1270		Leprosy 1329		
	No.	%	No.	%	*p* value
Don't know	655	51·6	266	20·0	<0·001
Evil spirit	381	30·0	97	7·3	<0·001
Punishment/curse from God	102	8·0	70	5·3	<0·001
Physical contact	64	5·0	333	25·0	<0·001
Born with it	63	5·0	514	38·7	<0·001
Febrile disease	3	0·2	44	3·3	
Accident	1	0·1	5	0·4	
Lightning	1	0·1			

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Table 5. Question: How should society take care of persons with epilepsy/leprosy?

Results	Respondents				
	Epilepsy 1214		Leprosy 1314		
	No.	%	No.	%	*p* value
Don't know	554	45·6	175	13·3	
Give alms	415	34·2	877	66·7	<0·001
Medicine to be provided	199	16·4	184	14·0	<0·001
Let own family help	20	1·6	25	1·9	<0·001
Government to take care	18	1·5	47	3·6	
Pray for them	6	0·5	1	0·1	
Give sacrifices to the spirits	2	0·2	1	0·1	
Employ them to be independent	—	—	4	0·3	

transmission and contagion as the factors most commonly associated with the causation of leprosy. This was significantly different ($p < 0·001$) from the beliefs found with epilepsy (Table 4).

The respondents' attitude on what society should do for the sufferers of leprosy and epilepsy was very revealing (Table 5). The need to provide conventional treatment was expressed by a modest 14–16% of respondents in both interviews. However, more interviewees (67%) thought that victims of leprosy should be dealt with by the offer of alms, as compared with 34% who had the same belief for the epileptics ($p < 0·001$).

Discussion

The study population in the rural sub-district of Butajira consists of mainly illiterate farmers who have very little exposure to scientific knowledge on diseases like leprosy and epilepsy. The prevalence of leprosy in the community was found to be 1/1000.[6] It is also an interesting point that 2·3% of the respondents in this survey admitted that a family member or a relative suffered from leprosy.

Less than 15% of the interviewees possess radios, the only means of access to mass media available to the community. It must also be pointed out that the Ethiopian mass media offer only limited programmes on health education. Thus, the views that the respondents express on leprosy and epilepsy represent largely the beliefs and practices which are indigenous and prevalent in the rural community, without much outside or foreign influence. It is quite obvious from this study that the rural community has stronger and more negative feelings toward leprosy compared with those toward epilepsy, particularly on such matters as physical contact and marriage with victims. What is indeed at the root of this strong social stigma toward leprosy?

The Ethiopian Amharic word qumtina used for leprosy is very similar in concept to the Arabic word judham derived from jadham, with the literal meaning of 'cutting', denoting the outcome of the disease.[7] The Amharic terms for leprosy the disease, and for the person with the disease, although widely used in the country, have derogatory and deeply entrenched discriminatory and stigmatizing connotations. For what it is worth,

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the less pejorative new terminology sega dewe, 'the disease of the flesh', is fortunately gaining wider acceptance. In this connection it is worth mentioning that, as part of the programme of destigmatization, Dogliotti proposed the replacement of the 'opprobrious term—leprosy' with the eponym 'hanseniasis',[8] though we are all aware that changing the name is not certain to change an attitude.

Nevertheless, in the rural farming community surveyed, it was our experience that leprosy patients do not in fact face outright segregation and ostracism. They seem in general to get a sympathetic reaction from their community. In a survey undertaken in the same community to detect neurological cases including leprosy,[6] we were impressed by the way leprosy patients were mixing and intermingling freely with others who did not openly discriminate against or reject them. This is very unlike the unfriendly reception that leprosy patients receive in the big towns and cities in Ethiopia.

It is also a common practice that in the peasant associations farmers with leprosy are allocated pieces of land equal to those of other peasants: they can cultivate these on their own or, if unable to do so, hire others to do the work for them. Like all other farmers, they can build their huts within the allocated village boundaries without any restriction or segregation. These conditions and observations suggest that leprosy patients in the rural community are better accepted or tolerated than in the towns, where they are invariably treated as outcasts.

In this attitudinal study on leprosy 13% of the respondents were from Butajira, the main small rural town, and from two other satellite towns within the study area. The attitudes of the respondents from these semiurban centres to different aspects of leprosy was not statistically different from that recorded in the rural villages.

As evidence in Table 5, the majority of the respondents are convinced that leprosy sufferers should depend on alms, which may explain why we find so many of leprosy sufferers among the multitudes of beggars around places of worship.

In a *Leprosy Review* editorial of 1977, Antia appropriately referred to leprosy as the 'disease which affects the body of the patient and the morale of the public'.[9] Indeed, leprosy has a profound effect on the patient, and carries a strong stigma in all cultures and societies.

In his analysis of the psychological aspects of leprosy, Davey identified the following main sources of stress in the leprosy patients: the stress of inherited idea, the stressful experience of leprosy related to its physical disabilities; and the stress of home and family life emanating from the threat of unemployment and problems of marriage.[10]

As evidenced in this study, there is a widely held concept that leprosy is congenital. Nearly half of the respondents in this survey thought that the disease was inherited, as compared to 5% who expressed the same belief about epilepsy. Such congenital transmission of leprosy is believed to extend through several generations, very similar to what has been documented among Hong Kong Chinese.[11] Traditionally, in many parts of Ethiopia, marriage with a leprosy sufferer would be allowed only after the families of each of the partners have independently convinced themselves that leprosy has not occurred for seven generations. Although this study did not address itself to the attitudes of the leprosy patients to their own disease, it was quite clear from our experience in the study area that those with leprosy face both rejection and isolation, particularly if they exhibit obvious amputations, ulcerations and disfigurement.

Edwards proposed that the origin of the social stigma of leprosy was a primitive fear evoking a guilt complex in both the sufferer and the observer, a rational fear of contagion, and the religious fear of divine punishment.[12]

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In previous studies of leprosy within the religious context, we come across persistent allegations of mistranslation and misinterpretations of writings on leprosy in holy scripture. References to leprosy are certainly made in the Bible. However, Browne, for one, argues that leprosy, as the currently well-defined clinical entity, is not explicitly or beyond doubt referred to in the Bible, although the word 'leprosy' and its cognates occur in translations from the original scriptures in Western languages.[13] In his review of the same subject, Mohamed in 1985 found that leprosy is also not mentioned in the Quran. What was erroneously translated from the Quran as leprosy was vitiligo. He further argues that the medieval type of persecution, isolation and segregation of leprosy patients, still practised in many Moslem communities, has no religious justification.[7]

Similarly, Skinsnes has cast serious doubts on the suggestion that the negative social reaction to leprosy is the result of biblical teachings, including possible mistranslation. Based on our experience and as confirmed by this study, we tend to agree with his conclusions that the negative social reactions encountered are largely derived from a 'wrongly perceived picture of a contagious, incurable disease which progresses and eventually results in deformities and mutilation'.[14]

In Zambia, witchcraft was believed to be an important cause of leprosy, and the disease was often believed to be a punishment, reminiscent of the beliefs in medieval Europe.[15] Yet these beliefs were not very prevalent in the Ethiopian rural community we surveyed. Only 12·6% implicated evil spirits and punishment from God as the cause of the disease. On the other hand, as mentioned earlier, the hereditary factor was considered very important. The fear of contagion was expressed by 48% of the respondents. Direct contact was believed to be the main method of transmission, while a minority also considered sexual contact to be a means. Similar strong fears of contagion have been documented in studies from communities in Mangalore, in south-west India.[16]

The conclusion to draw from this study is that the rural community as a whole needs to be provided with correct information on the cause and outcome of leprosy. There is a real need to impress on the public that the disease is not genetically transmitted. This necessitates intensive health education to convince the population that, as an infectious disease, leprosy can be cured, and if detected very early can be cured without deformities. The absence of strong negative religious beliefs, and the observed tolerance and understanding of the community toward leprosy sufferers would certainly contribute positively to the success of such health education. A campaign of education should, as Dogliotti suggested, extend to medical, paramedical, social, religious and educational institutions.[8] It is emphasized that the education of those in the medical profession should precede that of the general public.

The integration of leprosy care into the general health services would help to reduce the segregation of leprosy patients. In this connection, we subscribe to the views of Antia that the specialized treatment of leprosy patients in isolation encourages the perpetuation of the stigma in the minds of the public and the medical profession.[9] The present existing leprosy control programmes, with better resources and trained manpower, should therefore help to strengthen the basic health delivery centres in the country, and also actively participate in the health stations in order to ensure that the follow-up of leprosy patients is not neglected.

While we educate communities in endemic areas to avoid being victims of the disease and to report when they experience the first sign of leprosy, it is absolutely vital that we also find ways of re-integrating those that have been successfully treated. In the context of

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developing countries, it is common knowledge that a disabled person with a skill has better chances of overcoming prejudices and getting social acceptance. As Frist has emphasized, attention must be given to create integrated vocational rehabilitation opportunities for leprosy patients.[17]

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APPENDIX

Attitude Questionnaire

Date Farmers/Urban Association House No. Interviewer

TO BE ANSWERED BY ONE MEMBER OF THE HOUSEHOLD, PREFERABLY BY THE HEAD OR WIFE

Name of informant Age Sex
Marital status: Married Single Divorced Widow
Number of children: Male Female Total
Occupation Income per month:
Education: Illiterate Read and write Grade
Religion: Christian Moslem Other

ATTITUDES TO LEPROSY

Have you heard or read about leprosy? Yes No
If yes, where?
How would you recognize a person with leprosy?
Is there in your language/dialect another name for a person with leprosy?
Yes No If yes, specify:

After giving a full description of the different manifestations of leprosy (skin lesions, deformities and amputations due to nerve damage), the enumerator tells the respondent: WE CALL THIS *LEPROSY (SEGA DEWE)* AND THAT IS THE TERM WE WILL USE IN THE QUESTIONS TO FOLLOW.

Have you ever seen a person with leprosy? Yes No
Have you among your relatives anyone with leprosy?
Yes No If yes, specify relationship
Do you think you know the cause of leprosy? Yes No
If yes, explain
Do you think that leprosy is inherited? Yes No
If yes, how?
Do you think that leprosy is contagious? Yes No
If yes, how?
Do you think leprosy is a form of insanity? Yes No
Do you know what to do for a person with leprosy?
Yes No If yes, how?
If a person with leprosy has been treated and his disease has been cured will you consider him/her to be an ordinary healthy person?
Yes No If no, why?
If you had the opportunity, would you employ someone with leprosy?
Yes No If no, why?
Are you willing to work with a person having leprosy?
Yes No If no, why?
Would you allow your child to play with a child having leprosy?
Yes No If no, why?

What would you do if you were forced to share accommodation with someone with leprosy?

Do you have a friend who has leprosy? Yes_____ No_____

Would you be a friend of someone with leprosy?
Yes_____ No_____ If no, why?

May anyone in your family marry someone with leprosy?
Yes_____ No_____ If no, why?

Are you afraid of someone who has leprosy?
Yes_____ No_____ If yes, why?

Should a family having a member with leprosy hide him/her from outsiders?
Yes_____ No_____ If yes, why?

Do you think a person with leprosy should use public transport?
Yes_____ No_____ If no, how should he/she travel?

Would you shake hands with a person known to have leprosy? Yes_____ No_____

How should society take care of persons with leprosy?

At the end of the interviews health education on leprosy is given to the respondent and his/her family by the enumerator.

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Attitude des populations rurals à l'égard de la lèpre dans le centre de l'Ethiopie et brève comparaison avec certaines observations sur l'épilepsie

R Tekle-Haimanot, L Forsgren, A Gebre-Mariam, M Abebe, G Holmgren, J Heijbel et J Ekstedt

Résumé Pour connaître la réaction du public face à la lèpre, un sondage porte à porte a été effectué auprès de 1546 foyers dans les communautés rurales d'agriculteurs de Meskan et de Mareko dans le centre de l'Ethiopie, où la fréquence des cas de lèpre est estimée à 1 pour 1000. Les attitudes à l'égard de la lèpre ont été comparées aux attitudes vis-à-vis de l'épilepsie, étudiées lors d'une précédente enquête dans la même communauté. Quatre-vingt-sept pour cent des personnes interrogées ont plus de 25 ans, et 59,5% sont des femmes. Le groupe étudié se compose d'un peu plus de musulmans (54%) que de chrétiens. La majorité des personnes interrogées (87%) sont des fermiers, et le taux d'analphabétisme est de 84%. Respectivement 95% et 83% ne souhaitent pas employer ou travailler avec une personne souffrant de la maladie. Soixante-quinze pour cent ne permettraient pas à leurs enfants de fréquenter un camarade de jeu atteint de la lèpre. Une analyse comparative, dans la même communauté, a montré que les attitudes négatives à l'égard de la lèpre étaient plus marquées que celles à l'égard de l'épilepsie, notamment en ce qui concerne les relations matrimoniales, le partage du logement et le contact physique avec une personne atteinte. Il semble que ces différences s'expliquent par le fait que la communauté croit profondément que la lèpre est à la fois héréditaire et contagieuse, opinion exprimée par 48% et 53% des personnes interrogées, respectivement. Pour mettre un terme à ces attitudes négatives, il faut éduquer la population et lui inculquer que la lèpre est une maladie infectieuse que se soigne, qu'elle n'est pas congénitale et qu'elle est guérissable si elle est décelée tôt. Cette étude renforce les propositions déjà formulées pour intégrer le traitement de la lèpre aux programmes généraux de santé, dans les pays en développement comme l'Ethiopie.

Actitudes de los habitantes rurales de Etiopía Central a la lepra, y una breve comparación con la epilepsia

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Resumen Se realizó un estudio de las actitudes públicas a la lepra, de casa en casa en 1546 residencias muestreadas en las comunidades agrícolas rurales de Mesken y Mareko, en Etiopía Central, en donde se calcula la frecuencia de la lepra en 1 por 1000. Se compararon las actitudes a la lepra con las actitudes la epilepsia determinados en un estudio anterior en la misma comunidad. 87% de las personas interrogadas tenían más de 25 años, y un 59,5% eran mujeres. Habían pocos más Musulmanes (54%) que Christianos. La mayoría de personas entrevistadas eran agricultores, con un nivel de analfabetismo de 84%. 95% y 83% respectivamente no estaban dispuestos emplear ni trabajar con una persona que padecía de la enfermedad. Un 75% no permitía que sus hijos se asocien con un compañero que sufría de la lepra. Un análisis comparativo de las actitudes en la misma comunidad indicó que las negativas a la lepra erán más fuertes que las contra la epilepsia, especialimente respecto a las asociaciones matrimoniales, la distribución de acomodación y los contactos físicos con un enfermo. Las razones por estas diferencias parecían ser debidas a la creencia intensa que la lepra era tanto hereditaria como contagiosa, expresada por 48% y 53% de los entrevistados respectivamente. Para reducir a un mínimo la perpetuación de las actitudes negativas, es necesario educar y convencer la población que la lepra es una enfermedad infecciosa tratable, que no se adquiere por razones congenitales, y que es hasta curable si se detecta temprano. El estudio refuerza las sugerencias propuestas anteriormente que en los países en desarrollo, como la Etiopía, se debe integrar el cuidado de la lepra a los servicios sanitarios generales.

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Rheumatic Heart Disease Prevalence among Schoolchildren of an Ethiopian Rural Town

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Prevalence
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Rheumatic heart disease

Abstract
Rheumatic heart disease (RHD) is the most important cardiovascular disease in hospital practice in Ethiopia. However, the prevalence rate of RHD at the community level remains unknown. The current survey was undertaken to estimate its prevalence among schoolchildren of a central Ethiopian rural town (Butajira). Accordingly, 92.8% of the entire schoolchildren (n = 3.235) in the town were screened. Their mean age was 13.4 ± 3.5 years. Fifteen children, accounting for a rate of 4.6/1,000, were noted to have findings consistent with RHD. Females and older children were more frequently affected. Only 2 of the 15 students were aware of their disease, and neither of them were on regular secondary prophylaxis. Our finding is consistent with the hospital-based reports that showed RHD to be a common disorder in clinical practice. At the same time, the lack of awareness about their disease noted among the cases is worrisome and deserves serious attention.

Introduction

Valvular heart disease, presumably of rheumatic origin, is responsible for 35–50% of all admissions to Ethiopian hospitals because of cardiovascular disease [1–3]. A similar pattern has also been noted in adult and pediatric cardiac clinics [4, 5]. However, all the reports, except for one study that involved a few hundred elementary school children [6], were hospital based and came from large referral centers that serve an unknown vast

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population. There were therefore no serious attempts to determine prevalence of rheumatic heart disease (RHD) in the community in this country.

Ideally reasonable estimates of RHD prevalence can be obtained by a prospective study of a nationwide random sample of children aged 5–19 years. Such a study is difficult to conduct in developing countries like Ethiopia due to lack of funds and logistic problems. Thus this study was undertaken to determine the prevalence of RHD within a defined community of schoolchildren in a typical rural Ethiopian town.

Materials and Methods

The study was conducted among elementary schoolchildren grade 1–8 of Butajira. Butajira is a town 130 km south of Addis Ababa, the national capital. The town has a total population of 12,600, the great majority of whom are poor and live on small scale trade and subsistence farming [7]. There are two elementary schools and a health center for the town and its surroundings. Of the total 3,485 students enrolled in grades 1–8 in 1989–90, 3,235 (92.8%) volunteered to participate in the study.

Students were examined in a sitting position by a cardiologist in a room provided by the school. Girls and boys were examined separately. Initial screening was done with a high index of suspicion. Students suspected of having heart disease were reexamined in a supine and sitting positions during inspiration and expiration. When indicated, changes induced by a Valsalva maneuver were determined. Due to logistic problems, chest X-ray, electrocardiography and/or echocardiography were not carried out to confirm the diagnosis. Although the initial screening was performed with a high index of suspicion, the final diagnoses were made only after re-examination using strict criteria.

The significance of apical systolic murmur was judged according to the standards of Feinstein et al. [8]. An aortic systolic murmur was graded as significant if it was 3 or more in intensity and well conducted into the neck. In the presence of an aortic diastolic murmur, a systolic thrill in the neck was required for the additional diagnosis of aortic stenosis. Pulmonary ejection systolic murmur was considered significant only if it had an intensity of grade 3 or more and was associated with abnormalities of the pulmonic component of second heart sound. However, isolated aortic valve lesion was categorized under congenital heart disease and not considered under this study. The intensity of murmurs was graded according to Levine and Harvey's scale [9].

Table 1. Age and sex distribution of Butajira schoolchildren, 1989–90

	Age, years				Total
	5–9	10–14	15–19	>20	
Boys	190	912	592	155	1,849
Girls	161	597	542	86	1,386
Total	351	1,509	1,134	241	3,235

Results

Ninety-three percent of the entire Butajira schoolchildren were screened. They had a mean age of 13.4 ± 3.5 years, with a male to female ratio of 1.3:1 (table 1). Ninety and 80% of the children were in the age group of 5–19 and 10–19 years, respectively. Thus, the susceptible ages for RHD were well represented. There were more boys among the refusals than girls, but their mean age was similar to the participants. The average number of individuals per household according to our survey was 4.5. Seventy-three percent of the houses had one or two rooms, one of which is used as a bedroom for all members of the family.

Sixty-two percent of the children examined had grade 1 or more systolic murmurs. Murmurs consistent with RHD were detected in 15 children, accounting for a prevalence rate of 4.6/1,000 population at risk.

The characteristics of each case with RHD are given in table 2. Their number is too small for detailed analysis. However, girls and older children between 15 and 19 years were af-

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Table 2. Characteristics of students with valvular heart disease

S No.	ID No.	Age years	Sex	Auscultatory valve dysfunction	Comment
1	626	15	boy	MR	–
2	633	17	boy	MR	mild CHF
3	639	16	girl	MR	–
4	649	16	girl	MR	–
5	659	15	girl	MR	displaced apex
6	3197	18	boy	MR	displaced apex
7	664	17	boy	MR	displaced apex
8	2215	9	boy	MR, AS, AR	displaced apex
9	886	11	girl	MS, AR	APN
10	939	10	boy	MR	–
11	951	13	girl	MR	–
12	1667	15	girl	MR, MS	–
13	1916	10	girl	MR	–
14	670	18	girl	MS	–
15	2217	15	girl	MR, AS, AR	–

S = Student; ID = identity; APN = active polyarthritis noted; MR = mitral regurgitation; MS = mitral stenosis; AR = aortic regurgitation; AS = aortic stenosis; CHF = congestive heart failure.

fected more frequently. Two thirds of the cases had isolated mitral insufficiency, and 4 cases had combined valve lesions. There was only 1 case of pure mitral stenosis. Clinical rheumatic reactivation was noted in 1 of the patients. Because of the absence of physicians in the health center prior to 1989, documented history of rheumatic fever was not obtainable. Only 2 of the cases were aware of their disease and neither of them were on regular penicillin prophylaxis. All the cases were referred to the newly recruited general practitioner at the health center for follow-up and prophylaxis.

Discussion

The age and sex distribution of the study population is similar to that of elementary schools elsewhere in the country [9]. However, since school attendance in Ethiopia is free but not obligatory, the population studied may not be representative of children in the community as a whole. How much this selective attendance affects our results is difficult to estimate.

The poor socioeconomic conditions, overpopulation and inadequate medical service favor a high prevalence rate of rheumatic fever and RHD.

The high prevalence rate of 4.6/1,000 obtained in our survey is consistent with the observation that RHD is a common cardiovascular disorder in clinical practice. It is 10–40 times higher than that of Japan, an economically developed country [10]. However, it is lower than that (6–11/1,000) reported from Egypt, Morocco and India [11, 12], but higher than that of the Ivory Coast [13].

As in many other reports, the mitral valve is the valve most commonly involved. Older

children and girls were more frequently affected, consistent with the findings of the majority of investigators [10–15].

The prevalence rate may even be higher in larger cities of the country with rapidly increasing population and declining standard of living. The lack of awareness of RHD among the patients is also worrisome. We therefore feel that RHD constitutes a preventable public health problem that deserves serious attention.

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ATTITUDE OF MEDICAL STUDENTS TO FUTURE PRACTICE CHARACTERISTICS

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ABSTRACT: In November 1990, 14.5% of the 271 medical students of the Gonder College of Medical Science (G.C.M.S.), Gonder, Ethiopia, were of peasant background. Only 10.2% of the 271 expressed willingness to serve for more than two years in the rural areas after graduation, and, of those not willing, a higher proportion (15.5%) were from the main towns than from rural areas (1.2%). Speciality choice of senior students showed obstetrics-gynaecology, other specialities such as dermatology, internal medicine and surgery as the most preferred career goals. In addition, 67.2% of the students agreed that there is a greater need for physicians in rural than urban settings, agreement being six times more frequent by Clinical Year I students than interns (referent group). Among twelve personal and professional variables suggested, continuing education, schools for children, and private practice were considered better in urban than in rural areas. The study has important implications for medical education.

INTRODUCTION

Speciality choices of medical students have been widely studied both in developed and developing countries (1-5). In Ethiopia, published reports on the subject are scarce (6), but, with an increase in the number of graduates, a high rate of specialization, and a rapid increase in private practice, there is a need for such a study.

Observations at the Gonder College of Medical Sciences (GCMS) have indicated that medical students have a negative attitude towards certain specialities. There is also a growing concern among national health policy makers that medical graduates are unwilling to work in rural areas, reflected by the high concentration of medical doctors in urban centres. In addition, in spite of an increase in the number of specialists, there is a critical shortage of manpower in certain specialities, both in the teaching and service areas. Since many of these problems have their roots in the social milieu of the medical school and the role of instructors as models in professional socialisation, it is useful to investigate the speciality choices and preferred future practice locations of medical students.

Such a study could help to identify deficiencies in the learning-teaching process and in the operation of the national health system. In addition, it can serve as baseline data for assessment of trends in speciality choice.

The purpose of this study was to survey the demographic characteristics, expected career goals and future practice location preferences of medical students of the GCMS.

METHODS

The study was conducted in November, 1990. The survey questionnaire was prepared and pretested for reliability, and modified where necessary. A total of 286 students were enrolled

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at the GCMS during the study period. Medical school lasts for six years but students spend their first year in Addis Abeba before coming to Gonder.

Information on demographic characteristics such as age, sex, main residence during high school, parental education and occupation, and reasons for studying medicine was gathered from all students. However, information relating to expected future career goals, attitude to rural practice, and factors affecting the choice of practice location was collected from interns and senior medical students (Clinical Years One and Two) because clinical exposure begins in these years. Response rates among the different cohorts of medical students were compared using odds ratios.

RESULTS

Demographic characteristics of 271 students showed a mean age of 20 years (SD±3.7). The majority were male (93.4%). Of all students in the study, 38.4% completed high school in Addis Abeba, 30.6% in main regional towns and 31% in rural localities. Reported parental education was university degree or diploma for 21.7%. Occupationally, 29.5% of parents were government employees, 24.5% businessmen and only 14.5% peasants.

The study also revealed that, of the 271 students, 241 (88.9%) were enrolled in the three medical schools on the basis of their first choice. The main reason for studying medicine was an interest in basic science for 36.1% and service to patients for 29.9% (Table 1). Table 2 shows that among 175 senior medical students who responded to the questionnaire, obstetrics-gynaecology, other specialty (dermatology, ophthalmology, ear-nose-throat), internal medicine and surgery were chosen as preferred career goals. However, among interns the other specialities and surgery were considered first and second choices. On the other hand, Clinical Year II students selected surgery as their second choice and internal medicine was the first choice of Clinical Year I students. Community health, paediatrics and preclinical specialities (biochemistry, physiology, microbiology, pharmacology and pathology) were the least preferred career goals, and only 1.2% chose to remain as general practitioners.

Concerning future practice location, 241 (88.9%) of the 271 students were willing to serve in the rural areas, 29.2% of them for one year, 49.8% for two years and only 10.2% for more than two years (11.6% were uncertain). In addition, of the 30 students who were not willing to serve in rural areas, 29 were from the main towns including Addis Abeba. The proportion of those students of rural origin who were unwilling to work in rural areas was much lower (1.2%) than of those from the main towns (15.5%).

Of the 183 Clinical Year students, including interns, 48.6% considered prevention the most important function of a physician, followed by curative service (41.5%) and research (0.9%). The majority (67.2%) agreed that there is a greater need for physicians in rural than in urban settings, while 19.1% disagreed. Moreover, clinical Year I students were six times more likely to agree than the referent group (Table 3); 57.4% of the students agreed that a well-trained medical graduate can function well in a rural setting, twice as many clinical Year I students as the referent group having agreed (Table 4).

Table 5 shows continuing education, schools for children, private practice, overall life style, job availability and prestige among colleagues were viewed as better in urban than rural settings. However, in the rural areas, prestige in the community, patient contact, job challenge and housing

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expenses were considered more favourable.

DISCUSSION

The study raises some important issues related to medical students' perceptions of various specialities and future practice locations. It shows that obstetrics-gynaecology, other clinical specialities such as dermatology, internal medicine and surgery are the most preferred specialities (Table 2). Among Nigerian students also obstetrics-gynaecology and surgery were rated high(2). Although comparison is difficult, studies done in the USA had similar results (7). Our study indicates that except for paediatrics, medical students have a positive attitude to clinical training. Clinical training has a strong dominance in medical education, and the curriculum of the medical school is hospital based, maintaining a strong emphasis on clinical practice. In addition, 80 to 90% of the available scarce budget is allocated to curative services.

The reason why paediatrics was reported among the least preferred specialities is not clear and may require further study. However, many children admitted to the paediatric ward are severe cases, posing considerable difficulty in management, partly as a result of low coverage and poor functioning of rural health services. We feel that, parallel to bedside teaching, there is a need to establish separate maternal and child health clinics attached to the outpatient department, to serve as training sites for students and to bring them into close contact with mother and child. Since protecting the health of the child is a priority, improving the attitude of students to paediatric practice deserves special attention.

With regard to career goals, community health and the preclinical specialities were rated low (Table 2). Similar observations are reported concerning community health from other studies (5,6,7). This problem is caused by a number of factors both within and outside of the medical school. In addition to reasons already stated, time allocated for community health in the medical curriculum is too little. The department is poorly staffed and under-financed. In addition, the conditions of rural health service have deteriorated. These and other factors may have contributed to the problem. Thus, changing the curriculum and strengthening the department may improve the situation.

The results have shown consistency in the choice of certain specialities among the different cohorts. However, it is difficult from such a study to distinguish between cohort and socialisation effects of the training experience. Thus, it would be useful to follow this cohort to observe trends in career choices.

In this study, the reasons for choosing a particular speciality were not explored. However, many investigators have stated that talent, clinical experience, age, sex, family status, social and financial attractiveness, and avoidance of stress are considered determinant factors in the selection of medical speciality (4,8,10).

The reason why a high proportion of interns chose medical specialities such as dermatology is partly explained by demand for these specialities at the teaching hospital in Gonder. In the case of Clinical Year One students who had only been exposed to internal medicine, the reasons for their choices are not clear. However, the influence of instructors and peers in the decision making process cannot be ruled out. The low proportion (6.6%) of female students may have influenced overall speciality priorities.

The study has also show that 98.8% of the students intend to specialize. The desire to specialize is caused by a number of factors such as salary, prestige, practice location and role model of the instructor. Such a trend will affect the performance of rural

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health services, and is reflected in the high turnover of medical graduates working in rural areas.

The very low proportion of medical students of peasant background (14.9%) is quite disturbing. The under representation is a reflection of the hardship conditions that exist in rural areas. Narrowing the gap in educational opportunities between rural and different social classes is highly desirable.

The fact that a high proportion of the students who were unwilling to work in rural areas were from the main urban areas is interesting. If this observation is true for the other Ethiopian medical schools (Addis Abeba and Jima), there is a need to introduce a policy that increases enrolment of students reared in rural areas. We are not certain how this could be done but admission policies based on personal and social characteristics as opposed to purely academic criteria might be considered. Such a change in policy could improve rural health services, rural origin being recognized as a frequent characteristic in the background of the rural health practitioner (11-13).

This study indicates that the odds ratio in favour of agreeing about the greater need for medical practitioners in rural than urban settings among Clinical Year One students as compared to interns was 6.4 (Table 3). The reason why such a high proportion of interns (48.4%) disagreed is not clear. However, in such a cross-sectional study it is difficult to know whether it is due to the effect of training, or the influence of their experience in rural community health practice, or both. We think there is a need for a cohort study to investigate the situation.

Furthermore, as indicated in Table 5, of twelve personal and professional variables listed, continuing education, schools for children, private practice and overall life style were viewed better in urban than rural areas, resulting in the choice of the urban area as the desirable future practice location. This is quite understandable as more opportunities for furthering personal and professional development exist in urban areas: this situation has greatly affected the development of rural health services. Thus, concrete action should be taken to improve the working and living conditions of health personnel working in rural areas.

There is a need to revise the regulation of the Ministry of Health which states that medical graduates are required to serve in rural areas for two years. In our opinion, this regulation damages the development of rural health services: this period should be extended if the medical graduate who is the leader of the health team is to make a significant contribution.

Finally, we suggest further research of this type both during under-and post-graduate studies. Also there appears to be a need to orient and assist students in their choice of specialities.

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TABLE 1. Reported reasons for studying medicine (N=241)

Reason	Number of responses	%
An interest in basic science	67	36.1
Service to patients	72	29.9
Financial and social security	29	12.0
Influence of friends	21	8.7
Family pressure	20	8.3
Others	12	5.0

TABLE 2. Preference of 175 senior medical students for the various medical specialities, GCMS, 1990*

Speciality	Interns n = 57 %	Clinical II n = 57 %	Clinical I n = 59 %	Total n = 175 %
Obstetrics-gynaecology	20.3	31.6	22.0	24.6
Other specialities	28.8	21.0	20.3	23.4
Internal medicine	10.2	15.8	35.6	20.6
Surgery	23.7	22.8	11.9	19.4
Community health	6.8	1.8	6.8	5.1
Paediatrics	8.5	-	1.7	3.4
**Preclinical specialities	1.7	7.0	1.7	3.5

*Questions distributed to all 183 students: 175 (95.6%) responded.
**Preclinical specialities include specialities such as biochemistry, anatomy, physiology, pathology and microbiology.

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TABLE 3. Response of students as to whether there is a greater need for medical practitionnairs in rural than urban areas (n = 183)

Clinical year students	Response agree N(%)	disagree N(%)	uncertain N(%)	Odds rRatio	95% Confidence Interval
*Interns	32(51.6)	20(32.3)	10(16.1)		
Clinical Two	40(70.2)	10(17.9)	7(12.3)	2.5	1.0, 6.1
Clinical One	51(79.7)	5(7.8)	8(12.5)	6.0	2.2,18.7
Total	123(67.2)	35(19.1)	25(13.7)		

N = Number
*Referent group

TABLE 4. Response of students as to whether a well trained medical graduate can function well in rural settings (N = 183)

Clinical year students	Response Agree N(%)	Disagree N(%)	Uncertain N(%)	Odds Ratio	95% Confidence Interval
*Interns	33(53.2)	22(35.9)	7(11.3)		
Clinical Two	33(57.9)	15(26.3)	9(15.8)	1.5	0.6,3.9
Clinical One	33(60.9)	14(21.9)	11(17.2)	1.9	0.7,5.0
Total	105(57.4)	51(27.9)	27(14.7)		

N = Number
*Referent group

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TABLE 5. Response of 183 senior medical students concerning conditions of urban and rural practice

Factor	Better in Urban setting %	Rural setting %
Continuing education	94.0	6.0
Schools for children	90.8	9.2
Private practice	89.1	10.9
Standard of living	88.0	12.0
Job availability	71.6	26.4
Prestige among colleagues	67.2	32.8
Salary	43.9	36.1
General living expenses	48.6	51.4
Housing expenses	42.9	57.4
Job challenge	37.2	62.8
Patient contact	37.2	62.8
Prestige in community	34.4	65.6

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Neurological Disorders

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Introduction

Often in clinical practice, overlaps occur in mental and neurological illnesses. The confusion between the two categories of illnesses is very prominent in Ethiopia, where the majority of the public is not yet clear about the individual characteristics of each illness. The terminologies used in Amharic have further complicated the issue. *Yenerve beshita* ("the disease of the nerves") is a phrase commonly used by Ethiopians to describe mental illnesses. In fact *nerve hognalehu* ("I have become nerve") means "I have gone nuts or become insane." The term "nerve" in the Ethiopian context refers to the brain, and peripheral nerves as well as a mental state, which makes it a very confusing concept. There was actually no specific Amharic term or phrase for neurological disease because the Ethiopian public was not aware of this separate clinical entity until recently, when a direct translation of the English words was introduced to refer to neurological diseases.

As a result of the public's ignorance of the difference between the two specialties, a person with an altered state of consciousness due to an organic disease such as meningitis might end up in a mental hospital, while another with behavioral problems due to psychosis might present to a neurological clinic. In Ethiopia, where there are shortages of specialists in the medical profession, the above-mentioned confusion can be detrimental to the care of patients who are tossed from one clinic to another in search of the correct specialist. Consequently, there is a need to educate the public on the difference between the two disciplines. In this connection, it is a welcomed development that the newly introduced Amharic phrase, *yeaamero beshita*, which genuinely reflects mental illness, is gaining acceptance over the previously mentioned *yenerve beshita*.

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Neurological services are very limited in Ethiopia. Two neurological units operate within the medical departments of major hospitals in Addis Ababa. At the present time, there are only four neurologists and one neurosurgeon in the country, and these specialists function without adequate neurodiagnostic facilities. Because of these shortcomings, the rural population is left virtually without any neurological services. This calls for a plan to give "neurological services without neurologists"--a plan which raises a number of questions. Can the existing health services be used to tackle common neurological problems like epilepsy? If so, what are the common and important neurological disorders? What are the magnitudes of the problems? A recent community-based neuroepidemiological study conducted in central Ethiopia addressed these questions.[1] The findings of this study are incorporated in the sections below.

Common Neurological Disorders in Ethiopia

Infections of the Nervous System

Infections of the central nervous system are the commonest neurological disorders in Ethiopia, as they are in many developing countries. They are also the commonest causes of coma, as demonstrated by analyses of admissions to the university hospital in Addis Ababa.[2]

Poliomyelitis. In Ethiopia, as in the other Third World countries, poliomyelitis is the major cause of motor disability. Its prevalence among Ethiopian schoolchildren was found to range from 2.5 to 2.7/1,000.[1,3]

Leprosy. Leprosy is the commonest cause of peripheral neuropathy in Ethiopia and other developing countries. The numerous studies on neuropathy in leprosy carried out in Ethiopia are in the bibliography by Kloos and Zein.[4]

HIV Infection. Cases with a positive serology for HIV were first detected in 1983-84. Subsequently, there has been an exponential rise in the HIV seropositivity rate and in the incidence of AIDS (see the chapter on AIDS). In the limited cases of HIV infections we have treated, neurological complications were common. They included mono- and polyneuropathies, Guillain-Barré syndrome and involvements of the central nervous system by HIV encephalitis and opportunistic infection and primary tuberculous meningitis.

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Epilepsy

Next to infection of the central nervous system, epilepsy is the most prevalent nontraumatic neurological disorder in Africa. The prevalence rate of the disease in Sub-Saharan African countries, as evidenced by population-based studies, generally varies from 4/1,000 to 7/1,000, although exceptionally high frequencies have been reported in Tanzania[5] and Liberia,[6] where genetic and other factors have been implicated. One community-based study showed the epilepsy prevalence rate to be 5.2/1,000, making it the most common neurological condition in Ethiopia.[7] The prevalence is similar to that found by studies in other African countries.[8] As has been demonstrated in our community-based survey, mortality from uncontrolled seizures is high in a community where anticonvulsant therapy is not readily available. The lack of treatment for epileptics in rural communities explains the finding that in 85% of the cases identified, the seizure frequency was at least one episode a month.

Because in Ethiopia the rural community has very poor knowledge of the causes and the nature of epilepsy, epileptics suffer from social deprivation and ostracization. Traditional views on the association between epilepsy and evil spirits and other incorrect etiologies are prevalent. An attitudinal survey in rural central Ethiopia found that 45% of the interviewees believed the disease to be contagious through physical contacts during an attack. Although there was sympathetic concern in the community for persons suffering from epilepsy, negative attitudes were strong on matrimonial associations, sharing of accommodations, and physical contacts with affected persons, particularly when they exhibited obvious signs and suffered frequent seizures.[9]

Mental Retardation

Unfortunately, most of the studies on mental retardation in Africa have been based on institutionalized retarded children, who may not represent the actual situation in African communities. Adequate epidemiological and etiological data do not exist, except for a few statistics gleaned from studies in South Africa. In a community-based study of an urban black community in South Africa, Power found a prevalence rate of 2.6-3.4/1,000 in children of school age.[10] Friedlander and Power reported a prevalence rate of 2.5/1,000 among black children under the age of 18 years.[11] In a community-based survey in rural central Ethiopia, the prevalence of moderate to severe mental retardation was 1.7/1,000.[1] In this latter study, the researchers believed that the prevalence rate would have been even higher if the neuroepidemiological screening instrument had been sensitive enough to

pick up mild mental retardation. Thus this common neurological problem has not received the attention it warrants. Integration of preventive and rehabilitative measures within the Primary Health Care System is badly needed.

Dementia in adults was found to be rare in the rural community that was studied in central Ethiopia.[1] Similar low rates have been observed in Nigeria.[12]

Cerebrovascular Accidents

There have been no major autopsy studies on cerebral vessels in Ethiopia. However, other African studies have indicated that atherosclerosis is rare in the African black.[13-15] As in the rest of Sub-Saharan Africa, hypertension, which is very common in Ethiopia,[16,17] is the leading single most important risk factor for cerebrovascular accidents, which consitute the major reason for neurological admission to hospitals.[18] Next to thrombotic cerebrovascular accidents (CVAs), hypertensive strokes are the neurological problem most commonly encountered.[19] Since rheumatic heart diseases are common, emboli from cardiac sources are important causes of CVAs. It is believed that these cases are underdiagnosed. Additionally, studies from Uganda have demonstrated that the embolic lesions were discovered only at autopsy.[15,20]

Myelopathies

Paraparesis and Tuberculous Spondylitis. Several causes of myelopathies and myeloneuropathies are found in Africa. Tuberculous spondylitis is the primary cause of paraparesis in Africa.[21,22] In the university hospital in Addis Ababa, it was found to account for 50% of the hospital admissions for paraplegia or paraparesis, followed by spinal and metastatic tumors, Guillain-Barré syndrome, tropical spastic paraparesis, and other causes, in that order. Neurolathyrism patients rarely come to hospitals, and, if they do, they are never admitted for neurological problems.

Tropical Spastic Paraparesis. The tropical myeloneuropathies are classified into (1) tropical ataxia neuropathy, (2) epidemic tropical spastic paraparesis, and (3) endemic tropical spastic paraparesis.[23,24] In Ethiopia the endemic tropical spastic paraparesis type manifests with predominant spastic motor weakness of the legs and minimal sensory signs and bladder dysfunction.

Recently, a strong association was discovered between this type of spastic paraparesis in Africa, South America, and Japan and the Human T-cell

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Lymphotrophic Virus type-1 (HTLV-1).[25-29] It is also obvious from most of the studies that the HTLV-1 seropositivity in those with TSP tends to correspond to the level of seropositivity in the general population. In Ethiopia, HTLV-1 appears not to be strongly associated with tropical spastic paraparesis, but HTLV-1 seropositivity in the general population is very low.[30-32]

Lathyrism. Another type of spastic paraparesis which occurs commonly in Ethiopia is lathyrism. This type of myelopathy is at the present time confined to certain endemic areas, primarily in India, Bangladesh, and Ethiopia.[33] It is caused by excessive consumption of grass-peas (*Lathyrus sativus*), which contain the neurotoxin beta-oxalylamino-L-alanine acid. International efforts are underway to breed out this toxin from hardy pulse crops.

Some areas in north and northwestern Ethiopia, particularly in Gonder Region, have endemic foci of lathyrism; epidemics have been reported during a locust-caused famine in the north[34] and flooding in the northwestern part of the country.[35] This region, including two subdistricts in the Lake Tana basin in Gonder Administrative Region, is particularly prone to flood and drought, and grass-peas are widely grown there because of their high drought resistance. In this area, lathyrism continues to manifest itself at an estimated incidence rate of 1.7/100,000, with some villages recording alarmingly high frequencies of the disease of up to 3%.[36] The epidemiological and clinical manifestations of lathyrism observed in Ethiopia are very similar to those reported from India.[37,38]

Neurofluorosis. The prevalence of neurological complications of skeletal fluorosis is increasing in Ethiopia due to rapid population growth in the Rift Valley and other lowland areas where fluorosis is endemic. The myeloradiculopathic complications that simulate cervical spondylosis in the majority of cases are progressive and crippling.[39]

Peripheral Neuropathies

A hospital-based study in Nigeria pointed out that the primary etiological factors in peripheral neuropathies were Guillain-Barré syndrome, diabetes mellitus, nutrition deficiencies, malignancy, and leprosy.[40] This concurs with our experience in Ethiopia. However, when the community at large in tropical countries is considered, leprosy is by far the commonest cause of peripheral neuropathy in areas where it is endemic. The afflicted persons often face rejection and ostracism because of myths and prejudices.

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Peripheral neuropathic complications of diabetes in Africa have prevalence rates ranging from 22% to 58%.[41,42] In Ethiopia, one study reported a prevalence of 54%.[43] The high prevalence of neuropathy in Africans may be due to poor biochemical control of diabetes because of late diagnosis and inadequate treatment.

Myopathies

In the past, it was believed that myopathies were rare among Africans.[44] Most probably this belief was due to underdiagnosis of the conditions. A recent study found that muscular dystrophies and inflammatory myopathies were not uncommon in Ethiopia. Myasthenia gravis, though rare, was seen mainly in young females.[45]

Rare Neurological Disorders

Neurosyphilis has been found to be rare in Ethiopia.[46] Recently, investigations among Ethiopian Jewish immigrants (Falasha) in Israel revealed a seropositivity of 12% for syphilis among the adults, while all the children examined were seronegative. A search for neurosyphilis did not reveal neuropsychiatric complications, even in the three persons whose cerebrospinal fluid tested positive.[47] Therefore, it can be concluded that despite the high luetic seropositivities reported, syphilis in Africa appears to run a relatively benign course and that neurosyphilis is a very rare complication.

Positive serologies for syphilis ranging from 10.4% to 75.6% have been found in hospital- and community-based surveys in different parts of the country.[48-50] Extremely high prevalence rates of seropositivity (above 40%) were found in communities in south and southwestern Ethiopia, where yaws is endemic.[50] Despite the high incidence of positive treponemal serology in communities in Jamaica,[51] neurosyphilis was found to be extremely rare. Similar reports have come from Zimbabwe.[52]

Primary demyelinating disorder is rare in Ethiopia, [53] as it is in other tropical countries in Africa.[44,54,55] Among the extrapyramidal disorders, Sydenham's chorea is commonly encountered in children with rheumatic fever, a condition which is common in African countries, including Ethiopia. Except for the impressions of Collomb et al.in Senegal,[56] Parkinson's disease is believed to be a rare condition in blacks in general,[57] and Africans in particular.[44,58] Similar observation has also been made in Ethiopia.[59]

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THE CHANGING PATTERN OF CARDIOVASCULAR DISEASES IN ETHIOPIA
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THE CHANGING PATTERN OF CARDIOVASCULAR DISEASES IN ETHIOPIA

M. MARU

SUMMARY

A total of 474 patients (216 males and 258 females) with cardiovascular diseases which were followed in the cardiac clinic of the Gondar College of Medical Science Hospital, Gondar, Ethiopia, between 1985 and 1988 were studied. The commonest form of heart disease in Ethiopians was found to be rheumatic heart disease (42%), and affects mostly young people, who often have advanced valvular lesions. Hypertension (38.1%) was the second most common cause of heart disease. It affects mostly young people and 77% of the cases are of essential type. The incidences of atherosclerotic and congenital heart disease have not changed but that of syphilitic heart disease and cardiomyopathy have markedly decreased in the last 20 years. The incidences of rheumatic and hypertensive heart diseases have shown a significant increase. However the rise in the incidence of myocardial infarction over a 20 year period from 0.88 per 1000 in 1963-68 to 6.4 per 1000 in 1985-88 is distinctively impressive.

INTRODUCTION

Cardiovascular diseases appear to be of considerable importance as causes of morbidity and mortality in Ethiopia. Congestive heart failure is commonly seen among hospitalized patients. Retrospective analysis of admissions from different hospitals have shown an incidence of cardiovascular diseases ranging from 5.0% to 12.9% of medical admissions(1,2). Studies of cardiovascular diseases from other African countries showed that the pattern of heart diseases in Africa is much different from that of the developed countries(3,4,5). This study was undertaken to determine the prevalence and assess if there is a change in the pattern of cardiovascular diseases in Ethiopia in the last 20 years.

MATERIALS AND METHODS

In order to assess the prevalence and determine the pattern of cardiovascular diseases, a prospective study was undertaken from 1985-1988. All patients with cardiovascular diseases were followed in the Cardiac Clinic of the Gondar College of Medical Science Hospital. The age, sex, clinical findings were recorded at the initial visit in the Cardiac Clinic. Electrocardiograms, echocardiograms, chest x-ray and when necessary phonocardiography were done on each patient. ASO titres, VDRL, serum potassium, BUN, creatinine,and VMA were done when indicated. M-mode and 2-D echocardiography was used to assess valvular structures, functions, the relative size of cardiac chambers and myocardial contractility. In the absence of the characteristic chronic or acute ECG and enzymatic changes, echocardiographic findings such as dyskinetic movements between the ventricular septum and posterior left ventricular walls or the apical portion of the left ventricle was used to diagnose ischaemic heart disease. The results of this study are based on the above clinical laboratory and special investigations. All patients have been evaluated and followed by the author.

RESULTS

A total of 474 patients with average age 36.3 years (range 10-87) were followed in the Cardiac Clinic. The age and sex distribution of the various cardiovascular diseases is shown in Table 1. The incidence of cardiovascular diseases was 4.1% of all medical admissions. Out of the 474 patients, 292(61.6%) were hospitalized. The rest of the patients were managed in the Cardiac Clinic. There were 16(3.4%) deaths during the study period. Sixty nine percent of the patients were from Gondar city and its vicinities, and 6.5% from Gojjam an adjoining province.

Rheumatic heart disease (RHD) was found in 206 patients. Three patients had acute rheumatic carditis. Valvular involvement is shown in Table 2. The average age was 32.9 years (range 10 to 80). The male to female ratio was 1:1.3.

Hypertension of 160/95 mmHg and above was the second commonest cause of cardiovascular diseases. There were 196(38.1%) patients.There was no particular sex bias. The average age was 35.3 years (range 20-80).

Ischaemic heart disease (IHD) was found in 31 patients (15 males and 16 females). The average age was 65.7 years (range 32-86). Sixteen patients had myocardial infarction (11 males and 5 females). There were eleven patients with hypertension and seven with atrial fibrillation.

Of the 24 cardiomyopathy cases, two patients had obstructive and 22 had dilated cardiomyopathy. The age range was from 28 to 70 years.

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Table 1

Age and sex distribution various cardiovascular disease

	Total	10-19	20-29	30-39	40-49	50-59	60-69	70>
RHD								
Males	90	21	27	15	13	4	6	8
Females	116	27	17	17	23	17	5	6
Total	206	48	44	32	36	21	11	14
Hypertension								
Males	93	1	9	14	18	17	27	7
Females	103	3	9	11	28	22	22	7
Total	196	4	18	25	46	39	49	14
IHD								
Males	15	-	-	1	3	1	3	7
Females	16	-	-	-	1	3	7	5
Total	31	-	-	1	4	4	10	12
Cardiomyopathy								
Males	10	-	3	1	3	2	1	-
Females	14	-	2	6	1	3	1	1
Total	24	-	5	7	4	5	2	1
Pericardial disease								
Males	11	2	3	3	1	-	-	2
Females	12	2	2	1	2	3	1	1
Total	23	4	5	4	3	3	1	3
Congenital heart disease								
Males	6	2	2	2	-	-	-	-
Females	5	3	2	-	-	-	-	-
Total	11	5	4	2	-	-	-	-
Syphililitic heart disease								
Males	5	-	-	1	1	1	1	1
Females	6	-	1	1	3	-	-	1
Total	11	-	1	2	4	1	1	2
Others								
Males	7	-	3	2	2	-	-	-
Females	5	-	3	1	1	-	-	-
Total	12	-	6	3	3	-	-	-

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Table 2

Valvular involvement in 206 patients with rheumatic heart disease

	No. of cases	%
Mitral regurgitation and stenosis	72	35
Mitral regurgitation	48	24
ure mitral stenosis	26	13
Mitral and aortic valves	29	14
ortic valve alone	14	7
Mitral, tricuspid and aortic valves	10	5
Mitral and tricuspid valves	5	2
	206	100

Table 3

Causes of pericardial diseases

	Cases
Tuberculosis	12
Viral	8
Idiopathic	2
Pyogenic	1
Total	23

Table 4

The changing pattern of cardiovascular diseases in Ethiopians

	1963-1968			1975-1979		1985-1989	
	Gondar	Addis Ababa		Addis Ababa		Inpatient	Both
	Molineaux (1966)	Tefera (1968)	Parry (1969)	Lester (1976)	G/Hiwot (1982)	only	In & out
RHD	32.6	33.3	34.8	37.6	49.3	45.5	40.2
Syphilitic heart dis.	17.4	2.5	16.8	-	7.9	2.3	2.1
Hypertension	13.3	18.5	16.3	32.7	15.4	28.6	38.1
IDH	17.4	6.2	-	7.2	7.4	6.5	6.0
Cardio-myopathy	-	18.5	13.6	11.6	8.8	6.2	4.7
Congenital heart dis.	1.7	-	-	2.4	3.0	2.3	2.1
Pericardial heart dis.	1.7	-	10.8	-	2.6	6.2	4.5
Others	13.2	16.1	6.1	-	2.2	2.4	2.3

Pericardial disease was found in 23 (6.2%) patients. heir age ranged from 17 - 86 years.The major causes e shown in Table 3. All had pericardial effusion.

Eleven patients had syphilitic heart disease. Two d echo proven aneurysm of the ascending aorta with rtic insufficiency. All had positive VDRL.

Congenital heart disease was found in 11 (2.1%) tients. Three patients had ventricular septal defect, atrial septal defect, one atrial septal defect and lmonary stenosis, and one patent ductus arteriosus. heir age ranged from 10 - 32 years.

The miscellaneous group consisted of 4 patients ith supraventricular tachycardia, two with adyarrythmia, two with paroxysmal atrial fibrillation d four with viral myocardits.

DISCUSSION

Rheumatic heart disease (RHD) was the most common and was seen in 45.5% of all cardiovascular admissions.This finding is similar to that reported by Parker and Gebrehiwot(5,6). Comparison of prevalences of RHD of previous studies of medical admissions from 1960–1979(2,6) showed a gradual increase from 23.5% to 49.3% (Table 4). Similar increase in the rate of RHD 18% to 50% from 1960 to 1970 was also observed in Kenya(7). As shown in Table 1, 23% of the patients were below the age of 20 years which is similar to that found in Kenya(7). The distribution of valvular lesions is shown in Table 2. The mitral valve is involved in 83.5%, the mitral valve alone was affected

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in 72% and pure mitral valve stenosis was found in 12.6%.This findings are similar to previous reports from Ethiopia(2,6,9) and Nairobi(3). Atrial fibrillation was found in 30.4% of patients. Of these, one had embolic stroke.

The most striking thing about RHD in Ethiopia is the lack of history of acute rheumatic fever and the absence of recurrence in adult patients. The possible explanations are that rheumatic infection are truly asymptomatic.

In order to formulate preventive measures against acute rheumatic attacks, epidemiological study of post streptoccocal immunological responses and streptococcal carriers should be undertaken.

Hypertension was found in 28.6% of admissions and in 38.5% of all patients seen in the Cardiac Clinic. Forty seven percent were below the age of 49 years. There was no particular sex bias. Essential hypertension was present in 77%, which is similar to the findings of Gebrehiwot(6). Thirty patients (15.3%) had cerebro-vascular accident with five deaths. Thirty patients had congestive heart failure.The prevalence of hypertension in the last 23 years has shown an increasing tendency(,10,11,12). These findings indicate that hypertension will continue to be a major cause of morbidity and mortality with increasing urbanization and associated stresses.

The 6.7% prevalence of IHD in this series is much lower than the 17.4% reported from Gondar(1); Table 4. The higher rate of IHD at that time was most probably due to inclusion of cases of cardiomyopathy. The prevalence of IHD in Ethiopia does not seem to have increased in the last 20 years(2,5,6,10).

Myocardial infarction is thought to be rare in Ethiopia. Analysis of medical admissions and outpatient records of 10,161 patients from 1960-1976(1,2,5,10,13) showed an incidence of myocardial infarction of 0.88 per 1000. Studies of medical admission and outpatient records of 4,198 patients from Addis Ababa(6,14,15,16) for the years 1977-1986 revealed an incidence of 6.4 per 1000. This is a seven fold increase.

Autopsy studies of 256 patients by Gabre Selasse(17) in 1984 showed a rate of myocardial infarction of 16 per 1000. A prospective study of 124 autopsies for myocardial infarction by Maru in 1989 showed an incidence of 65 per 1000(18).

These studies are highly indicative that the prevalence of myocardial infarction in Ethiopia and other African countries is on the increase(8,19). Even then, it is still much lower than in the West. However, it would not be too long, before it also becomes a major health hazard in indigenous Africans, unless appropriate preventive measures are taken as as soon as possible.

The prevalence of pericardial disease seems to have increased from 1.7% in 1963 to 6.2% in this series. This rate is similar to that reported from Addis Ababa(2), and Kenya(7) but higher than that reported by Gebrehiwot(6). The increase is most likely due to improved diagnostic methods.

The aetiology of cardiomyopathy has been a cause of considerable controversy. One notable difference from Kenya is the apparent rarity of endomyocardial fibrosis in Ethiopians(7). The prevalence of cardio-myopathy seems to have markedly decreased from 18.5% in 1960 to 6.2% in this series(6). A similar trend was also observed by Isaacson(8). It is not clear at this time whether the decrease is a true decrease in the prevalence or whether it is due to improved diagnostic techniques.

The incidence of syphilitic heart disease in Ethiopia in the last 20 years has been downwards(1,2,6,9). This is similar to the findings of Isaacson in South Africa(8). The decrease in the incidence would be expected with increased availability of health services.

In conclusion, the study clearly indicated that rheumatic valvular heart disease, hypertension and coronary heart disease are on the increase in Ethiopia. In order to start appropriate primordial preventive measures, it is necessary to do representative population surveys to determine the prevalence of these diseases and identify the risk factors.

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Mulugetta Mengistu. 1993. *Ethiop Med J* 31,

THE PATTERN OF THYROID DISEASES IN ADULT ETHIOPIANS AND EXPERIENCE IN MANAGEMENT

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ABSTRACT: *During the study period, between February 1986 and July 1991, a total of 373 thyroid patients (68.3% of the total endocrine cases) were seen in the weekly endocrine referral clinic of Tikur Anbessa Hospital (TAH); 258 (69.2%) came from Addis Abeba, 41 were males and 332 females (M:F=1:8.1) and 71.9% were below 40 years of age. Thyrotoxicosis was seen in 43.7% of the patients, followed by euthyroid solitary nodules (23.6%) and simple goitres (22.3%). Euthyroid multinodular goitre was seen in 6.7% while hypothyroidism and thyroiditis were less frequent. Graves' disease was the main cause (41.7%) of thyrotoxicosis, followed by toxic multinodular goitre TMNG (31.9%), toxic solitary nodule (22.1%), Jodbasedow phenomenon (3.1%) and thyroiditis (1.2%). All thyrotoxic patients responded to the treatment, but 4 of 21 Graves' cases with relative triiodothyronine (T3) elevation relapsed after treatment was discontinued. Nine thyrotoxic patients had surgery after euthyroid state was attained; 1 each became hypothyroid and hyperthyroid a year later, 6 remained euthyroid and 1 did not return. Fine needle aspiration biopsy (FNAB) was helpful both as a diagnostic and therapeutic tool. Of 42 cystic nodules, 30 were repeatedly aspirated; 6 were cured and the rest had a reduction in size by 50%. Nine cases of solitary nodule, 3 cystic and 6 solid, were operated and the histology confirmed the cytology diagnosis in all but 1; in that one case, the cytology showed a benign lesion while the histology revealed papillary carcinoma.*

INTRODUCTION

Clinical as well as community studies (1-3) indicate that endemic goitre is common both in mountainous and non-mountainous regions of Ethiopia. Recent clinical studies (4-6) indicate that, contrary to previous reports (6-8), thyrotoxicosis is quite common among Ethiopians. Thus, although there have been isolated reports on individual thyroid diseases in Ethiopian patients, there is no report to date on the pattern of thyroid diseases. The purpose of this study is to document the type and frequency of thyroid diseases as seen in an endocrine specialty clinical at the TAH, the main teaching and referral centre in

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Addis Abeba. Although the data source is obviously hospital-based, it will nevertheless be a valuable information source for launching a community-based study of a much wider scope.

MATERIALS AND METHODS

The study was conducted between February 1986 and July 1991 in a weekly endocrine referral clinic. During this period, a total of 550 endocrine patients were seen. This figure does not include patients with diabetes mellitus who were seen on a separate day. Among the 550 endocrine patients, there were 2 female Indians with hypothyroidism and 2 Sudanese, 1 female and 1 male, with Graves' hyperthyroidism who were excluded from the study. Of the remaining 546 endocrine patients, 373 (68.3%) had thyroid disease and were prospectively studied. Each patient was entered in a prepared register where demographic, clinical and biochemical data were also recorded. The patients were assessed periodically at subsequent clinic visits and the findings documented.

Blood was drawn from the antecubital vein and the serum was separated and stored at -20°C until hormonal assay was made. The serum thyroxine (T_4) and triiodothyronin T_3 were determined by the radio-immunoassay (RIA) method and thyrotropin (TSH) by the immuno-radiometric assay (IRMA) technique using RIA-T_4, RIA-T_3 and IRMA-TSH diagnostic kits obtained from the North East Thames Region Immunoassay (NETRIA) Unit, and radioactivity was measured by the gamma counter and automatic changing system (UK), and NE 1612 Turbo Gamma Counter (UK). The assays were run in duplicate in the Nuclear Medicine Unit of TAH. The normal reference ranges were as follows: T_4, 58-160 n moles/L; T_3, 1.1-3.2 n moles/L and TSH, 0.38-4.8 mU/L.

Other investigations done whenever indicated and/or available included FNAB, ultrasonography of the thyroid, ^{131}I thyroid scan and uptake, red blood cell indices and morphology, erythrocyte sedimentation rate (ESR), white blood cell count and differential, and thyroid autoantibodies.

Thyrotoxicosis was clinically diagnosed using the Newcastle Index (9). In the case of Graves' hyperthyroidism, the diagnosis was made when a diffusely enlarged goitre of short duration was encountered with or without eye manifestations or dermopathy or both, and in the presence of other clinical findings compatible with thyrotoxicosis (9). TMNG was diagnosed when the goitre had multiple nodules and was of longer duration but in the presence of signs and symptoms of thyrotoxicosis (9). The diagnosis of Jodbasedow phenomenon was made in patients with prior clinical and biochemical euthyroid goitre but in whom thyrotoxicosis was induced by the intake of iodine. Subacute thyroiditis was diagnosed when there was fever, neck pain, tender goitre and high ESR.

In the analysis of the pretreatment serum T_3 and T_4 concentration, calculations were made to find out by how

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many fold each hormone was raised above the upper normal level; then the one with the higher fold was said to be increased relative to the other.

RESULTS

The majority of the patients (69.2%) came from Addis Abeba while the remaining (30.8%) came from different parts of the country (Table 1).

The types of thyroid disease and the prevalence in relation to age and sex are shown in Tables 2 and 3. There were 41 (11.0%) males and 332(89.0%) females, making the overall M:F ratio of 1:8.1. Of the total, 199(53.4%) patients were euthyroid while 163 patients had thyrotoxicosis of different causes, and 11 patients were hypothyroid.

Euthyroid Thyroid Diseases

1. **Solitary nodules:** Eighty-eight of the 199 patients (44.2%) in euthyroid state had solitary nodules which were cystic in 42 and solid in 32 patients; the nature of the nodules in 14 other patients was unknown. Two patients with solid nodule had papillary carcinoma without metastasis. The mean age was 32.8 ± 10.0 (± SD) years and the range 18-74 years. The peak age affected was the group 20-29 years (Table 2) and over 72% of the patients were below 40 years.
2. **Simple goitre:** This was seen in 83 patients, accounting for 41.7% of the total euthyroid cases. The mean age was 24.3 ± 8.4 (± SD) years with a range of 13-50 years. The peak incidence was in the age group 20-29 years (Table 2) and over 98% of the patients were below 40 years.
3. **Multi-nodular goitre:** There were 25 patients with this condition. The mean age was 38.8 ± 8.1 (± SD) years, the range 17-50 years, and 14 patients were above the age of 40 years.
4. **Thyroiditis:** There were 3 patients who had thyroiditis in euthyroid state.

Thyrotoxicosis: This condition was seen in 163 (43.7%) of the patients (Table 3). The clinical presentation, reported in part previously (4-5), were similar to other reported series (10).

1. **Graves' disease:** This was the most frequent cause, accounting for 41.7% of the total thyrotoxic patients (Table 3). The mean age was 27.1 ± 8.4 (± SD) years and the range 15-50. The age group most affected was 20-29 years and the great majority (89.7%) were below 40 years (Table 2).
2. **TMNG:** There were 52 patients with TMNG, accounting for 31.9% of the total cases of toxicosis, and of those 36 (69.2%) were over 40 years (Table 2). The mean age was 46.3 ± 13.5 (± SD) years with a range of 22-77, the peak incidence being in the age group 40-49 (Table 2).
3. **Other causes:** There were 5 patients (3.1%) with Jodbasedow phenomenon and 2 cases (1.2%) of thyroiditis with toxic manifestations.

Hypothyroidism

There were a total of 11 patients with hypothyroidism of whom 8 have been previously reported (11). The majority of the patients were over 40 years of age, the mean being 41.3 ± 11.4 (± SD) years and the range 26-

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50. In one patient the hypothyroidism was part of a polyglandular failure in which the gonads and adrenals were also involved.

Laboratory data: The TSH, T_4 and T_3 were all normal in those patients with clinically euthyroid goitres (diffuse or multinodular) and solitary nodules. The TSH was suppressed in all thyrotoxic patients; T_3 was elevated in all, while the T_4 was elevated in all but 7 patients, in whom there was isolated elevation of T_3. Pretreatment analysis of T_4 and T_3 values showed that the majority (63.8%) %) had T_3 elevation relative to the T_4 (Table 4). There were 7 patients with isolated T_3 elevation; 3 had Graves' disease and 2 each had toxic solitary nodule and toxic multinodular goitre. The TSH was elevated in all hypothyroid patients; the mean value was 59.7 mU/L (range, 10.9-107.3 mU/L). Antimicrosomal and antithyroglobulin antibodies were checked in 6 patients and in 4 the test was positive for one or both. None of the hypothyroid or Graves' patients had megaloblastic anaemia. The white blood cell count and differential were normal but the ESR was elevated in patients with thyroiditis.

Thyroid scan was done in 43 patients with euthyroid solitary nodules and in 36 the scan showed "cold" nodules of which 18 were cysts. FNAB was done on 73 solitary nodules and of these 42 were cysts; the majority of those remaining were benign adenomas. The details of solitary nodules will appear in another communication. Ultrasonography was rarely available at the time and hence was done on only 22 patients; in 9 the nodule was cystic and in 13 the nodules solid; this was consistent with the clinical findings.

Treatment and outcome: *Thyrotoxicosis:* All patients but 4 with thyrotoxicosis were put on conventional doses of prophylthiouracil (PTU), and in most instances propranolol 40-120 mg. daily was added in the initial phase of treatment. All the patients responded to the treatment, and the PTU was later reduced to a maintenance dose and continued for 18-24 months. No major side effect was encountered. Nine patients, 5 with Graves' disease, 2 with Jodbasedow phenomenon and 2 with TMNG, were operated after they became euthyroid on the antithyroid drug and of those, one of the Graves' cases became hypothyroid one year after operation and was put on permanent thyroxine therapy, while another one became thyrotoxic a year after surgery and was restarted on PTU. One of the Graves' cases did not return subsequently and hence the outcome of surgical treatment was unknown. The remaining 6 patients were euthyroid when last seen 3 1/2 years after surgery.

Solitary thyroid nodule: Of 42 known cystic nodule cases, 30 had needle aspiration; of these, 6 were cured and the remaining had a reduction of the cyst size by over 50%. Five of the 30 patients presented with sudden onset of severe neck pain; all had immediate relief after needle aspiration. Three of the cystic cases were operated and the histology confirmed the diagnosis.

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Among the 31 known solid nodule cases, none received any form of medical treatment, but 5 had surgery; 2 of those had follicular adenoma, 2 had papillary carcinoma and 1 had benign thyroid histology; the histologic finding was consistent with the cytologic diagnosis in all but one of the papillary carcinoma cases whose cytology showed a benign lesion.

Simple goitre: Of 83 patients, 9 were put on thyroxine and 10 on Lugol's iodine; 2 of the former and 1 of the latter had resolution of the goitre, while the remaining had a reduction in the size of the goitre, with the exception of 2 cases in the Lugol's group who were refractile to the treatment; they were both switched to thyroxine and showed marked reduction of the goitre. Two patients had surgery and both had colloid goitre.

Multinodular goitre: There were 25 patients in this category, and the only treatment available was surgery. However, for logistic reasons, only a few had it. It is perhaps time to consider introduction of treatment with small doses of radioiodine in Ethiopia.

Others: The hypothyroid patients were put on thyroxine replacement therapy while those with thyroiditis were given analgesics for the pain and fever; all showed improvement.

DISCUSSION

The results of this study indicate that euthyroid solitary nodules, goitre and thyrotoxicosis constitute the bulk of thyroid diseases seen in an endocrine referral clinic. The study may not reflect the true picture in the community where endemic goitre is probably the main thyroid disease, particularly in areas where iodine deficiency exists (1-3). Nevertheless, as this is the first study of its kind, the data may be useful as a starting point for launching a community-based study of a much broader scope.

Females predominate in this study (M:F=1.0:8.1); whether this is also true in the community awaits further study, even though surveys on endemic and sporadic goitres indicate a preponderance of females (1-2). A similar observation was also noted in other studies (12-13), but the high female preponderance in the present study is at variance to the 5.3:1.0 reported by Gitau (12) and 4:1 by Kungu (13).

Over 70% of the patients were below 40 years of age; this youthfulness is a reflection of the main age group utilizing the hospital service (6), although other reasons may have to be considered. The majority of the patients (89.5%) had euthyroid solitary nodules and simple goitres, and thyrotoxicosis. Euthyroid solitary nodules and simple goitres alone account for 45.8% of the total; furthermore, 146 (39%) of those cases were below 40 years. The main reason for seeking medical help by the euthyroid solitary nodule and goitre cases is aesthetic, although acute neck pain was a reason in 5 of the solitary nodule cases. Surgery is the main treatment, which should be available for euthyroid solid nodules and goitres to alleviate the aesthetic anxiety but cur-

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rent problems prohibit the full utilization of that mode of therapy. As an alternative, small doses of radioiodine therapy may perhaps have to be used for selected cases, after ensuring the applicability of radiation safety measures.

The usefulness of fine needle aspiration deserves special mention in the context of limited hospital beds in Ethiopia and similar countries. Although it has some limitations, fine needle aspiration is an important diagnostic procedure, as well as a useful tool in the treatment of cystic thyroid nodules. It is simple, inexpensive and associated with minimal risk. In this study, 30 patients had needle aspiration and, of these, 5 presented with acute pain; 2 of the latter and 4 others had no recurrence of the cyst, while the remaining had a reduction of the cyst by over 50% of the original size. Fine needle aspiration is also used in other centres (14-16) in spite of the availability of alternative modes of therapy. Tetracycline, as a sclerosing agent for cystic nodules, appears to be useful (17); the outcome of this mode of therapy in Ethiopian patients remains to be seen.

Thyrotoxicosis is a common condition in this study, even though earlier reports suggest the contrary (6-8). Indeed, the results of this study show that an average of 24.3 cases were seen annually in a weekly endocrine clinic. The rarity of toxicosis in Africa has been observed by other authors (18-24) but more recent studies indicate that the disease is no longer as rare in Africans as was previously thought (12-13, 25-27). McGill (28) studied the prevalence of autoantibodies in Kenyan Graves' patients and found that 16% were positive; this was much lower when compared with the 40 to 60% in their Caucasian counterparts. Based on this finding, McGill (28) concluded that the reason for the rarity of thyrotoxicosis in Africans was that the great majority were not mounting autoantibodies; this view is difficult to accept for the following reasons. Firstly, insulin-dependent diabetes mellitus (Type I), which is believed to be auto-immune-mediated, is a common metabolic disease, although Tulloch (29) commented to the contrary. Secondly, Graves' disease is the most common cause of hyperthyroidism in this study, accounting for about 42% of the total thyrotoxicosis cases; this is also true in other reports (12-13, 25-27). Thirdly, there were 11 patients with hypothyroidism in this study (Table 2), and 4 patients with Addison's disease were seen during the study period: some of these were positive for auto-antibodies (11). Fourthly, in a recent study, premature primary ovarian failure was found in 32.7% of infertile women (30); although auto-antibodies were not determined, due to lack of facilities, it is conceivable that some of them may be positive. Thus, for the above reasons, it is hard to accept McGill's conclusion (28) and further study on the prevalence of auto-antibodies in Graves' patients is warranted.

About 90% of Graves' cases were below 40 years; the median age was 21.

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In contrast, 69% of the patients with TMNG were over 40 years and the median age was 46. This finding is in keeping with younger age incidence of Graves' hyperthyroidism and older age incidence of TMNG. The fact that there were more Graves' cases in this study than the expected higher incidence of TMNG in an endemic area confirms the suggestion that auto-immune diseases are probably not rare in Ethiopia.

Five patients were seen with Jodbasedow phenomenon. This condition is seen both in endemic and non-endemic goitre areas (31-33). The gland has escaped the normal mechanism; hence, when sufficient substrate iodine becomes available excess thyroid hormone is produced, leading to thyrotoxicosis (31-32). The 5 patients received iodine for their goitre and subsequently developed thyrotoxicosis. We do not know how many of those who received iodine developed thyrotoxicosis, but with the planned introduction of iodized salt to control endemic goitre, it is important to be aware of a possible increase in Jodbasedow's phenomenon (31).

Seven patients (4.3%) had isolated T_3 toxicosis; 3 had Graves' disease and 2 each had toxic nodule and TMNG. Hollander *et al* (34) reported that 4% of the thyrotoxic patients had T_3 toxicosis; this finding is similar to the 4.3% in this study. Although T_3 thyrotoxicosis has been increasingly reported (35) since its first recognition in 1957 (10), it is nonetheless not a common condition.

Hormonal analysis showed that in about 66%, the T_3 was elevated relative to the T_4 (Table 4). Increased T_3 concentration relative to T_4 concentration is a known pretreatment finding, especially in those with Graves' hyperthyroidism (36-37). Uller and van Herle (38), in a small series of 19 patients, found higher pretreatment T_3 levels in those who later relapsed. Among the 26 Graves' cases in whom the treatment was discontinued, 21 had increased pretreatment T_3 levels and of those, only 4 have relapsed.

Finally, from the results of this study, the following conclusions can be made:

1. The main thyroid diseases seen were thyrotoxicosis (43.7%) of various causes, euthyroid solitary nodules (23.6%) and simple goitres (22.3%).
2. The majority (71.9%) of the patients were below 40 years of age and females predominant.
3. Jodbasedow phenomenon was seen in 5 patients and hence caution has to be taken with the introduction of iodized salt, although the latter is important in the prevention of endemic goitre.
4. FNAB is a useful diagnostic and therapeutic tool in the management of solitary nodules of the thyroid and hence should be widely applied.
5. Thyrotoxicosis in general and Graves' disease in particular are not as rare among Ethiopians as previously thought.

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TABLE 1. Address of 373 Ethiopian patients with thyroid diseases

Place	Number	Percent
Addis Abeba	258	69.2
Shewa	37	9.9
Gonder	14	3.8
Harerghe	10	2.7
Sidamo	10	2.7
Kefa	8	2.1
Welo	8	2.1
Eritrea	6	1.6
Bale	5	1.3
Tigary	5	1.3
Gojam	4	1.1
Welega	3	0.8
Ilubabor	2	0.5
Arsi	1	0.3
Asseb	1	0.3
Gamu Gofa	1	0.3
Total	373	100.0

TABLE 2. Incidence of thyroid diseases in relation to age in 373 Ethiopian patients

Age (yr.)	Solitary Nodule		MNG		Diffuse Goitre		Hypothyroid	Thyroiditis	JB	Total
	E	T	E	T	E	T				
<20	4	3	2	-	31	12	-	-	1	53
20-29	36	6	4	4	39	37	2	2*	4	134
30-39	24	11	5	12	12	12	2	3*	-	87
40-49	18	8	11	17	1	6	4		-	65
50-59	5	3	3	11	-	1	2		-	25
60+	1	5	-	8	-	-	1		-	15
Total	88	36	25	52	83	68	11	5	5	373

MNG — Maltinodular Goitre
E — Euthyroid
T — Toxic
JB — Jodbasedow phenomenon

TABLE 3. Type of thyroid diseases and incidence in relation to sex in 373 Ethiopian patients

Type of disease	Male (%)	Female (%)	Total (%)
Disease in euthyroid state	23 (6.2)	176 (47.2)	199 (53.4)
Simple goitre	8	75	83
Solitary nodule	13	75	88
Multinodular goitre	1	24	25
Thyroiditis	1	2	3
Diseases causing thyrotoxicosis	17 (4.6)	146 (39.1)	163 (43.7)
Graves' disease	10	58	68
Toxic multinodular goitre	1	51	52
Toxic solitary nodule	5	31	36
Jodbasedow phenomenon	-	5	5
Thyroiditis	1	1	2
Hypothyroidism	1 (0.2)	10 (2.7)	11 (2.9)
Total	41 (11.0)	332 (89.0)	373(100.0)

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TABLE 4. Pretreatment relative hormone elevation in 156 Ethiopian thyrotoxic patients

Diseases causing thyrotoxicosis	Hormone relatively elevated			Total
	T_3	T_4	Neither	
Graves' disease	3	46	15	64
Toxic multinodular goitre	11	36	4	51
Toxic solitary nodule	7	23	4	34
Jodbasedow phenomenon	2	3	-	5
Thyroiditis	2	-	-	2
Total	25	108	23	156

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ACUTE LEUKAEMIAS IN ADULT ETHIOPIANS IN A TEACHING HOSPITAL

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ABSTRACT: *Eighty-two consecutive cases of acute leukaemias in adult Ethiopians were admitted to the Tikur Anbessa (Black Lion) Hospital, a teaching and referral hospital in Addis Abeba, Ethiopia, from January 1982 to December 1992. These cases were studied to describe the clinical and haematological findings, response to therapy and prognosis. The age range was 13–78 (mean 29.6) years. The male to female ratio was 1.6:1.* Acute myeloblastic *(AML) and acute lymphoblastic (ALL) leukaemias occurred in 53.7% and 46.3%, respectively. The commonest symptoms were anaemia, fever and bleeding tendencies. The commonest signs were pallor, fever, sternal tenderness and purpura. Splenomegaly was more commonly seen in ALL patients. The haematological findings were anaemia (mean Hgb 6.35g%), leucocytosis (mean WBC count 88,507/mm^3) and thrombocytopenia (mean platelet count 31,700/mm^3). Of the patients eligible for evaluation treated with chemotherapeutic agents, only 38.4% of ALL and 6.2% of AML achieved complete remission. Twenty-seven patients with ALL died from one day to 84 (median 1.0) months after diagnosis. Ten are lost to follow-up from two weeks to 36 (median 2.5) months, one is still alive 40 months after diagnosis. Thirty-nine of the AML patients died from one day to nine (median 0.3) months after diagnosis. Five are lost to follow-up from two weeks to two and a half (median 2.0) months. The causes of death were sepsis and bleeding, separately or in combination. Increasing numbers of acute leukaemia patients are being referred to this centre. Therefore, attempts should be made to equip it for the treatment of such cases.*

INTRODUCTION

Leukaemias in general and acute leukaemias in particular occur world-wide, although their incidences appear to be different in various countries (1). It is said that leukaemias were less common in blacks compared to whites in the USA (1). In the 1960's, reports from Africa suggested that leukaemias were uncommon (2), some even suggested that African children resisted leukaemias (3). Subsequent studies, however,

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have shown that leukaemias were more common than previously suggested (4–11). Analysis of medical admissions to various hospitals in Ethiopia in the 1960's reported low figures for leukaemias (12–16). Recent studies on haematological disease admissions and pattern of leukaemias in adults (17–18) found higher proportions of leukaemias. The current study includes the 38 acute leukaemia cases previously reported (18) and attempts a detailed description in terms of age, sex, types, clinical and haematological presentations, response to therapy, and follow-up results, and compares the findings with studies of similar nature.

PATIENTS AND METHODS

This study is based on the analysis of 82 consecutive new cases of acute leukaemia admitted to the adult medical wards of the Tikur Anbessa (Black Lion) Hospital, Addis Abeba University's teaching and referral hospital, between January 1982 and December 1992. Acute leukaemia cases from other hospitals whose bone marrows were reviewed by the author were not included in this study. All patients with acute leukaemias were admitted for investigations and management.

The age, sex, address, date of diagnosis, type of acute leukaemia, clinical, haematological, biochemical, radiological, bone marrow aspiration results, response to therapy, follow-up and outcome were recorded. The diagnosis of acute leukaemia was based on clinical and haematological findings, mainly the morphology of the peripheral blood and bone marrow stained with Wright's Stain (19). The classification of AML and ALL was according to the French-American-British (FAB) classification (20).

The treatment regimens used for ALL were:

1. CP (21) cyclophosphamide 5.0 mg/kg per day p.o for four weeks with prednisolone 2.2 mg/kg per day p.o. for four weeks, and discontinued after an additional seven day decremental schedule.
2. VP (22) vincristine 1.5 mg/m² IV weekly for four to six weeks with prednisolone 40 mg/m² per day p.o. for four to six weeks.
3. OAP (23) vincristine 1.5 mg IV weekly for four weeks, doxorubicin 45 mg IV weekly total of 550 mg with prednisolone 60 mg/m² for four to six weeks.

AML was treated with:

1. Modified POMP regimen (24):
   6-mercaptopurine (parenteral) not available
   Vincristine 2 mg/day IV-day 1
   Methotrexate 7.5 mg/m² per day IV, days 1–5.
   Prednisolone 200 mg/day p.o. days 1–5.
2. AD-OAP (25):
   Doxorubicin 30 mg/m² per day IV days 1–3.
   Vincristine 1.5 mg/m² per day IV days 1 and 5.
   Cytosine-arabinoside (not available)
   Prednisolone 40 mg/m² per day p.o. days 1–5.
   Repeat at day fourteen if complete remission is not attained.

The responses in both types of leukaemias were defined according to Pinkel (26):

Complete remission (CR): Absence of clinical symptoms and signs of leukaemia; neutrophil count of more than 500/mm³ and bone marrow blasts less than 5%.

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Partial remission (PR): Bone marrow blasts 5–25%.

No response (NR): Bone marrow blasts greater than 25%.

ALL patients who attained complete remission were given central nervous system (CNS) prophylaxis with intrathecal methotrexate at doses of 10mg/m² twice weekly for five doses (27). Maintenance treatment was with six mercaptopurine 100 mg orally daily and methotrexate 30 mg orally weekly until relapse or for 30 months (28). Patients achieving remission were discharged from hospital and followed at the haematology clinic.

RESULTS

During the study period, 82 cases of acute leukaemia were admitted to the adult medical wards of the Tikur Anbessa Hospital. There were 51 males and 31 females giving a male to female ratio of 1.6:1. The age range was 13–78 (mean 29.6) years. Table 1 shows the age and sex distribution of acute leukaemia in adults. The majority of acute leukaemias (87.8%) occurred below the age of 51 years and more commonly in males than in females.

The age groups and types of acute leukaemia are shown in Table 2. Acute myeloblastic leukaemia (AML) and acute lymphoblastic leukaemia (ALL) accounted for 53.7% and 46.3%, respectively. Patients with ALL were relatively younger than those with AML. The mean age for ALL was 22.1 years compared to 34.3 years for AML. Of the acute myeloblastic leukaemia, 8 (18.2%) were M1, 17 (38.4%) M2, 2 (4.5%) M3, 14 (31.8%) M4, 3 (6.8%) M5 and no cases of M6 or M7. Attempts were not made to classify ALL morphologically or immunologically.

The clinical presentations are shown in Table 3 and 4. In both types of acute leukaemia, symptoms of anaemia, fever, bleeding and bone pain or tenderness were the common manifestations. Patients with ALL had splenomegaly more commonly than AML patients. Gum hypertrophy was seen in three patients with acute myelomonocytic leukaemia (M4).

Table 5 shows the haematological data at the time of diagnosis; 75% of the patients had severe anaemia (Hgb less than 8g%), 75% had elevated leucocyte count, 41% had counts above 100,000/mm³. The platelet counts ranged between 5,000–140,000/mm³ and were less than 50,000/mm³ in 85%.

Management with blood and/or platelet transfusion was started as required as soon as the patients were admitted. Broad spectrum antibiotics (usually ampicillin and gentamycin) were initiated empirically in all febrile patients after appropriate cultures were taken when feasible. After stabilising the patients, the available chemotherapeutic agents were given according to the diagnosis.

In the initial phase of the study, (1982–1983) ALL patients were treated with cyclophosphamide and prednisolone (CP) while no definitive treatment was given for AML patients. Of the six patients with ALL treated with CP, two had complete remission (CR) and the rest attained partial remission (PR). From 1985 to 1987, ALL patients were treated with vincristine and prednisolone (V.P). Of the 11 patients so treated, five (45.5%) had CR, four (36.4%) PR, one had no response while one could not be evaluated. During the same period, five patients with AML were treated with modified POMP, of whom only one had complete remission and survived for nine months. From 1988 to 1992, ALL was treated with vincristine, doxorubicin and prednisolone (OAP). Of the 13 treated with

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this regimen, five (41.7%) had CR five (41.7%) PR, two had no response while one was not eligible for evaluation. In the same period, 11 patients with AML were treated with modified AD-OAP, since there was no cytosine-arabinoside. No patient had CR, three (50%) had PR, three had no response and five could not be evaluated.

Of the ALL patients only one is alive 40 months after diagnosis. Ten are lost to follow-up two weeks to 36 months (median 2.5 months). Four were in CR, three in PR and three in relapse. Twenty-seven patients with ALL died in hospital one day to eighty-four months after diagnosis (median 1.0 month). Five patients with AML are lost to follow up two weeks to two and a half months (median 2.0 months) after diagnosis; three were in PR and 39 died at one day to nine months (median 0.5 month).

The causes of death were similar in both types of acute leukaemia. Bleeding and sepsis in combination accounted for 33.3%, while sepsis and bleeding separately accounted for 31.6% and 22.8% respectively. In most instances, the sites of sepsis could not be identified. Intracranial bleeding was a common terminal event in both sexes, while females had additional uncontrollable pelvic bleeding.

DISCUSSION

Acute leukaemias accounted for 21% of all leukaemia cases (18), and 40% of deaths due to haematological diseases in adult Ethiopians (17). This proportion is much lower in Caucasians (1) and some African countries (4,8,10). The paucity of acute leukaemias in African populations is attributed to under diagnosis and patients dying at home before reaching medical services (2,4,18). The younger ages of our patients compared to that of Caucasians is explained by the younger age of the general population.

In this study, AML and ALL occurred in 53.7% and 46.3% respectively. In adult Caucasians, AML accounts for 75-85% (1), while in adult Africans it accounts for 55-80% (4,6,8,10). The FAB classification of AML was in agreement with those reported in Caucasians (1,25). The clinical presentations were similar with those of Caucasians (1) and other African populations, except that bleeding tendencies, in particular petechiae, were said to be rare in Kenyans and Nigerians (4,10,11). In this study petechiae were found in 51.2% of patients. The severe anaemia and thrombocytopenia seen in 75% and 89% respectively in this study are in agreement with figures reported from other African countries (4,10,11).

Using the available drug combination regimens, CP, VP and OAP for the treatment of ALL, complete remission was achieved in 33.3%, 45.5% and 36.4% respectively. Overall remission rate was only 38.4%. The median survival after complete remission was nine months. These results are very low compared to what is achieved in children and adults elsewhere (complete remission rates of more than 90% and 70-90% respectively). Cure is possible in 50-60% of children and 15-25% of adults (22,23,26-31). In this study, only one patient lived for 84 months, 27 (71%) died in hospital and median survival was only two months.

The treatment of AML is even more frustrating. Only one patient (6.2%) achieved complete remission and survived for nine months, while five (50%) had partial remission. Thirty nine (88.6%) patients died in hospital, median survival was only two weeks. These results are in contrast to

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In this study, AML and ALL occurred in 53.7% and 46.3% respectively. In adult Caucasians, AML accounts for 75-85% (1), while in adult Africans it accounts for 55-80% (4,6,8,10). The FAB classification of AML was in agreement with those reported in Caucasians (1,25). The clinical presentations were similar with those of Caucasians (1) and other African populations, except that bleeding tendencies, in particular petechiae, were said to be rare in Kenyans and Nigerians (4,10,11). In this study petechiae were found in 51.2% of patients. The severe anaemia and thrombocytopenia seen in 75% and 89% respectively in this study are in agreement with figures reported from other African countries (4,10,11).

Using the available drug combination regimens, CP, VP and OAP for the treatment of ALL, complete remission was achieved in 33.3%, 45.5% and 36.4% respectively. Overall remission rate was only 38.4%. The median survival after complete remission was nine months. These results are very low compared to what is achieved in children and adults elsewhere (complete remission rates of more than 90% and 70-90% respectively). Cure is possible in 50-60% of children and 15-25% of adults (22,23,26-31). In this study, only one patient lived for 84 months, 27 (71%) died in hospital and median survival was only two months.

The treatment of AML is even more frustrating. Only one patient (6.2%) achieved complete remission and survived for nine months, while five (50%) had partial remission. Thirty nine (88.6%) patients died in hospital, median survival was only two weeks. These results are in contrast to

Table 2. Age group and types of acute leukaemia

Age group* (years)	Type of leukaemia		Total	
	ALL	AML	No.	%
11–20	21	10	31	37.8
21–30	12	10	22	26.8
31–40	3	11	14	17.1
41–50	–	5	5	6.1
51–60	2	5	7	8.6
61–70	–	2	2	2.4
>70	–	1	1	1.2
Total	38	44	82	100.0

*Children are seen in children's hospital and clinics.

Table 3. Presenting symptoms of acute leukaemia

Symptom	Type of leukaemia		Total	
	ALL	AML	No.	%
Anaemia	29	35	64	78.0
Fever	29	35	64	78.0
Bleeding	28	30	58	70.7
Bone pain	7	8	15	18.3
Weight loss	3	7	10	12.2
Cough	4	4	8	9.8
Jaundice	2	3	5	6.1
Sore-throat	3	1	4	4.9
Swelling in the neck	2	2	4	4.9
Neck stiffness	1	–	1	1.2

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Table 4. Presenting signs of acute leukaemia

Sign	Type of leukaemia		Total	
	ALL	AML	No.	%
Pallor	31	35	66	80.5
Fever	30	29	59	72.0
Sternal tenderness	22	20	42	51.2
Purpura	19	23	42	51.2
Lymphadenopathy	25	12	36	43.9
Splenomegaly	16	9	25	30.5
Hepatomegaly	7	7	14	17.1
Retinal haemorrhage	8	7	15	18.1
Gum hypertrophy	1	3	4	4.9
Others	7	5	12	14.6

Table 5. Haematological data in acute leukaemia patients

Parameter	Type of leukaemia	
	ALL	AML
Hgb (g%)		
Range	2.4–13.4	3.3–11
Mean ± 2SD	7.0 + 2.77	6.0 + 2.25
WBC/mm³ (x10)		
Range	1.0–704	4.2–385
Mean ± 2SD	113.0–161.6	67.4 + 85.6
Platelet/mm³ (x10)		
Range	0.05–1.40	0.1–1.0
Mean ± 2SD	31.6–33.1	31.9–21.2
Blasts (%)		
Range	16–95	10–100
Median	70	75

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A SURVEY OF ANTIBODIES TO HEPATITIS C VIRUS IN ETHIOPIA

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Abstract. Antibodies to hepatitis C virus (HCV) were measured in 1,580 Ethiopian subjects representing urban and rural populations. Sera found positive by a repeated second generation enzyme immunoassay (EIA) were subjected to three additional confirmatory tests. The overall confirmed seroprevalence was 2.0%. Less than 1% were confirmed to be seropositive in rural communities, with 1.4% positive among blood donors, 1.6% positive among patients with dermatologic disorders, 3.6% among leprosy patients, and 6.0% among patients attending a University Hospital clinic for neurologic disorders. The patients in the groups with leprosy and neurologic disorders have most likely been in ill health for many years and have sought relief by traditional healers or treatment at poorly equipped clinics. This group of patients demonstrated a high prevalence of antibodies to HCV. In Ethiopia, especially in small clinics, there is a shortage of syringes and needles and they have to be reused many times often with inadequate sterilization. Therefore, these syringes and needles may be contaminated, thus being a risk factor for HCV and HIV infection.

In Ethiopia, as in the other sub-Sahelian countries, the prevalence of liver diseases is high. They account for 12% of the hospital admissions and 31% of the mortality in the medical wards of Ethiopian hospitals.[1,2] In Africa, infection with hepatitis B virus (HBV) plays a major role in the etiology of most liver diseases, but recent reports indicate that infection with hepatitis C virus (HCV) occurs in chronic hepatitis and in primary hepatocarcinoma.[3–5] The frequency of markers of HCV infection has also been shown to be high among leprosy patients.[6]

In this study, we determined the frequency of antibodies to HCV in 1,580 sera collected in urban and rural Ethiopia. We used a second generation enzyme immunoassay (EIA) and three confirmatory tests.

SUBJECTS AND METHODS

Serum samples from three groups of individuals were assayed for antibodies to HCV. The first group consisted of 250 patients under treatment for histologically confirmed leprosy, 248 patients with various dermatologic conditions that were not related to leprosy,[7] 82 bacteriologically negative former leprosy patients seen in a follow-up of the study of Duncan and others on the association of pregnancy and leprosy,[8] and 166 subjects attending the neurology clinic of the Addis Ababa University Hospital. All of the 580 leprosy and dermatology patients had been examined at the hospital division of the All Africa Leprosy and Rehabilitation Training Centre (ALERT) in Addis Ababa.

The second group was composed of 276 residents from the outskirts of Addis Ababa. These individuals, 116 adult females and 160 children and teenagers, were the leprosy-free control population of the prospective study of leprosy mothers and their children conducted by Duncan and others.[8] They were found to be free of leprosy and the human immunodeficiency virus. Two hundred twenty volunteer blood donors attending the National Blood Transfusion Center in Addis Ababa were also included in this group.

The third group consisted of a cross-sectional sample of 338 of 2,234 inhabitants from Aba Roba, district of Konso (5°7′N, 37°35′E), a remote area in the lower Ethiopian Rift Valley. This population has been under study since 1982 as part of a control program for visceral leishmaniasis[9] and represents a rural population of Ethiopia.

Sera collected from January until May 1991 were separated from whole blood within 4 hr after collection. They were stored in multiple aliquots at −23°C and sent on dry ice to Limoges, France and kept frozen until testing. The serum samples were screened for antibodies to HCV by

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a second generation EIA (Abbott Diagnostika, Wiesbaden, Germany). Samples that were reactive twice in the EIA were further analyzed by three confirmatory assays. The first assay was a recombinant immunoblot assay (RIBA-2HCV test; Chiron Corporation, Emeryville, CA). Sera reactive with two or more of the four RIBA antigens (5.1.1, C-100-3, C-33-c, and C-22-3) were considered positive for HCV. The second assay was a semi-automated dot blot immunoassay (MATRIX; Abbott Laboratories, North Chicago, IL) using the C-100 antigens expressed in yeast and *Escherichia coli*, and the C-33-c and C-22-c recombinant antigens. A positive reaction with two of the three proteins was required before the samples were scored as positive. The third assay was a confirmatory EIA (HCV-EIA complementary assay; Abbott Laboratories) using two polystyrene beads, one coated with a structural protein (core protein) and the other with nonstructural proteins (NS-3 and NS-4 regions). Specimens reacting with one or both beads were considered anti-HCV positive.

Using the second dot blot immunoassay and the third confirmatory EIA, it was possible to classify as positive sera that were indeterminate in the RIBA-2 immunoblot assay.

Comparisons of proportions were performed using the chi-square test with Yates' correction and comparison of odds ratios according the method of Mantel and Haenszel; the 95% confidence limits were calculated using the exact method, and linear trends in proportion were determined according to the methods of Yates.[10]

RESULTS

The composition of the three cohorts, as well as the prevalence of serum antibody to HCV for each group and age class, is given in Table 1. Fifty-four percent of the serum samples reactive in the EIA with an optical density 0.3 units above the mean of the negative controls were found to be positive in the confirmatory tests.

In this survey of 1,580 serum samples, the overall confirmed prevalence of antibodies to HCV was 2.02% (95% confidence interval [CI] 1.3–2.7); all children less than 10 years of age were seronegative. Excluding this age class, which was unevenly distributed among the various groups, the prevalence of antibodies to HCV ranged between 1.64% and 6.02% in the cohort of patients attending hospitals (group 1). This prevalence differed at a P level of < 0.005 from that observed in the comparison groups; it was 1.01% for the population residing in Addis Ababa (group 2) and 0.93% for the population from southwestern Ethiopia. The crude odds ratio for the presence of anti-HCV antibody between group 1 and groups 2 and 3 was 3.52 (95% CI 1.5–8.2). Since the mean age of groups 2 and 3 was less than that of group 1 (25.7 and 34.3 years, respectively), when adjusted for age, the odds ratio decreased to 2.41 ($P = 0.08$, 95% CI 0.95–7.1). Nonetheless, a linear trend for increase of antibody to HCV with age was observed ($P < 0.001$) when the analysis included all three groups, although comparisons between adjacent age classes remained nonsignificant (Table 2).

The 32 HCV seropositive were composed of 17 females and 15 males. They ranged in age from 14 to 75 years with a mean age of 41.3 ± 18.8 years. The patients' history failed to reveal particular risk factors, e.g., major surgery, blood transfusion, or an admitted sex-related profession. Three HCV-positive patients were found to be coinfected with human immunodeficiency virus type-1 (two men 20 and 67 years of age and one 39-year-old woman). Infection with HCV of both mother and child (group 2) was not observed.

DISCUSSION

Although the population studied was not truly representative of the demographic pattern of Ethiopia, in which 57.3% of the inhabitants are less than 20 years of age and 87.9% are classified as rural inhabitants[11] (in this report, 37.1% and 21.4%, respectively), the prevalence of antibodies to HCV of 2.0% is likely to reflect a valid estimate of exposure to HCV in Ethiopia. This 2% prevalence rate is based on two consecutive EIAs with positive samples confirmed by assaying specific antibodies to structural and nonstructural (C-100 and 33C) antigens of HCV. This study also revealed that HCV is present in deeply rural areas of Ethiopia. The 2.0% prevalence rate recorded here is markedly less than the 11% value determined earlier in a group of Ethiopian blood donors.[12] However, this value was based only on a first-generation ELISA enzyme-linked immunosorbent assay. Our seroprevalence value is in accordance with a recent analysis carried out in a neighboring country, the Yemen Arab Republic. In Yemen, a prevalence of 2.6% was

TABLE 1
Prevalence of antibodies to hepatitis C virus (HCV) in the Ethiopian populations

Age (years)	Group 1															Group 2						Group 3						Group 2 and 3
	Active leprosy				Cured Leprosy				Dermatology patients				Neurologic outpatients			Addis Ababa controls						Rural southwestern Ethiopia						
																Nonleprosy mothers and children				Blood donors							
	M	F	Total	No. (%) HCV+	M	F	Total	No. (%) HCV+	M	F	Total	No. (%) HCV+	M	F	Total	M	F	Total	No. (%) HCV+	M	F	Total	No. (%) HCV+	M	F	Total	No. (%) HCV+	Total (no. HCV+)
<10	1	0	1	0	0	0	0	0	2	2	4	0	0	0	0	0	0	0	0	67	55	122	0					123
10–19	17	28	45	1 (2.2)	0	0	0	0	19	28	47	0	11	14	25	1 (0.7)	37	43	80	0				65	44	109	1 (0.9)	341 (2)
20–29	33	28	61	3 (4.9)	0	1	1	0	34	43	77	1 (1.3)	23	18	41	0	47	21	68	2 (2.9)				7	21	28	0	103 (2)
30–39	42	18	60	3 (5.0)	0	53	53	0	38	27	65	1 (1.5)	19	9	28	1 (1.3)	19	12	31	0				16	32	48	0	154 (1)
40–49	28	13	41	0	0	25	25	2 (8.0)	18	6	24	0	23	5	28	0	12	5	17	0				13	2	15	0	70
50–59	22	5	27	1 (3.7)	0	1	1	0	13	7	20	2 (10.0)	16	8	24	0	6	2	8	0				6	3	9	0	18
>60	10	4	14	1 (7.1)	0	0	0	0	7	4	11	0	5	3	8	0	3	1	4	1 (25.0)				4	3	7	1 (14.3)	11 (2)
Unknown	0	1	1	0	0	2	2	0	0	0	0	0	8	4	12	0	9	3	12	0				0	0	0	0	14
Total	153	97	250	9 (3.6)	0	82	82	2 (2.4)	131	117	248	4 (1.6)	105	61	166	10 (6.0)	133	87	220	3 (1.4)	178	160	338	2 (0.6)				834 (7)

TABLE 1
Continued

Age (years)	Group 2												Group 3						Group 2 and 3
	Addis Ababa controls												Rural southwestern Ethiopia						
	Nonleprosy mothers and children				Blood donors														
	M	F	Total	No. (%) HCV+	M	F	Total	No. (%) HCV+	M	F	Total	No. (%) HCV+	M	F	Total	No. (%) HCV+	M	F	Total (no. HCV+)
<10	1	0	1	0	0	0	0	0					67	55	122	0			123
10–19	61	91	152	1 (0.7)	37	43	80	0					65	44	109	1 (0.9)			341 (2)
20–29	0	7	7	0	47	21	68	2 (2.9)					7	21	28	0			103 (2)
30–39	0	75	75	1 (1.3)	19	12	31	0					16	32	48	0			154 (1)
40–49	0	38	38	0	12	5	17	0					13	2	15	0			70
50–59	0	1	1	0	6	2	8	0					6	3	9	0			18
>60	0	0	0	0	3	1	4	1 (25.0)					4	3	7	1 (14.3)			11 (2)
Unknown	0	2	2	0	9	3	12	0					0	0	0	0			14
Total	62	214	276	2 (0.7)	133	87	220	3 (1.4)					178	160	338	2 (0.6)			834 (7)

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TABLE 2

*Prevalence of antibodies to hepatitis C virus (HCV) in relation to age**

Age (years)	No. of HCV positive subjects/no. tested	% HCV positive	95% confidence interval prevalence
<10	0/128	0	0–2.8
10–19	4/458	0.87	0.4–2.2
20–29	6/283	2.21	1.1–4.5
30–39	7/360	1.94	0.8–3.9
40–49	3/188	1.60	0.3–4.5
50–59	5/90	5.56	1.8–12.4
>60	7/44	15.91	6.6–30.5
Total	32/1,551	2.06	1.4–2.9

* The linear trend in proportion with a Z value = 5.07 ($P < 0.001$) demonstrates the increase in antibody to HCV with age. The 29 subjects whose age was unspecified have been omitted from the calculations.

found using an EIA plus a recombinant immunoblot assay.[13] Furthermore, these values are similar to those observed for blood donors in Saudi Arabia[14] and in Mozambique.[15]

The trend of increased prevalence of HCV antibodies with age seems to be a general observation in Africa, as well as in the northern hemisphere.[6, 13] The most striking finding was the difference in prevalence for patients attending hospitals (group 1) versus individuals less prone to frequent health centers and hospitals (group 2). The higher prevalence of antibodies to HCV among leprosy patients as reported by Denis and others in a multicenter survey[6] has been confirmed in this study.

A common denominator among patients in group 1 is the duration of their disease, in particular, the time that probably elapsed between the occurrence of the initial signs and complaints and the referral to a teaching hospital. During these months or years of lingering illness, Ethiopians often chose to visit traditional healers, drugs vendors, and/or small and poorly equipped health centers, where they were at risk of exposure to contaminated scalpels, needles, and syringes. Transmission through these means would parallel the route played in parental drug abuse, which in industrialized countries are responsible for up to 40% of the HCV infections.[16] It must be noted that among the bacteriologically negative leprosy patients and the mother-child group, in which the prevalence for HBV surface antigen was 12.3%, no HBV-HCV coinfection was found.

This survey indicates that in Ethiopia HCV infection has reached a critical level. This finding calls for careful studies on the mode of transmission of HCV and on cost-effective strategies for the screening of blood donors for HCV.

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PATTERN OF *LATHYRUS SATIVUS* (GRASS PEA) CONSUMPTION AND *BETA-N*-OXALYL-α-ß-DIAMINOPROPRIONIC ACID (ß-ODAP) CONTENT OF FOOD SAMPLES IN THE LATHYRISM ENDEMIC REGION OF NORTHWEST ETHIOPIA

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ABSTRACT

Grass pea, a legume whose consumption is associated with human lathyrism, is an important food crop among the poorer sectors of society in many parts of Ethiopia. A nutritional survey, focussing on the preparation and consumption of grass pea, in 224 families of two villages of a lathyrism endemic area in northwestern Ethiopia has been undertaken. Grass pea is grown in only one of the two villages. Raw as well as cooked food samples were collected and the levels of ß-ODAP determined by the OPT method. Grass pea foods were also prepared in the laboratory following methods used in the villages and analyzed for their toxin level to derive information if certain procedures were capable of reducing the level of toxin. Steeping grass pea in excess water leaches out *ca* 30% of the ß-ODAP. Grass pea bread (*kitta*) and roasted seeds (*kollo*) showed elevated levels of ß-ODAP compared to the seeds used in the preparation of these foods. Lower levels of ß-ODAP were found in boiled snacks (*nifro*) and the flour form (*shiro*).

KEY WORDS: Grass pea, *Lathyrus sativus*, Lathyrism, Paraparesis, ß-N-oxalyl-L-α,ß-diaminopropionic acid (ß-ODAP)

INTRODUCTION

Lathyrism, which is characterized by spastic paraparesis, is a neurotoxic disorder caused by excessive consumption of chickling or grass pea (*Lathyrus sativus*) (1,2).

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Epidemics of the disease have been reported following acute food shortages during drought or after floods (3-5). Recent studies have confirmed that ß-N-oxalyl-L-α, ß-diaminopropionic acid (ß-ODAP), [synonym: ß-N-oxalylamino-L-alanine (BOAA)] is the neurotoxic principle in *L. sativus* responsible for the neurodegenerative condition (6).

Although lathyrism has in the past been reported from other parts of the world, including Europe, it is at present known to be endemic in India (7), Bangladesh (8) and Ethiopia (9). In Ethiopia, the disease occurs in the northern and central parts of the country with recurrent outbreaks reported from the Lake Tana basin of the north-west Administrative Region of Gondar.

As part of a multidiscipilinary project for the improvement of *Lathyrus sativus* and the control of lathyrism, we undertook an epidemiological survey of the Dembia and Fogera subdistricts of the Lake Tana basin (10). A nutritional survey was also carried out in two peasant associations within the project area to find out the feeding habits of the inhabitants particularly in relation to the preparation and consumption of grass pea. Food samples were collected and assayed for (ß-ODAP) levels. This paper reports on our findings.

MATERIALS AND METHODS

In the subdistrict of Fogera of the Gondar Administrative Region, two peasant associations were selected for the nutritional survey. Shina (pop. 6,142) is a village in a grass pea cultivating area, while Montura (pop. 2,560) situated 50 km north of Shina is a non-grass pea growing village. Both villages are about 600 km north of Addis Ababa. In Shina, most of the farmland invariably gets flooded during and after the heavy rainy months of July to September. Farmers therefore resort to the cultivation of the hardy crop, grass pea. On the other hand, Montura which is situated on the highlands, has a more fertile and productive land where cereals like *teff* (*Eragrotis teff*), wheat, barley and millet are cultivated.

For the nutritional survey of the two villages, a questionnaire was developed to get the following essential information: supply and preparation of food, distribution and consumption of food and infant feeding, with particular emphasis on grass pea. The questionnaire was carefully designed to obtain the comparative dietary pattern of the target populations of the two villages.

The questionnaire, initially prepared in English, was translated into Amharic, the local language spoken in the region. Based on pilot studies, the questionnaire was further modified to formulate the questions in accordance with the cultural background and educational levels of the population.

Ten female research assistants were recruited from among the secondary school graduates of Woreta, a town situated between the two villages. These enumerators were trained for two weeks by nutritionists of the research team on the concept and techniques of dietary field survey. As the enumerators were recruited locally, a fairly reliable rapport and confidence was developed between them and the respondents. As females, they

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were readily accepted by housewives into the kitchens. The activities of the enumerators were supervised closely by the three experienced nutritionists of the research group (March-April 1989).

The purpose of the nutritional study was explained and discussed with the elders and local leaders of the peasant associations. After obtaining the consent and support of the community, a total census of the two villages was performed initially.

Random samples of 110 and 114 families from Shina and Montura peasant associations respectively were taken into the study. The survey was undertaken during harvesting season of grass pea (March-April).

The dietary history was obtained by determining the average food intake of an individual during the 24 hours preceding the interview. The survey was conducted for seven consecutive days by daily visits to the families.

During the survey the enumerators and nutritionists made close observations and recorded the methods used in the preparation and consumption of cereals, legumes and drinks. The consumption of guests and absence of the family members were taken into account.

In most parts of Ethiopia, particularly northern regions, *teff (Eragrotis teff)*, wheat, barely, maize and sorghum, either singly or in combination, are used to produce a fermented, sour pancake-like leavened bread called *enjera*. The dough used for *enjera* is usually fermented for less than three days. The *enjera* is eaten together with *wott*, which is the Ethiopian sauce traditionally prepared by cooking, in a clay pot, a mixture of onions, hot pepper blended with several spices and butter or vegetable oil, meat, vegetable, eggs, or legumes. When the hot pepper is omitted from the preparation of the *wott*, the sauce so prepared is called *alitcha*. To the *alitcha*, green pepper is added for flavour and turmeric (*Curcuma longa*) for colour (11). *Shiro* is the flour prepared from legumes and used for the preparation of *wott* or *alitcha*, generally in poor families. *Kitta* is the unleavened bread prepared from the flour of cereals or legumes or their mixture. For snacks, cereals, legumes or their mixture are served either roasted (*kollo*), or boiled (*nifro*).

The raw and cooked food items were weighed or measured. Samples of food containing grass pea were collected from some families. These samples were refrigerated and transported to the Chemistry Department of the Addis Ababa University for the determination of ß-ODAP.

Determination of ß-ODAP

The method employed for the analysis of ß-ODAP is that of Rao [12], with slight modification, which involves a neutralization step prior to addition of the chromogenic reagent (13).

Extraction of ß-ODAP. Samples of bread, *nifro*, *kitta* and *wott* samples were dehydrated to constant weight, in an oven at 40°C and 120°C. Whole and decorticated seeds were finely powdered prior to extraction. Solutions obtained by boiling grass pea seeds were

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diluted one hundred fold prior to analysis.

Absorbances were measured on a Beckman model 24 spectrophotometer.

Diaminopropionic acid hydrochloride (DAP.HCl) and *ortho*-phthalaldehyde (99% and 97% respectively) were purchased from Aldrich; mercaptoethane was acquired from Hopkin and Williams. Water was redistilled from an all-glass set-up. Ethanol (60% aq.) was used for extraction.

Preparation of reagent. *Ortho*-phthalaldhyde (OPT) reagent was prepared by dissolving 100 mg of the aldehyde in 1 ml ethanol and 0.1 ml mercaptoethane. This was added to 99 ml of 0.1 M sodium tetraborate buffer. In all cases a freshly prepared reagent was used.

ß-ODAP analysis. The extracts were filtered and taken in duplicate (0.1 ml each), treated with 3N KOH (0.2 ml) and kept in boiling water bath for 30 min. After cooling to room temperature, 3N HCl (0.2 ml) was added and the final volume made to 1 ml with water. A sample blank was prepared with the extract (0.1 ml) and water (0.9 ml) to account for any interference from the reaction between the OPT reagent and other constituents of the extract.

The OPT reagent (2 ml for each sample) was added to the hydrolysed and control samples and absorbance measured at λ_{max} = 476 nm after 30 min. Reagent blank was prepared by diluting the OPT reagent (2 ml) with water (1 ml). ß-ODAP concentration was calculated from a calibration curve prepared by using commercial DAP.HCl and assuming 100% conversion of ß-ODAP to DAP at the given conditions of hydrolysis [12].

Statistical method

The t-test was employed for comparing two means.

RESULTS

Numbers and types of meals (Table 1)

Most families (95%) in both peasant associations had two main meals during the day. The meals were served in the middle of the day and in the evening. The main dishes in both communities were *enjera* and *wott*. The *enjera* was most often prepared from finger millet alone and sometimes millet was mixed with *teff*, corn, and sorghum. The *wott* made of *shiro* was mainly prepared from grass pea alone or mixed with chickpea (*Cicer anietinum*) in both villages. In some families, lentil was also used for *wott*.

In Montura, potato was added to *wott* (in addition to legumes). Other foods like *nifro* and *kollo* were prepared from grass pea and consumed as snacks. *Kitta* was also consumed by a few of the families studied.

TABLE 1

Dietary Habits of the Inhabitants of the *L. Sativus* Growing Village of Shina and Montura

Type of Food		Daily consumption gm/person/day (% of total)	
		SHINA	MONTURA
Enjera			
	Millet	578.3 (50.8)	375 (23.1)
	Teff	283.0 (24.8)	320 (19.6)
	Sorgum	160.5 (14.1)	231 (14.2)
	Corn	117.5 (10.3)	372 (22.8)
	Barley	----	332 (20.4)
L. sativus			
	Nifro	91.3 (49.5)	38 (100)
	Kollo	72.1 (39.1)	----
	Kitta	21.0 (11.4)	----
	Shiro	consumed with every meal	same
Vegetables			
	Potato	----	139 (51.1)
	Kale	----	133 (48.9)

Different methods are used in the preparation of grass pea for *shiro*. The most common methods used are as follows:

1. After removal of foreign particles, grass pea is lightly toasted on a clay or metal pan, transferred into cold water in a wooden trough or clay pot and thoroughly washed. The wet grass pea is toasted until browned and set aside for cooling. The husk is then removed by the use of a stone handmill (*woftcho*). The split grass pea is again washed, set in the sun for a while, and then mixed with peeled onion, garlic, ginger and basil. The mixture is pounded in a wooden mortar and set in the sun for final drying. It is then ground into flour. This method is mostly used in Montura.

2. Grass pea, free of all foreign particles, is added to boiling water on the stove, removed from heat after a few minutes and kept aside overnight. The following day, the liquid is discarded and the grass pea toasted until browned. After cooling for a while, the toasted grass pea is dehusked and thoroughly washed. The washed split grass pea is then set in the sun for a while. The rest of the preparation until the final flour product is as described above (under 1).

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3. Cleaned grass pea is toasted and dehusked. The split grass pea is washed and set in the sun to dry. It is then ground into *shiro*.

Grass pea, *shiro wott* preparation differed from house to house in the two peasant associations. The most common methods are as follows:

1. Water is poured into a washed clay pot and placed on a stove. When the water starts to boil, grass pea *shiro* is added a little at a time while stirring the mixture continuously. Salt is added and the sauce cooked until done. When ready the *wott* is eaten warm or cold with *enjera*.

2. Peeled and chopped onion is fried in a clay pot by adding a little water at a time until browned. If oil or water from crushed oil seeds is available, it is added while frying. Enough water is then added into the frying onion to boil. When the water starts to boil, *shiro* is added while stirring continuously. It is then cooked until done. This may take 20 to 30 minutes.

Boiled grass pea (*nifro*) is most often consumed in Shina. Different methods are used for *nifro* preparation. The most common methods are as follows:

1. Grass pea is cleaned and washed with cold water. Water is added and the grass pea cooked for a short time. The water is then drained off. Fresh water is added and the legume cooked until tender. Sometimes, chickpea or whole wheat is added to the grass pea before adding water the second time.

2. Grass pea is washed 2-3 times with hot water. Cold water is added and the legume cooked until it is soft enough to eat.

3. Grass pea is soaked in cold water, left overnight, and the liquid discarded the following day. It is then thoroughly washed, water added, and cooked.

4. Cleaned grass pea is thoroughly washed with cold water. Enough water is added and then the legume is cooked until done.

The roasted form of grass pea snack (*kollo*) was prepared in two alternative ways:

1. Grass pea is added into boiling water and boiled for sometime. Excess water is decanted and the grass pea is roasted over a hot clay or iron griddle.

2. Grass pea is soaked in cold water for some time and excess water is decanted. roasting is carried out as in 1.

Very few people consumed grass pea unleavened bread (*kitta*) during the survey period. *Kitta* is eaten mainly at times of acute food shortages. It is prepared in the following

manner:

Grass pea is cleaned and set in the sun for sometime. The husk is removed in a stone mill (*woftcho*). The split grass pea is ground into fine flour. Water is added a little at a time and the moistened flour kneaded to make a dough. Salt is added to taste. The thick dough is spread over hot clay or metal griddle by hand and baked on both sides for about 10 minutes.

Reliability check on chemical analysis

The results of assays obtained at the Addis Ababa University Department of Chemistry on identical samples were in excellent agreement with those of a reference laboratory at the Albert Einstein College of Medicine, New York.

The Rao method involves an initial hydrolysis of ß-ODAP to 2,3- diaminopropionic acid (DAP) which is then reacted with *ortho*-phthalaldehyde to generate the derivative whose concentration is determined by measuring its UV absorbance. The limitation of this method lies in its lack of selectivity to ß-ODAP in the presence of other species like α-ODAP which would give rise to DAP during hydrolysis. This is particularly important since α-ODAP is claimed to be non-toxic (14-16). However, the natural presence of the α-ODAP in the seeds of grass pea is believed to be very small (ca 5%). A further concern in dealing with the analysis of processed grass pea foods is the possibility that some of the ß-ODAP may transform into the α-form (17). However, such transformations are not expected to occur in solid food samples where the ß-ODAP exists in solid matrices. As a result it is felt that the analytical data generated for the food items considered in this study (with the possible exception of the *wott* samples, and these are only few cases) may approximate the actual levels of ß-ODAP present in them.

Levels of ß-ODAP

The ß-ODAP levels of whole seed samples collected randomly from the study areas ranged from 0.2 - 0.8%. The values of dehusked samples were 0.2-0.7%. The flour contained ß-ODAP in the range of 0.15 - 0.4%.

Although the sample sizes were small,the levels in the *shiro* sauce made of the flour form and the boiled grass pea were 0.1 - 0.3% and 0.1 - 0.7% respectively. As the preparation of *shiro* involved some degree of steeping and later dehusking, the ß-ODAP level of *shiro wott* was on the average lower by 40% than the whole seed.

In the preparation of *wott*, volume dilution by the addition of various ingredients may account for the observed lowering of the ß-ODAP level by 30% compared to the *shiro* used for the sauce preparation (Table 2).

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TABLE 2
ß-N-Oxalyl, ß-diaminopropionic acid (ß-ODAP) content in different grass pea food samples from Shina and Montura peasant associations

Sample type	Size of samples	ß-ODAP content (mg/100g)		
		Higest	Lowest	Average
Whole seed	63	810	282	455
Decorlicataed seed	10	690	239	444
Shiro-flour	50	429	155	270
Shiro-sauce	13	338	113	190
Nifro-boiled	13	704	70	471

TABLE 3
ß-ODAP content of boiled grass pea prepared in the laboratory using different methods of boiling.

Code	ß-ODAP content (mg/100g)				
	Dry seed	1	2	3	4
36	488	282	239	261	331
37	549	211	211	232	553
38	387	338	378	465	408
39	514	465	444	401	521
40	394	380	373	359	331
41	514	402	373	373	324
42	528	394	429	420	345
43	429	275	330	380	401
44	359	246	389	450	317
45	253	211	218	268	183
46	514	387	380	373	408
Mean	488.1	326.5	342.2	362.0	374.7
S.d.	91.8	86.0	82.5	77.3	101.7

1. Grass pea boiled for a short time, excess water drained. Then boiled with fresh water.
2. Grass pea washed with boiling hot water 3 times and then boiled with fresh water.
3. Grass pea soaked overnight, excess water discarded. Then boiled with fresh water.
4. Grass pea washed with cold water and then boiled with fresh water.

Simulated kitchen experiments confirmed that steeping grass pea in a large volume of water for 3 minutes and decanting the excess water leeched out approximately 30% of ß-ODAP. Improved detoxification was achieved when the boiled snack, *nifro*, was prepared from grass pea boiled directly with hot water as compared to that prepared from grass pea soaked overnight in cold water. This was statistically verified, (Tables 3 and 4).

Roasting grass pea preceded by steeping of the seeds achieved some degree of ß-ODAP reduction. On the other hand, when grass pea roasting was done after only soaking the seeds, there was an increase in the ß-ODAP level in six of 11 samples

(Table 5). Although the absolute differences were not statistically significant, neverthless the trend in the increase of ODAP level could not be ignored.

Higher levels of ß-ODAP were observed in the grass pea bread produced by the kitchen experiment compared with the original grass pea samples. The increase, which was found in 14 out of 20 identical experiments, ranged from 4.1-48.9 % (Table 6). However, due to the high variability in ODAP levels of the bread samples, the differences were not statistically significant.

TABLE 4

ß-ODAP content of boiled grass pea (*nifro*) samples prepared in the kitchen laboratory by two different methods: boiling directly and after soaking

Samples	ß-ODAP content (mg/100 g)					
		Soaked and boiled seed			Boiled seed	
	Dry seeds	Wet seed	Discarded water	Boiled seed	Discarded water	Boiled seed
1	901	739	3.5	683	300	479
2	831	732	8.2	676	420	324
3	1,042	936	10.9	429	598	697
4	824	697	9.7	634	655	408
5	739	789	11.5	704	662	387
6	796	634	8.7	514	535	331
7	591	380	4.4	338	275	253
8	367	282	1.3	334	264	246
9	475	252	1.7	343	387	317
10	598	343	8.1	264	370	229
Mean	716.4			491.9		367.1
S.d.	206.0			107.9		139.8

DISCUSSION

Food legumes, including grass pea, form a major part of the protein source and nutrients of the Ethiopian diet. Grass pea, though considered a poor person's food, is cultivated quite extensively in areas of the country subject to adverse agricultural conditions, particularly flooding and drought. Grass pea production is concentrated in the northwest region of Ethiopia, and is also cultivated in northeast, central and southeast regions.

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TABLE 5

ß-ODAP content of grass pea roasted (*kollo*) by two different methods

Raw grass pea		Roasted Sample 1			Roasted sample 2		
			ß-ODAP (mg/100g)			ß-ODAP (mg/100g)	
Code	ß-ODAP mg/100gm	Time (min)	Discarded water	seed	Time (min)	Discarded water	seed
50	704	1.15	9.9	651	4.38	8.6	739
51	500	3.15	7.0	591	3.33	6.3	584
52	943	4.15	21.8	831	5.50	14.6	1133
53	789	5.00	16.9	866	5.25	22.8	894
54	725	4.05	12.7	667	3.40	8.7	588
1/1	608			476			770
2/1	436			488			405
3/1	606			867			732
4/1	829			656			613
5/1	681			503			433
6/1	676			596			603
Mean	681.6			653.8			681.3
S.d.	144.4			145.3			207.4

It ranks fifth in total area among Ethiopian food legumes with a mean of 60,030 ha of land (8.7%) and 42, 200 t (7.6%) of grain (18). Probably as a reflection of the repeated food shortage situations in Ethiopia, the production of grass pea increased by 20% between 1981 and 1987 (19). Sporadic cases of lathyrism continue to appear in the northwest part of the country (10).

In the area studied here, grass pea is mainly used to produce the flour (*shiro*) used in the preparation of the Ethiopian sauce or gravy, *shiro wott*. This was the case in both villages studied. The pulse is also used as snacks in the roasted and boiled forms, mainly in Shina, the village where lathyrism is endemic at a prevalence rate of 3% (10). The bread form is consumed widely only in extreme famine situations as was the case during the major lathyrism epidemic of the Fogera and Dembia districts in 1976/77 (5). The consistent view that transpires from interviews of consumers of grass pea is that the pulse has an excellent taste. In the flour form, it possesses the unique water-absorbing and expansive properties which are advantageous during the preparation of the gravy, *wott*. As a result, in central parts of Ethiopia where grass pea is not cultivated, the pulse is presently popularly used as an admixture in the production of *shiro*. Food adulteration, with *Lathyrus sativus* seeds have been reported from India (20).

There are only a few studies that have addressed the potential neurotoxicity of

different food preparations of grass pea with reference to ß-ODAP content. Dwivedi and Singh have suggested that the Indian staple, *ghotu*, prepared by cooking a mixture of *Lathyrus sativus* and rice in water to form a stiff porridge (paste balls) precipitated lathyrism more rapidly than *chapati*, the unleavened bread form. This was based on an epidemiological observation. The researchers further suggested that the presence of water in the *ghotu* permitted the toxic component to be released in solution providing a more rapid absorption (21). To our knowledge ß-ODAP levels have not been systematically assayed in the different grass pea food preparations, thus this hypothesis has not been tested.

Our kitchen experiments have demonstrated that the Ethiopian unleavened bread, *kitta*, which in its form and preparation is equivalent to the Indian *chapati*, has higher detectable levels of ß-ODAP than the dry grass pea seeds from which it is prepared. We have also epidemiological evidence that in the lathyrism outbreaks and epidemics of northwest Ethiopia, the bread (*kitta*) form was consumed in large quantities in addition to other types of grass pea-derived foodstuffs. Gebre-ab *et al.* writing about the 1976/77 lathyrism epidemic in northwest Ethiopia, when over 2500 persons were affected, observed that the commonest form of grass pea consumed by the affected population included *kitta*, *nifro* and *kollo*. They also commented that the *kitta* form was then a new introduction into the area of the epidemic (5). In normal times, as was the case during our survey, villagers in the lathyrism-endemic area used grass pea commonly as snacks in the boiled and roasted forms and very little as bread.

Similarly, we have shown that the roasted form (*kollo*), if roasted without prior aqueous steeping, may contain higher levels of ß-ODAP than the native seeds. The conclusion drawn from these experiments, which were designed to simulate the condition in the villages, is that the level of ß-ODAP is maximal in the bread and roasted forms of grass pea. The level is lower in the boiled snacks, particularly when the process of steeping is employed. The flour form, *shiro* and the sauce prepared there from, contained relatively lower levels of ß-ODAP and thus may not be so hazardous.

Detoxification of the grass pea through aqueous leeching of the toxic component (i.e. steeping) has been described previously (22). Mohan *et al.* have suggested the removal of the toxin from *L. sativus* seeds through two alternative methods: steeping the dehusked seeds in hot water for several hours and boiling the seeds in water and draining out the supernatant. This removed 70-80% of the neurotoxin (23). Moslehuddin *et al.* also found that washing the seeds partially removed the neurotoxin while fermentation, steaming or autoclaving appeared to have little effect (24).

Ayyagari *et al.*, based on analysis of a limited number of samples, concluded that the ß-ODAP content did not decrease much in prepared food. Dry heating, roasting, deep frying, or boiling did not alter the ß-ODAP levels (25). On the other hand, Rao *et al.* recorded that the roasting of grass pea for about 15-20 minutes at 140°C rendered the seed free of neurotoxin. Howevere, they observed that chapati making made the

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grass pea foodstuff more toxic (26). However, in the case of the roasting they did not mention whether the seeds were washed or boiled before roasting.

TABLE 6

ß-ODAP content of bread (*kitta*) prepared in the laboratory from different *L. sativus* samples

Dry grass pea			Bread sample		Bread preparation	
CODE	ß-ODAP mg/100gm	% moisture	ß-ODAP mg/100gm	grass pea wet sample (gm)	water for mixing (ml)	baking time (min)
36	488	70.8	394	80	60	7
37	549	76.5	426	80	60	7
38	387	63.1	429	80	60	7
39	514	65.4	584	80	60	7
40	394	62.8	521	80	60	6
41	514	70.8	535	80	75	7
42	528	62.7	786	80	60	7
43	429	69.8	583	80	60	10
44	359	67.0	472	80	60	10
45	253	70.8	331	80	55	8
46	514	71.4	401	80	60	7
67	367	66.7	510			
68	475	65.3	542			
69	452	64.3	590			
70	598	77.5	678			
71	299	65.3	502			
1/1	416		493			
1/2	416		244			
1/3	416		224			
1/4	416		227			
Mean	439.2		473.6			
S.d.	85.5		145.5			

However, a serious and challenging question that will arise out of our findings will be why have higher ß-ODAP levels been recorded in the bread and roasted forms of grass pea? How does direct heat increase ß-ODAP content of the grass pea?

A plausible explanation relates to changes in the extractability of the ß-ODAP by thermally introduced processes. Other workers who have been studying the extractability of the toxin by imbibing with water over prolonged periods and determining the levels of ß-ODAP in the imbibed seeds, as well as in the fluid, have found that the two values when added up differ from the level of toxin found by direct analysis of seeds [Lambien, F. personal communication]. Heat treatment may induce enzymatic changes, damage lipid membranes or even alter the nature of the counterions that may be associated with the toxin. It is possible to speculate changes in the composition and availability of counterions, K+, Na+, Mg++ that may be induced by heat. For

instance, the potassium salt of ß-ODAP is more extractable than the sodium salt. Little or no information is available on the relative extractabilities of other divalent metal salts of the toxin.

Although there have been suggestions that the reduction of over 65% in ß-ODAP content could be considered safe, the non-toxic levels of ß-ODAP have not yet been established (20). In fact, it will not be easy to set such a cut of standard because of the different concentration of ß-ODAP in germplasm lines of *L. sativus*. For instance, in the field samples we collected the ß-ODAP contents varied from 128 to 985mg/100 gm of dry seeds. Thirty or thirty-five per cent of the most toxic sample may still contain a significant amount of ß-ODAP.

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EXPERIENCE IN THYROID SCINTIGRAPHY WITH ETHIOPIAN PATIENTS

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ABSTRACT: *One thousand and thirty-seven thyroid scintigraphy examinations done in the Nuclear Medicine Unit of Tikur Anbessa Hospital, Addis Abeba, Ethiopia between December 1984 and September 1989 were analyzed to assess their diagnostic value. Thirty-one percent of the referrals were to investigate clinically detectable solitary nodules, and of these fifty-six percent had "cold" nodules and twenty-three percent "hot" nodules. Fifty-five percent of the referrals for evaluation of goitre were for multinodular goitres and twelve percent for diffuse. Thirteen of fifty-three cases with suspected ectopic thyroid tissue were positive. Little useful information was obtained in the evaluation of goitre. It is concluded that thyroid scintigraphy was an unnecessary investigation in the evaluation of goitres in euthyroid patients. Its primary role was in the investigation of the solitary nodule, ectopic thyroid tissue and the retrosternal goitre. Therefore, only selected patients should be investigated with thyroid scintigraphy.*

INTRODUCTION

The Nuclear Medicine Unit of the Department of Internal Medicine in Tikur Anbessa Hospital, Addis Abeba, serves as the referral centre for thyroid scintigraphy for patients from all over Ethiopia. Radioiodine-123 (123-I) scintigraphy is a well established and widely available technique for investigating regional thyroid function. However, since 123-I is not available in our Unit, radioiodine-131 (131-I) is used which reveals the same information. A few drawbacks, such as exposure to radiation associated with 131-I use and its longer half life, were well recognized by the investigators.

Indications for thyroid scintigraphy had been circulated to the majority of practising physicians at the different hospitals. The indications were:

1. palpable thyroid nodule
2. enlarged thyroid gland
   a. presence of nodular component
   b. presence of residual tissue following thyroidectomy
3. evaluation of soft tissue masses in the neck and mediastinum
   a. lingual thyroid
   b. ectopic cervical thyroid
   c. substernal thyroid

The contraindications were pregnancy and breast feeding.

The present analysis was undertaken to assess the extent of adherence to the

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guidelines circulated by the Unit, the reasons for referral, and the contribution made by scintigraphy to subsequent clinical management.

PATIENTS AND METHODS

The period of study was from December 1984 to September 1989. Relevant history and physical examinations were done by a physician in the Unit prior to imaging. Pregnant and lactating women were excluded. No special informed consent was obtained because all studies were performed on patients referred for the investigations by their physicians.

Twenty-four hours after oral administration of 40-60 uCi of 131-I (sodium iodine solution), anterior views were obtained. Thyroid scan was performed using Gamma Muvic Rectilinear Scanner with 85 holes, collimator of 0.5m/-min speed and "R" time constant.

The interpretation of the images was made after correlating palpatory findings in the thyroid gland with the images, but without knowledge of the clinical impression. Homogeneous distribution of the tracer in each lobe measuring up to approximately 5 cm by 2 cm was interpreted as normal. Homogeneous distribution of the tracer in both lobes but with increased size was taken as diffuse goitre. Multinodular goitre exhibits heterogeneous distribution pattern of the tracer with both lobes enlarged. A "hot" nodule is a hyperfunctioning nodule which demonstrates greater activity than the adjacent gland. A "cold" nodule is a hypofunctioning nodule which demonstrates little or no activity.

A solitary palpable nodule may demonstrate activity equal to adjacent thyroid gland. If the scintigram is heterogenous, then these cases are classified in the multinodular group, and if the palpable nodule appeared to be a part of one of the thyroid lobes, then these cases are classified in the normal group.

RESULTS

More than 76% of the patients were referred from Tikur Anbessa Hospital, which offers endocrinology services to patients with thyroid disease referred from all over Ethiopia. Table 1 shows the indications in 1037 patients referred for thyroid scintigraphy: 62% were for evaluation of goitre.

Table 2 shows age and sex distribution. The female to male ratio is 3.7:1. The mean age was 33 years with a range of 7 to 74. Sixty one percent of the patients were from 20 to 40 years of age, and of these 82% were females. Seventeen percent of all the patients were below 20 years of age.

Tables 3, 4 and 5 show the results of 1037 consecutive thyroid scintigraphy examinations grouped according to the reason of referral. The diagnostic contribution of the procedure to the subsequent medical management of the patients was also analyzed.

Thirty one percent of the total requests (n=323) were for the investigation of solitary nodules. Confirmation of "cold" (56%) or "hot" (23%) nodules was made in 255 cases. "Cold" and "hot" nodules were also detected in

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18% and 9% of those referred with a diagnosis of goitre respectively.

Of the 640 patients referred for evaluation of goitre, multinodular goitre, diffuse goitre and normal thyroid were found in 55%, 12% and 6% respectively.

In the 1037 referrals, "cold" nodules were found in 294 (31%) patients, suggesting a need for further diagnostic work up, such as needle aspiration.

DISCUSSION

The unique biological properties of iodine and the availability of its radioactive isotopes enable clinicians to study thyroid function by isotopic nuclear methods.

Twenty five percent of solitary nodules may harbour malignancy (1-4). Thus, the finding of a "cold" nodule is an indication for early biopsy or surgical removal. In addition, in most series, a palpable solitary nodule is the commonest indication for scintigraphy (5-7). In our study, 31% have "cold" nodules which suggest that further histological examination is required. The study of Maxon et al (6) suggested that, prior to fine needle aspiration cytology and/or biopsy, thyroid imaging should be performed to direct the tissue sampling to proper locations. While not absolutely diagnostic in so far as thyroid malignancy is concerned, the procedure is extremely useful in conjunction with other clinical information in the rational management of the patient with a thyroid nodule. Therefore, a palpable solitary nodule or the presence of a dominant nodule in a goitre is the most important indication for scanning, because the scan can confirm the presence of a nodule and whether it functions or not. In addition, this study revealed 23% "hot" nodules and 21% normal thyroid scans amongst those referred as cases of palpable nodule: thyroid scintigraphy indicated that further invasive investigation was not warranted in these patients.

A survey was done by the Ethiopian Nutrition Institute (ENI) in 1979/81 which revealed an overall prevalence of goitre from 0.4 to 66% with a mean of 25.1% (8), demonstrating that the problem of goitre is of great public health significance, especially in the northern, western, and central regions of the country which are characterized by high altitude. In view of the high incidence of goitre in Ethiopia, it is clear that thyroid scintigraphy must be used selectively. This has been supported by our study in which 55% of those referred for evaluation for goitre had multinodular and 12% diffuse goitres. This information is no greater than that which could be obtained from careful clinical palpation. Only 27% (171) of 640 thyroid scintigraphies gave useful information by eliciting "hot" and "cold" nodules. Tindall et al (9), in their study of 131 patients, have also shown that thyroid scintigraphy has little practical value in the management of euthyroid patients with diffuse or multinodular goitre, unless there is a prominent thyroid nodule. For example, our study revealed "cold" nodules in 18% of patients referred for evaluation 330

of goitre.

Very few patients are referred for retrosternal goitre and ectopic thyroid tissue: there are only 2 positive scans in twenty-one suspected cases of retrosternal goitre. Nevertheless, thyroid scintigraphy is useful in evaluating whether retro-sternal goitre is functional or not. The finding of ectopic thyroid in only 13/53 (25%) could be due to the palpable gland being cystic or non-functioning. However, thyroid scintigraphy is indicated if there is a clinical impression of ectopic thyroid tissue to find out whether it is functional or not.

Our study confirms the recommendations of Tindall et al (9) and Reasner et al (10) that the indications for thyroid scintigraphy should be:

1. presence of solitary nodule
2. confirmation of suspected autonomous nodules
3. presence of a prominent thyroid nodule in a euthyroid goitre patient
4. demonstration of ectopic thyroid tissue
5. suspected retro-sternal goitre.

Thyroid scintigraphy should be an essential investigation for patients with solitary nodule, ectopic thyroid tissue and/or retrosternal goitre. It has little practical value in euthyroid patients with diffuse or multinodular goitre. In addition, it should be emphasized that the pattern of functioning thyroid, as seen on the scan, provides guidelines rather than diagnosis in the management of thyroid disorders.

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TABLE 1. Indications for thyroid scintigraphy of 1037 patients

Indication	Number (%)
1. Evaluation of goitre	640 (62)
2. Solitary nodule	323 (31)
3. Suspected retrosternal goitre	21 (2)
4. Suspected ectopic thyroid tissue	53 (5)
Total	1037 (100)

TABLE 2. Age and sex distribution

Age (Years)	Sex		Total
	Male	Female	Number (%)
1-9	2	3	5 (0.5)
10-19	45	126	171 (16.0)
20-30	64	287	351 (34.0)
31-40	49	229	278 (27.0)
41-50	37	103	140 (14.0)
51-60	10	53	63 (6.0)
61-70	8	16	24 (2.0)
>70	2	3	5 (0.5)
Total	217	820	1037 (100)

TABLE 3. Thyroid scintigraphy results in 323 patients referred for evaluation of solitary nodules

Solitary nodule	Number	Scintigraphy Result (%)		
	Number	"Hot" nodule	"Cold" nodule	Normal thyroid scan
Right side	188	53	98	37
Left side	135	20	84	31
Total	323	73 (23%)	182 (56%)	68 (21%)

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TABLE 4. Thyroid scintigraphy results in 640 patients referred for evaluation of goitres

Result	Number (%)
Multinodular goitre	354 (55)
Diffuse goitre	76 (12)
"Cold" nodule	112 (18)
"Hot" nodule	59 (9)
Normal thyroid gland	39 (6)
Total	640 (100)

TABLE 5. Thyroid scintigraphy results in 74 patients referred for evaluation of soft tissue masses in the mediastinum and neck

Reason for request	Number	Scintigraphy Result	
		Present	Absent
Suspected retrosternal goitre	21	2	19
Suspected ectopic thyroid tissue	53	13	40

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THE EPIDEMIOLOGY OF LATHYRISM IN NORTH AND CENTRAL ETHIOPIA

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ABSTRACT: *Lathyrism is a neurotoxic disorder caused by excessive, prolonged consumption of the hardy, environmentally tolerant legume, the grass-pea,* Lathyrus sativus, *which contains the neurotoxic amino acid beta-N-oxalylamino-L-alanine acid (BOAA). The disease develops after heavy consumption of grass-pea for over two months. It is uniformly manifested by a predominantly motor spastic paraparesis with varying degrees of disability. A door-to-door epidemiological survey for the disease using trained lay health workers was carried out in the major areas of northwest* and central *Ethiopia where* L. sativus *is grown. For security reasons, some of the other endemic areas were not accessible for the survey. The survey involved a population of 1,011,272. A total of 3,026 affected persons were identified. The disease was found to be widespread in the northwest and central highland areas of the country. The prevalence rates ranged from 1/10,000 to 7.5/1,000. The highest prevalences were in North and South Gonder, and East and West Gojam. The male:female ratio of cases was 2.6:1; the females exhibited a milder form of the disease. The cultivation of* L. sativus *is increasing in Ethiopia, which makes the development of low-BOAA strains very important in order to control the high incidence of lathyrism, a crippling disease which affects the productive young members of the society.*

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INTRODUCTION

Lathyrism is a neurotoxic disorder caused by excessive, prolonged consumption of grass-pea *(Lathyrus sativus)*. Much of our knowledge about this pulse and the disabling disease it causes comes from studies in India (1-4). The neurotoxic culprit, beta-N-oxalylamino-L-alanine acid (BOAA) has been identified and characterized (5). Although in the past the disease occurred in Europe, North Africa, the Middle East and Asia (6), it is at present endemic in India (7), Bangladesh (8) and Ethiopia (9). In Ethiopia, it has been known for many years. Its leg-paralysing features have gained descriptive local names such as "sebre", "gayu" and "gwaya". Although known to be associated with *L. sativus*, the paralysis has given rise to false local beliefs concerning the method by which the disease is acquired. Outbreaks of lathyrism have occurred in the northern parts of the country associated with famine (10, 11), and the disorder remains endemic in several parts of the country, with the occurrence of new cases recently recorded in the northwest (12).

The purpose of this study is to give a general epidemiological overview of the lathyrism problem in the endemic regions of Ethiopia with the aim of providing information essential for the prevention and possible eradication of the disabling disease. It was undertaken as part of a multidisciplinary approach to study the agricultural, medical and nutritional aspect of the disorder (13).

Study areas (Figure 1): Grass-pea (*L. sativus)* is grown in the Ethiopian highlands at altitudes ranging from 1700 to 2220 m and a maximum temperature of 15 - 20 C. Its production is mainly in areas affected by severe natural disasters such as moisture stress, water logging and flooding. Grass-pea cultivation is concentrated predominantly in the northwest zone (58%), while the central and northeast zones produce 16.3% and 12.8% respectively. The northern and southeast regions produce the balance (14).

The survey: Field investigations carried out between 1988 and 1990 were concentrated on the major grass-pea producing administrative regions of North and South Gonder, West and East Gojam and West Shewa. For security reasons, the survey was unable to cover Welo, Tigray, Eritrea, Harer, and parts of Shewa Administrative Regions. There were also inaccessible grass-pea growing districts in North and South Gonder.

In each administrative region, the research team contacted the regional officers of the Ministry of Agriculture as well as the local administrative authorities responsible for crop production. Up-to-date information on grass-pea cultivation and production was obtained. A twenty-per-cent random sampling of the Peasant Associations of grass-pea cultivating districts was made. Later on in the survey, the random sampling had to be reduced to 10%, due to security considerations and the need to complete the survey before the major military escalations of late 1991 in the survey areas. The results of a

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neuro-epidemiology survey from the Butajira district of South Shewa, a region which does not grow grass-pea (15), were included for control purpose.

Locally recruited lay health workers (6 males and 4 females) were trained in the use of questionnaires and the recognition of motor disabilities in the legs, including the different stages of paraparesis due to lathyrism. Pilot studies were undertaken in every survey area whenever a new group of enumerators was recruited.

Village elders and leaders of the different Peasant Associations were informed about the objectives of the field investigation, and their consent was obtained. The elders were interviewed individually and in groups on the dietary habits of the community, with particular reference to grass-pea consumption.

During their door-to door interviews, the enumerators collected census data including age, sex, religion, marital status, occupation and food habits of households in each village. They also recorded information on the amount and period of grass-pea consumption in households, and the onset of walking difficulties. In the majority of cases, the age of individuals and the age of onset of symptoms were determined using local event calendars. Two physicians trained to recognize and diagnose cases of lathyrism screened all subjects with walking difficulties identified by the enumerators. The neurologist in the team saw sampled groups of cases in order to validate diagnosis. After a period of experience, the agreement between the physicians and neurologists was excellent.

Inclusion criteria included leg weakness and spasticity of subacute or insidious onset and history of heavy grass-pea consumption prior to and at onset of the disease. The following were considered to be exclusion criteria: sensory deficit in extremities, marked asymmetrical leg weakness, continuing bladder and/or bowel dysfunction, and presence of peripheral gangrene in the limbs (12). Resulting disability was classified according to Acton (2) with some modifications.

Stage 1: mild spastic gait with no use of a stick; increased stiffness and exaggerated deep tendon reflexes (DTR) of the lower limbs; ankle clonus present, Babinski's sign present.

Stage 2: spastic gait, with use of one stick; lower limbs exhibit increased stiffness; mild rigidity; exaggerated DTR; ankle clonus present, Babinski's sign present.

Stage 3: spastic gait, with use of two sticks; crossed adductor gait; lower limbs exhibit exaggerated DTR; ankle clonus present; Babinski's sign present.

Stage 4: crawling or bedridden state; loss of leg use, with contracture; arms strong; and pyramidal signs present.

Concurrent with the medico-social field surveys, the team collected samples of grass-pea from the local market and some of the households. A total of 200 grass-pea seed and food samples collected from the surveyed areas were sent to the Addis Abeba Universtiy's Department of Chemistry for analysis of BOAA content using the

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calorimetric ophthaldehyde (OPT) fluorescent dye method (16, 17).

Statistical Methods: the two-tailed test was used to test for statistical significance.

RESULTS

Table 1 shows the 1988 production and yield of grass-pea cultivation in Ethiopia as depicted by the Central Statistics Office (CSO) (18). East Gojam, South Gonder, West Gojam, and South Welo are, in that descending order, the major grass-pea producing regions, followed by East Shewa, North Welo, North Gonder and Arsi. Beta-N-oxalylamino-L-alanine acid (BOAA) levels in the 200 samples collected from the survey areas ranged from 0.2 to 0.96 mg/100gm of dry grass pea. High BOAA content was registered from grass-pea samples collected from Gonder and Gojam. The highest were from the sub-district of Adet (West Gojam). The grass-pea samples in Shewa are in general less toxic. The prevalence of lathyrism was highest in the subdistricts of Yilmana and Deinsa (West Gojam), Dembia (North Gonder) and Fogera (South Gonder).

In all the lathyrism endemic areas, agriculture, including cattle rearing, was the main occupation, and the chief source of livelihood, for over 90% of the affected persons. Socio-economically the population was poor (i.e. below the average Ethiopian per capita GNP of 120 US dollars per year) and individuals had a hand-to-mouth existence.

The age and sex distribution (Fig. 2) demonstrates that males were affected much more than females (2.6: 1). Onset of the disease took place below 10 years of age in 26.7%, between 10 and 20 years in 27.1%, between 21 and 40 years in 29.9%, and above 40 years in 16.3 per cent. Thus, 83.7% were below the age of 40 years at onset. It is noteworthy that, in females, 69.2% of cases had their disease onset before the age of 20 years as compared to 47.7% in males ($p < 0.001$).

In over 80% of the cases, the disease developed in the months of May to August (the majority in July), after 3 to 6 months of grass-pea consumption in 65%, 2 to 3 months in 60% and one month or less in 15%. In Ethiopia, grass-pea is sown in October/November and harvested in March/April. Consumption is from May to October, with the maximum amount recorded in the months of June and July.

The annual distribution of cases was found to be relatively constant except in situations of acute food shortage and famine when epidemics of lathyrism have been recorded. One such epidemic occurred in the Dembia and Fogera subdistricts in 1976/77 (11).

The clinical setting of the paralysis was recalled in only 30% of the patients, who remembered the prodromal symptoms of rheumatic pain and tightness at the waist. Painful spasms of the leg muscles, the so-called myospasm, was rarely recalled. The majority experienced stiffness and heaviness of the legs at and around the time of the paralysis of the legs, which occurred in a sub-acute manner in 65%

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of the cases and acute (occurring all of a sudden) in 25%. The sub-acute onset refers to the presence of prodromal symptoms before the manifestation of the paralysis and gradually increasing stiffness of legs over a month or more. Concerning disabilities, 52.2% and 41.5% belonged to stage 1 and 2 respectively. Stage 3 and 4 together formed only 6.3%. Sixty-five percent of the females had the mild stage 1 disability (Table 2).

The dietary interviews revealed that grass-pea was commonly consumed as snacks in the boiled "nifro" and roasted "kollo" forms. The flour form was used to prepare the Ethiopian sauce or gravy called 'shiro wot'. In a typical grass-pea-producing village, this was the predominant type of sauce consumed with the injera, a pancake type of leavened bread prepared from finger-millet, sorghum or rarely, from barley, wheat and tef *(Eragrostis eff)*, depending on the region and socio-economical standing of the household. Tef and wheat are generally expensive cereals that require good soil and a great deal of agricultural input. The bread (kitta) form of grass-pea is consumed only during acute food shortages, and in some of the villages that were repeatedly affected by flooding.

When interviewed about the connection of grass-pea and lathyrism, the majority of the victims were not clear that the onset and severity of the paralysis had a direct relationship to the amount and period of grass-pea consumption. The belief that the paralysis was precipitated or accentuated by exposure to vapour or smoke from grass-pea being boiled or fried was very common. Walking in a grass-pea field, as well as drinking milk together with the pulse, was thought to be dangerous. The interviews further revealed that the afflicted peasants continued to consume grass-pea despite a clear understanding of its paralysing properties. When asked why they persisted in eating the "poisonous" pulse, they replied that there was no alternative.

The clinical signs of the spastic paraparesis were uniformly similar to the classical descriptions of neurolathyism. The victims manifest varying degrees of disability which cause difficulties with mobility and hinder their occupation as farmers. The common precipitating factors identified by these surveys were heavy physical labour, febrile illness and diarrhoea.

DISCUSSION

Ethiopia has been undergoing serious political turmoil for the last twenty years. Because of military conflicts, many areas of the north, and later the central regions of the country, were inaccessible to civilians. Our epidemiological surveys were therefore hampered from operating in some of the administrative regions where lathyrism was known to be prevalent. Nevertheless, the results now reported represent the best obtainable data on the lathyrism problems of the major grass-pea growing regions of the country.

Lathyrism is a real and serious problem which has not received the attention

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it deserves, either from the Ethiopian people or from its health authorities. The disease continues to claim more and more victims in direct proportion to the increasing cultivation and consumption of grass-pea. Those that have succumbed to the disease remain permanently disabled and are without opportunities for social and physical rehabilitation. Since young men are relatively commonly affected there is a major loss of critical manpower for peasant families.

The high prevalence rates of lathyrism in the Lake Tana basin (Table 1) are very strongly influenced by several factors. First, the area is repeatedly flooded during the rainy seasons (June to October), when cereals fail because of waterlogging. Second, the area is populated by very poor peasants who live on subsistence farming, using primitive agricultural practices such as oxen ploughing. Their diet is cereal based, with legumes being used for preparation of snacks and sauces. There was hardly any intake of milk, protein or vegetables (19).

In the 1988/89 re-survey of the districts of Dembia and Fogera of north-west Ethiopia, a region that had been affected by an epidemic in 1977 (11), we found that the prevalence of lathyrism in some villages was as high as 3%. This was most alarming when we consider that the mean annual incidence of the disease in the same region was 0.6% (12). Although the prevalence of the disease in other regions may be lower, the disease was nevertheless found to be widespread, with its maximal concentrations in northwest Ethiopia, particularly in the administrative regions of West and East Gojam and South Gonder.

The high prevalence figures correspond to the cultivation and production of grass-pea. The high BOAA levels of grass-pea from these regions may also have promoted disease outbreaks (Table 1). Unfortunately, for reasons mentioned earlier, we have been unable to survey the administrative regions of North and South Welo and North Shewa, where grass-pea production is recorded to be high.

The characteristics of the affected populations, their consumption of grass-pea, the onset and the clinical manifestations of the disease are very similar to those in the classical reports from India (2-4, 19-20) and Bangladesh (21).

As shown in Fig. 2, the prevalence of the disease in females is low and their degree of infirmity is less severe. This is similar to the results of epidemiological studies in India (2,4). It is not because women consume less, as Acton suggested (2); our dietary enquiry confirms that their consumption is not less than that of men. The reason for the relative protection of females, particularly of child-bearing age, may be hormonal (oestrogen), as proposed by Dwivedi and Prasad (4).

In India, legislation to ban the production and sale of grass-pea has proved to be difficult to implement (22). Whereas in India serious attempts have been made to tackle the problem of lathyrism, in Ethiopia very little attention has been given to the preven-

tion of this crippling disease. With natural and man-made calamities so commonly encountered in Ethiopia, the production of the hardy pulse is increasing, and is bound to increase further particularly in drought-prone and flood-prone areas. For instance, in 1988/89 the annual production of grass-pea in the country, from 37,800 hectares of cultivated land, was estimated to be 410,000 quintals (18).

Lathyrism is a very serious social problem because it cripples the young and productive age groups. Disease prevention is an important public health response. Acton, in his meticulously executed investigation of lathyrism in North Rewah, India (2) proposed measures that are both appropriate and feasible in the Ethiopian situation:

1. The public should be educated about the toxicity of grass-pea, and instructed in ways of processing it to help reduce the toxicity. It is now well documented that soaking or boiling and discarding the excess water reduces the toxic BOAA in the seed (23).
2. During poor harvest and famine situations, communities in lathyrus growing areas should get external relief supplies free, or cereals should be made available to them at affordable prices.

Recently, interest and hopes have been raised by a more effective and far-reaching approach to solving the lathyrism problem. This will involve the development of low BOAA varieties of grass-pea. It is interesting to observe that Acton, even in 1922, had alluded to this, suggesting that "the small-grained *kesari* is less toxic than the large grained Bhagalpur *dal*, so that every effort should be made to grow sufficient quantity of indigenous grain to meet local requirements" (2).

There are now very active breeding programmes in a number of countries, including Ethiopia (14), to develop and disseminate low-BOAA varieties of grass-pea. This is part of an international multidisciplinary collaborative effort to improve *L. sativus* and eradicate lathyrism (13).

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TABLE 1. The prevalence of lathyrism in the surveyed areas compared with the *Lathyrus sativus* production and content of beta-N-oxalylamino-L-alanine acid (BOAA) of dry grass-pea samples.

Administrative region	Cases/pop. surveyed	Prevalence per 1,000	L. sativus prod*		BOAA in grass-pea samples (mg/100gm)
			area '000 ha	prod.'000 qt.	
North Gonder			1.4	10.3	0.4-0.85
Dembia	999/160,000	6.2			
South Gonder			11.4	69.1	0.5-0.96
Fogera	767/123,500	6.2			
Simada	175/46,028	3.8			
Kemkem	113/62,927	1.8			
Dera	169/174,904	1.0			
Este	61/75,295	0.8			
West Gojam			8.1	77.8	0.45-0.85
Yilmana Deinsa	401/53,389	7.5			
Bahr Dar Zuria	148/44,433	3.3			
Mecha	33/33,739	1.0			
Dega Damot	15/20,919	0.7			
Jabir Quarit	17/42,376	0.4			
Achefer	1/14,162	0.1			
East Gojam			13.1	102.1	0.38-0.78
Mota	29/14,546	2.0			
Bichena	29/17,715	1.6			
Enesie	9/16,549	0.5			
Dejen	14/30,910	0.5			
Enarj-Enawga	1/8,440	0.1			
West Shewa			3.5	31.6	0.2-0.50
Becho	45/19,620	2.3			
South Shewa			0.28	1.8	
Butajira	0/60,820		(0.5)	(4.9)	

* Production figure in hectares (ha.) and quintals (qt.) are from Agricultural Sample Survey 1988/89; Central Statistics Office (CSO), 1990.

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TABLE 2. Degree of disability by sex

Stage	Males		Females		Total	
	No.	%	No.	%	No.	%
1. No stick	621	47.1	339	65.1	960	52.2
2. One stick	607	46.1	157	30.1	764	41.5
3. Two sticks	54	4.1	15	2.9	69	3.8
4. Crawler	36	2.7	10	1.9	46	2.5
Total	1,318	100.0	521	100.0	1,839	100.0

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Tubercle and Lung Disease

Community acquired pneumonia in adults in Addis Ababa: etiologic agents and the impact of HIV infection

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SUMMARY. Setting: Black Lion Hospital, a tertiary care referral hospital in Addis Ababa, Ethiopia.
Objective: To determine the prevalence of HIV infection in patients with Community Acquired Pneumonia (CAP) and compare the etiologic agents, clinical and radiographic presentation and outcome of the disease in HIV positive and negative patients.
Design: A hospital based prospective study on 110 adult patients consecutively coming to Black Lion Hospital between August 1987 and July 1989.
Results: 8% of patients with pneumonia versus 2.4% for the general population ($P < 0.05$) were seropositive for HIV-I. *Streptococcus pneumoniae* was the most common offending pathogen. HIV positive patients were more likely to be male, young and of urban residence. They had fewer chills, increased bilateral and multilobar lung involvement, frequent association with pulmonary tuberculosis and recurrent chest infiltrate.
Conclusion: The incidence of Community Acquired Pneumonia in patients with HIV infection is likely to increase with the rapid rise in HIV infection. Future studies should therefore look further into (a) the pattern of etiologic agents, (b) unusual clinical patterns which may help set criteria for screening for HIV infection, and (c) the use of pneumococcal vaccine in selected groups of patients.

RÉSUMÉ. Cadre: Black Lion Hospital, un hôpital de référence de soins de santé tertiaire à Addis Abeba, Ethiopie.
Objet: Déterminer la prévalence de l'infection VIH chez des patients atteints d'une pneumonie communautaire (CAP), et comparer les agents étiologiques, la présentation clinique et radiographique, et l'issue finale de la maladie chez des patients VIH positifs et VIH négatifs.
Schéma: Etude prospective hospitalière d'une série de 110 malades adultes se présentant à l'Hôpital Black Lion entre août 1987 et juillet 1989.
Résultats: 8% des patients atteints d'une pneumonie, versus 2,4% dans la population générale ($P < 0,05$), étaient séropositifs pour le VIH-1. *Streptococcus pneumoniae* était le pathogène le plus commun. Les patients séropositifs étaient le plus souvent masculins, jeunes et habitants d'une région urbaine. Ils souffraient moins de frissons, avaient plus souvent une atteinte pulmonaire bilatérale et multilobaire, ainsi qu'une association fréquente avec la tuberculose pulmonaire et un infiltrat thoracique récidivant.
Conclusion: L'incidence d'une CAP chez des patients atteints d'une infection VIH va vraisemblablement croître avec l'augmentation rapide de l'infection VIH. D'autres études devraient ainsi approfondir a) les caractéristiques des agents étiologiques, b) les caractéristiques cliniques inhabituelles susceptibles d'établir des critères pour le dépistage de l'infection VIH, et c) l'utilisation de vaccin pneumococcique dans des groupes de malades choisis.

RESUMEN. Cuadro de referencia: El Hospital Black Lion, hospital de referencia de atención terciaria en Addis Ababa, Etiopía.
Objetivo: Determinar la prevalencia de infección VIH en pacientes con neumonia adquirida en la comunidad (CAP) y comparar los agentes etiológicos, la presentación clínica y radiográfica y la evolución final de la enfermedad en pacientes VIH positivos y negativos.

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***Método*: Estudio prospectivo hospitalario de una serie consecutiva de 110 enfermos adultos que se presentaron al hospital Black Lion entre agosto de 1987 y julio de 1989.**

***Resultados*: Un 8% de pacientes con neumonia, versus un 2,4% en la población general ($P < 0,05$) eran seropositivos para el VIH-1. *Streptococcus pneumoniae* era el agente causal más común. Los pacientes VIH positivos eran más frecuentemente de sexo masculino, jóvenes y con residencia urbana. Presentaban con menos frecuencia escalofríos, más frecuentemente un compromiso pulmonar bilateral y multilobar, una asociación frecuente con tuberculosis pulmonar y un infiltrado torácico recidivante.**

***Conclusión*: La incidencia de CAP en pacientes con infección VIH aumenta muy probablemente con el aumento rápido de la infección VIH. Estudios futuros deberán investigar a) las características de los agentes etiológicos, b) las características clínicas inhabituales que podrían contribuir a establecer criterios para la detección de la infección VIH y c) la utilización de la vacuna neumocócica en grupos seleccionados de pacientes.**

INTRODUCTION

Community Acquired Pneumonia (CAP) tends to occur more frequently in patients with AIDS than in those without AIDS.[1–4] Infection occurs either before or after an AIDS-defining diagnosis and entails increased morbidity and mortality.[5–7] The latest expanded surveillance case definition for AIDS by the Centers for Disease Control (CDC) classifies recurrent pneumonia as an AIDS-defining disease.[8] The pneumococcus and *Haemophilus influenzae* are the most common pathogens isolated although other organisms including *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Rhodococcus equi*, Legionella species, etc., have occasionally been isolated. The clinical presentation of patients with pneumonia is similar to that of HIV-negative patients except that HIV-positive patients tend to have one or more recurrences, increased incidence of bacteremia and multilobar involvement.[2] In Ethiopia, CAP is the second most common cause of adult medical admissions, with a case fatality rate of 17%.[9] The most common lung infection in HIV positive patients is pulmonary tuberculosis.[10] Opportunistic lung infections caused by *Pneumocystis carinii* are rarely diagnosed. The etiologic agents of CAP in general and in HIV-positive patients in particular and the seroprevalence of HIV in patients with CAP is not known. We therefore determined the HIV status of patients with CAP and compared the etiologic agents and clinical and radiographic presentation in the two groups. We also looked for factors that might affect the outcome of the disease in HIV positive patients.

PATIENTS AND METHODS

110 consecutive adult patients (age > 14 years) admitted to the Black Lion Hospital with a diagnosis of CAP between August 1987 and July 1989 were included in the study. Black Lion Hospital is a tertiary care referral hospital in Addis Ababa, Ethiopia. All patients had a detailed clinical and radiologic examination according to a prepared questionnaire. Final clinical evaluation and control X-ray were done 6–8 weeks later. All patients were examined and followed-up by the author.

Sputum specimens were collected in a sterile bottle and later spread over 3 slides, 2 for gram stain and one for acid fast stain (AFS). A sputum specimen was considered adequate whenever there were > 25 pus cells/low power field (LPF). 43 patients had transthoracic needle aspiration (TTNA) of the pneumonic area as determined by clinical and radiologic means. The aspirate was then studied for gram stain, acid fast stain and culture. Only 39 out of the 43 were found adequate for interpretation. 64 and 40 patients had blood and lung aspirate (LA) culture done respectively. All patients underwent serologic testing for HIV by ELISA and those positive were later confirmed by the Western blot. Pneumococcal serotyping of sputa, sera, urine and other biologic fluids including cerebrospinal fluid (CSF), pleural fluid (PF) and lung aspirate was performed in 43, 40, 93 and 6 patients respectively. Acute and convalescent sera were studied for mycoplasma, Influenza A and B, adenovirus, Q fever and psittacosis/LGV in 104 patients each. Indirect immunoflorescence test (IFA) for Legionella was done in 40 patients but in none of the patients who were positive for HIV. The results of the etiologic agents, clinical presentation, chest X-ray findings and outcome of HIV positive and negative patients were then compared. Statistical analysis was performed using the chi-square test for proportions and the T-test to compare the means. The Fisher's exact test was employed wherever appropriate.

RESULTS

Of the 110 patients, 62 were male. The mean age was 35 years (range 14–73). 9 of the 110 patients (8%) were seropositive for HIV. The seroprevalence of HIV for the general population as determined from blood donors during the same period was 2.4% ($P < 0.05$).

Etiologic agents

The pattern of etiologic agents for the 110 patients is shown in Table 1. The majority of patients had gram-positive diplococci in their sputa (68%) and lung aspirate (69%). *Streptococcus pneumoniae* was grown from blood and lung aspirate culture in only 4 cases. The organism was sensitive to penicillin and other

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Table 1. Etiology of CAP in 100 patients

Type of test	No. of patients tested	Positive N (%)
Gram-positive diplococci		
Sputum	108	72 (68%)
Lung aspirate (LA)	39	27 (69%)
Pneumococcal Antigen		
Sputum	43	17 (42%)
Pleural fluid, CSF, LA	6	3 (50%)
Urine	93	0
Sera	40	0
Blood and LA culture		
Streptococcus pneumoniae	60	4 (6%)
Staphylococcus aureus	60	4 (6%)
Enterobacteriaceae	60	3 (5%)
Others	60	3 (5%)
Complement fixation test		
Mycoplasma	104	3 (3%)
Influenza A	104	4 (4%)
Influenza B	104	3 (3%))
Adenovirus	104	0
Q-Fever	104	0
Psittacosis/LGV	104	4 (4%)
Immunoflorescence antibody		
Legionella	40	0

CAP = community acquired pneumonia; LGV = lymphogranuloma venereum.

commonly used antibiotics. There was no case of *H. influenzae* isolated.

The etiologic agents for HIV-positive and negative patients as determined from sputum and lung aspirate gram stain is shown in Table 2. Gram positive diplococci were demonstrated in 78% and 60% of the sputa and lung aspirate of HIV-positive patients respectively. These percentages were comparable to those of HIV negative patients. Only 5 HIV-positive patients underwent TTNA, of whom 3 were positive for gram-positive diplococci. 2 had pus cells only. In the remaining 4 patients, 2 had gram positive diplococci in their sputa and the other 2 remained undiagnosed. Blood and lung aspirate culture done in 6 and 5 patients respectively grew no organism.

Table 2. Etiology of CAP in HIV-positive vs HIV-negative patients

	Sputum		Lung Aspirate	
	HIV +ve (N = 9)	HIV –ve (N = 101)	HIV +ve (N = 5)	HIV –ve (N = 34)
Gram-positive diplococci	7 (78%)	66 (66%)	3 (60%)	24 (70%)
Gram-negative	–	3	–	
Gram-positive clusters	–	3	–	
Pus cells only	–	12	2 (40%)	9 (26%)
Acid-fast	–	1	–	
Absent sputum	2 (22%)	15	–	

4 of these 6 patients had already taken antimicrobials before culture was done. None of the HIV-positive patients had evidence for other bacterial or non-bacterial pathogens. 1 patient had a co-infection with *S. pneumoniae* and Influenza A.

Clinical and chest X-ray findings

There were 38 clinical and radiological variables looked for. The results of some of these were shown in Table 3. 75% of HIV-positive patients were male and all were from the capital city, Addis Ababa. HIV-positive patients were younger ($P < 0.01$), had fewer chills and were more likely to be male and of urban residence. Amongst a total of 6 patients with associated pulmonary tuberculosis, 2 were positive for HIV ($P < 0.05$). 33% of HIV-positive patients had bilateral and 55% multilobar involvement. The corresponding figure for HIV-negative patients was 17% ($P = 0.07$) and 15% ($P < 0.01$). In 8 of the 9 patients, the chest X-ray pattern was either lobar or segmental. One patient had bilateral patchy interstitial and alveolar infiltrate. In 2 patients there was a delay in both the clinical and radiologic resolution. The

Table 3. Clinical characteristics

	HIV +ve N = 9	HIV –ve N = 101	Confidence Internal	*P*-value
Demographic characteristics				
Gender –% male	7 (77%)	55 (55%)	2.7 (0.59, 12.4)	$P = 0.15$
Age – mean (SD)	30.5 (8.1)	35.5 (15.4)		$P < 0.01$
Residence -% urban	9 (100%)	89 (88%)		$P = 0.33$
Symptoms				
Chills	4 (57%)	69 (75%)	0.41 (0.12, 1.42)	$P = 0.14$
Chest pain	7 (100%)	90 (90%)	0.47 (0.11, 2.02)	$P = 0.31$
Associated tuberculosis	2 (22%)	4 (4%)	4.95 (1.3, 18.85)	$P < 0.05$
Signs				
Consolidation (% with)	8 (87.5%)	85 (84%)	1.46 (0.2, 19.95)	$P = 0.71$
Hypotension (% with)	2 (25%)	24 (25%)	1.05 (0.23, 4.78)	$P = 0.91$
Complications				
Parapneumonic effusion	2 (22%)	12 (12%)	1.96 (0.45, 8.5)	$P = 0.32$
Meningitis/Encephalitis	1 (11%)	2 (2%)	4.46 (0.79, 25.24)	$P = 0.22$
Chest X-ray (Total = 100 patients)				
Lobar/segmental	8 (87.5%)	89 (98%)	1.07 (0.15, 7.9)	$P = 0.71$
Bronchopneumonia	0	2 (2%)		$P = 0.84$
Interstitial	1 (11%)	0 (0%)	13.6 (6.9, 26.5)	$P < 0.001$
Bilateral	3 (33%)	11 (12%)	4.05 (0.99, 16.35)	$P < 0.065$
Multilobar	5 (55%)	15 (15%)	5.63 (1.66, 19.1)	$P < 0.01$
Outcome				
Death (%)	1 (12.5)	10 (11%)	1.13 (0.15, 8.18)	$P = 0.62$

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response to treatment in these 2 patients was suboptimal initially but they later responded fully. One patient had a recurrence of the chest infiltrate 3 months after completion of treatment. Bronchoscopy did not show endobronchial lesions in this patient. 1 patient was admitted unconscious, probably due to HIV encephalopathy, and later died. CSF study in this patient was negative for both bacterial and cryptococcal meningitis. The remaining 8 patients did not fulfill the revised CDC criteria for the diagnosis of AIDS. The 2 groups were comparable in all other clinical characteristics including duration of hospital stay and outcome of treatment. The mortality in both groups was 11%.

DISCUSSION

Our study demonstrated that CAP occurred significantly more frequently in HIV positive patients and that *S. pneumoniae* was the most commonest offending pathogen. This finding is in keeping with the findings of several investigators in the past.[2,3] *Haemophilus influenzae* is another commonly described pathogen,[2,3,11] but there was no evidence for this organism in our study. It should, however, be noted that the rate of recovery of bacterial pathogens from blood and LA culture in our series was lower than in most studies. Furthermore, 38% of our patients had taken antimicrobials before they came to hospital. Inadequate culture facilities also partly account for the poor recovery. We evaluated, in the same study, the utility of sputum gram stain for the diagnosis of CAP by comparing it to LA gram stain (unpublished data). The sensitivity was 95%, specificity 55% and positive predictive value 84%. We therefore relied on sputum and lung aspirate gram stain for diagnosis in this study.

It is now an established fact that patients with AIDS have lower levels of protective antibody.[12,13] It has also been shown that natural retrovirus infection in animals is associated with impaired B-cell function.[14] Defects in both humoral and cellular immunity occur in AIDS patients.[15] However, systematic study of the stage of HIV infection as measured by CD4 lymphocyte numbers has not been performed until recently.[8] Our study demonstrates that HIV-positive patients are at risk of acquiring CAP before the development of full blown AIDS. Besides the recognition of gram positive diplococci as a major pathogen, the increased prevalence of multilobar involvement and the recurrence of an infiltrate on a chest raentgenogram are consistent with findings from other places.[2,3,13,16] Additional observations in our study include younger age group, bilateral lung involvement, associated tuberculosis and fewer chills. Our patients were also more likely to be male and of urban residence although the difference did not reach significant level. Contrary to previous studies, our patients were less bacteremic and there was no case of *H. influenzae* isolated. The outcome of the illness was unaffected by the HIV status.

HIV infection is rapidly spreading in Eastern and Central Africa, including Ethiopia. Our data suggests that the incidence of CAP is likely to increase with the increase in HIV infection. At present, apart from the increase in morbidity, the outcome of the disease appears to be unaffected by the HIV status. There are not, however, many studies that have looked into this. Earlier studies have shown that unusual pathogens such as *Pneumocystis carinii* and *Rhodococcus equi* could be important pathogens in patients with AIDS. These pathogens do not respond to the usual form of treatment for CAPs. Unusual manifestations, including recurrence of a chest infiltrate and suboptimal response to treatment, have been observed in this study and several others in the past. As we join more and more of the AIDS pandemic, the frequency of these unusual findings is likely to increase. In view of the impact of HIV infection on CAP, the possible benefits of immunization against pneumococcal infection in HIV infection may need to be considered in prospective studies.

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Susceptibility Alleles at HLA-DRB1, -DQA1, and -DQB1 Loci in Ethiopian Childhood Insulin-Dependent Diabetes Mellitus

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We report the following additional interesting details pertaining to the pattern of susceptibility alleles at HLA-DRB1, -DQA1, and -DQB1 loci in the 39 Ethiopian childhood-onset type-1 diabetic patients (and 39 controls) whose findings had been published earlier [1]. Both patients and controls were from the Shoan region (in the geographic center of Ethiopia). The controls were from the Centralized School of Nursing in Addis Ababa. The chi-squared test with Yates adjustment and Woolfe's method for the odds ratio were used in the statistical analysis.

Among the well-known susceptibility alleles at DQA1, both DQA1•03 (Arg-52) and •0501 (Arg-52) were significantly more common in patients than in controls (25 in patients versus seven in controls for •03, odds ratio 4.5, $\chi^2 = 11.3$, $P < 0.001$; 29 in patients and six in controls for •0501, odds ratio 6.6, $\chi^2 = 17.8$, $P < 0.0005$). At DQB1, the difference in the frequency of •0201 (Ala-57) and •0302 (Ala-57) was not significant between patients and controls (44 versus 31 for •0201, odds ratio 1.95, $\chi^2 = 3.7$, P NS, and ten versus three for •0302, odds ratio 3.3, $\chi^2 = 3.0$, P NS). But statistical significance was reached for DQB1•0201 + •0302 (54 in patients versus 34 in controls, odds ratio 2.9, $\chi^2 = 9.4$, $P < 0.005$) in contrast to the sum of Val-57 alleles (not shown in the Table 1) consisting of DQB1•0501, •0604, and •0605 (17 in patients versus 26 in controls, odds ratio 2.6, $\chi^2 = 2.1$, P NS). The total number of alleles was 76 at each locus in all instances. DR3/DR4 heterozygosity (seven patients, 17.9%) was confined to patients; among DQβ non-Asp-57/non-Asp-57 patients and controls, 18 patients (46.2%) and seven controls (17.9%) were Ala-57/Ala-57 ($\chi^2 = 5.9$, $P < 0.025$), 13 patients (33.3%) and 12 controls (30.8%) were Ala-57/Val-57, and one patient and three controls were Val-57/Val-57. As shown in Table 1, DRB1•0301 was in linkage disequilibrium with DQB1•0201 and DQA1•0501; DRB1•04 (•0405 being the most frequent subtype in our patients) was in linkage disequilibrium with DQB1•0302 (Ala-57) or •0201 and DQA1•03. Only ten (40%) of 25 DRB1•04 alleles were found in association with DQB1•0302 (DQw8) in our patients in contrast to the finding of over 90% in Caucasoids [2]. Fourteen of the remaining 15 DRB1•04 alleles in the patients (all subtype) and all of the DRB1•0301 (DR3) were associated with DQB1•0201 (DQw2). DRB1•07 (DR7) was in linkage disequilibrium with DQB1•0201 and DQA1•0201 (non-Arg-52) and was significantly more frequent in controls than in patients.

On the other hand, DR1, DR6, and DRw10, which were not significantly associated with diabetes, were in linkage disequilibrium with DQβ Val-57 and DQα non-Arg-52 encoding alleles (not shown in Table 1).

The restriction of significant diabetes susceptibility to DQβ Ala-57 within the non-Asp-57 group in our study agrees with the results of studies of in Caucasoids by Baisch et al. [3] and Vallet-Collom et al. [4], while the higher frequency of DRB1•0405 among DRB1•04 subtypes, which is generally considered rare, is similar to the Sudanese and Zimbabwean (and Mediterranean) par-

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TABLE 1 Linkage disequilibrium pattern of DRB1*0301, *04, and *07 alleles with alleles at DQB1 and DQA1 in 39 patients and 39 controls[a] and association with insulin-dependent diabetes mellitus[b]

DRB1	(DR)	DQB1	DQA1	Patients		Controls		OR	χ^2	P
				n	%	n	%			
*0301	(3 DRw17)	*0201(A)	*0501(R)	26	33.3	7	9.0	4.8	12.5	<0.0005
*0401	(4 Dw4)	*0301(D)	*03(R)	0	0	1	1.3	0.3	1.0	NS
*0401		*0302(A)	*03	3	3.8	2	2.6			
*0403	(4 Dw13)	*0302	*03	0	0	1	1.3			
*0404	(4 Dw14)	*0302	*03	1	1.3	0	0	3.0	1.0	NS
*0404		*0402(D)	*03	1	1.3	0	0			
*0404		*0402(D)	*03	1	1.3	0	0			
*0405	(4 Dw15)	*0201(A)	*03	14	17.9	3	3.8	4.9	6.6	<0.025
*0405		*0302(A)	*03	6	7.7	0	0	14.0	4.5	<0.05
X	(4)	*0402(D)	*0401(R)	1	1.3	0	0			
*07	(7)	*0201(A)	*0201(H)	4	5.1	20	25.6	0.2	11.1	<0.001
*07		*03032(D)	*0201	0		2	2.5			

[a] The total number of alleles is 78 (39 × 2) for patients and controls, respectively.

[b] DR, DR antigens and subtypes corresponding to the respective SSO specificities; numbers under patients and controls indicate number of alleles and not number of patients; OR, odds ratio; *, SSO specificity numbers; A and D in the DQB1 column, alanine and aspartic acid at position 57, respectively; R in the DAQ1 column, arginine at position 52; and X, unspecified DR4.

terns. The linkage of DRB1*0405 with DQB1*0201, however, was found in Ethiopians and Sudanese, but not in Zimbabweans [5, 6]. Furthermore, unlike in other black populations [2], DRB1*07 (DR7) does not show a significant association with insulin-dependent diabetes mellitus in Ethiopians [7]. This could be related to its linkage with DQA1*0201 (His-52) in this population as in Caucasoids.

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The Etiology of Community Acquired Pneumonia in Adults in AddisAbaba

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Summary

Over a two year period, we prospectively studied 110 adult patients with Community Acquired Pneumonia (CAP) who presented to the Black Lion Hospital, Addis Ababa, Ethiopia. Pneumococcal infection was diagnosed in 41% by the detection of pneumococcal antigen in sputum and other biologic fluids; in 72% by Gram stain of Lung Aspirate (LA) and in 67.5% by Gram stain of sputum. Blood and Lung Aspirate culture grew Streptococcus Pneumoniae in 4 cases (6%), Staphylococcus Aureus in 4 (6%), Enterobacteriacae in 3(5%), Pseudomonas, Klebsiella Pneumoniae and Strep. Viridans in one case each. Other non-bacterial causes included Mycoplasma Pneumoniae in 4 (4%) Influenza A in 4 (4%), Influenza B in 3 (3%) and Psittacosis/LGV in a 4 (4%). There was no case of Legionnaires disease. 39% had taken treatment before coming to hospital. The mortality was 11%. The study showed that antibiotic treatment during the preceding 36 hours did not affect the outcome of the Gram stain.

Key Words: *Etiology, Pneumococcal infection.*

Résumé

Nous avons fait une étude prospective sur 2 ans de 110 malades presentant une pneumonie acquise en milieu urbain et ayant consulté à l'Hôpital 'Black Lion'. à Addis Abeba, Ethiopie. Une infection pneumoncoccique fut diagnostiquée dans 41% des cas par la detection d' antigéne pneumococcique dans les crachats et autres liquides biologiques, dans 72% par la coloration de gram des produits d'aspiration pulmonaire et dans 67.5% des cas par la coloration de Gram des crachats.

L'hémoculture et la culture des produits d'aspiration pulmonaire révélèrent du Streptocoque Pneumoniae dans 4 cas (6%), Staphylocoque doré dans 4 cas (6%), Enterobacter dans 3 cas (5%), Pseudomonas, Klebsiella Pneumoniae et Streptocoque Viridans 1 cas de chaque.

D'autres causes non bacteriennes comprenaient: Mycoplasme Pneumoniae dans 4 cas (4%), Influenzavirus de type A dans 4 cas (4%), Influenzavirus de type B dans 3 cas (3%), Psittacose/LGV dans 4 cas (4%). Nous n'avons pas trouvé de case de legionellose.

Trente neuf pour cent des malades ont eu un traitment avant de venir en consultation a l'hôpital. La mortalité fut de 11%. Notre étude montre qu'une antibiotherapie pendant les 36 heures avant l'examen, n'affecte pas les resultats de la coloration de Gram.

Correspondence

Introduction

Community acquired Pneumonia (CAP) is the second most common cause of adult medical admission in Addis Ababa with a mortality of 17%[1]. In many parts of the tropics including Nigeria and Zambia[2,3,4,5], it is the commonest cause of admission to hospital medical wards. Globally, CAP is a major medical problem despite the introduction of antibiotics. Before the advent of antibiotic therapy, pneumonococcus caused more than 95% of lobar pneumonia[6]. Recent studies largely from Europe and North America have shown a marked variation in the prevalence of the isolated pathogens with pneumococci accounting for 11.5% to 76% of the isolates[7]. Strep. pneumoniae is the usual cause of lobar pneumonia in Africa[8]. However, between 10% and 31% of patients with lobar pneumonia do not respond promptly to penicillin. This finding has suggested that other micro-organisms may also be responsible for the causation of CAP. It is possible that this major global shift in the etiology of CAP might have affected Africa too.

Mycoplasma pneumoniae has been reported from Nigeria, South Africa and Egypt. The evidence from Tropical Africa is scanty if any. The same is true for viral etiologies and legionnaires disease. In countries where the diagnosis of CAP rarely exceeds the use of sputum gram stain, it is imperative to know the pattern of the etiologic agents in order to reasonably and adequately interpret a gram stain and initiate appropriate treatment. We have thus performed a clinical and laboratory study of the cause of CAP in Addis Ababa. We have also evaluated the effect of prior antibiotics therapy on the accuracy of the Gram stain of Lung Aspirate.

Patients and Methods

One hundred and ten adult presenting consecutively to the Black Lion University Teaching Hospital between 1987 and 1989 with clinical and radiologic features consistent with CAP were included in the study. All patients were examined and followed by the author.

Microbiologic Method

Sputa specimen are collected in a sterile bottle and immediately spread over 3 slides - two for Gram stain and one for Acid fast stain (AFS). Transthoracic needle Aspiration (TTNA) of the pneumonic area as determined by clinical and radiologic means was performed in 43

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spinal needle as described by Davidson[9]. The aspirate was then spread over two slides. Both sputa and LA gram stain were considered acceptable for interpretation whenever there were more than 25 pus cells per low power field. The slides were examined by two observers, the author and a bacteriologist. The sensitivity, specificity and positive predictive value of the sputum Gram stain was determined by comparing it to the Gram stain of the LA.

Blood and Lung Aspirate cultures for the common bacterial pathogens were done in 63 and 40 cases respectively according to standard laboratory methods.

Indirect fluorescent antibody staining (IFA) for legionella was done in 40 specimen.

Countercurrent Immunoelectrophoresis (CIE) and Serological tests

All specimens of purulent sputa, acute and convalescent sera, urine and other biologic fluids (CSF, pleural fluid and Lung Aspirate) were collected on admission and were stored at -20C until they were transported to Great Britain by air, but temporary thawing was inevitable. On arrival they were stored at -40C until further testing. It took several months before it was tested. All available samples were tested for pneumococcal polysaccaride antigen by the CIE method using pneumococcal omniserum as described by Tugwell and Greewood[8]. Pneumococcal antigen sero-typing was not done.

All acute and convalescent sera whenever available were tested for Mycoplasma. Influenzae A and B, adenovirus, Q. fever and psittacosis/LGV by the complement fixation test (CFT) at the Royal Victoria Infirmary, Department of Virology, a WHO collaborating centre for Reference and research on rapid laboratory viral diagnosis.

Criteria for the diagnosis of Infection

A diagnosis was considered to be "definite" if the pathogen was isolated from a blood or LA culture; if the organisms were demonstrated on LA gram stain; if pneumococcal antigen was detected by CIE in any of the sputa, sera, urine or other biologic fluids and if there was a titre of >/ 1/160 or a four fold or greater rise in titre in any of the serological tests. A diagnosis was considered "probable" if the gram stain of the sputa demonstrated single or predominantly single organism.

A history of antimicrobial use prior to coming to hospital including dose and type was carefully documented, although in some instances patients didn't know the name or the dose.

Results

Of the 110 patients, 62 were male and the mean age was 35 years (range 14 — 75 years). 38 patients (39%) had received antibiotic before they arrived to hospital. 35% had underlying illness of which 21% were related to chronic chest diseases. Complications due to TTNA included one major pneumothorax and 2 minor pneumothoraces. 3 patients had minor haemoptysis which resolved spontaneously.

Bacterial Causes

Pneumococcal infection was diagnosed in 28 of 39 patients (72%) by LA gram stain. (Table 1). The gram stain showed purely gram positive diplococci and was therefore highly diagnostic. 72 of 108 patients (67.5%) demonstrated either all or predominant gram positive diplococci on sputum gram stain. 12 patients had mixed organisms, 3 had predominant gram negative rods and in another 3 gram positive in clusters. In 17 patients the sputum was inadequate to make any bacteriologic diagnosis. The accuracy of the sputum gram stain in predicting the etiology of the pneumonia was determined by comparing it to the findings of the Lung Aspirate (Table II). The sensitivity of the sputum gram stain was 93% and the specificity 55%. The positive predictive value was 84%. The interobserver variability in the interpretation of the Gram stain was 5%.

Strep. Pneumoniae was grown in 4 out of 63 (6.3%) blood and LA culture.

Table 1 Results of Gram stain of sputa and Lung Aspirate in 110 and 39 patients

	Sputa		Lung Aspirate	
	No.	%	No.	%
Gram positive diplococci	72	67.5	28	71.8
Mixed organisms	12	11	—	—
Gram negative rods	3	3	1	2
Gram positive clusters	3	3	—	—
No bacteria/pus cells only	—	—	10	26
Scanty sputum	17	15	—	—
Mycobacterium TB	1	1	—	—
Total	108	100	39	100

Table 2 Sputum gram stain by Lung Aspirate gram stain

Sputum	Gram positive seen	Gram positive not seen	Total
Gram positive seen	26	5	31
Gram positive not seen	2	6	8
Total	28	11	39

Sputum Gram Stain:
Sensitivity = 26/28 = 92.8% Specificity = 6/11 = 54.5
Positive predictive value = 26/31 = 84%

Pneumonococcal antigen was detected in 17 of the 43 sputa specimen (41%) and in none of the 40 sera and 93

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urine specimen (Table III). It was also detected in 3 of the 6 (50%) CSF, pleural fluid and LA samples.

Table 3 Results of pneumococcal antigen and legionella

Titre	Pneumococcal antigen				Legionella
	Sputum	Serum	Urine	Others	
Positive	17	0	0	3 CSF PF* LA**	0
Negative	26	40	93	3 (PF)	40
Total	43	40	93	6	40

*PF = pleural fluid **LA = Lung Aspirate

Other bacteria grown in blood culture include *Staph Aureus* in 4 patients, and Enterobacteriacae in another 3 patients, Strep viridans and Pseudomonas in one each. Klebsiella pneumonia was grown in one patient from both blood and LA culture in one patient.

There was no case of legionella species detected by IFA. There were two cases of tuberculous pneumonia. One of them expired immediately after admission and the diagnosis was made postmortem. Five more patients with pneumonia had co-infection with tuberculosis.

Non-bacterial causes (Table IV)

(a) Viral. Q fever (table IV).

Four patients for influenza A and 3 patients for influenza B had a titre of >/ 1/160. 2 more patients for influenza A and for influenza B had borderline results (titre >/1/80). It was interesting to note that 3 of the 6 patients with influenza A and one with influenza B had gram positive diplococci in the gram stain of both LA and sputum, suggesting a double infection. In two patients with influenza A and 3 with influenza B, the sputum gram stain showed either scanty or absent organisms. There was no case of adenovirus or Q fever pneumonia.

Table 4 Etiology of CAP — Non-bacterial Causes

Type of pathogen	Titre				
	>/1/160 or four fold rise	Borderline (1/80)	</1/80	Negative (<1/10)	Total
Influenza A	4	2	60	38	104
Influenza B	3	3	44	40	90
Adenovirus	0	—	30	74	104
Q. fever	0	—	21	83	104
Mycoplasma	3	1	83	17	104
Psittacosis/LGV	4	—	48	51	103

(b) Mycoplasma, psittacosis/LGV

Mycoplasma Pneumoniae was diagnosed in 3 patients. There was one borderline case (titre 10:40). One of these 4 patients grew strep. pneumoniae in blood culture and therefore had a double infection. In 2 patients - the sputum gram stain demonstrated scanty and mixed organisms.

Four patients had a titre >/1/320 for psittacosis/LGV. One of these was positive for gram positive diplococci in LA gram stain. The sputa gram stain were inconclusive in two.

Effect of prior antibiotic therapy

Five of the 10 patients (50%) with negative LA gram stain had taken antimicrobial for a duration of /< 36 hrs. prior to coming to hospital. On the other hand, 21 of the 29 patients (71%) with positive LA gram stain had taken antibiotics used were procaine penicillin G, oral tetracycline, ampicilline and cotrimexazole.

Discussion

Bacteriologic diagnosis of pneumococcal pneumonia continues to present difficulties and can be made only by blood culture which is positive in less than 1/3 of the cases. As a result, several investigative methods including CIE. Latex agglutination, CoAg, Blood culture, Lung aspirate Culture and stain, sputum gram stain and serologic methods are employed to determine the infective agent. Undoubtedly, the problem of diagnosis in Africa is tremendous.

In this study, LA gram stain demonstrated gram positive diplococci in 72% and it was the most sensitive and specific diagnostic test. This probably represents the true prevalence of pneumococcal infection amongst our patients. It is also interesting to note that comparable proportion of patients (67.5%) demonstrated diplococci in the sputum gram stain. The sputum gram stain was highly sensitive (93%) and had a remarkable positive predictive value (84%). In developing countries, where diagnostic facilities rarely exceed the use of sputum gram stain, I suggest that sputum gram stain should be used prudently for the diagnosis of CAP.

The results of blood culture, as is usually the case, was disappointing. This is especially so in developing countries where culture facilities are not only inadequate but also unavailable. The use of antibiotics prior to coming to hospital adds to the enormity of this problem.

The yields of pneumococcal antigen in the sputa of our patients was 41%. This figure is relatively small compared to findings from Nigeria[4] and London[10]. Besides, pneumococcal antigen was not detected in both the sera and urine of our patients. This was probably due to the inadequate handling of the samples. (Specimens were kept for several months before testing). Technical difficulties in the methodology could partly account for the low yield too.

Strep. Pneumonia accounted for 50% and 64% of the etiology of lobar pneumonia in Nigeria[4,8]. Data from 6

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separate studies[11] have shown that bacterial causes of CAP accounted for 47% to 74%, of which strep. pneumoniacae was responsible in 62% to 94%. Our study conforms with the results of these studies.

The prevalence of non-pneumococcal bacterial pneumonias in Tropical Africa is not well documented. Our study showed 4 cases of *Staph. Aureus* 3 cases of Enterobacteriacae, and one of klebsiella, pseudomonas and *S. Viridans*. There was no case of Haemophilus influenzae.

Legionella pneumonia accounts for between 2 to 20%[7,12] of all pneumonias in the temperate climates. It appears the growth requirement of this bacteria (> 25 C) is better met by the weather in the tropics[13]. However, there has been no report of legionella from Africa. In this study too, there was no evidence for legionella pneumonia. Despite this , we have to continue to search for this pathogen.

Mycoplasma pneumonia has been reported from Nigeria (17%), Egypt and South Africa. The prevalence in our series was 4%. It is probable that this organism will continue to stand out as an important etiologic agent in the future. The presence of associated pneumococcal infection in 50% of the cases was consistent with observations from Nigeria[4]. None of the patients with M. pneumoniae had non-respiratory systemic manifestation or a difference in the clinical and radiologic presentation compared to cases of pneumococcal pneumonia. The finding of scanty or absent organisms in an adequate sputum sample should therefore lead physicians to suspect atypical pneumonias including mycoplasma pneumonia. Our study also confirmed that pneumonia caused by psittacosis/LGV, though rare, is prevalent in this country. To our knowledge, this is the first report from Africa.

Two patients had tuberculous pneumonia, of which one died. Given the high prevalence of tuberculosis in developing countries, the prevalence of TB pneumonia is low in our series. This is probably not surprising because tuberculous pneumonia occurs as a primary infection while almost all adult pneumonia in developing countries are due to reactivation.

Our study also showed that antibiotic treatment during the preceding 36 hrs did not affect the outcome of the gram stain. The dose however, used by most patients was small. It is probable that the outcome of LA and blood culture will be affected by prior use of antibiotic. It is therefore encouraging to most physicians to use the gram stain regardless of a history of prior use of antibiotics.

Acknowledgements

The author wishes to thank Ato Shiferaw Terefe and Ato Zerga Biza both from the Department of Microbiology, Addis Ababa University for the Gram stain and AFS of Sputa and LA.

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CASE REPORT

ADULT PNEUMOCOCCAL MENINGITIS WITH NO INFLAMMATORY CELLS IN THE CSF

Guta Zenebe, MD[1]

ABSTRACT: *An 18 year old male patient was admitted to the Medical Intensive Care Unit of the Tikur Anbessa Hospital in October 1988. He was in deep coma and had findings consistent with a left lobar pneumonia. Lumbar puncture revealed a turbid CSF. Gram stain on both centrifuged and uncentrifuged specimens revealed plenty of gram positive diplococci with no single inflammatory cell. CSF culture proved the organism to be* Streptococcus pneumoniae. *The patient was put on combination of high doses of intravenous sodium-penicillin and chloramphenicol with all appropriate supportive management. However, the patient died only after three hours of stay in the hospital. The condition of diminished to absent inflammatory response in the CSF associated with pneumococcal meningitis in adults is discussed with a review of the literature.*

INTRODUCTION

Mortality from pneumococcal meningitis remains as high as 20 to 30% despite early treatment with potent antibiotics (1). The mortality becomes even higher when there is a history of short duration of illness, altered state of consciousness at presentation and a concomitant pneumonia. High mortality rate is positively correlated with increased levels of CSF fibrinogen degradation product (FDP), lactate, protein, bacterial load, pneumococcal polysacharide antigen titre, reduction or absence of CSF white cell count and low levels of CSF glucose (1–5).

CASE REPORT

An 18 year old male patient from Addis Abeba was admitted in deep coma to the Medical Intensive Care Unit of Tikur Anbessa Hospital in October 1988. Proper history could not be obtained as none of the persons who accompanied the patient knew enough about him. He was reportedly well three days prior to his hospital admission.

Physical examination revealed a critically

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sick looking patient in deep coma. The blood pressure was 100/70 mmHg, the pulse 132/min, respiratory rate of 40/min and temperature 39°C.

He was not pale or icteric. The tongue was dry and coated. The neck was stiff. There was no sign of trauma to the head. He had bronchial breath sound and pleural friction rub on the mid-zone of the left lung posteriorly. There were coarse crepitations bilaterally in the mid and lower lung zones.

The jugular venous pressure was flat, with normal cardiac sounds and there was no murmur or gallop rhythm. His abdomen was flat and soft with no palpable mass or organomegaly. The pupils were of normal size and reactive to light. The Doll's eye movement and ciliospinal reflexes were preserved. The muscle tone was diffusely spastic. The deep tender reflexes were brisk. The plantars were upgoing bilaterally. He had bilateral sustained clonus. The fundi were normal.

Laboratory results revealed haemoglobin of 13.5 gm%, white blood cell count of 3,000/ mm^3 and random blood glucose by dextrostic was within the range of 90–130 mg%. Blood film for haemoparasites was negative. Urinalysis was remarkable for proteinuria of plus two.

A lumbar puncture revealed a turbid CSF which came under normal pressure. The CSF analysis showed no inflammatory cells, glucose of 4mg% and protein of 300mg%. A wet smear of the CSF revealed numerous bacteria without white cells. A Gram stain showed sheets of gram positive diplococci (Figure 1). The CSF culture proved the organism to be *Streptococcus pneumonia*. The chest X-ray showed a left mid-zone homogeneous opacity with air bronchogram.

A diagnosis of pneumococcal meningitis with lobar pneumonia was made. Appropriate supportive management, high doses of intravenous penicillin 3 mega units every three hours and chloramphenicol 1 gm every six hours were initiated. Despite these measures, the patient deteriorated and subsequently developed signs of mid-brain dysfunction and expired three hours after admission.

DISCUSSION

The observation of 20–30% mortality from pneumococcal meningitis in developing countries and around 50% in the less privileged societies within developing countries calls attention for further evaluation and analysis of this problem. This high mortality occurs in spite of availability of potent antibiotics. Apart from lack of accessible health services with qualified health professionals in many African countries black patients seem to be susceptible to pneumococcal infections. The disease is also believed to be caused by virulent organisms (1,2).

The patient had several of the known risk factors and poor prognostic signs. He came with an apparently short duration of illness in a comatose state with concomitant pneumonia. His CSF analysis showed no inflammatory cells with high bacterial load, high protein and low glucose.

It was cited by some authors that rapidly progressive clinical course over 24 hr period ending up with the demise of the patient was an occasional encounter. This rapidly advancing clinical course was attributed to mid-brain compression (3–5). The concomitant presence of pneumonia may imply that the patient acquired meningitis following a haematogenous spread from a primary focus in the lung. The higher mortality rate of pneumococcal meningitis when associated with pneumonia is presumed to be due to the hypoxic state

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produced by alveolar hypoperfusion leading to a reduction in the oxygen supply of the brain favouring anaerobic glycolysis. This was indirectly measured by increased lactate level in CSF which is also known to be related to increased mortality (11).

The absence of any inflammatory cell either in the wet smear or Gram's stain of both centrifuged and uncentrifuged specimen which were teeming with bacteria is quite interesting. The turbidity was due to the bacteria and the high protein in the CSF. This type of response has not been described in other types of bacterial meningitis and why it occurs particularly in pneumococcal meningitis is not known. It was speculated that reduction or absence of CSF white cell count results from the presence of a potent leucocidin in the CSF. However, leucocidin was also found in other types of bacterial meningitis (4).

Fulminant pneumococcal infection in an asplenic host has been encountered where the dual function of the clearance of foreign particles from the circulation by phagocytosis and elaboration of early appearing antibody by the spleen is impaired. A similar situation is frequently observed in sickle cell disease (6,7).

The relatively high mortality in blacks with pneumococcal meningitis led to the belief that genetic factors may play a role (7). HLA association was also documented as a contributing factor (8). High mortality (17.3%) rates were observed by Quaade et al (2) even in settings which provided early diagnosis and treatment.

Weinstein (9), in his 30 years of experience had come across six immunocompetent patients with pneumococcal meningitis with absent CSF inflammatory response. Except for one patient who subsequently developed significant leucocytosis in the CSF and recovered; the rest expired shortly after initiation of treatment.

Although death is at least five times more likely in a patient with pneumococcal than meningococcal meningitis, factors contributing to the high mortality rate have not been identified (5,10).

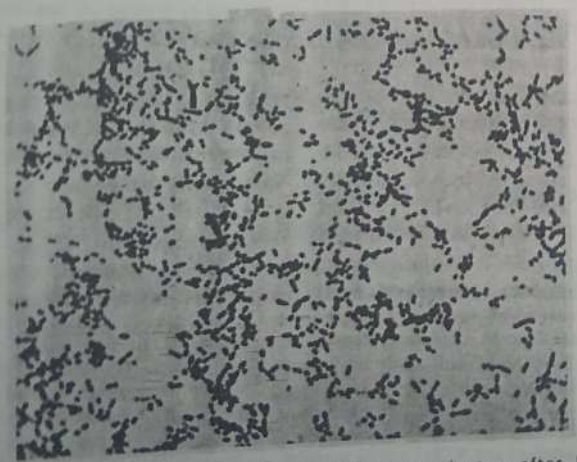


Figure 1. Gram stain of uncentrifuged CSF few minutes after lumbar puncture showing multiple Gram positive diplococci without inflammatory cells. 359

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while being treated with a 10-day course of clarithromycin for otitis media. *Clostridium difficile* toxin B was identified by tissue culture assay. Pseudomembranous enterocolitis was suspected, clarithromycin was stopped, and vancomycin was given orally at a dose of 150 mg four times daily (50 mg/kg per day) for 7 days. Diarrhoea improved within 2 days and no relapse was observed within 4 weeks.

It is important to note that clarithromycin can trigger pseudomembranous enterocolitis because this macrolide is increasingly used in immunocompromised patients, including HIV-infected subjects, for treatment of non-tuberculous mycobacteriosis.[2] Diarrhoea occurs frequently in HIV-infected patients, and the cause often remains unknown.[3] Patients with HIV infection and clarithromycin treatment must therefore be monitored for *Clostridium difficile* and its toxins in the stool as soon as diarrhoea develops.

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Successful in-vitro cultivation of *Borrelia recurrentis*

SIR—Sundnes and Tekle Haimanot report (Nov 13, p 1213) louse-borne relapsing fever in Ethiopia. We have successfully cultivated a strain of *Borrelia recurrentis* isolated from a patient with louse-borne relapsing fever in Addis Ababa.

A 24-year-old seaman who had been resident in Addis Ababa for two months was admitted to the Black Lion Hospital, as part of a study of louse-borne relapsing fever. He gave a 3-day history of fever, chills, headache, dizziness, cough, chest pain, musculoskeletal aches, abdominal pain, anorexia, nausea, and vomiting. He had 14 000 spirochaetes per µL in blood. His serum was cultured in Kelly's[1] growth medium for *B recurrentis* and in BSK II medium, for growth of Lyme borreliae.[2] Cultures were incubated at 35°C and examined by dark-field microscopy. BSK II medium yielded an isolate that has now survived eighteen in vitro passages, producing a growth yield of 10^7 organisms per mL with a generation time of 8–9 h. Although Obermeier first described *B recurrentis* in 1867, attempts to maintain this spirochaete in culture have failed.[1,3]

Pulsed-field electrophoresis of the isolate showed a chromosome of about 1 megabase and six plasmids of 184·3, 54·56, 46, 39·6, 30·2, and a faint band at 15·6 kilobase. This pattern was distinct from that of other borrelial species tested including *B hermsii*, *B turicatae*, and *B burgdorferi* (data not shown). Similarly, the Coomassie blue stained protein profile of the strain was distinct from that of other borreliae tested with a major band detected at 47 kDa (figure). Serum samples from 16 patients with louse-borne relapsing fever were highly reactive with an isolate of both *B recurrentis* and *B burgdorferi* when tested by immunoblotting. These samples would have been falsely reported as positive in Lyme borreliosis serological tests with *B burgdorferi* antigens.[4] This finding should be considered when investigating patients from relapsing fever endemic regions for Lyme borreliosis (see Fry and Kenny, Sept 11, p 689).

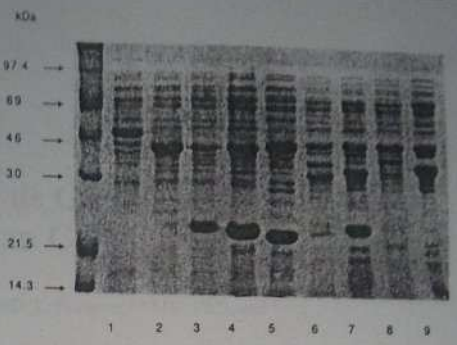


Figure: **Coomassie blue stained SDS PAGE gel**

Lane 1 = *B recurrentis*; 2 = *B hermsii* strain HS1; 3 = *B hermsii* strain Man1; 4 = *B hermsii* strain Con1; 5 = *B turicatae*; 6 = *B burgdorferi* strain B31; 7 = *B garinii*; 8 = *B burgdorferi* strain V5461; 9 = *B burgdorferi* UK isolate.

This strain was highly susceptible to penicillin (minimum inhibitory concentration [MIC] 0·2 µg/mL; minimum bactericidal concentration [MBC] 0·75 µg/mL), tetracycline (MIC and MBC 0·06 µg/mL), and erythromycin (MIC 0·04 µg/mL; MBC ≤0·02 µg/mL). This finding contrasts with values for tetracycline and tick-borne relapsing fever strains which gave MICs of 1–4 µg/mL (three *B hermsii* and one *B turicatae*), whereas *B burgdorferi* gave MICs of 0·12–0·5 µg/mL for tetracycline (low and high passage strain B31); MBC values ranged from 2–4 µg/mL for tick-borne relapsing fever and 0·25 to 1 µg/mL for *B burgdorferi*. The exquisite antibiotic susceptibility of this isolate supports the use of single dose treatment of louse-borne relapsing fever.

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Chronic fatigue syndrome or myalgic encephalitis

SIR—Although we agree with David and Wessely (Nov 13, p 1247) that the term benign myalgic encephalomyelitis (ME) is no longer accurate, we do not share their enthusiasm for the suggested replacement, chronic fatigue syndrome (CFS). CFS means different things in different countries. In Australia, it is synonymous with ME; in America, it covers several disorders, including ME, chronic fatigue and immune dysfunction syndrome, giardiasis, fibromyalgia, and masked depression, whereas in the UK it has become a dustbin diagnosis for all cases of unexplained chronic fatigue.

In a sense, ME is to CFS what migraine is to headaches: it is much more disabling, it is aetiologically more complex, and it is often more difficult to treat. The confusion between ME and

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Blood Pressure Patterns and its Correlates in Schoolchildren of an Ethiopian Community

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Summary

This study was undertaken to define blood pressure pattern in a sample of schoolchildren in an Ethiopian rural community. All schoolchildren below the age of 15 years in Butajira town formed the study population. Blood pressure measurement which was made according to the recommendations of the American Task Force on blood pressure control in children was found to be unimodal with almost symmetrical distribution. The mean systolic and mean diastolic blood pressure for both sexes combined was 106 ± 14.8 and 70.5 ± 4.5 mmHg, respectively. The mean systolic and mean diastolic blood pressures increased with age in both boys ($P < 0.05$) and girls ($P < 0.01$). Girls had significantly higher mean systolic and mean diastolic blood pressures than boys ($P < 0.001$). Similarly, girls had significantly higher pulse rate and arm-girth than boys which may partly explain the higher mean pressures in the girls. A multiple regression analysis showed that height, body mass index, arm-girth, and heart rate were significant in explaining the variations in systolic and diastolic blood pressures. In conclusion, except for the higher blood pressure in girls, our findings are similar to the majority of the reports from Africa and other parts of the world.

Introduction

Information on blood pressure and hypertension in Ethiopia in general is scanty. The mean blood pressure values recorded for rural adult Ethiopians according to the few studies available is one of the lowest.[1,2] Regional differences in children's blood pressure levels have also been postulated by some investigators.[3,4] However, data on blood pressure levels in Ethiopian children at various ages is not available for comparison.

The present study was undertaken to provide basic information on blood pressure patterns and its correlates in schoolchildren in a typical Ethiopian rural town.

Materials and Methods

Population

The study was conducted between February and June 1990 among schoolchildren below 15 years of age at Butajira, a rural town 130 km south of the national capital, Addis Ababa. The town has a total population of 12 600, the great majority of whom are poor and live on small scale trade and subsistence farming.[5] There are two elementary schools and a health center which serves the town and the sub-district of Meskan and Mareko (population 182 000). About 60 per cent of children of school age in the town attended school. The majority of the students had no prior contact with health personnel and detailed information and demonstration was done to reduce their apprehension. Eight trained lay-health workers recruited locally went into each class room explaining and demonstrating the procedure. Of the 2058 eligible students 1850 (90 per cent) participated in the study. Two-hundred-and-eight students refused to participate in the study without specifying their reasons.

Measurement

Students were examined in the presence of their classmates after 10 min of rest in a classroom provided by the school. Girls and boys were examined separately. Blood pressure was measured with a mercury sphygmomanometer on right arm with subject seated and arm extended over a coach or a desk at heart level. Cuffs of different sizes were available. A cuff bladder long enough to surround most of the circumference of the arm and wide enough to cover at least two-thirds of the upper arm was used. A single observer, made all the readings to avoid inter-observer variation. Systolic

Acknowledgements

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TABLE 1

Mean standard deviation of systolic blood pressure in 1850 schoolchildren 7 to 14 years old (Butajira Southern Shewa, 1990)

Age (years)	Boys mean ± SD (range)	No. of boys	Girls mean ± SD (range)	No. of girls	Total no.	*P* value
7	96.64 ± 12.62 (76–120)	25	103.50 ± 12.21 (80–120)	20	45	
8	99.79 ± 13.20 (70–130)	65	104.41 ± 16.06 (70–150)	64	129	
9	102.54 ± 12.88 (80–130)	96	105.07 ± 13.05 (80–130)	73	169	
10	101.77 ± 12.25 (70–140)	212	109.92 ± 13.35 (70–154)	148	360	
11	102.86 ± 15.46 (60–140)	140	112.75 ± 12.72 (80–140)	94	234	
12	104.53 ± 13.68 (66–140)	229	113.43 ± 15.09 (80–150)	126	355	
13	104.35 ± 14.27 (70–140)	158	111.35 ± 15.27 (80–150)	117	275	
14	104.11 ± 15.50 (70–170)	172	111.41 ± 14.43 (82–140)	111	283	
Total	103.06 ± 13.99 (60–170)	1097	110.19 ± 14.89 (70–154)	753	1850	<0.001

and diastolic blood pressure values were read to the nearest 2 mmHg. First and fourth Korotkoff sounds were recorded. Attempts were made to avoid digit preferences. The average of two casual blood pressure readings were recorded for analysis.

Heart rate was counted and cardiovascular examination was done before blood pressure measurements were made. Weight, height and arm-girth were measured using standard techniques.[6]

Statistical methods

Statistical significance for analysis of differences was settled at the level = 0.05. Two-tailed tests of statistical significance have been used throughout.

Results

Ninety per cent of the entire schoolchildren at the schools below the age of 15 years at Butajira were studied (Tables 1 and 2). They had a mean age of 11.3 ± 1.9 years. Fewer girls with a female to male ratio of 1:1.5 attended school as in other rural towns in Ethiopia.[7]

The combined mean systolic and diastolic blood pressures for both the sexes were 106.0 ± 14.8 and 70.5 ± 4.5 mmHg, respectively. The girls had a mean systolic blood pressure of 110.2 ± 14.9 and a mean diastolic blood pressure of 72.0 ± 12.1. The blood pressure levels for the boys were lower with the mean systolic and diastolic values of 103.1 ± 13.0 and 69.1 ± 11.4, respectively. Tables 1 and 2 also show the mean systolic and mean diastolic blood pressure according to age and sex. The mean systolic and mean diastolic blood pressure increased significantly with age in both boys ($P < 0.05$) and girls ($P < 0.01$).

The mean blood pressure was unimodal and almost symmetrically distributed except for some digit preferences (Figs 1 and 2).

Relations with other variables measured

The multiple linear regression analysis of systolic and of diastolic blood pressure on height, body mass index weight (kg)/height (m), pulse rate, arm-girth, and age is shown on Table 3. Height, body mass index, pulse rate, and arm-girth correlated positively with mean blood pressure values. When the other variables were taken into consideration, age was not significantly associated with mean systolic and mean diastolic pressures. Height, weight and arm-girth increased significantly with age in both sexes (Table 4). However, the girls had significantly higher arm-girth and pulse rate than boys ($P < 0.001$). The regressors, as shown by the square of multiple correlation coefficients, accounted for 16 per cent of variation in systolic blood pressure and 7 per cent of variation in diastolic blood pressure.

Discussion

The age and sex distribution seen in this report is typical of schoolchildren in the Ethiopian countryside.[7] Height, relative weight, and arm-girth correlated with blood pressure independent of age. However, age lost its significance after controlling for

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TABLE 2

Mean standard deviation and range of diastolic blood pressure (Phase IV) in 1850 schoolchildren 7–14 years old (Butjira Southern Shewa, 1990)

Age (years)	Boys mean ± SD (range)	No. of boys	Girls mean ± SD (range)	No. of girls	Total no.	*P* value
7	60.96 ± 9.04 (44–80)	25	67.50 ± 8.10 (50–80)	20	45	
8	69.14 ± 10.58 (40–90)	65	67.94 ± 11.12 (40–90)	64	129	
9	70.40 ± 9.67 (50–90)	96	71.70 ± 10.69 (40–100)	73	169	
10	69.83 ± 10.14 (44–94)	212	72.23 ± 11.92 (40–100)	148	360	
11	70.86 ± 11.48 (38–90)	140	74.21 ± 9.89 (50–96)	94	234	
12	71.00 ± 12.23 (40–110)	229	73.30 ± 11.32 (40–106)	126	355	
13	68.03 ± 12.76 (30–100)	158	72.48 ± 11.32 (40–100)	117	275	
14	68.13 ± 11.40 (38–110)	172	70.97 ± 12.10 (40–100)	111	283	
Total	69.13 ± 11.44 (30–110)	1097	71.97 ± 12.10 (40–106)	753	1850	<0.001

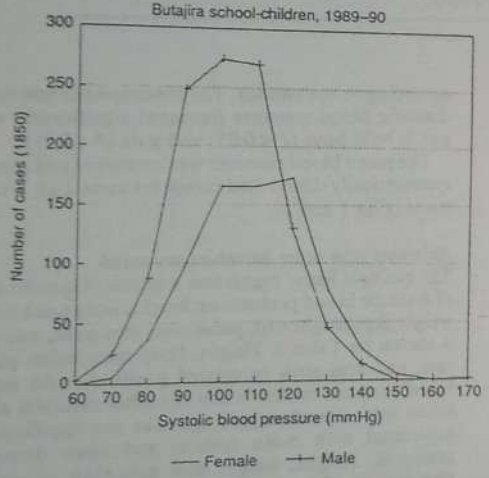


FIG. 1.

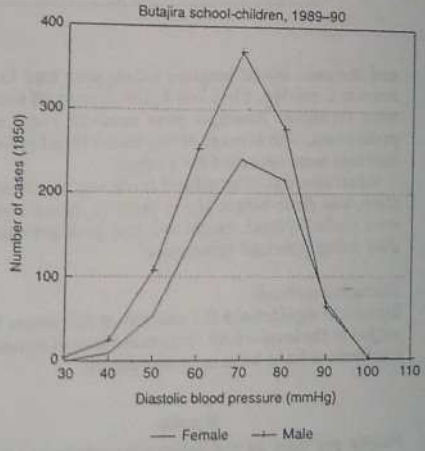


FIG. 2.

the variables mentioned above. Such findings are similar to the reports from the USA and elsewhere.[8,9] The mean blood pressure values reported here are similar to the ones recorded for Nigerian schoolchildren.[10] There are no similarly conducted Ethiopian studies on children for comparison.

The higher mean blood pressure values found in girls in this study may partly be explained by their higher pulse rate and arm-girth both of which correlated with the blood pressures. Interdepartmental Committee on Nutrition for National Defence that recorded blood pressure in Ethiopian children as part of Nutrition survey has also noted higher blood pressure in girls.[1] Higher mean blood pressure values in girls as compared to boys between 10 and 15 years of age have also been reported by several other investigators.[9–13] However, many investigators did

TABLE 3

Multiple regression of blood pressure on selected anthropometric variables and pulse ($n=1850$)

Source	Systolic standardized regression coefficient	*P* value	Diastoalic standardized regression coefficient	*P* value
Pulse	0.37		0.23	
Arm-girth	0.15		0.12	
Height	0.63	<0.01	0.75	<0.01
Body mass index	0.65		0.49	
Age	0.05*		0.06*	
$R^2=0.161$	<0.001	$R^2=0.067$	<0.001	

* $P>0.1$.

TABLE 4

Weight, Height, Arm girth by age in both girls and boys Butajira school-children, 1989–90 ($n=1850$)

	Girls			Boys		
Age (y)	Weight (kg)	Height (cm)	Arm girth (cm)	Weight (kg)	Height (cm)	Arm girth (cm)
7	19.3±1.9	115.4±4.4	15.7±1.0	19.9±2.0	118.0±4.2	15.7±1.0
8	22.1±2.1	122.5±5.1	16.4±1.1	22.0±2.4	122.2±6.6	16.0±1.1
9	24.3±2.6	127.6±6.4	17.0±1.3	24.5±2.5	127.7±5.2	16.7±1.2
10	27.6±4.2	134.6±6.8	17.6±1.5	27.5±4.7	133.3±8.0	17.3±1.3
11	30.2±4.8	138.9±7.7	18.4±1.9	29.4±4.7	137.0±7.6	17.7±1.5
12	32.5±5.7	141.5±7.6	19.1±2.0	31.7±5.2	141.3±8.3	18.2±1.6
13	37.2±5.6	148.7±8.3	20.0±1.8	35.5±6.2	147.7±9.7	18.8±1.9
14	41.9±6.6	152.1±7.1	21.4±2.3	40.1±7.5	154.1±10.2	20.1±2.2
Total	31.4±8.0*	138.8±12.1*	18.7±2.4*	31.0±7.6*	139.3±12.7*	18.0±2.0*

* Arm girth $P<0.001$.

not demonstrate a sex blood pressure difference in prepubertal children.[14]

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CASE REPORT

FAMILIAL POLYPOSIS IN TWO ETHIOPIANS

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ABSTRACT: *Cases of familial polyposis coli and Peutz-Jeghers syndrome are reported for the first time in Ethiopia. One case seemed to have the defect as a new mutation in his gene while the other possibly inherited from his father. The one with polyposis coli had transmitted the disease to his offspring. This patient had total colectomy for prophylaxis against a potential carcinoma of the colon.*

INTRODUCTION

The familial polyposis syndromes are hereditable autosomal dominant diseases and, depending on their histology, are divided into adenomatous or hamartomatous polyposis (1). The inherited polyposis syndromes are characterized by the development of many hundreds of polyps in the gastrointestinal tract and the various clinical entities are differentiated by the presence of other distinguishing features. Familial polyposis syndromes have never been reported in Ethiopia. We present here two cases of familial polyposis syndromes, one of familial polyposis coli and the other, a case of Peutz-Jeghers syndrome.

Case 1: A 46-year-old man was referred to the Gastrointestinal Clinic of Tikur Anbessa Hospital in June of 1990. Patient's clinical history revealed that he was last well in 1980 when he started to notice change in his bowel habits. He felt an urge to defecate at odd times and always after meals. His stool progressively became loose and there was urgency in bowel motions. In 1990, at the time of presentation, he had frequent bloody diarrhoea during the day as well as at night, even when he took no food. He lost 24 kg in about six months before he was referred to us. Retrospective family history revealed that his father died of bloody diarrhoea with considerable weight loss. His mother was alive and healthy. He is the second child in a family of four siblings.

The oldest brother died of unknown disease but had no diarrhoea or gastrointestinal symptoms. His younger brother has a similar illness. A sister is quite healthy and so was another youngest

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brother.

On physical examination, he was pale and chronically sick looking. The abdomen was scaphoid and soft. There was no finding on digital rectal examination. The rest of the examination was within normal limits. Except for haemoglobin of 7 g%, the laboratory tests for WBC, urinalysis, stool for ova and parasites were normal.

Endoscopic examination of the colon revealed multiple polyps of various sizes (Figure 1). Upper GI endoscopy was normal. Biopsy specimen was taken from the polyps and this was reported as adenomatous polyps.

A barium enema was performed to see the right colon which was not viewed on colonoscopy. It also showed that the entire colon was studded with polyps (Figure 2). At this point, it was agreed that the patient had familial polyposis coli although the family history was not definite. He was subjected to total colectomy and the rectum was spared. The patient had follow-up for two years. He was seen last in June 1992. He came complaining of diarrhoea and proctoscopy showed suspicious lesion in the rectum. Biopsy of the rectal mucosa revealed carcinoma in situ.

His parents and siblings were not available for colonoscopic examination. His first son was a 15-year-old school boy who underwent colonoscopic examination. He too had exactly the same picture as that of his father except the polyps were smaller in size. The father declined to bring his other children after he was informed of the findings of his son; he was extremely sad. Biopsy taken from the polyps of the son showed tubular adenoma. In March 1992 skull x-ray showed an osteoma which was sclerotic (Figure 3). He also alleged that in the past a mass was removed from the left mandible with a chisel. His previous medical record could not be retrieved and the nature of this mass could not be ascertained. However, one can deduce that he had an osteoma that required a chisel to remove it.

Case 2: A 20-year-old male patient was referred from Mekele Hospital, Northern Ethiopia, in 1987. He complained of cramping abdominal pain, diarrhoea, nausea and vomiting since childhood. His diarrhoea started to be bloody since the last two years. He also indicated mucocutaneous pigmentations of the lips, face, upper and lower limbs. He denied a similar illness in his ten siblings and parents. His father died ten years ago due to unknown cause. His mother lives in Saudi Arabia.

Physical examination revealed a chronically sick looking and emaciated person who looked younger than his stated age. The positive findings were black spots on the lower lip and mucocutaneous junctions laterally (Figure 4). Similar pigments were observed on the skin of the face, palms and soles. The abdomen was flat and there were visible waves of peristalsis in the epigastrium; succussion splash was elicited. The rest of the examination was normal.

Laboratory tests included hemogram, liver function tests, BUN, stool for ova and parasites, urinalysis, total protein, electrophoresis and d-xylose absorption test. All were normal except for haemoglobin, total protein, and d-xylose test. The haemoglobin, total protein, and d-xylose test were 9 g/dl., 5.1 g% (NR=5-8.5), and 16.7 mg/dl blood (NR=25 mg/dl in blood) respectively. d-Xylose in urine was 3.27 g in five hours (NR>4).

Radiological investigation included barium meal with follow-through, barium enema, and chest x-ray. The barium meal and follow-through showed multiple filling

defects in the stomach and upper small intestine. The barium enema revealed few filling defects in the sigmoid area. The chest x-ray was essentially normal.

Endoscopic investigation of the upper and lower intestinal tract showed multiple polyps of various sizes in the stomach. There was a large single polyp in the sigmoid region. Histopathology of the polyps was hamartomatous.

Taking all the available evidence together, that is mucocutaneous pigmentation, polyps in the stomach, small intestine and colon, the diagnosis of Peutz-Jegher syndrome was made. The patient was eager to join the rest of his family in Saudi Arabia and he left before surgical management was possible.

DISCUSSION

Familial polyposis coli (FPC) or familial adenomatous polyposis (FAP) is an autosomal dominant condition which is transmitted by a Mendelian pattern of inheritance with a high degree of penetrance (1). Therefore, offspring of a case of FPC are at 50% risk of inheriting the defective gene and developing FPC. Forty percent of FPC cases arise de novo due to new mutations (1). The patient we present here has findings compatible with FPC. His family history, colonoscopic, radiographic and histological findings confirm this diagnosis. Presumably, the patient inherited the abnormal gene from his father and has transmitted the same to his son. His siblings and his other children have not yet been screened and this step is important as it has serious consequences. Recently, cytogenetic methods are being developed to detect family members who have a high or low risk of developing FPC. This predictive test helps to determine which of the family members require regular surveillance and which ones do not need very close follow-up (2). This is based on the knowledge that the abnormal gene for FPC is located on the long arm of chromosome 5, which is already mapped. Additional associated finding in this condition is the presence of congenital hypertrophy of the retinal pigment epithelium, a sign of FPC (2). Another extracolonic manifestation of FPC is mandibular osteoma and or dental abnormalities(1). Our patient had a mass in the left mandible which was removed with a chisel. Skull x-ray revealed a sclerotic osteoma.

The only differential diagnosis to be considered is Gardner's syndrome. Both conditions have so much in common that, in fact, they are considered to be the forme fruste of the same disease with variable expressions (1). This patient does not have many of the extra-colonic manifestations found in Gardner's syndrome. Both share metabolic and cellular abnormalities of failure of normal cellular differentiation in colonic crypt epithelium and malignant characteristics of skin fibroblast culture (1). All points considered, Gardner's syndrome cannot be ruled out in this patient. The management of this case was dictated by the knowledge of the natural course of the disease. There are two ways to deal with such a case. The first is to do subtotal colectomy and ileorectal anastomosis. The second is to do total proctocolectomy with ileostomy. The first option assumes that the patient will be screened periodically and polyps that develop in the rectum will be dealt with by fulguration. However, this approach is not considered adequate for all patients and many hold the view that cases of FPC should undergo total proctocolectomy (1). The acceptability of such a radical procedure would be very low in our

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cultural setting.

Peutz-Jeghers (P-J) syndrome is a genetically transmitted rare disorder which is characterized by gastrointestinal polyposis and pigmentation of the lips, buccal mucosa, face and digits. This condition is transmitted by autosomal dominant gene with variable penetrance. About forty percent of the patients with this condition have no family history of the disorder and are believed to be due to new mutation (1). The patient we presented here has no family history and we believe that this is due to new mutation. Most patients become symptomatic in their teens and the most common presenting symptom is abdominal pain caused by intussusception secondary to intestinal polyps. Signs and symptoms of obstruction, palpable mass, and gastrointestinal bleeding which may be occult or massive are present (4). Some patients may manifest only polyposis without pigmentation or pigmentation without polyps. However, most patients have both. The P–J polyps are generally multiple and are found mostly in the small intestine without colorectal and gastric areas being affected in descending order of frequency (5). The polyps are thought to be adenomas but are now established to be hamartomas. P–J polyps are potentially premalignant (6). Studies have shown that patients with P–J syndrome carry a slightly increased risk of gastrointestinal carcinoma. P–J syndrome is associated with primary carcinoma of the breast and tumours of various organs such as ovary, testes, and gallbladder (7–9).

The barium meal and follow-through study did not reveal mucocal abnormality other than the polyps. The low value of d-xylose absorption and excretion is most likely due to vomiting and delayed gastric emptying. The patient had symptoms and signs of upper gastrointestinal obstruction such as persistent vomiting and succussion splash.

This patient fulfils the clinical criteria of Peutz-Jeghers syndrome with the classical features of oral, facial, and digital pigmentation and polyposis of the gastrointestinal tract. The abdominal pain with symptoms and signs of gastrointestinal obstruction and anaemia are all present in our patient and are typical features of this condition (5). It is unfortunate that a follow-up of this case was not possible, because he went to Saudi Arabia.

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We wish to express our gratitude to the departments of Pathology, Radiology and Audiovisual Centre of the Faculty of Medicine. Many thanks go to W/o Fantaye Takele for her technical assistance.

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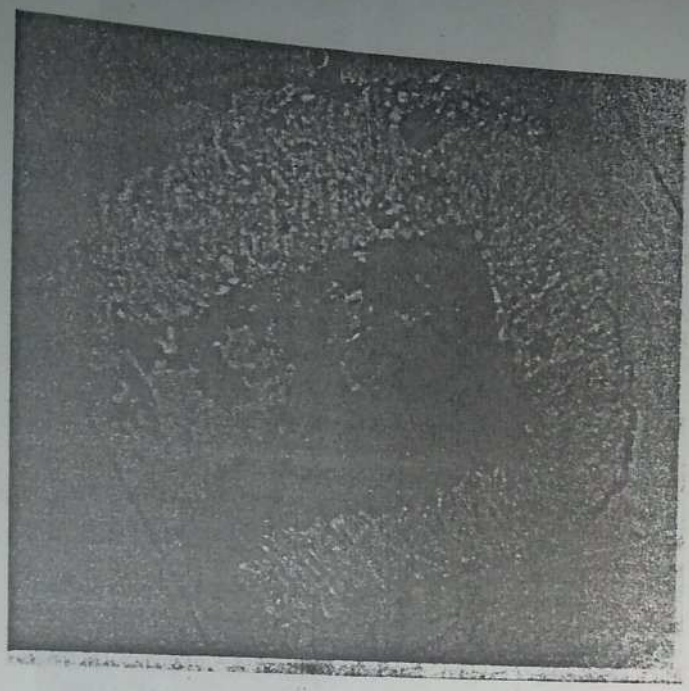


Figure 1. Polyps as seen after the colon was resected and cut exposing the mucosal surface.



Figure 2. A barium enema to show the polyps on the right side of the colon.

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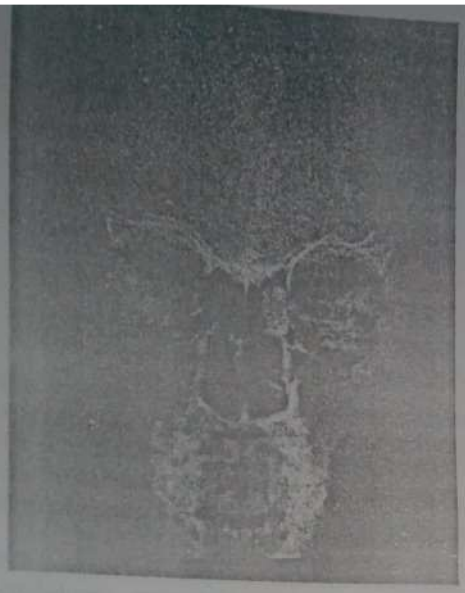


Figure 3. A-P skull x-ray indicating a sclerotic osteoma.

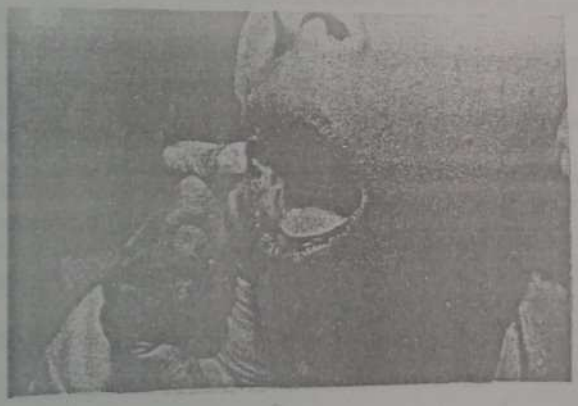


Figure 4. Muco-cutaneous junction pigments in the Peutz-Jeghers syndrome.

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ACUTE RENAL FAILURE IN ADDIS ABEBA, ETHIOPIA: A PROSPECTIVE STUDY OF 136 PATIENTS

Worku Zewdu, MD[1]

ABSTRACT: *The causes and clinical course of 136 cases of acute renal failure (ARF) consecutively treated in the Renal Unit of Tikur Anbessa Hospital, Addis Abeba, Ethiopia, between January 1989 and December 1992 are described. There were 106 women and 30 men with mean age of 26.9 ± 7.2 and 40.7 ± 14.9 years respectively. Septic abortion is still the leading cause of ARF (71 patients) followed by falciparum malaria (29 patients) and nephrotoxic agents (12 patients). One-hundred-seventeen patients (86%) required dialysis. The overall case fatality rate was 33.8%, with similar mortality rates in septic abortion (36.6%) and falciparum malaria infection (37.9%), but a much lower rate (16.7%) in acute renal failure secondary to nephrotoxic agents. Septicaemia and pneumonia were leading causes of death. Derangement of liver function was associated with higher mortality rates in patients with septic abortion and malaria, whereas leukocytosis was found to be a poor prognostic finding in the latter. Non-oliguric ARF was seen in 33.8% of cases and was found commonly in patients with malaria (75.9%) or in nephrotoxin-induced ARF (83.8%). Mean duration of oliguria was 18.9 ± 11 days. Compared to the previous report from the same centre, this larger series identified important clinical settings other than septic abortion which predispose to ARF. As renal function tests are not performed routinely in many Ethiopian hospitals and as many patients have non-oliguric ARF, cases may be being missed. Measures to prevent septic abortion and malaria, and the judicious use of nephrotoxic agents, may decrease the incidence of ARF.*

INTRODUCTION

Despite the introduction of dialysis therapy and intensive general care, acute renal failure (ARF) remains an important and potentially lethal complication of many serious obstetric, medical and surgical conditions. The clinical settings in which ARF develops have changed over the years in the developed world. Three decades ago, the leading causes of ARF were pregnancy related (1,2) but now the renal failure often follows severe trauma, surgery or medical conditions (3–6). Although

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reports are few, obstetrical and medical complications are still the main clinical settings in which ARF occurs in developing countries (7–9).

A decade ago, Habte et al (10) reported their three years' experience in Tikur Anbessa Hospital, Addis Abeba, in a small number of patients with ARF. A prospective study of a larger number of patients having only intrinsically reversible renal failure would give a clearer picture of the clinical pattern and the clinical settings in which renal failure develops. It was for this purpose that the present study was conducted in the same hospital which has the sole civilian dialysis centre in the country.

PATIENTS AND METHODS

A total of 136 patients with established intrinsically reversible ARF were managed in the Renal Unit of Tikur Anbessa Hospital between January 1989 and December 1992. Cases of ARF secondary to other causes such as glomerulonephritis, interstitial nephritis and obstructive uropathy were excluded. The diagnosis of ARF was based on clinical presentation, course of the illness, and an acute persistent elevation of the blood urea nitrogen (BUN) above 40mg/dl and/or serum creatinine above 2mg/dl in spite of correction of the underlying precipitating factor.

Patients who had oliguria for more than four weeks and patients whose clinical presentation did not suggest acute intrinsically reversible renal failure were subjected to renal biopsy to exclude other causes. Every attempt was made to obtain postmortem renal biopsy as well.

In cases of falciparum malaria infection, the parasite density was estimated by counting parasitized red cells in a thin blood smear as percentage of total red cells counted.

In the majority of patients, dialysis was performed when severe gastrointestinal symptoms, impaired cerebral function, acidosis, pulmonary congestion, pericarditis, bleeding tendency or hyperkalemia occurred. Both haemodialysis and peritoneal dialysis were performed as indicated and depending on availability at the time.

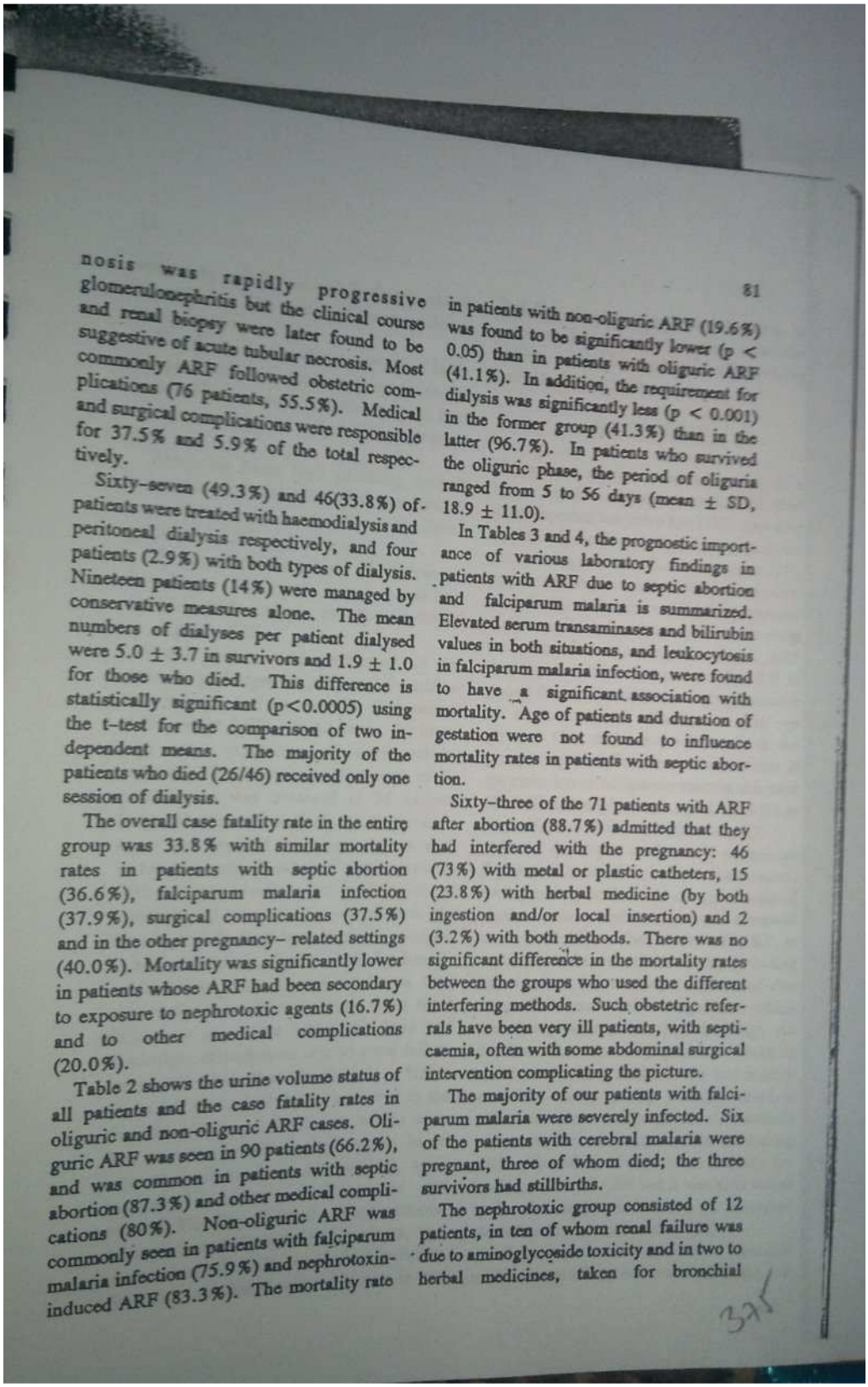
Patients were categorized into either oliguric (less than 400ml urine per 24 hours) or non–oliguric (more than 400ml urine per 24 hours) ARF. The period of diuresis dates from the day when urine volume reaches one litre in 24 hours. The clinical course of each patient was followed closely until the time of discharge or death. Those discharged were followed in the outpatient renal clinic until their renal function returned to normal, as measured by serum urea and creatinine levels.

Statistical analysis of the data was performed by the Fisher's t-test and Chi-square tests as appropriate.

RESULTS

The clinical course of 136 patients with ARF was analyzed. There were 106 women and 30 men with mean age of 26.9 ± 7.2 and 40.7 ± 14.9 years respectively. Sixty–five per cent of the patients were referred from other centres. Two–thirds of these were from hospitals in Addis Abeba and the rest from outside the city. The clinical states precipitating ARF in all but one patient could be classified into three categories (Table 1). Septic abortion (71 patients), falciparum malaria infection (29 patients) and exposure to nephrotoxic agents (12 patients) accounted for 82.3% of the total. The precipitating factor in one patient could not be identified, her admission diag-

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nosis was rapidly progressive glomerulonephritis but the clinical course and renal biopsy were later found to be suggestive of acute tubular necrosis. Most commonly ARF followed obstetric complications (76 patients, 55.5%). Medical and surgical complications were responsible for 37.5% and 5.9% of the total respectively.

Sixty-seven (49.3%) and 46(33.8%) of patients were treated with haemodialysis and peritoneal dialysis respectively, and four patients (2.9%) with both types of dialysis. Nineteen patients (14%) were managed by conservative measures alone. The mean numbers of dialyses per patient dialysed were 5.0 ± 3.7 in survivors and 1.9 ± 1.0 for those who died. This difference is statistically significant ($p<0.0005$) using the t-test for the comparison of two independent means. The majority of the patients who died (26/46) received only one session of dialysis.

The overall case fatality rate in the entire group was 33.8% with similar mortality rates in patients with septic abortion (36.6%), falciparum malaria infection (37.9%), surgical complications (37.5%) and in the other pregnancy- related settings (40.0%). Mortality was significantly lower in patients whose ARF had been secondary to exposure to nephrotoxic agents (16.7%) and to other medical complications (20.0%).

Table 2 shows the urine volume status of all patients and the case fatality rates in oliguric and non-oliguric ARF cases. Oliguric ARF was seen in 90 patients (66.2%), and was common in patients with septic abortion (87.3%) and other medical complications (80%). Non-oliguric ARF was commonly seen in patients with falciparum malaria infection (75.9%) and nephrotoxin-induced ARF (83.3%). The mortality rate

in patients with non-oliguric ARF (19.6%) was found to be significantly lower ($p < 0.05$) than in patients with oliguric ARF (41.1%). In addition, the requirement for dialysis was significantly less ($p < 0.001$) in the former group (41.3%) than in the latter (96.7%). In patients who survived the oliguric phase, the period of oliguria ranged from 5 to 56 days (mean ± SD, 18.9 ± 11.0).

In Tables 3 and 4, the prognostic importance of various laboratory findings in patients with ARF due to septic abortion and falciparum malaria is summarized. Elevated serum transaminases and bilirubin values in both situations, and leukocytosis in falciparum malaria infection, were found to have a significant association with mortality. Age of patients and duration of gestation were not found to influence mortality rates in patients with septic abortion.

Sixty-three of the 71 patients with ARF after abortion (88.7%) admitted that they had interfered with the pregnancy: 46 (73%) with metal or plastic catheters, 15 (23.8%) with herbal medicine (by both ingestion and/or local insertion) and 2 (3.2%) with both methods. There was no significant difference in the mortality rates between the groups who used the different interfering methods. Such obstetric referrals have been very ill patients, with septicaemia, often with some abdominal surgical intervention complicating the picture.

The majority of our patients with falciparum malaria were severely infected. Six of the patients with cerebral malaria were pregnant, three of whom died; the three survivors had stillbirths.

The nephrotoxic group consisted of 12 patients, in ten of whom renal failure was due to aminoglycoside toxicity and in two to herbal medicines, taken for bronchial

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asthma by one patient and for haemorrhoids by another. The nature of these medicines is not known.

The surgical procedures performed in the six patients were abdominal operation for bullet injury in two, hysterectomy in two, myomectomy in one and cholecystectomy in one.

Relapsing fever (two patients), typhoid fever (two patients) and typhus (one patient) were found to be associated with the development of ARF in five cases.

Three patients transfused with incompatible blood developed severe haemolytic reactions with urticaria and fever followed by oliguric ARF.

Renal biopsy was performed in ten patients; prolonged oliguria was the indication in nine and in one the diagnosis of ARF was in doubt. In all cases, the histology was suggestive of acute tubular necrosis. Postmortem confirmation of the renal lesion was obtained in 24 patients (septic abortion 15, malaria six, nephrotoxic agent one, typhoid fever one, typhus one). In two seriously ill cases of septic abortion, with evidence of severe ischaemic insult and disseminated intravascular coagulation, the histological findings were cortical necrosis.

In the majority, deaths could be directly attributed to other complications as they occurred either after recovery from renal failure or at a time when the fluid and electrolyte disturbances due to renal failure were well controlled by dialysis. Sixty-seven per cent of all deaths occurred in the first three days of admission to the unit. The causes of death include sepsis in 16 patients, pneumonia in six patients, adult respiratory distress syndrome in six patients, bleeding dyscrasia in six patients, pulmonary embolism in two patients, and severe cerebral malaria in four patients. The cause of death was unknown in six patients. Urinalysis and renal function, as assessed by serum urea and creatinine values, returned to normal in all surviving patients during follow-up.

DISCUSSION

The present report represents a study of a larger number of patients with ARF than those reported ten years ago (10), seen over a relatively brief period of time. As in the previous report from the same centre (10), and in reports from other developing countries (7–9), obstetric complications, particularly septic abortion, were the most common clinical settings in which ARF developed. The occurrence of ARF in young females is due to the high prevalence of septic criminal abortion in this age group. One major respect in which the present report differs from the previous is the inclusion of falciparum malaria infection (21.3%) and nephrotoxic agents (8.8%) as major factors in the causation of ARF.

In the developed world, ARF complicating obstetric disorders has become a rarity, owing mainly to the near disappearance of septic abortion and to improved antenatal care (6,11,13). The causes of ARF in septic abortion are multifactorial, including hypotension, haemorrhage, sepsis and disseminated intravascular coagulation which are often present in this clinical setting. As the law of the country prohibits abortion and contraceptive methods are not readily available, many young patients interfere with their unwanted pregnancies, resulting in a number of complications including ARF. Therefore, abortion was not only the leading cause of ARF but it was also found to be the commonest cause of maternal mortality in the same centre (14).

All patients with falciparum malaria infection were from non-endemic areas and

no patient had the clinical manifestations of blackwater fever. The majority of them (75.9%) had non-oliguric ARF with mild haemolysis and heavy parasitaemia as found elsewhere (15-17). It was also reported from Gondar, northwestern Ethiopia, that one of the leading causes of death in severe and complicated falciparum malaria had been ARF (18,19).

Aminoglycoside antibiotics have become one of the leading causes of ARF encountered in a general hospital (20,21). This may be due to an increasing exposure of patients to these nephrotoxic agents.

In contrast to the developed world (4,5), post-surgical or post-traumatic ARF was not commonly seen in our centre. This may be partly due to lack of resuscitative measures for severely injured patients who often die before they develop overt clinical or biochemical uraemia. The near non-existence of cardiovascular surgery in Ethiopia may be another reason.

It is also interesting to note that ARF induced by causes common elsewhere, such as haemodynamic alterations (severe hypotension, severe dehydration and heart failure) and exposure to non-steroidal antiinflammatory drugs (NSAIDs) and contrast media, were not seen in our patients. This may be due to lack of awareness and failure to determine renal function as these clinical states would be expected here as well.

The rate of oliguria in patients with septic abortion (87.3%) was similar to the rate documented previously (10). Due to the high prevalence of non-oliguric ARF in patients with falciparum malaria infection and in those exposed to nephrotoxic agents, common causes of ARF in this series, the overall rate of non-oliguric ARF is higher than that reported previously.

The overall case fatality rate in this series is similar to other reports of ARF following medical and obstetric complications (6,8). Elevated serum transaminase and bilirubin levels were found to be associated with higher mortality in patients with septic abortion and falciparum malaria infection, possibly reflecting the severity of the underlying illness and its systemic complications. As leukocytosis appears to be associated with poor prognosis in patients with falciparum malaria infection, identifying and promptly treating its causes, such as secondary bacterial infection, may alter the outcome. The role of sepsis in the mortality of ARF is well recognized; it was the most common cause of death in our patients (34.8%). Generally our patients were referred late in a critical state which was reflected in the number of deaths which occurred in the first few days after admission to the dialysis unit.

As routine renal function tests are not performed in many health institutions in Ethiopia even in severely ill patients and those who are exposed to known nephrotoxic agents, it is not possible to assess the incidence of ARF in our setting. Usually only patients who develop oliguria or clinically overt uraemic symptoms are subjected to renal function studies. As the majority of patients with ARF following falciparum malaria infection or exposure to nephrotoxic agents have adequate urine output and a less severe clinical course of their renal failure, the diagnosis may not be suspected. It has to be emphasized that progressive azotaemia is the hallmark of ARF, and the urinary volume may be highly variable. One has to be aware of the clinical settings in which ARF commonly develops for early diagnosis and prompt management.

A number of reports indicate that the survival of patients with ARF changed little

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in the past three decades in spite of improvements in dialytic and supportive therapy (22). In developing countries, where medical resources are meagre, preventive measures to minimize the incidence of ARF are mandatory. As seen in the developed world, the incidence of pregnancy related ARF may be decreased if satisfactory antenatal care is available and if septic abortion can be prevented by the liberalization of abortion or by other measures such as ready availability of family planning programmes to all women of childbearing age. Non-immune individuals should be taught to take preventive measures when they go to malarious regions; also cautious use of nephrotoxic drugs in severely ill patients no doubt will decrease the incidence of ARF.

ACKNOWLEDGEMENTS

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Table 1. Clinical observations in 136 patients with acute renal failure

Clinical setting	No.	Sex		Percentage of total	Case fatality rate
		Male	Female		
Pregnancy related	76			55.9	28/76
Septic abortion	71		71	52.2	26/71
Toxaemia of pregnancy	2		2	1.5	0/2
Postpartum haemorrhage	2		2	1.5	1/2
Perpeural sepsis	1		1	0.7	1/1
Medical conditions	51	26	25	37.5	15/51
Falciparum malaria	29	18	11	21.3	11/29
Nephrotoxin	12	5	7	8.8	2/12
Transfusion related	3	-	3	2.2	0/3
Acute febrile illness	5	3	2	3.7	2/5
Volume depletion	2	-	2	1.5	0/2
Surgical conditions	8	4	4	5.9	3/8
Post surgery	6	2	4	4.4	1/6
Burns	2	2	-	1.5	2/2
Unknown	1	-	1	0.7	0/1

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Table 2. Urine volume status of the 136 patients and case fatality rates in non-oliguric ARF

Clinical setting	Total no. of patients	Non-oliguric ARF		Oliguric ARF	
		Total	Deaths	Total	Deaths
Pregnancy related	76	9	1	67	27
Septic abortion	71	9	1	62	25
Others	5	-	-	5	2
Medical conditions	51	34	8	17	6
Falciparum malaria	29	22	7	7	4
Nephrotoxic agents	12	10	1	2	1
Others	10	2	-	8	1
Surgical conditions	8	3	-	5	4
Unknown	1	-	-	1	-
Total	136	46	9	90	37

Table 3. Prognostic significance of laboratory findings in patients with acute renal failure following septic abortion

Findings	Survivors (n=45)	Fatal cases (n=26)	P
Haemoglobin < 8gm%	40	23	***0.62(NS)
WBC > 10,000/cumm	38	20	**0.22(NS)
Elevated transminases*	11	17	**0.002(S)
Bilirubin > 3mg%	16	20	**0.002(S)
BUN > 150mg%	16	8	**0.88(NS)

*Above two times the upper limit of normal.
**Chi-square test. Yates correction.
***Fisher's exact test.

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Table 4. Prognostic significance of laboratory findings in patients with acute renal failure following falciparum malaria infection

Findings	Survivors (n=45)	Fatal cases (n=26)	P
Haemoglobin < 8gm%	16	10	***0.68(NS)
WBC > 10,000/cumm	2	6	**0.02(S)
Heavy parasitaemia*	11	8	**0.41(NS)
Bilirubin > 3mg%	3	8	**0.004(S)
Elevated transminases**	4	7	**0.03(S)
BUN > 150mg%	9	5	****0.88(NS)

*5% or more RBC's parasitized.
**Above two times the upper limit of normal.
***Fisher's exact test.
****Chi-square test.

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The Jarisch–Herxheimer reaction: a paradigm of the cytokine cascade in man

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INTRODUCTION

The discovery and rapid expansion of our knowledge of cytokines in human and experimental infection has been one of the most fundamental advances in pathophysiology. For the first time, mechanisms of classic parameters of infection, such as fever and weight loss, have been clearly defined and consequently new therapeutic avenues are being opened as the mechanistic links between immunological response and metabolic changes seen in infection are understood. However, as is often the case in scientific advance, rapid expansion of knowledge in a particular field tends to make what initially appeared simple observations much more complex. Such complexity now exists in the field of cytokines, in which it is difficult to understand how the body integrates information from the prolific cascade of release of cytokines now known to exist.

The initial knowledge, gained particularly from animal experiments (Tracey et al, 1986; Mathison et al, 1988) involving discrete models of infection, for example endotoxin infusion, gave a great deal of information concerning the release of cytokines into the circulation and the appearance of the classic features of the acute-phase response induced in such models. Experiments using such well-defined models demonstrated that the release of tumour necrosis factor (TNF-α) into the circulation was exquisitely controlled, and experiments on cells in culture demonstrated that control was principally exerted at the transcriptional level. The extremely precise control of TNF release is clearly very important, since the random release of such a potent molecule would clearly be disadvantageous to the host. The release of TNF into the circulation in response to endotoxin administration in both man and animal models is evident with 15–30 min, peaks at about 2 h, and baseline values are seen after around 4 h. It was therefore not surprising that

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a complex picture of plasma cytokine profiles was detected in humans with serious bacteraemia. Such complexity of plasma cytokine profiles detected in the course of wild-type human bacteraemic situation (Waage et al, 1989), compared with the highly reproducible cytokine patterns detected in animal model experiments, has restricted our knowledge and understanding of the control and significance of cytokine release in human infection. However, some clarification has been obtained in experiments in which endotoxin was infused into volunteers under controlled conditions: similar patterns of cytokine release (TNF-α) (Michie et al, 1988) to those detected in rabbit and rat models were detected in plasma. However, these human experiments involving experimental endotoxin administration received extensive criticism on ethical grounds, and it is likely that they may not be repeated in certain institutions.

The purpose of this chapter is to describe experiments involving the Jarisch–Herxheimer reaction (J–HR), a clinical phenomenon described almost a century ago, which have led to important observations of the cytokine cascade in humans and have, for the first time, given insight into the biochemical mediation of this phenomenon (Negussie et al, 1992).

THE JARISCH–HERXHEIMER REACTION

The J–HR is a clinical syndrome occurring soon after the first adequate dose of an antimicrobial drug to treat an infection. This clinical phenomenon was first described at the turn of the century: mercurial treatment of syphilis caused a severe worsening of symptoms within 24 h, consisting of fever, malaise and worsening of rash (Herxheimer, 1902; Jarisch, 1895). It is now recognized that such a constellation of clinical phenomena often occurs after the first dose of an antimicrobial to treat serious bacterial infection (Bryceson, 1976) or protozoal infections, for example African trypanosomiasis (Whittle and Pope, 1972). Bacterial infections commonly associated with J–HR are those caused by spirochaetes such as syphilis, relapsing fever, leptospirosis, yaws, Lyme disease and Vincent's angina. Clinical studies measuring changes in body temperature, peripheral blood white cell count, blood pressure and constitutional symptoms following antibiotic treatment of syphilis and relapsing fever have defined the evolution of the J–HR, its time course and severity. Interestingly, as will be described, the J–HRs associated with these different infections are clinically different in both of these respects.

LOUSE-BORNE RELAPSING FEVER

Clinical features

Louse-borne relapsing fever presents in endemic areas (Ethiopia, Bolivia) as a severe febrile illness resembling malaria. The infection is caused by the organism *Borrelia recurrentis*, which lives in the haemolymph of body

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lice and gains access to the human body through skin. The disease is essentially a condition of poor socio-economic circumstances in an endemic area. The name, relapsing fever, describes the clinical course of infection, in which the first episode of fever resolves spontaneously by crisis after about 10 days, to return about 5–6 days later. Each remission is accompanied by production of immunoglobulins G and M (IgG and IgM) specific for bacterial strains causing relapse, and up to four relapses may occur during the course of a non-fatal infection. The diagnosis of relapsing fever is relatively simple and is made by microscopic observation of spirochaetes, morphologically typical of *B. recurrentis* on Wright's stained blood smears. The level of bacteraemia may be intense with densities up to $10^5/mm^3$.

Jarisch–Herxheimer reaction

The J–HR of relapsing fever occurs in highly predictable form following the treatment of this infection with penicillin or tetracyline (Parry et al, 1970; Warrell et al, 1970; Perine et al, 1971; Zein, 1987). Clinical characteristics of the J–HR are shown in Figure 1 and consist of a rise in body temperature of some 1.5°C associated with rigors and peaking at 90 ± 15 min after the intramuscular administration of penicillin, a transient rise and fall of mean arterial blood pressure and a fall of peripheral blood white cells (Negussie et al, 1992). In the study illustrated in Figure 1, spirochaetaemia disappeared in all patients within a mean time of 4.5 h after antibiotic treatment was given. The J–HR encountered in louse-borne relapsing fever may be fatal, unlike that encountered in syphilis or Lyme disease, and mortality of up to 40% has been described.

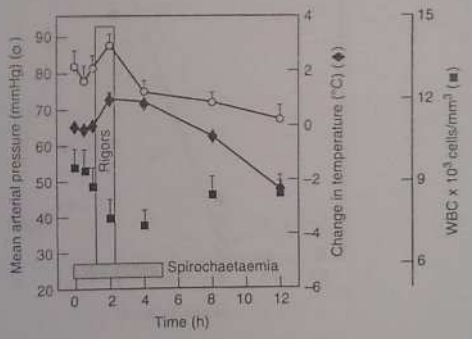


Figure 1. Clinical characteristics of the Jarisch–Herxheimer reaction. At the indicated time points after administration of penicillin to patients with blood-smear proven relapsing fever, venous blood samples were drawn and cytokine levels were measured in plasma. Each value is the mean ± SEM for 6–14 patients at each time point. Values on the second line represent the range observed at each time point. WBC, white blood cells.

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The severe predictable pathophysiological changes associated with the J–HR of relapsing fever have provided a paradigm for clinical investigation. Initial studies of serum from individuals experiencing J–HR revealed, by bioassay in rabbits, the presence of a pyrogen (Bryceson et al, 1972). However, whilst it was clear from further experiments that such a pyrogen was not lipopolysaccharide, its chemical nature was not defined. It was not until the discovery of the aetiological relationship between plasma TNF and septic shock in animals (Tracey et al, 1987) that the chemical nature of the mediation of J–HR in louse-borne relapsing fever was investigated in terms of the cytokine cascade.

Plasma cytokine profile in Jarisch–Herxheimer reaction

The exquisitely reproducible time course and severity of pathophysiological change measured in the J–HR resemble those of acute administration of endotoxin in man and provide an excellent model to study the cytokine cascade in human subjects. Measurement of plasma TNF and interleukins-6 and 8 (IL-6 and IL-8) in relation to the severe physiological changes occurs in the course of this clinical phenomenon revealed a single peak of TNF, IL-6 and IL-8 detectable in peripheral blood (Figure 2). Absolute values of

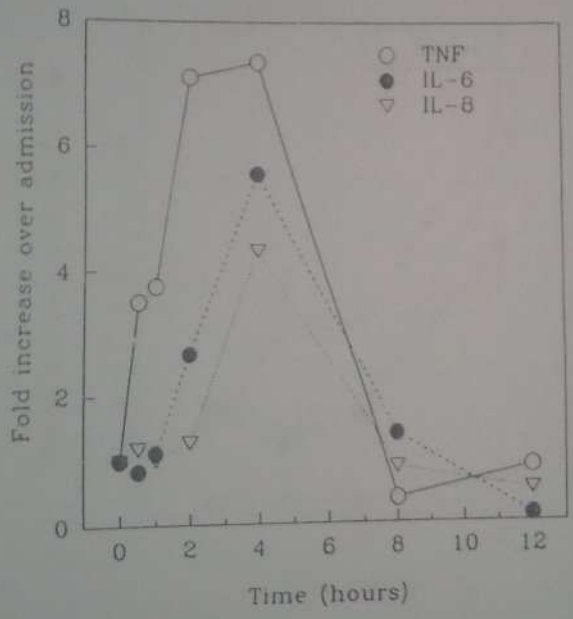


Figure 2. Kinetics of cytokine release in the Jarisch–Herxheimer of louse-borne relapsing fever. Data are expressed as fold increase over admission levels of tumour necrosis factor (TNF) and interleukins-6 and 8 (IL-6 and IL-8) measured in plasma. Compared with baseline levels, TNF showed the most rapid induction, and attained the greatest relative increase. The TNF level was significantly increased over baseline by 1 h, IL-6 by 2 h and IL-8 by 4 h.

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plasma TNF, IL-6 and IL-8 are shown in Table 1 and Figure 3. Transient release of all three cytokines was detected in plasma, with peak values occurring within 2–4 h after intramuscular penicillin administration. Twelve hourse after administration of penicillin, when all of the clinical parameters had returned to normal, plasma levels of the measured cytokines had fallen dramatically. These data clearly indicate that TNF was most rapidly induced and showed the greatest fold increase relative to pre-antibiotic plasma levels.

In addition, a detailed analysis of the early phase of the rise in plasma cytokine concentration in relation to rise in body temperature and onset of rigors revealed that plasma TNF was elevated at 1 h after penicillin administration, whereas plasma levels of IL-6 and IL-8 remained unchanged above baseline at this time (Figure 3). Such findings may indicate an aetiological role of TNF in the evolution of fever in this condition. Thus the evolution of the cytokine cascade in the J–HR of louse-borne relapsing fever occurred in a discrete temporal sequence, with an early rapid rise in TNF being sequentially followed by IL-6 and IL-8, the plasma levels of which appear to peak simultaneously.

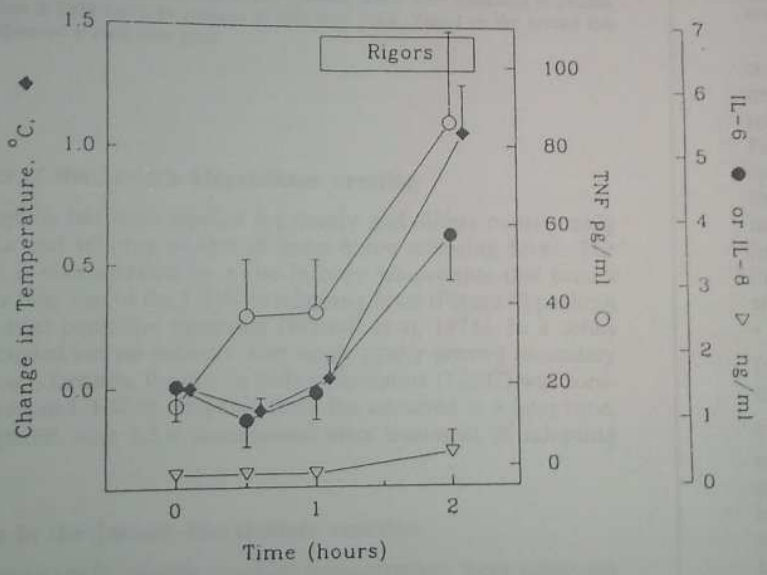


Figure 3. Early kinetics of cytokine release and development of symptoms of louse-borne relapsing fever. The change in temperature, and development of rigors is shown relative to the evaluation of plasma cytokine concentration. The rise of plasma tumour necrosis factor (TNF) concentrations preceded the elevation in temperature and development of rigors, whereas elevation of plasma interleukin-6 (IL-6) coincided with these symptoms. Elevation of plasma IL-8 concentration lagged behind the development of symptoms. Each value is the mean ± SEM for 10–14 patients.

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Table 1. Peripheral blood cytokine levels during the Jarisch-Herxheimer reaction of Louse borne relapsing fever

Time (h)	TNF (pg/ml)	IL-6 (pg/ml)	IL-8 (pg/ml)
0	15 ± 5	1,478 ± 527	173 ± 65
	0–55	0–6,673	0–848
0.5	37 ± 14	1,020 ± 369	171 ± 67
	0–142	0–5,358	0–1,001
1	38 ± 13	1,375 ± 435	168 ± 56
	0–137	0–4,940	0–871
2	86 ± 23	3,836 ± 651	503 ± 330
	0–232	1,261–9,975	0–4945
4	126 ± 38	9,578 ± 1,808	8,102 ± 4,991
	0–469	2,262–28,447	109–70,000
8	8 ± 4	2,003 ± 696	216 ± 111
	0–40	66–9,403	0–1,567
12	12 ± 7	289 ± 159	178 ± 69
	0–51	0–1,841	0–639
24	14 ± 10	40 ± 21	ND
	0–47	0–245	

At the indicated time points after administration of penicillin, to patients with blood smear proven relapsing fever venous blood samples were drawn and cytokine levels were measured in plasma. Each value is the mean ± SEM for 6–14 patients at each time point. Values on the second line represent the range observed at each time point.

SYPHILIS

Clinical features of the Jarisch–Herxheimer reaction

The J–HR of syphilis has been studied previously and differs considerably in its time course and severity of that of louse-borne relapsing fever. The J–HR of syphilis is characterized by a rise in body temperature that occurs considerably later than that of the J–HR of relapsing fever (Figure 4) peaking at around 6–8 h after penicillin treatment (Warrell et al, 1971). In a series of experiments carried out on patients with serologically proven secondary syphilis in Kingston, Jamaica, the rise in body temperature (1.2°C) was comparable to that seen in J–HR of relapsing fever but occurred at a later time, namely 6 h compared with 1.5 h documented after treatment of relapsing fever.

Cytokine release in the Jarisch–Herxheimer reaction

In the same Jamaican study, plasma cytokine concentrations were measured in the plasma of the treated syphilitic patients and compared with the measured physiological parameters. In these experiments no TNF, IL-6 or IL-8 was detected at any time over the 24 h protocol, in sharp contrast to the high plasma concentration of these cytokines detected in the J–HR of relapsing fever (G. E. Griffin, unpublished data). In the light of the much less

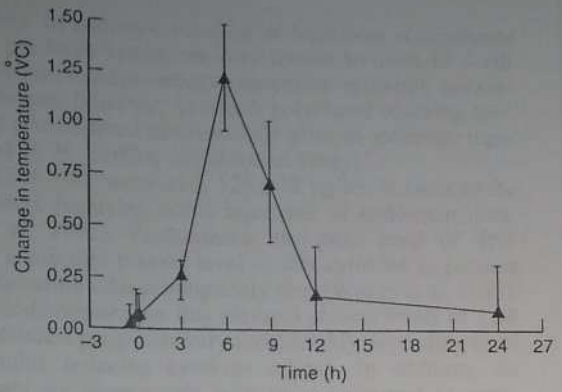


Figure 4. Temperature changes in the Jarisch–Herxheimer reaction of syphilis. Patients (n = 14) with serologically proven secondary syphilis were treated with intramuscular penicillin at t = 0. Rectal temperature was taken at the times indicated following administration of the antibiotic. No rigors were observed in any patient. A maximum rise of body temperature of 1.2°C was recorded 6 h after the administration of penicillin. Blood was taken at the same time as temperature was measured and plasma tumour necrosis factor (TNF) and interleukin-6 and -8 (IL-6 and IL-8) were assayed in serum at each time point and found to be undetectable.

severe pathophysiological changes recorded in the J–HR of syphilis, these negative findings suggest that the clinical magnitude of the J–HR may be related to the appearance of cytokines such as TNF, IL-6 and IL-8 in plasma. Plasma cytokine cascades have not yet been described in detail in other spirochaetal diseases such as leptospirosis or Lyme disease but their characteristics and their relationship to clinical symptomatology is clearly of great interest and pathophysiological significance. It may be that, in the less severe forms of J–HR, plasma levels of cytokine are not elevated and the change in clinical parameters is brought about by local release and action of cytokine at paracrine and autocrine level.

PATHOPHYSIOLOGY OF THE JARISCH–HERXHEIMER REACTION

The J–HR is a well-known but infrequently diagnosed complication of antimicrobial chemotherapy for a wide range of infections but classically is associated with spirochaetal infection. Until the studies described above, the biochemical mediation of the J–HR remained largely a mystery; however, the investigations of the cytokine cascade in patients experiencing J–HR associated with louse-borne relapsing fever have clearly indicated that cytokines are likely to have at the least an accessory if not aetiological role (Negussie et al, 1992). A similar reaction to the J–HR, consisting of fever and profound constitutional disturbance, occurs in renal transplant patients receiving monoclonal antibody against OKT-3 as treatment for rejection and transient elevation of TNF has been recorded in plasma of such patients

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(Abramowicz et al, 1989). In addition, infusion of high-dose recombinant TNF in cancer patients produces symptoms very similar to those of J–HR (Spriggs et al, 1988). Definitive experiments concerning aetiology are currently in progress in Ethiopia, however, in which polyclonal blocking antibodies to TNF are being administered intravenously prior to antibiotic treatment (D. A. Warrell and G. E. Griffin, unpublished study).

The peak plasma level of TNF measured, 126 ± 38 pg/ml, is close to the level detected in volunteers receiving bolus injections of endotoxin intravenously (Negussie et al, 1992). Furthermore, the peak level of TNF recorded is close to the admission plasma level of this cytokine in patients with meningococcal septicaemia who subsequently died (Waage et al, 1989). These findings are a clear demonstration that elevated plasma levels of TNF associated with adverse clinical prognosis vary considerably depending upon the condition and stimulus inducing cytokine release. In addition, the recorded peak IL-6 levels are comparable with those measured in septic shock and bacteraemia (Waage et al, 1989) but considerably higher than those recorded in human volunteers receiving bolus ingestion of lipopolysaccharide (Martich et al, 1991). Similarly, plasma levels of IL-8 recorded in the J–HR of louse-borne relapsing fever are some ten times higher than those seen following endotoxin infusion into humans (Van Zee et al, 1991). However, a clear point which does emerge from evaluation of the cytokine profile in J–HR is that the plasma concentrations of all the three cytokines measured (Figure 2 and Table 1) exhibit a transient peak of kinetics similar to that seen after bolus endotoxin infusion, suggesting similar control mechanisms may be implicated (DeForge and Remick, 1991). It is likely that such control is exerted at the transcriptional level, since similar profiles have been detected in cells stimulated with endotoxin in vitro and these closely relate to the levels of mRNA extracted from those cells.

The stimulus for the sudden release of cytokines in the J–HR is not yet understood. Not unreasonably, endotoxin *per se* was initially implicated but not chemically detected. Indeed, when endotoxin preparations were made from isolated *B. recurrentis* and injected intravenously into rabbits, none of the pathophysiological changes associated with J–HR were detected (Young et al, 1982). Since the J–HR is induced by antibiotic and correlates with rapid removal of spirochaetes from the circulation, it is tempting to postulate that *en masse* phagocytosis of organisms made abnormal by the cell–wall action of penicillin causes overwhelming stimulation of macrophages, likely to be Kupffer's cells in liver, to produce and release cytokines. Experiments in the present authors' laboratory have shown that phagocytosis of intracellular pathogens by macrophage cell lines or peripheral blood derived monocyte/macrophages is a potent stimulus of cytokine release (Friedland et al, 1992, 1993). This hypothesis is strengthened by the demonstration of a heat-stable particulate pyrogen isolated from *B. recurrentis* (Bryceson et al, 1972). In addition, a study of the interaction of Lyme disease spirochaetes with human adherent macrophages or macrophage cell lines demonstrated potent production of interleukin-1 (Habicht et al, 1985).

THERAPY FOR THE JARISCH–HERXHEIMER REACTION

Various attempts have been made to ameliorate the J–HR of louse-borne relapsing fever and syphilis using pharmacological agents. Intravenous hydrocortisone was ineffectual (Warrell et al, 1970) and meptazinol, a partial opiate agonist, was only partially successful (Taklu et al, 1983). In addition, therapeutic trials of prednisolone, more potent pharmacologically than hydrocortisone, were unsuccessful in the management of the J–HR of syphilis (Gudjonsson and Skog, 1968). It is tempting to speculate that specific monoclonal antibodies directed against cytokines, such as TNF or IL-6 might be therapeutically efficacious in reducing the clinical severity of J–HR, since they have been shown to have protective effects in animal models of sepsis (Tracey et al, 1987; Starnes et al, 1990).

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THE VALUE OF SPUTUM GRAM STAIN IN THE DIAGNOSIS OF PNEUMOCOCCAL PNEUMONIA

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ABSTRACT: *The utility of sputum Gram stain in identifying Gram positive diplococci and other bacteria was studied in 39 patients with community acquired pneumonia (CAP). The results of the Gram stain of the sputum were compared to the Gram stain of the lung aspirate (LA). Of 28 patients whose LA smear showed Gram positive diplococci, 26 (95%) had the same organisms, either exclusively or predominantly, in their sputum. One patient had Gram negative rods both in the sputum and lung aspirate. Seventy-one per cent of patients with positive LA stain versus 50% with negative LA stain had taken antimicrobials for less than 36 hours prior to coming to hospital. We conclude that sputum Gram stain is a sensitive method for the diagnosis of pneumococcal pneumonia and is unaffected by a short period of prior antimicrobial treatment.*

INTRODUCTION

Initial antimicrobial therapy for CAP is usually based on a presumptive aetiologic diagnosis utilizing available epidemiologic, clinical, radiologic and microbiological information. The importance of the presence or absence of Gram positive diplococci in the expectorated sputum has been disputed over the years (1–4); sputum culture is non-specific (5) and blood culture is not sensitive. Both these tests are quite expensive for routine use in developing countries and, even if used, results would not be available at the time of treatment initiation. On the other hand, sputum Gram stain is useful because results are immediately available. In addition, it may demonstrate Gram positive diplococci not detected by routine culture methods because of stringent growth requirements, inhibition by other bacteria, or previous antimicrobial treatment.

The Quellung reaction, counter current-immunoelectrophoresis (CIE), coagglutination (COAG) and latex agglutination tests (6–8) have been found to be helpful in the rapid identification of pathogens. The clinical applicability of these newer tests compared to sputum Gram stain, however, has not been established.

Many patients with CAP come to hospital

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after using antimicrobials, usually for a short period, a problem encountered frequently by physicians in developing countries. The effect of prior antibiotic therapy on the accuracy of sputum Gram stain is not known. To determine the value of sputum Gram stain and the impact of prior antibiotic use, we prospectively compared the Gram stain findings in lung aspirates and sputa of 39 patients.

MATERIALS AND METHODS

Forty-three consecutive patients with CAP diagnosed by clinical and radiological means were prospectively studied between August 1987 and July 1989. All patients were treated either as inpatients or in the emergency room and had a detailed clinical examination and chest roentgenography. Sputa specimens were collected in sterile bottles and immediately spread over three slides, two for Gram stain and one for acid fast bacilli (AFB) stain. Transthoracic needle aspiration (TTNA) of the pneumonic area was performed using a number 20 gauge, 8.8 cm long, thin walled spinal needle as described by Davidson (5). The aspirate was then spread over two slides. Culture of LA and blood was attempted but the results were not interpretable for technical reasons. Both sputa and LA Gram stains were considered acceptable for interpretation whenever there were more than 25 pus cells per low power field. The slides were examined independently by two observers, the author and a microbiology technician. The sensitivity, specificity, positive predictive value and negative predictive value of Gram stain were then determined.

A history of antimicrobial use prior to coming to hospital, including dose and type, was carefully documented, although in some instances patients did not know either the name or the dose.

RESULTS

Out of 43 patients, four were excluded because the LA contained neither organisms nor pus cells, suggesting that the TTNA might have missed the lesion. Of the remaining 39 patients, 23 were male, and the mean age was 35 years. Complications due to TTNA included one major pneumothorax and two minor pneumothoraces. Three other patients had minor haemoptysis immediately following the procedures and all resolved spontaneously in less than an hour.

Sputa specimens were available in all 39 patients. It is interesting to note that many patients produced sputum only after repeated persuasion to do so. The results of sputa and LA Gram stains are shown in Table 1. Twenty-eight (72%) patients had lancet shaped Gram positive diplococci in their LA. Twenty-six (93%) of these had either exclusively or predominantly similar organisms in their sputa Gram stain. One patient had Gram negative rods both in his sputum and LA. Both blood and LA culture grew *Klebsiella* spp. in this particular patient. In the remaining ten patients, the LA Gram stain was negative. This might have been due to the use of antimicrobials prior to coming to hospital or because the pneumonia was caused by other non-Gram stainable organisms. The sputum Gram stain of these ten patients showed Gram positive diplococci in five, mixed organisms in three and no bacteria in the remaining two. The sensitivity of sputum Gram stain was 93%, the specificity 55%, the positive predictive value 84% and the negative predictive value 75% (Table 2). The inter-observer variability in the interpretation of the Gram stain

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was calculated to be 72% using the Kappa statistics.

Twenty-one of the 29 patients (71%) with positive LA stain had taken antimicrobials for a duration of less than 24 hours prior to coming to hospital (Table 2). On the other hand, five of the ten patients (50%) with negative LA stain had taken antibiotics for a similar duration of time. The commonest antibiotics used were procaine penicillin G given intramuscularly, or oral tetracycline, ampicillin or co-trimoxazole. These drugs were taken for less than three doses in the majority.

DISCUSSION

The utility of the sputum Gram stain in identifying organisms has varied greatly in previous studies. The sensitivity has ranged from 50% to 96% and the specificity from 17% to 100% (9–12). Not all the studies however used standard methods of collection and interpretation. Our study emphasizes the need for persistence and persuasion in order to get an adequate sputum sample. Blood, LA and pleural fluid cultures are the gold standards for the identification of etiologic agents in pneumonia. In the present study, both blood and LA culture were found technically difficult to perform and interpret. Gram stain of lung aspirate was highly specific for comparison purposes. In this particular study, the sputum Gram stain was very sensitive and sufficiently specific to help initiate treatment. The positive predictive value was also remarkably high. The inter-observer variability with a Kappa score of 72% is considered as in good agreement.

Early diagnosis and a decision to initiate treatment in lobar pneumonia is important because adverse outcomes commonly occur during the first 72 hours of illness. It is therefore imperative to make a reasonable choice of antimicrobials based on clinical, radiological and bacteriological findings. Blood culture in pneumonia is positive in only 10 to 30% and the result usually arrives too late to help initiate treatment. In this respect, sputum Gram stain provides very quick and reliable information. Other modes of diagnosis, including CIE, COAG, Latex agglutination and the Quellung reaction, have been advocated recently based on several studies. The relative importance of these tests compared to sputum Gram stain, however, is not yet established. The clinical applicability of such tests in developing countries is also debatable. Any consideration of the use of such highly technical diagnostic means needs a justification of the cost to benefit ratio. In this era of tremendously expensive diagnostic sophistication, sputum Gram stain stands as the time tested inexpensive diagnostic tool.

Unfortunately, many physicians have lost their skill in both performing and interpreting the Gram stain (13). As a result, they depend less and less on sputum Gram stain and resort to the so-called "blanket treatment", often using very expensive anti microbials.

Sputum Gram stain, unlike the other diagnostic methods, is important for the following reasons:

a) it can be done with reasonable confidence by the medical student, resident or staffman by the bedside;
b) coupled with the clinical and radiological findings, it will help the physician to decide on the choice of antibiotics;
c) it is inexpensive, and therefore most suited for developing countries; and
d) a negative gram stain will remind the physician to consider other causes of pneumonia.

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In this respect, sputum Gram stain is complementary to other modes of diagnosis. In this study, 10 of 39 patients who had lung aspirate had negative stain for organisms. It is probable that some of these patients had atypical pneumonia and therefore it would be justified to initiate treatment with erythromycin. Our study also showed that antibiotic treatment during the preceding 24 hours did not affect the outcome of the Gram stain. However, the dose used by most patients was small. It is probable that the outcome of LA and blood culture could have been affected by prior use of antibiotics.

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Table 1. Results of Gram stain of sputa and lung aspirate in 39 patients

	Sputum No. (%)	Lung aspirate No. (%)
Gram positive diplococci	31(75.6)	28(71.7)
Mixed organisms	3(10.8)	
Gram negative rods	1(2.7)	1(2.6)
Pus cells, no bacteria	4(10.8)	10(25.6)
Total	39(100.0)	39(100.0)

Table 2. Sputum Gram stain compared to lung aspirate Gram stain

Sputum	Lung Aspirate		
	Gram positive seen (No.)	Gram negative not seen (No.)	Total No.
Gram positive organisms seen	26	5	31
Gram positive organisms not seen	2	6	8
Total	28	11	39

Sputum Gram stain	= 26/28	= 92.8%
Sensitivity	= 6/11	= 54.5%
Specificity	= 26/31	= 84.0%
Positive predictive value	= 6/8	= 95.0%
Negative predictive value	= 32/39	= 82.0%
Accuracy		

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HIV infection and leprosy: a four-year survey in Ethiopia

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Between 1988 and 1992 three cross-sectional surveys for antibodies to HIV were done in 644 Ethiopian patients with histologically proven leprosy. Whereas the frequency of HIV-1 infection gradually increased from 3·2% to 6·5%, the clinical presentation, number of new patients, and frequency of relapse did not differ between HIV negative and positive patients. Thus HIV appears unlikely to have a significant impact on the incidence of leprosy in sub-Sahelian populations.

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The few epidemiological surveys on HIV and leprosy in countries in which both are endemic showed that coexistence of HIV and *Mycobacterium leprae* infections did not raise the incidence of leprosy.[1] These studies, however, were not confirmed on repeat survey. In an on-going investigation of retroviral infections in different groups of Ethiopian patients,[2] three consecutive cross-sectional serological studies were done over 4 years, during which the prevalence of HIV-1 infection in the general Ethiopian population increased three-fold.[3,4] Here we report on the involvement of HIV status in leprosy.

Between October, 1988, and September, 1989, between April and December, 1990, and between February and November, 1992, all patients attending the clinics of the All-Africa Leprosy and Rehabilitation Training Centre (ALERT), Addis Ababa, who underwent a diagnostic skin or nerve biopsy and gave consent were enrolled in the study (table). They were mainly new or recently treated cases (< 1 year) or patients with a complication. In the 1990 survey, 61 biopsy specimens were taken for the assessment of possible relapse in 45 patients previously treated with dapsone and in 16 defaulters from multidrug therapy; relapse was confirmed in 34 of the former and 11 of the latter. The number of patients investigated for reversal reaction was 0, 13, and 22 in the three surveys, respectively; and for erythema nodosum leprosum, 2 in the 1990 and 1992 surveys.

Concurrently, 607 patients with no clinical or histological evidence of leprosy were also studied. They were a group of non-leprosy patients attending the same hospital. Age and sex in the two groups were similar (eg, 49·0% of the leprosy patients were aged 20 to 39 years versus 49·6% in the non-leprosy group), but these populations differed in geographic origin: 83% of the leprosy patients were referred from provincial centres whereas 72% of the non-leprosy group indicated Addis Ababa as their site of residence. (Fuller epidemiological data can be obtained from the secretariat of AHRI.)

Serum was separated from whole blood within 4 hours of collection, split and stored at −23°C, sent on dry ice to Limoges, and kept frozen until tested. Serum samples were screened for antibodies to HIVs with a recombinant HIV-1/HIV-2 enzyme immunoassay (Abbott recombinant HIV-1/HIV-2 EIA). Positive samples were confirmed by western-blot HIV-1 and HIV-2 (Newlav blots I and II, Pasteur Diagnostics). Criteria for positivity were: for HIV-1, the presence of antibodies directed against env-encoded glycoproteins (gp160, gp110, gp41) and core proteins (p55, p25, and p18); and for HIV-2, presence of antibodies to gp140, gp110, gp36, and p56, p26, and p16.[5] 95% CI were calculated with the exact method.

Over the 4 years surveyed, the frequency of antibody to HIV-1 increased by a factor of two in leprosy patients: from 3·2% (95% CI 1·2–5·6) in the 1988–89 survey to 6·5% (3·5–10·0) in the 1992 survey. However, the distribution of HIV negative and HIV positive leprosy patients into multibacillary, paucibacillary, and indeterminate forms did not vary (table). 19 males and 12 females were seropositive; they belonged mainly to the 20–39-year age class (74%). In patients with reversal reaction, the rate of seropositivity was 11% (4/35, 95% CI 2·9–22·9), for those with confirmed relapse 2% (1/45, 0·0–6·7), and zero for the 4 cases of erythema nodosum leprosum (0·0–6·0), rates which are close to that of the entire group (4·8%, 3·3–6·5). The number of patients with well-documented, pure neural involvement was too small to draw conclusions. No Kaposi's sarcoma was observed in leprosy patients, but 6 cases were diagnosed in the non-leprosy group.

The political unrest in Ethiopia until early 1992 resulted in a substantial loss of follow-up by ALERT's leprosy

	Survey				
	1988–89	1990	1992	1988–92*	Total HIV positive*
Leprosy					
All cases	250 (8)†	194 (10)	200 (13)	644	31 (4·8%)
Multibacillary	74 (3)	83 (5)	77 (2)	234 (36·3%)	10 (4·3%)
Paucibacillary	130 (3)	86 (3)	96 (8)	312 (48·4%)	14 (4·5%)
Indeterminate	46 (2)	9 (1)	25 (3)	80 (12·4%)	6 (7·5%)
Inactive‡	0 (0)	16 (1)	2 (0)	18 (2·8%)	1 (5·6%)
Non-leprosy	201 (7)	206 (13)	200 (24)	607	44 (7·2%)

*As percentage of 644 or 607 for leprosy and non-leprosy totals, respectively. †Number of HIV positive cases. ‡Patients with histologically proven leprosy, treated with dapsone or multidrug therapy, released from treatment for ≥ 3 years, and studied for possible relapse.

Table: **Distribution of patients according to simplified classification plus indeterminate form**

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control division. The war prevented reliable follow-up of patients found seropositive in 1988–90. In a parallel but more limited survey on women with leprosy released from treatment,[6,7] 3 of the 5 women found seropositive in 1990 had died within 12 months with presumed diagnosis of infection by *M tuberculosis*, salmonella, and *Plasmodium falciparum*, respectively, but with no signs of resurgent leprosy.

In the non-leprosy patients the rise in frequency of HIV infection was greater: 3·5% (1·0–6·0) to 12·0% (7·5–16·5). The increase involved the same age class (68% aged 20–39) but a greater proportion of Addis Ababa residents (57% versus 14·5%). Antibodies to HIV-2 were not detected in either group.

This analysis in an urban reference centre for leprosy and skin diseases is not truly representative of the situation in Ethiopia. Nonetheless, we confirmed the overall rise in HIV seropositivity and the increase of dual infection by *M leprae* and HIV. The finding, however, was that so far the outbreak of HIV has not substantially altered the course of leprosy because the rate of detection of new cases and the age of clinical diagnosis are stable,[8] as are the ratio of multibacillary to paucibacillary forms, and the frequency of reversal reaction and of relapses among the HIV negative and HIV positive leprosy patients.

In sub-Sahelian populations, severe HIV-induced immunosuppression seems not to last long enough to promote the clinical expression of latent infection by *M leprae*, a slow-growing organism, or to predispose to the development of leprosy.

Although there is a need for continued surveillance of the *M leprae* and HIV interaction, it appears unlikely that HIV will have a serious direct impact on the incidence of leprosy.[1] The HIV pandemic may, however, have deleterious consequences on the resources and personnel available to leprosy control programmes.

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COMMUNITY ACQUIRED PNEUMONIA IN ADULTS IN ADDIS ABEBA: ETIOLOGIC AGENTS, CLINICAL AND RADIOGRAPHIC PRESENTATION

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ABSTRACT: *We prospectively studied 110 adult patients coming to Black Lion Hospital between August 1987 and July 1989 with community acquired pneumonia (CAP) for various etiologic agents and clinical and radiographic presentation.* Streptococcus pneumoniae *was the most common offending pathogen in 72% and 67.5% from sputum and lung aspirate (LA) Gram stain respectively, and in 41% by pneumococcal serotyping of sputum. Blood and LA culture grew* Streptococcus pneumoniae *in 4 (6%),* Staphylococcus aureus in 4 (6%), Enterobactericae *in (3%),* Pseudomonas, Klebsiella *and* Streptococcus viridans *in one case each. Non-bacterial pathogens included* Mycoplasma pneumoniae *in 3 (3%),* Influenza A *in 4 (4%),* Influenza B *in 3 (3%) and psittacosis/LGV in 4 (4%). Fever, cough, chest pain, tachypnea and coarse crepitations/bronchial breathing were the most common presenting signs and symptoms. Thirty per cent had associated diarrhoea and vomiting initially and 9% had altered state of consciousness at admission. Six patients came in a state of shock. Thirty-nine per cent had underlying illnesses. Ninety-three per cent had either segmental or lobar consolidation. Parapneumonic effusion occurred in 14%. The mortality was 11%. Tachypnea, the presence of underlying illness, altered state of consciousness, extreme leucocytosis and the presence of bilateral and multilobar lung involvement were found to be signs of poor prognosis. Our finding is similar to those from other African countries, except that we are reporting psittacosis/LGV for the first time in Africa.*

INTRODUCTION

Respiratory diseases comprise 11–17% of medical admissions to general hospitals in Ethiopia (1–3). Community acquired pneumonia (CAP) is the second most common cause of adult medical admissions in Addis Abeba and the leading cause of respiratory admission with a mortality of 17% (4). It is also a common cause of medical admissions in other parts of Africa including Zaria, Northern Nigeria and Zambia (5,6). Globally, the pneumococcus has been shown to be the most common cause of CAP (7,8). In West Africa, clinical and laboratory studies have shown *Strep. pneu-*

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moniae to be the commonest etiologic agent; *Mycoplasma pneumoniae* accounted for 17% of the causes of CAP (5,9). In Ethiopia, *Strep. pneumoniae* has been assumed to be the most common cause of CAP. Apart from analysis of the pattern of respiratory diseases in a general hospital in Addis Abeba (4), there has not been any systematic study which attempted to define the various etiologic agents and the clinical and radiographic presentation of the disease (4). The present study was designed to look at these and several aspects of CAP.

PATIENTS AND METHODS

Study population: From August 1987 to July 1989, 110 adult patients with CAP, consecutively coming to Black Lion Hospital, were admitted to the wards or the emergency room and examined by the author. Pneumonia was defined as an acute illness with radiological pulmonary shadowing, at least segmental or present in more than one lobe.

Data collection: Clinical data was collected on a specially designed form to record demographic data, symptoms, pre-existing illness, habits, physical signs, laboratory investigations, complications, treatment and outcome. Patients were closely followed while in hospital and appointed to come six to eight weeks after discharge.

Microbiologic methods: Sputa specimens were examined with Gram and acid fast stain (Zeihl-Neelson). Transthoracic needle aspiration (TTNA) of the pneumonic area was performed in 43 patients following an informed consent and the specimen studied with Gram stain, acid fast bacilli (AFB) stain and culture. Thirty-nine out of the 43 specimens were found adequate for study with Gram stain, AFB and culture. Blood and lung aspirate (LA) culture was done in 63 and 40 patients respectively. Counter current immunoelectrophoresis for the detection of pneumococcal antigen was done using pneumococcal omniserum as described by Tugwell and Greenwood (5) in 43 of sputa, 40 of sera, 93 of urine and six of pleural fluid, CSF and LA samples. All acute and convalescent sera, whenever available, were tested for mycoplasma, influenza A and B, adenovirus, Q-fever and psittacosis/LGV by the complement fixation test at the Royal Victoria Infirmary, Department of Virology, Newcastle, UK, a WHO Collaborating Centre for Reference and Research on Rapid Laboratory Viral Diagnosis. A single titre of $\geq$ 1/160 or a $\geq$ 4 fold rise was considered indicative of a diagnosis. Indirect immunoflorescence antibody testing for Legionella was done in 40 specimens.

Roentgenography: A postero–anterior and lateral chest X-ray was available for 100 patients at admission. In the remaining ten either a chest X–ray was done late in the course of the illness or the X-rays were lost in between. Control chest X–ray was done towards the completion of treatment in the majority and six to eight weeks after discharge.

Haemoglobin, total blood leucocyte count and erythrocyte sedimentation rate were performed in 95,104 and 39 patients respectively.

Statistical methods: Statistical analysis was performed using the chi–square test for proportion and the t–test to compare the means. The Fisher's exact test was employed wherever appropriate.

RESULTS

Of the 110 patients, 62 were male and the mean age was 35 years (range 14–75 years). Seventy–five per cent of the

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patients were below 45 years of age, 88% were either poor or had average income. Most had been ill for less than a week. The mean duration of illness prior to coming to hospital was 4.7 days. Thirty-eight patients (35%) had received antibiotics before they arrived in hospital. The most common antibiotics used were penicillin, oral tetracycline, ampicillin and cotrimoxazole.

The principal presenting symptoms and signs at admission are shown in Tables 1 and 2. Of the 91 patients with productive cough, 63% had blood streaked sputum and only 3% had frank haemoptysis. Single chills were observed in 35%. Twenty-nine per cent presented with associated diarrhoea and/or vomiting. This, however, did not last more than a day or two in the majority. Thirty-nine per cent admitted to the presence of an underlying illness. Chronic chest diseases, including pulmonary tuberculosis, bronchial asthma, chronic bronchitis and chronic obstructive lung disease (COPD), accounted for 23% of the underlying illnesses. The remaining 16% had non-respiratory underlying illnesses. These included diabetes mellitus, essential hypertension and heart diseases in three patients each, splenomegaly in two patients and chronic liver disease, chronic lymphocytic leukaemia, intracranial space occupying lesion, relapsing fever, malaria and HIV infection in one patient each.

Eight patients arrived in a state of shock probably related to bacteraemia. All responded to intravenous fluid administration and antibiotics in less than 12 hours. Twenty more patients had associated hypotension at admission. Cyanosis and intercostal indrawing were noted in 11% and 26% of the patients respectively.

Of the twenty patients with intercostal indrawing, 12 patients had clinically severe pneumonia and four died. Three of the nine patients with cyanosis had underlying COPD and asthma and two patients expired.

Ten patients had altered state of consciousness at arrival. Of these, three patients came in shock, four patients each had *Klebsiella pneumoniae* bacteraemia, *Strep. pneumoniae* bacteraemia, *Pneumococcal meningitis* and HIV associated meningoencephalitis and all expired. Two patients had *Staph. aureus* bacteraemia and *Falciparum malaria*. Altered state of consciousness was found to be a sign of poor prognosis.

Etiologic agents: The results of tests for the various etiologic agents are shown in Table 3. Excluding sputum Gram stain, a microbiological diagnosis was established in 59 of 110 patients (54%). Pneumococcal infection was diagnosed in 28 of 39 patients (72%) from LA Gram stain and in 72 of 108 patients (67.5%) from sputum Gram stain.

Pneumococcal antigen was detected in 17 of the 43 sputa specimens (41%) and in three of the six (50%) CSF, pleural fluid and LA samples. Pneumococcal antigen was detected in none of the sera and urine samples. Non-bacterial pathogens were detected in 14 patients. In five of these 14 patients, *Strep. pneumoniae* was also identified either by LA Gram stain or culture, suggesting a double infection.

Roentgenographic findings: The results of the chest X-ray in 99 patients are shown in Table 4. Ninety-three per cent had either segmental or lobar consolidation. Fourteen patients (14%) had associated parapneumonic effusion. Therapeutic thoracentesis was performed in only one patient. None of these patients developed empyema thoracis or lung abscess. The right lung was involved in twice as many patients (57%) as the left side (27%). Both lungs

were involved in 15%. The most common sites of involvement were the right lower lobe (22%), the right upper lobe (17%) and the left lower lobe (12%). Most patients had either a partial or complete resolution of the chest infiltrates towards the end of treatment. Slightly less than 30% of the patients came for a follow-up exam six weeks after completion of treatment and in the majority the chest X-ray had completely cleared. One patient who had a recurrence of the chest infiltrate three months after completion of treatment was found to be seropositive for HIV-1 infection.

Laboratory investigation: The mean (SD) haemoglobin was 12.5 gm% (2.5). The mean (SD) WBC count was 13,056/dl (9,106). Leucocytosis (>10,000/dl) was noted in 60%. In 8% the count was more than 25,000/dl. There was only one patient with leucopaenia. The mean (SD) erythrocyte sedimentation rate during the first hour was 68mm (45). Follow-up ESR was not done.

Complications, treatment and outcome: The mean duration of hospital stay was 12 days (range 1-35 days). The most important complications encountered were shock (10%), parapneumonic effusion (14%), meningitis (3%) and jaundice (4%). One patient with underlying diabetes mellitus developed ketoacidosis. Meningitis was observed in three patients. In one patient, the CSF culture grew *Strep. pneumoniae*. The second had *Staph. aureus* septicaemia and the third had meningoencephalitis on the background of retroviral infection. In this patient, the CSF was sterile with pleocytosis and was negative for *Cryptococcus neoformans*. There were no cases of arthritis, pericarditis or endocarditis.

Ninety-four patients (83%) were treated with parenteral penicillin alone. The remaining 16 patients were treated with one of a combination of penicillin and gentamycin, cloxacillin or erythromycin based upon the clinical, radiologic and aetiologic findings.

Eleven patients (10%) died. Seven of these (64%) had underlying illnesses. These included pulmonary tuberculosis in two patients and diabetes mellitus, severe asthma, intracranial space occupying lesion, hypertension and HIV infection with meningoencephalitis in one patient each. Two patients (22%) had *Strep. pneumoniae* bacteraemia. All four patients with *Staph. aureus* pneumonia survived although in two cases the course of the illness was protracted for more than two weeks. In one of these patients the portal of entry was presumably from a skin infection and the chest X-ray showed bilateral multiple opacities which subsequently cavitated. None of the patients with a diagnosis of non-bacterial pneumonia died.

The signs and symptoms identified as poor prognostic factors are shown in Table 5. Tachypnea, duration of illness more than one week prior to coming to hospital, altered state of consciousness at arrival, extreme leucocytosis exceeding 20,000/mm^3, and multilobar or bilateral lung involvement were significantly related to adverse outcome.

DISCUSSION

This is the first detailed study of CAP in adult Ethiopians. As in many developing countries, our patients were young as expected from the population pyramid characteristic of developing countries. While old age is a well recognized poor prognostic factor (10), despite the fact that our patients were young, the mortality was comparable to that in developed countries where pneumonia tends to occur at a rela-

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tively older age.

Rigors were observed more frequently in our patients (74%) than in the patients from Zambia (6) and Nigeria (11). Single chills occurred in 35% and all had Gram positive diplococci in their LA and/or sputum. Diarrhoea and vomiting occurred in 29% of our patients but never appeared as presenting complaints to mislead the diagnosis. Herpes labialis was noted in only six patients.

A microbiologic diagnosis was made in 54%, slightly less than the reports from elsewhere (12,13). *Strep. pneumoniae* was the most common organism identified from both the sputum and lung aspirate Gram stain. Blood and LA culture grew organisms in only 14%. This is a very low yield as is the case in most developing countries where culture facilities are either unavailable or grossly inadequate. Besides, 35% of our patient had taken antibiotics prior to coming to hospital and this might have compounded the problem.

Mycoplasma pneumoniae has been reported from Nigeria (17%). Although the prevalence in our series is low (3%), it certainly exists as a cause of CAP and physicians should be on the lookout in patients with atypical radiologic presentation, strong epidemiologic history and poor response to penicillin treatment. Psittacosis/LGV was diagnosed in four patients. One of these patients had a double infection with *Strep. pneumoniae*. To our knowledge this is the first report from Africa (14).

There were seven cases (6%) of pulmonary tuberculosis (TB). The diagnosis was made late in all except one patient in whom the sputum was positive for acid fast bacilli. The delay in diagnosis was probably due to the superinfection which masked the TB. It is therefore worthwhile to check all sputa for AFB and perform further tests, including pleural biopsy, in those patients who show a delay in both the clinical and radiographic response. Alternatively therapeutic trial may be necessary in patients difficult to diagnose.

Lobar/segmental consolidation occurred in 93% and this is probably typical for developing countries where *Strep. pneumoniae* continues to be the most frequent offending pathogen. A recent study of CAP in adults in British hospitals (12) showed that lobar and segmental pneumonia occurred in 43% and 21% respectively. The prevalence of parapneumonic effusion in our series (14%) was comparable to the findings by Safowora and Onadeko from Nigeria (11). Unlike the studies from Nigeria (11) and Zambia (6) however, none of our patients developed frank empyema. Amongst 142 patients with CAP from Ethiopia, empyema and lung abscess occurred in three and four patients respectively (4). None of our patients developed a lung abscess.

Four patients (4%) developed jaundice with tender hepatomegaly. One of these had mycoplasma pneumonia and another had pneumococcal pneumonia. In the remaining two an etiologic diagnosis was not made. Jaundice and tender hepatomegaly have been noted in 20% of Nigerian patients and described as one of the misleading signs of lobar pneumonia (15). Trowell (16) has suggested that the African with pneumonia may be particularly liable to become jaundiced. However, both our data and those from Zambia (6) and Nigeria (11) have shown that jaundice is not a particularly frequent finding in Africans.

Eleven patients died (10%), of whom seven had underlying illness. This is probably slightly less than the 17% mortality reported from Ethiopia (4). Excluding the

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seven patients with underlying illness, the adjusted mortality is 4%. The mortality rate of pneumonia was 4.2% in Zambia (6), 22.7% and 3.5% in Ibadan (11,17), 1.3% in Nairobi (18) and 5.7% in the recent British hospitals study (12). Most of our patients who died did so within three to five days after admission.

In conclusion, this is the first clinical and radiographic description of CAP in adult Ethiopians. Our study has also shown that *Strep. pneumoniae* is the commonest offending pathogen and sputum Gram stain is a cheap and valuable test to be done before initiation of treatment. However, the possibility of other bacterial and non-bacterial pathogens has to be considered, especially in patients with negative sputum examination, atypical radiographic presentation and poor response to penicillin treatment.

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Table 1. Symptoms and underlying illnesses

Symptoms		Patients examined (No.)	Patients with symptom No.(%)
Cough		106	91(86)
	Abundant sputum		67(63)
	Haemoptysis	107	97(91)
Chest pain		104	77(74)
Chills			36(35)
	Single		41(39)
	Multiple	105	85(81)
Headache		106	31(29)
Diarrhoea/vomiting		102	40(39)
Underlying illnesses			7(7)
	Pulmonary TB		6(6)
	Bronchial asthma		6(6)
	Chronic bronchitis		2(2)
	COPD		1(1)
	Sinusitis		1(1)
	Bronchogenic carcinoma		17(17)
	Non-respiratory		
Habits	Smoking	107	12(11)

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Table 2. Physical signs

Signs	Total No. of patients	Patients with No. (%)
Respiratory rate ≥ 30/min	90	33(37)
Shock	104	8(8)
Hypotension	104	20(19)
Fever (≥ 37.5%C)	104	77(74)
Cyanosis	83	9(11)
Intercostal retraction	78	20(26)
Coarse crep/bronchial breathing	101	89(88)
Jaundice	105	4(4)
Altered state of consciousness	110	10(9)
Herpes labialis	106	6(6)

Table 3. Etiology of CAP in 100 patients

Type of test	Patients tested (No.)	Positive No.(%)
Gram positive diplococci		
Sputum	108	72(68)
Lung aspirate (LA)	39	27(69)
Pneumococcal antigen		
Sputum	43	17(42)
Pleural fluid, CSF, LA	6	3(50)
Urine	93	0
Sera	40	0
Blood and LA culture		
Strep. pneumoniae	60	4(6)
Staph. aureus	60	4(6)
Enterobacteriacae	60	3(5)
Others	60	3(5)
Complement fixation test		
Mycoplasma	104	3(3)
Influenza A	104	4(4)
Influenza B	104	3(3)
Adenovirus	104	0
Q-fever	104	0
Psittacosis/LGV	104	4(4)
Immunoflorescence antibody		
Legionella	40	0

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Table 4. Chest X-ray findings in 99 patients

Chest X-ray finding	Number of patients No.(%)
Lobar/segmental	
Right upper lobe	17(17)
Right middle lobe	7(7)
Right lower lobe	22(22)
Left upper lobe	5(5)
Lingula	1(1)
Left lower lobe	12(12)
Right multilobar	7(7)
Left multilobar	7(7)
Bilateral	14(14)
Bronchopneumonia	4(4)
Intersititial pneumonia	2(2)
Parapneumonic effusion	14(14)

Table 5. Poor prognostic factors

Signs and symptoms	Patients with		Patients without		p-value
	Patients No.(%)	Deaths No:(%)	Patients No. (%)	Deaths No.(%)	
Tachypnea (RR > 30/min)	46	9(20)	44	1(2)	$p < 0.05$
Duration of illness (> 1 week)	30	9(30)	79	2(3)	$p < 0.001$
Altered state of consciousness	10	4(40)	93	6(6)	$p < 0.01$
Underlying illness	40	7(18)	60	4(7)	$p = 0.08$
Extreme leucocytosis (>20,000/mm³)	15	4(27)	89	7(8)	$p < 0.05$
Multiloboar involvement	28	6(21)	71	5(7)	$p < 0.05$
Bilateral involvement	14	6(43)	85	5(6)	$p < 0.001$

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Byssinosis and tuberculosis among textile mill workers in Bahar Dar, Ethiopia

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A cross-sectional study was conducted in 1991 on 433 workers of a cotton mill in Bahar Dar, northern Ethiopia. The study consisted of symptom evaluation using a standardized questionnaire, lung function tests, chest x-ray, and measurement of dust concentration in the various work areas. A hundred non-exposed hospital workers were included as control group. The overall prevalence of byssinosis among the exposed subjects was 45.5%, being highest among carding (57.9%) and ring frame workers (57.1%). Lower prevalences were found in weavers (36.7%) and those working in the preparatory unit (32.1%). Chronic bronchitis occurred in 48.8% of workers in the carding section, and in none of the control group. Bronchial asthma occurred in 11.5% of workers in the carding and ring frame sections, and in 28.6% of the workers in the waste section. Twelve per cent of the control group had bronchial asthma. Tuberculosis was prevalent in 5.3% of the mill workers and in 2.1% of the control group. Ventilatory capacity (FEV1 and FVC) was significantly reduced in the exposed workers ($p<0.05$). The study revealed that the prevalence of byssinosis and other respiratory disorders was extremely high among the cotton mill workers. In view of the above findings preventive measures deserve a high priority.

Key words: byssinosis, cotton mill, tuberculosis, Ethiopia

Byssinosis is an occupational respiratory disease in cotton and soft hemp workers. It is characterized by chest tightness and breathlessness at work after weekend break and may lead after several years of exposure to chronic respiratory impairment.[1,2] These symptoms are associated with measurable changes of pulmonary functions. The exact pathogenesis is unknown but endotoxins from bacteria contaminating cotton are thought to be central in causing bronchial obstruction.[3,4] The prevalence of respiratory symptoms and byssinosis was reported to be highest among card and blow room workers in cotton spinning mills.[5,6]

Tuberculosis is considered to be an occupational disease when the infection occurs because of occupational exposure. Even though contracting tuberculosis is significant in pneumoconiosis, workers did not yet suffer unduly from tuberculosis as a complication of byssinosis.[7]

Cotton textile industry has become an important economic sector in many developing countries including those in tropical Africa. However, only few investigations on the occurrence of occupational diseases have so far been published. The objective of this study was to assess the prevalence of byssinosis and tuberculosis as well as other respiratory disorders among workers exposed to cotton dust in Bahar Dar textile mill, northwest Ethiopia.

SUBJECTS AND METHODS

Population

From the workforce (n=1237) of the textile mill in Bahar Dar, Northwestern Ethiopia, 433 (35%) textile workers (233 males, 200 females) aged between 22 and 55 years were selected. Random number tables were used for selection. One hundred hospital workers (51 males, 49 females) living in the same geographical area were included as controls.

Medical examination

A modified questionnaire of the British Medical Research Council[8] was used for obtaining information on age, smoking habits, duration of work, occupational history and respiratory symptoms. Each worker was physically examined with emphasis on the cardiopulmonary system and signs and symptoms suggestive of tuberculosis. All examinations were done by the same physician without prior knowledge of exposure status. Byssinosis was diagnosed and graded according to the criteria used by Schilling et al.[1], that comprises four grades of severity.

Subjects suffering from recurrent cough or phlegm production for at least three months each year for not less than two successive years were diagnosed as having chronic bronchitis.[9]

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Lung function tests

Pulmonary function tests were carried out using a vitalograph spirometer after providing careful instructions. Forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were recorded after weekend break at the beginning of the shift and after a minimum exposure of four hours. The recordings were taken with the subjects standing. Five expiratory efforts were taken and the highest two values were averaged. All volumes were corrected to body temperature and pressure saturated with water vapour (BTPS). The predicted normal values of FEV_1 and FVC for each subject was obtained using a normogram for healthy African descendants.[9]

Bacteriologic examinations

Each subject was provided with a plastic container and asked to supply early morning sputum. Specimen were investigated the same day by the laboratory of the factory's clinic. A smear was made from the specimens stained by Ziehl-Neelsen method and examined by microscopy for acid fast bacilli.

Radiological examination

Chest x-rays were done on 243 randomly selected mill workers as well as on 97 controls. Parenchymal changes compatible with tuberculosis were recorded according to the WHO scheme.[7]

Subjects considered to be tuberculous were those showing infiltrations grade I, II or III and treated accordingly.

Environmental measurements

Levels of total dust and of the respirable fraction (<7 micro equivalent diameter) had been measured by Mentisnot[10] in the various work places: highest levels (above 3 mg m^{-3}) were found in the blowing and carding sections; concentrations between 1 and 2 mg m^{-3} were reported in the simplex, ring frame and waste units, and levels lower than 1 mg m^{-3} in the weaving and weaving preparatory areas. Personal dust sampling was carried out in order to estimate the actual exposure of the workers. The results of these measurements were in general about 10% higher than the ones obtained by area sampling.

Data analysis

The prevalence of byssinosis, chronic bronchitis, bronchial asthma and pulmonary tuberculosis was determined. Mean values for the different groups were compared by multiple t–tests. For all tests, a p–value <0.05 was considered significant.

RESULTS

Population

Marital status, family size and income were similar in all groups. The results of the physical characteristics are summarized in *table 1*. Blowers and carders were significantly taller and older than the other workers and the controls. Weavers and blowers were found to be significantly heavier than the other groups.

Lung function and respiratory impairments

Observed and predicted mean values of FEV_1 and FVC of all groups are summarized in *table 1*. There was a significant difference in FEV_1 between exposed and non-exposed subjects. The workers from the blowing and carding units had the lowest mean FEV_1/FVC %.

The prevalence of non-specific chronic cough, chronic bronchitis, and bronchial asthma are shown in the *figure*. Prevalence of chronic bronchitis was highest among ring frame operatives (48.8%), and lowest among weaving preparatory workers (2.5%). The overall prevalence of bronchial asthma among exposed and controls was the same (12.0%). Significantly increased prevalence was noted in the waste room workers (28.6%).

Considerable numbers of workers from the various sections of the mill suffered from byssinosis *(table 2)*. Highest prevalences were recorded among workers in the carding (57.9%), ring frame (57.1%), and blowing (55.0%) areas. Workers

Table 1 Physical characteristics, pulmonary function data, observed and predicted forced expiratry volume in one second (FEV_1) and forced vital capacity (FVC) of subjects at Bahar Dar textile mill and controls Mean ± SD

Section	N	Age (years)	Height (m)	Weight (kg)	Observed FEV (1/sec)	Observed FEV (1)	Observed FEV/FVC %	Predicted FEV (1/sec)	Predicted FVC (1)	Predicted FEV/FVC %
Blowing (1)	20	46.4 ± 4.76	1.66 ± 0.08	62.5 ± 10.2	2.4 ± 0.60	3.2 ± 0.61	70	2.8 ± 0.40	3.2 ± 0.53	88
Carding (2)	19	45.1 ± 4.06	1.65 ± 6.2	59.3 ± 7.64	2.2 ± 0.61	3.1 ± 0.38	71	2.8 ± 0.30	3.2 ± 0.37	88
Simplex (frame) (3)	56	40.7 ± 7.55	1.60 ± 9.5	58.7 ± 10.0	2.1 ± 0.63	2.7 ± 0.67	77	2.81 ± 48	3.1 ± 0.60	90
Ring frame (4)	126	40.3 ± 6.28	1.60 ± 0.8	55.3 ± 0.20	2.0 ± 0.58	2.6 ± 0.66	77	2.6 ± 0.38	2.8 ± 0.48	92
Waste (5)	14	42.9 ± 6.28	1.61 ± 0.09	54.9 ± 8.27	2.0 ± 0.63	2.5 ± 0.76	80	2.5 ± 0.39	2.8 ± 0.51	89
Weaving preparatory (6)	78	40.1 ± 6.58	1.61 ± 3.8	56.9 ± 10.4	1.9 ± 0.77	2.6 ± 0.79	73	2.6 ± 0.41	2.8 ± 0.49	92
Weaving (7)	120	42.0 ± 6.48	1.67 ± 3.6	60.1 ± 9.33	2.3 ± 0.69	3.1 ± 0.70	74	2.9 ± 0.34	3.2 ± 0.42	91
Total	433				2.5 ± 0.58	3.0 ± 0.60	83	1.8 ± 0.40	3.1 ± 0.50	90
Control (8)	100	35.1 ± 9.04	1.62 ± 4.8	58.8 ± 9.09						

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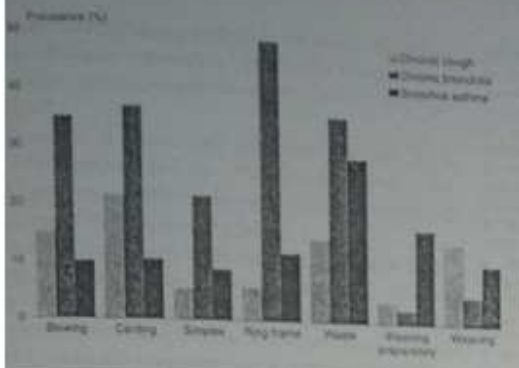


Figure Prevalence of non-specific chronic cough, chronic bronchitis and bronchial asthma of subjects studied in Bahar Dar textile mill

from sections in which the dust levels were lower than in other areas, such as weaving and weaving preparatory, showed the lowest rates of byssinosis, 36.7% and 32.1%, respectively. The overall prevalence of byssinosis of all grades was 45.5%. Byssinosis grade II was found in 52% of the affected individuals of the weaving preparatory group compared to 50% in the waste and weaving section, 45% in the carding, and 27% in the blowing groups. The number of individuals suffering from byssinosis grade I was lowest in weavers (27%) while the highest (54%) was observed among blowers.

As the mean duration of exposure was similar in all workers (21.7 years; SD=6.7 years) it was not possible to investigate the dose-response relationship (*table 2*).

Of 321 sputum specimen examined under direct microscopy six (1.9%) were positive for acid fast bacilli. X-ray examination revealed fibrosis and calcifications in 25 (10.2%) workers and in three controls (3.0%). Infiltrates with cavities and without (grade I to III) were noted in 16 workers. Individuals with infiltrates grade I to III and positive acid fast bacilli were considered tuberculous. Overall, 16 workers (5.3%) and one control (2.1%) were diagnosed as having tuberculosis.

DISCUSSION

The study group of this investigation comprised workers who had been exposed to high levels of cotton dust over many years. Mean duration of exposure was similar (21.7 years; SD =6.7 years) in all groups and 'labour turnover' was very low. These facts might have lead to the observed high prevalence of byssinosis (45.5%) in this work force. Relevant figures from cotton mills in Egypt and Sudan were 7% and 37%, respectively.[7,11]

Dust concentrations in the various sections of the mill had been measured previously[10], and were found to be very high; the lowest levels found in the weaving and weaving preparatory rooms were about 20% higher than the limit levels of 0.75 mg m^{-3} as recommended in the United States[12] for industrial weaving units. However, the concentrations observed in the blowing and carding areas were four to five times higher than recommended standards. The high prevalence of byssinosis in the carding (57.9%), ring frame (57.1%), and blowing (55.0%) areas in the Bahar Dar textile mill corresponds with the observed high dust levels in these areas and is also in agreement with previous reports.[13,14]

Byssinosis grade I was two to three times as prevalent in the highly exposed groups (blowing and carding areas) than in the relatively moderately exposed groups. Also, byssinosis grade II was found highest in the carding group. However, in blowers prevalence was lower than in groups working in areas where dust levels were much lower; the reason for the latter finding is unclear.

The occurrence of chronic bronchitis followed a similar pattern as that of byssinosis; while none of the controls exhibited relevant symptoms, the frequency of chronic bronchitis increased, in general, with exposure to cotton dust.

Bronchial asthma occurred as often in workers as in controls (12%). The reason for the parallelly high prevalence in the latter group could only be speculated upon: firstly, a relatively high endemic prevalence is found in the Bahar Dar region[15], and secondly, in Ethiopia it is a tradition that those with chronic diseases tend to aggregate in health centres where medication is easily available. Most frequently bronchial

Table 2 Prevalence of byssinosis and mean duration of exposure in years of all subjects studied in Bahar Dar textile mill

Section	N	Grade 0 n	Grade 0 %	Grade 1/2 n	Grade 1/2 %	Affected Grade I n	Affected Grade I %	Grade II n	Grade II %	Total affected n	Total affected %	Mean duration of exposure (years)
Blowing	20	9	45.0	2	10.0	6	30.0	3	15.0	11	55.0	22.8 ± 7.00
Carding	19	8	42.1	2	10.5	4	21.1	5	26.3	11	57.9	21.7 ± 4.65
Simplex (frame)	56	28	50.0	2	3.6	12	21.4	14	25.0	28	50.0	20.5 ± 7.12
Ring frame	126	54	42.9	11	8.7	32	25.4	29	23.0	72	57.1	22.0 ± 6.08
Waste	14	8	57.1	1	7.1	2	14.3	3	21.4	6	42.8	21.9 ± 6.73
Weaving preparatory	78	33	67.9	2	2.56	10	12.8	13	16.7	25	32.1	22.1 ± 6.36
Weaving	120	76	63.3	10	8.3	12	10.0	22	18.3	44	36.7	21.5 ± 7.44
Total	433 (100%)	236	54.5	30	6.9	78	18.0	89	20.6	197	45.5	21.7 ± 6.65

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asthma was observed among workers in the waste unit, where all forms of wastes accumulate. Endotoxin contaminated dusts and dust byproducts might have contributed to this high prevalence.[4]

The prevalence of tuberculosis accounted for only 5.1% among textile workers and was, thus, low compared to the national prevalence of 40%[16], a fact which could be explained by the so-called 'healthy worker effect'.

A drawback of the present study was that endotoxin levels could not be measured in the various sections; bacterial endotoxins are known to be an important aetiologic factor in the causation of acute and chronic respiratory reactions and occur in considerable concentration in cotton mills.[3,4] The issue whether respiratory impairments in cotton mill workers are more closely related to dust concentrations or endotoxin levels has so far not been clarified.

In conclusion, it is of paramount importance to implement protective measures such as installation of hoods and dust filters, ventilators and use of vacuum cleaners in the various factories. Additionally, supply of respirators might be considered in areas with high dust levels. As stated by Parker 'the contribution of medical surveillance is small, but control of spreading dust is much greater'.[17] In future, regular surveillance of air dust levels as well as regular medical surveillance of the workers in order to identify those with early signs of impairments should be undertaken.

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THE NEUROLOGICAL MANIFESTATIONS OF HIV-2 INFECTION

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The symptoms and clinical signs associated with infection by HIV-2 are similar to those described for infection with HIV-1 (3,4), but the epidemiological studies suggest that the evolution of infection by HIV-2 is slower than that determined by HIV-1 with, in particular, much longer survival (1,4,5).

Affection of the nervous system is frequent with infection by HIV; depending upon the clinical stage, the population studied and the location of the study, it may vary between 10% and 70% (6 to 9), but if we refer only to post mortem examination data, the prevalance of the neurological affections appears much greater, observed in 70% to 80% of cases, whether concerning the central nervous system or the peripheral nervous system (10,11). Most studies concern patients infected with HIV-1; similar affections have been reported in patients with HIV-2 (3, 4, 12 to 18), but their frequency is unknown. Neurological manifestations during HIV-2 infections, as for HIV-1, are either secondary to the direct attack on the nervous system by the virus or secondary to an infection by an opportunistic or tumoral affection due to the immunodepression caused by the retrovirus.

NEUROLOGICAL MANIFESTATIONS ASSOCIATED WITH HIV-2 NEUROTROPY

Subacute encephalitis

This is the most frequent form of attack to the nervous system described in infections by HIV-1 (19). It is observed in 30% to 60% of patients in the AIDS stage (20,21). In Africa, it has been particularly well observed in Tanzania (6) and, with a lower frequency, in Zaire (7). This subacute encephalitis has also been found in patients infected with HIV-2 (3,17).

The clinical symptomatology is identical whichever virus is concerned; the start is progressive, characterised by cognitive problems, often with memory problems, difficulty in ideomotor concentration and a slowing down of mental processes. In a more evolved stage, the picture is that a veritable servere dementia where a bedridden state progressively appears. The evolution takes place of some few month, leading to death. The diagnosis is made after elimination of other causes of dementia. Complementary investigations show up nothing specific, their interest being to find a possible associated pathology. Definite diagnosis of the encephalopathy rests on the anatomico-pathological examination.

Myelopathies

They are much less frequent than encephalitis and have been seen in cases if HIV-2 infection (15,16). The clinical signs are usually discrete: they are associated with a pyramidal corticospinal syndrome with hypotonia, osteotendonous hyperactivity, paraplegia and, sometimes, ataxia when the posterior medullar cords are affected. In HIV-1 infections, neuropathological tests have shown a diffuse colliquation affecting the white matter of the posterior and lateral cords. There does not seem to have been any neuropathological examinations in the case of VIH-2 myelopathies.

SECONDARY NEUROLOGICAL MANIFESTATIONS DUE TO IMMUNODEPRESSION

Opportunistic infections

• Cerebral toxoplasmosis

This is the most frequent opportunistic infection of the central nervous system found in HIV-1 patients (22). In western countries, its prevalance is between 20% and 40% in patients with AIDS. It is 23% in a series of African post mortem examinations (23), but its frequence appears to be increasing.

This complication has also been described in patients with HIV-2 (4,12 to 14). As for HIV-1, it is most likely secondary to the reactivation of a latent infection by Toxoplasma gondii. In the majority of cases, it appears as signs of a localised attack to the brain: partial epileptic attacks, hemiparesis, language difficulties. In fact, the signs depend upon the localisation of the lesions.

Exceptionally, this diffusion of lesions is the origin of the encephalopathy picture, sometimes with dementia.



The neurological manifestations associated with HIV-2 are probably identical to those observed with HIV-1, but with a slower evolution.

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The cerebral CAT scan is the preferred examination for revealing the presence of small multiple hypodensities, usually situated in the central grey nucleus. These lesions are always shown up by injection of a contrast product, which determines a ring contrast. Modifications of the cerebro-spinal fluid (CSF) are usual, as well as positivity of immunological tests which, however, may be negative in patients having an immunodepression.

In the absence of formal diagnostic proof, if a toxoplasmosis is suspected in a patient suffering from AIDS, it is preferable to institute a treatment (association of pyrimethamine and sulphonamides). Clinical improvement is often the best diagnostic criterium. This treatment should be maintained for several weeks.

• Cryptococcal meningitis

In the United States, cryptococcosis with AIDS appears in 5% to 10% of cases (24). It is particularly frequent and much higher in Africa, particularly in Central and East Africa (25). This complication was reported in the USA by Ruef, et al. in 1989 in a patient infected by HIV-2 (12). The clinical manifestations appear similar whichever retrovirus is the cause. They are consistent in the early stages in a change in the general state, with anorexia and tiredness which occur within a context of fever and intermitent headaches. Then the meningitis picture appears with headaches, photophobia, vommiting and rachidial stiffness (26). In Africa, the patients are usually hospitalised at this late stage. Certain diagnosis rests on evidence of cryptococcosis by analysis of the cerebro-spinal fluid after colouring with Indian ink. In the case of doubt, it is necessary to make cultures and a search for cryptococcosis antigens both in the blood and in the cerebro-spinal fluid, where the result is almost always positive.

• Multifocal progressive leukoencephalopathy (PML)

This complication is associated with the JCV virus of the papovirus family. Its frequency is 0.5% to 1% in HIV-1 AIDS patients (27). It also exists with HIV-2 infections (18). The usual signs are personality change accompanied by problems of the superior functions with, in particular, aphasia. The CAT scan shows hypodense lesions in the white matter without mass effect not taking the contrast. Certain diagnosis evoked by clinical and radiological observation is given by cerebral biopsy, but there is no specific treatment available at present.

Tumoral Process

This essentially concerns primitive lymphoma of the type immunoblastic B. Frequent in Europe in cases of HIV-1 (10% of patients with neurological problems) (24), it has been described in a patient infected by HIV-2 (3). Its prevalence is not the same as in Africa.

The clinical picture is that of an expansive intracerebral process: focalised deficiency, convulsions and problems of conscience are frequent. Usualy the symptoms are multifocal. The CSF may show a lymphocytic reaction with immature yellow cells, but most often they are normal or without any specific anomaly. On CAT scan, spontaneous hypodense lesions appear, shown up by contrast, thus differenciating from those observed in PML. The lymphomas may, on the other hand, be difficult to differenciate from a toxoplasmosis. The heterogeneous nature of the lesions, their size greater than 3 cm, and the invasion of a ventricle, may suggest a lymphoma rather than a toxoplasmosis. Whatever the case, an anti-toxoplasmosis treatment should be systematically instituted. The inefficacity of the treatment is an indication for the biopsy which allows confirmation of a lymphoma. Radiotherapy is effective, but the prognostic is, in any case, unfavourable.

CONCLUSION

In 1994, there is very little data concerning neurological manifestation associated with infection by HIV-2. The first publications allow us to think that they are probably identical to those observed for HIV-1 with, however, a slower evolution. But, their prevalence is unknown. Perhaps the future will allow us to confirm these first remarks.

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Zeube

CLINICAL ASPECTS OF SEIZURE DISORDERS AT OUAGADOUGOU — BURKINA FASO RETROSPECTIVE STUDY OF 532 CASES.

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SUMMARY

A retrospective analysis of 532 patients with seizure disorders seen in the Internal Medicine department of Yalgado OUEDRAOGO hospital, Ouagadougou, over a seven years period is presented. The commonest type of epileptic seizure encountered was generalized elilepsy of the tonic-clonic type (61.5%), 35.5% had partial seizures, petit-mal type was seen in only 3%. Possible etiologies has been identified in 29.7% of the cases. Aspects of treatment are briefly discussed. These results are compared with the experiences in other African countries.

RESUME

A partir d'une série de 532 observations de patients colligées dans le service de Médicine Interne du CHU de Ougadougou, pendant une période de 7 ans, les Auteurs décrivent les aspects cliniques des crises épileptiques rencontrées; il s'agit de 108 patients hospitalisés (dont 44% d'état de mal épileptique), et de 424 patients ambulatoires. La répartition des types cliniques de crises montre une prédominance des crises généralisées tonico-cloniques (61,5%); les crises partielles suivent avec 35,5%. Les absences de l'enfant ne font que 3%.

Des étiologies possibles sont identifiées dans 29,7% des cas, dominées par les causes traumatiques et les séquelles d'infection du systéme nerveux central. Le traitement medicamenteux utilisé plus souvent le phenobarbital a' cause de son coût peu élevé.

Key Words: Epilepsy — Burkina Faso

INTRODUCTION

Epilepsy is one of the commonest neurological disorders world-wide, and it is more common in developing countries than in developed countries. Epilepsy is not well studied in Africa. Most studies on epilepsy in Africa have been based on hospital attending patients. In Burkina Faso, there is no hospital-based study concerning epilepsy up to now. This study was carried out to describe the different clinical aspects of seizure disorders in Burkina Faso.

PATIENTS AND METHODS

It is a retrospective study in which the medical records of all patients with seizure disorder seen on out-patient and/or in-patient basis, in the department of Internal Medicine of Yalgado OUEDRAOGO Hospital, between October 1, 1987 and December 31, 1994 were reviewed. All the children included in this study were seen on consultation, and subsequently followed in the paediatrics department. A total of 532 patients has been identified. From the medical records of these patients all the available clinical, laboratory, and other informations have been collected and analysed. The classification of seizures was done on the basis of history using the International League Against Epilepsy (ILAE) classification (1981) (10). Electroencephalography results were not available.

RESULTS

Of the five hundred thirty two patients who have been included in this study: 108 were in-patients and 424 were out-patients. Of these, 87 were children between the age of 0-14 years (46 boys, 41 girls). Of the total number of patients, 68.4% were males and 31.6% were females. The distribution according to the age and sex is presented in Table 1.

TABLE 1 Age and Sex distribution of patients.

AGE GROUP (YEARS)	MALE		FEMALE		TOTAL	
	No.	%	No.	%	No.	%
0 - 9	27	7.4	26	15.5	53	10
10 - 19	49	13.5	46	27.4	95	17.8
20 - 29	92	25.3	31	18.4	123	23.1
30 - 39	84	23.2	31	18.4	115	21.6
40 - 49	62	17.1	14	8.3	76	14.3
50 - 59	25	6.9	9	5.4	34	6.4
60 - 69	19	5.2	7	4.2	26	4.9
70 & above	5	1.4	5	3.0	10	1.9
TOTAL	363	100	169	100	532	100

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The distribution according to the clinical type of seizure is presented in Table 2. Generalized seizures of the tonic-clonic type was the commonest type seen (61.5%), followed by secondary generalized seizures (18.8%), and partial complex seizures (10.3%). Petit-mal seizure type was rarely encountered (3%).

TABLE 2 Clinical types of seizures

TYPE OF EPILEPSY	NUMBER OF CASES	%
Generalized seizures	**343**	**64.5**
* Tonico-clonic	327	61.5
* Petit-mal (Absence)	16	3.0
Partial seizures	**189**	**35.5**
* Simple	34	6.4
* Complex	55	10.3
* Secondary generalization	100	18.8

Probable etiologies have been identified in 158 patients. The list of identified etiologies is shown in Table-3. History of the head injury and chronic alcoholism were obtained in 28.5% and 17.7% cases respectively. A history suggestive of central nervous system infection wa obtained in 20.2% cases. 9.8% of the patients had antecedent of cerebrovascular accidents. 6.3% of the patients had intracranial space-occupying lesions.

TABLE 3 Probable etiologies of seizures in 158 patients.

ETIOLOGY	No cases	%
Head injury	45	28.5
Chronic alcoholism	28	17.7
CNS infections	32	20.3
Cerebrovascular accident	17	10.7
HIV infection (AIDS)	14	8.9
Intracranial-space occupying lesion	10	6.3
Cysticercosis	10	6.3
Hypoglycemia	2	1.3
TOTAL	**158**	**100**

8.9% had advanced HIV infection (AIDS); 6.3% had neurocysticercosis. Besides, past history of febrile convulsions has been noted in 21 patients.
Among the 108 hospitalised patients, 48(44.4%) had status epilepticus. In five of these patients this was the initial presenting manifestation.

329 of the patients have been taking their treatment regularly. The drugs prescribed were the following : phenobarbitone, 250 patients (76%), sodium valporate, 42 patients (12.8%); carbamazepine, 32 patients (9.7%); phenytoin, 5 patients (1.5%). Patients with status epilepticus has been treated with diazepam or clonazepam in perfusion.

DISCUSSION

A part from the 5 patients with inaugural status epilepticus, the other patients could be considered epileptic patients.

In this series a male predominance has been observed with sex ratio 2.6. This is similar to the findings of other studies from Africa (1, 2, 5, 11, 13). The degree of male predominance is less marked in developed countries (10). The possible explanations for this male over representation are the tendency in Africa for males to seek medical attention more readily than females and the migration of men to cities due to economic and social reasons (6, 12).

As in other hospital series in Africa (1, 11, 12), in our series the majority of the patients were young. 82.1% of the patients being below 40 years of age and only 6.8% of the patients were above 60 years of age.

The pattern of the epilepsy found in this study is similar to what has been reported in the literature from other African countries (4, 5, 11, 12, 13) generalized seizures of the tonic-clonic type being the most frequent type of seizures seen. On the other hand petit-mal epilepsy was rare. The relative rarity of absence seizures in our study and other studies from Africa (5, 13) could be due to underdiagnosis of the disorder because of its relatively subtle clinical features.

In this series possible etiologies has been identified in 158 cases. Past history of head injury was the commonest disorder identified accounting for 28.5% of these cases, followed by sequalae of cerebral infection in 20.2%, and chronic alcoholism (17.7%). It is important to note that 10 patients had clinical evidence of cysticercosis, and their seizures were

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probably consequences of central nervous system involvement of the cysts.

Among the 48 patients with status epilepticus, in 44%, the precipitating factor was cerebral malaria; in the others, the discontinuation of the antiepileptic drugs was the precipitating factor identified. The attitude of the population towards epilepsy and epileptics make treatment and follow-up of the patients difficult. Among the antiepileptic drugs, phenobarbitone is the one which is widely used, because of its reasonable price.

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ELSEVIER

BRIEF COMMUNICATION

Novel HLA-DPB1 Alleles Detected in the Ethiopian Population

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ABSTRACT: The number of identified HLA-DPB1 alleles increased rapidly by application of DNA-based typing techniques. PCR–SSO typing indicated the presence of possible new HLA-DPB1 variants in the Ethiopian population. The use of the SBT technique, which considers polymorphic as well as constant regions in the second exon of HLA genes, allowed direct identification of two new allelic variants. Moreover, a recently identified HLA-DPA1 variant was also present in this population. The newly defined allelic HLA-DPB1 sequences found in five individuals of the Ethiopian population were confirmed by cloning and subsequent sequencing of the cloned DNA. One of the new alleles was shown to segregate in a family and was also present in unrelated individuals. Both new DPB1 alleles represent new combinations of existing polymorphism in the hypervariable regions. In different populations the frequency of these new HLA-DP variants remains to be determined. *Human Immunology 42, 181–183 (1995)*

ABBREVIATIONS

IHWS	International Histocompatibility Workshop	SBT	sequencing-based typing
PCR	polymerase chain reaction	SSO	sequence-specific oligonucleotide

INTRODUCTION

The allelic diversity of HLA-DPB1 is considerable; 48 alleles have been officially recognized by the WHO Nomenclature Committee for factors of the HLA system [1]. New allelic variants are detected mainly in isolated populations, such as in The Gambia, New Guinea, Australian Aborigines, Kyoto (Japan), Java (Indonesia), and Santa Cruz Island (Solomon Islands) [2–6]. Most of the newly identified HLA-DPB1 alleles are the result of different combinations of the six hypervariable regions within the polymorphic second exon.

DNA-based typing methods are commonly used in HLA class II typing. Especially in HLA-DPB1 typing, the polymerase chain reaction–sequence-specific oligonucleotide (PCR–SSO) typing method is used routinely due to scarcity of DP antisera [7]. We report here the identification of two new DPB1 variants by use of PCR–sequencing-based typing (SBT) [8, 9] and the detection of a recently described DPA1 allelic variant [10]. This SBT method considers all nucleotides of the polymorphic exon and shows directly the new sequences. The new variants have been confirmed by sequencing of cloned DNA, which demonstrated the value of SBT as a direct approach for the identification of new alleles.

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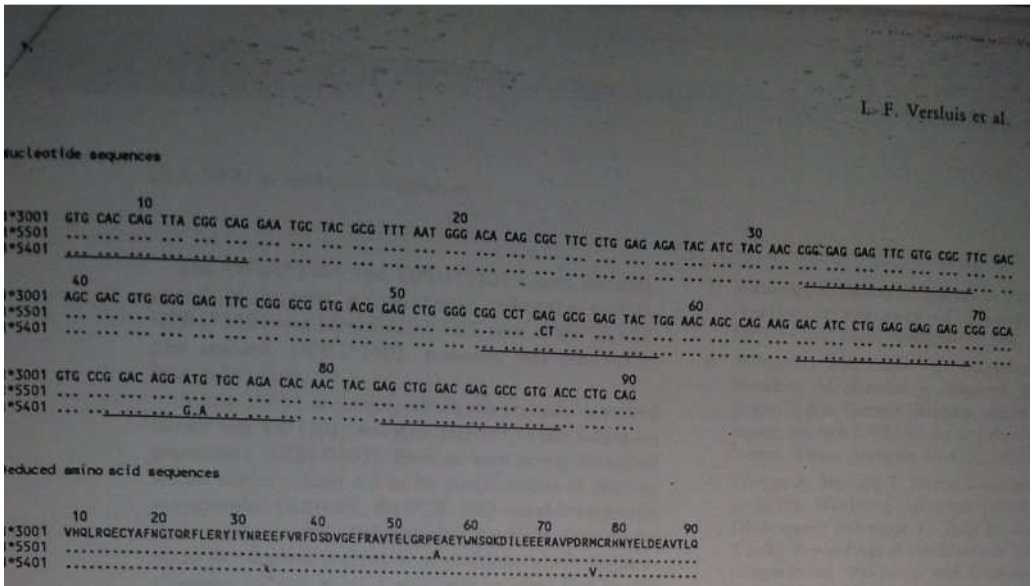
*Accession numbers EMBL: X78042 = ETH-0222 = DPB1*5401 and X78041 = ETH-0271 = DPB1*5501. The names DPB1*5401 and DPB1*5501 (ETH-0222 and ETH-0271, respectively) have been officially assigned by the WHO Nomenclature Committee in March 1994. This follows the agreed policy that, subject to the conditions stated in the most recent Nomenclature Report (Bodmer et al., 1992), names will be assigned to new sequences as they are identified. Lists of such new names will be published in the following WHO Nomenclature Report.*

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URE 1 DPB1 exon 2 sequences of the new alleles B1*5401 and DPB1*5501 with DPB1*3001 as the consus sequence: (A) nucleotide sequences and (B) the deduced ino acid sequences. Sequence homology is indicated by *dots* *numbers* above indicate the position of the corresponding ino acid in the mature protein. The *underlined* regions are oligonucleotide sequences that were used in PCR–SSO g, defining the unusual hybridization patterns. The new les differ at codons 55 and 76, respectively, from the consus allele.

ATERIALS AND METHODS

a part of the disease component of the 11th International Histocompatibility Workshop (IHWS), 96 Ethiian individuals (insulin-dependent diabetes mellitus tients, relatives, and controls) were studied [11]. NA was extracted from frozen peripheral blood mononclear cells and PCR–SSO typing for the different HLA ss II loci was performed, according to the protocol of 11th IHWS [7]. The SBT method for DPA1 was plied as described by Rozemuller et al. [10]. The SBT thod for DPB1 typing described by Versluis et al. [8] applied on samples that showed unusual PCR–SSO bridization patterns in the DPB1 typing. In order to blish homozygous sequence data of the new allelic uences, the amplified products were cloned into a smid vector and subsequently sequenced. In principl, the primers for DPB1 amplification are as described pt for the modification in the upstream primer, ch was extended with the recognition site for the striction enzyme EcoRI. The obtained PCR fragment digested on solid phase by EcoRI and PstI, thus lting in a fragment size of approximately 400 bp. his fragment was ligated in the multiple cloning site of pUC19 vector and introduced into competent *Escher- coli* JM109. Small-scale plasmid isolation according the CTAB method [12] revealed the DNA template r automated sequencing [13] using an ABI 373 DNA sequencer (ABD, Foster City, CA, USA). Distinct individual clones were sequenced in sense orientation using dye-labeled 21M13 primer as well as in reverse orientation using dye-labeled M13RP1 primer.

RESULTS AND DISCUSSION

Among the 96 samples, two unusual PCR–SSO patterns were displayed indicating previously unknown combinations of known DPB1 sequence motifs (Fig. 1). One pattern was shown to segregate in a family and was detected in two unrelated individuals as well; the other unusual pattern was found once in the panel studied.

Sample ETH-0271 appeared to be heterozygous for DPB1: the DPB1*0401 allele in combination with a new sequence, which was later officially named DPB1*5501. The ETH-0222 sample contained the DPB1*1301 allele together with another new allelic DPB1 variant (later officially named DPB1*5401). PCR products of both alleles of these samples have been cloned and sequenced in both orientations. Both new variants appear to be closely related to the DPB1*3001.

The combination of sequences is shown in Fig. 1, with DPB1*3001 as the consensus sequence. Fig. 1A shows the nucleotide sequences, whereas Fig. 1B reflects the deduced amino acid sequences. DPB1*5501 (ETH-0271) differs from DPB1*3001 at codon 55. DPB1*5401 (ETH-0222) differs from DPB1*3001 at codon 76. Also, both intronic sequences upstream to exon 2 are identical to the DPB1*3001 (data not shown). In Fig. 1B the high degree of homology of DPB1*5401 and DPB1*5501 to DPB1*3001 is shown at the amino acid level. DPB1*5401 (ETH-0222) carries a valine (V) at codon 76 instead of a methionine (M) in DPB1*3001. DPB1*5501 (ETH-0271) is identical to DPB1*3001 except for codon 55, which carries an alanine (A) instead of an aspartic acid (E).

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The DPB1*5401 and DPB1*5501 alleles are composed of known polymorphic sequence motifs. DPB1*5501 was identified by SBT once in the 96 samples studied. DPB1*5401, however, was detected in four individuals.

A new DPA1 sequence, which was recently described in cell line SK [10], was also detected in the Ethiopian population (ETH-0203). Because both newly identified DPB1 alleles turned out to be combinations of existing polymorphic positions, the PCR–SSO was able to predict these new variants. Polymorphic positions that might occur in constant regions or at positions where oligonucleotides are not applied will only be identified by the SBT method. Moreover, the value of the SBT system as a direct sequencing approach was demonstrated, as all results are concordant with sequences obtained from cloned DNA. The DPB1*3001 allele was detected in five out of 96 Ethiopian individuals. Both new alleles are closely related to DPB1*3001; whether these new alleles are specific for the Ethiopian population remains to be tested.

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MYELOPATHIES IN ETHIOPIA
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MYELOPATHIES IN ETHIOPIA

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SUMMARY

From December 1990 to December 1993, 130 patients who had a lesion localized to the spinal cord were admitted to the Tikur Anbessa Hospital, Department of Internal Medicine, Addis Ababa. These patients accounted for 18.0% of all neurological admission to this department. The male/male female ratio was 1:8:1; the mean age was 40 years for these patients; 52% were from Addis Ababa City and 48% of them were coming from the rest of the country. Paraparesis or paraplegia (77%) and quadriparesis or quadriplegia (23%) were the commonest presenting complaints. Sensory level, sphincter dysfunction and bedsores were found in 70%, 54% and 14% of the cases respectively. Tuberculous spondylitis was found to be the leading cause accounting for 35 (26.9%), and HIV-1 myelopathies was the second common type accounting for 22 (16.9%) of spinal cord disease. Metastatic cord compression, tropical spastic paraparesis, (progressive non compressive myelopathy), cervical spondylosis, primary cord tumours and transverse myelitis were also not uncommon. Death related to sepsis or other causes were documented in 14 (10.8%). Follow-up was arranged on discharge, and only 45 (38.8%) patients were able to attend at least once the neurology referral clinic. Myelopathy is an important neurological disease and currently HIV-1 associated myelopathy has become the second important presumed cause.

INTRODUCTION

Spinal cord disorders are one of the commonest disabling neurological disease in Africa, from the compressive myelopathies, tuberculous spondylitis is the leading preventable and treatable aetiology(1-4). The same statement holds true also in India(5,6). Currently the HIV-1 associated myelopathy is frequently encountered, and it is the second most common neurological manifestation due to HIV-1(7,8). In Ethiopia neurological manifestation have accounted for 20.7% of all patients who are seropositive for HIV-1(9). The other cause of non compressive myelopathy is the tropical spastic paraparesis.

In many parts of the world, higher percentage of HTLV- antibody positively have been found among the patients, 100% in Martinique, Japan, Chili, Zaire, France and South Africa; 94.5% in Colombia; 90% in Great Britain; 85% in Sychelles and 63% in Jamaica(10-13). However, the situation in Ethiopia is different because the HTLV-1 antibody positively in the serum among patients with tropical spastic paraparesis is only 9%(14). The prevalence rate of tropical spastic paraparesis in central rural community is 10/100,000 population(15). The prevalence rate among paraparetic patients admitted to a hospital was 9.8%(1). The aim of this study was to determine the current aetiologies of myelopathies in Ethiopia.

MATERIALS AND METHODS

All patients who are admitted to the department of internal medicine Tikur Anbessa Hospital, Addis Ababa due to neurological diseases are registered into a separate file prepared by the neurology unit of this department. Patients who had a diagnosis which was related to the spinal cord disease admitted consecutively to the ward between December 1990 and December 1993 were selected and their charts were reviewed. Essential demographic and clinical data, diagnoses, treatment outcome and follow up were filled into a pre-prepared protocol.

RESULTS

Demographic data: From December 1990 upto December 1993, 723 patients who had neurological disease were admitted to the department of Internal Medicine, Faculty of Medicine, Addis Ababa University. Of these, 130 patients have neurological lesion located to the spinal cord which accounted for 18% of all neurological admission to this department. The male to female ratio was 1.77:1. 68 (52.3%)patients were from Addis Ababa city; the remaining 63 (47.7%) patients were from outside of Addis Ababa. The age ranges was 13 year to 69 year and the mean age for the group was 40 year.

Clinical features: Muscle weakness in the pattern of paraparesis or paraplegia was noted in 100 (76.9%)

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and quadriparesis or quadriplegia in 30 (23.1%) patients. Muscle tone was increased in 78 (60%), normal in 36 (30%) and decreased in 6 (4.6%) of the cases. Muscle atrophy was noted in 10 (7.7%), in the rest 120 (92.3%) there was no muscle atrophy. Muscle stretch reflexes were increased in 100 (76.9%), normal in 8 (6.2%) and decreased in 22 (16.9%). Plantar response was extensor in 76 (58.5%), equivocal or flexor in 54 (41.5%). Sensory level was detected in 91 (70%). Sphincter dysfunction was present in 60 (53.8%). Pressure sore was encountered in 19 (14.6%).

Table 1

Clinical features seen in 130 patients who had spinal cord disease

Clinical findings		No.	Percentage
Paraparesis/paraplegia		100	76.9
Quadriparesis/quadriplegia		30	23.1
Muscle tone	increased	78	60.0
	normal	36	30.0
	decreased	6	5.0
Muscle atrophy	absent	120	92.3
	present	10	7.7
Muscle stretch reflexes	increased	100	76.9
	normal	8	6.2
	decreased	22	16.9
Plantar response	extensor	76	58.5
	flexor/equivocal	54	41.5
Sensory level	detected	91	70.0
	not detected	39	30.0
Sphincter dysfunction	present	70	53.8
	absent	60	46.2
Pressure sore	present	19	14.6
	absent	111	85.4

Different diagnostic tests were performed, these were chest x-ray, spinal x-ray, myelography, CSF study, serology for HIV I and histology of biopsy tissue. Accordingly 35 (26.9%) cases tuberculous spondylitis, 22 (16.9%) HIV I associated myelopathy, 20 (15.4%) metastatic cord compression, 18 (13.8%) tropical spastic paraparesis, 12 (9.2%) cervical spondylosis 11 (8.5%) primary cord tumour, 7 (5.4%) transverse myelitis and 5 (3.8%) other non-cerebrovascular disorders were found to be causes of spinal cord diseases (Table 2).

Fourteen (10.8%) patients had died in the hospital, 116 patients had been discharged and only 45 (38.8%) were available for follow up.

Tuberculous spondylitis as the leading cause of spinal cord disease, the mean age for this group was 36 and the median 30 years. The male to female ratio was 1.9:1, other system involvement was noted in 30% of these cases. The ESR level was elevated almost in all except two patients. The mean ESR level in the first hour was 74 mm. Different antituberculous drugs combinations were used to treat these patients, 30 (85.7%) have since known a significant improvement on medical treatment alone. Three patients have not shown any improvement after 2 months of medical treatment, two patients were subjected to decompressive surgery and no significant improvement noted. Two patients died from sepsis related with bladder infection.

Table 2

Causes of myelopathies in 130 patients

Serial No.	Causes	Cases	Percentage (%)
1.	Tuberculous spondylitis	35	26.9
2.	HIV-1 associated myelopathy	22	16.9
3.	Metastatic cord compression	20	15.4
4.	Tropical spastic paraparesis	18	13.8
5.	Cervical spondylosis	12	9.2
6.	Primary cord tumour	11	8.5
7.	Transverse myelitis	7	5.4
8.	*Others	5	3.8
Total		130	99.9

* Others: 3. Myelopathic lateral sclerosis
4. Subacute combined degeneration of the spinal cord
1. Fibrous band cord compression

HIV-I associated myelopathy as the second common cause in 22 patients with a mean age of 31 year, the male to female ratio 2.1:1 and mean ESR level of 68 mm in the first hour.

Metastic cord compression was seen in 20 patients, the male to female ratio was about the same and the mean age for these patient was found to be 53 years. The mean ESR level in the first hour was 81 mm.

Hepatoma, lymphoma and multiple myeloma were found to be the primary source to give metastasis to the spinal cord, each accounting for 3 cases. Prostate (2 patients), thyroid (2 patients) lung (1 patient) were other sources of metastatic lesion to spinal epidural space. In 6 patients the primary source was unknown, accounting for 30%.

Tropical spastic paraparesis (progressive non-compressive myelopathy) was found in 18 patients. The male to female ratio was 5:1 as compared 1.5:1 for the other myelopathies excluding tropical spastic paraparesis. Eleven (61.6%) patients came outside of

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Addis Ababa, as compared with 45.5% for other places.

Apart from one patient, 10 patients came from Northern and Western part of the country particularly from Gojam (5 patients). Regarding the marital status, 13 (72.2%) were married, three (16.7%) divorced, and two (11.1%) were single. The duration of illness was from 5 months to 4 years (mean: 18 months and median 12 months). The mean ESR levels was 25mm/hr. Eight patients were on follow up; of these 4 remained in the same state and 4 deteriorated.

Cervical spondylosis was diagnosed in 12 patients with a mean age of 53 years and male to female ratio of 6:1. Evelen patients were operated, 9 showed improvement, 2 patients remained in the same state; one patient refused to a have operation.

There were 11 patients with primary cord tumour. The mean age was 39 years, the male to female was about the same. Meningioma, glioma and neurofibroma was found in 5, 3 and 2 patients respectively, and one patient refused operation. Of the 10 operated cases six showed improvement, three remained unchanged and three had died.

Transverse myelitis was seen in 7 patients with a mean age of 36 years and male to female ratio of 2.5:1. Other miscellaneous five cases were encountered, these were: three cases of amyotrophic lateral sclerosis, one case of subacute combined degeneration and one case of fibrous band cord compression.

DISCUSSION

Spinal cord diseases are important and common problem accounting for 18% of all neurological patients requiring hospital admission. The predominant clincial findings are muscle weakness, increased muscle tone and muscle stretch reflexes. Extensor plantar response and sphincter dysfunction was found in half of these cases. Sensory level was detected in 70% and only 14% of them had associated pressure sore (Table 1). Common causes of myelopathy in Ethiopia are tuberculous spondylitis, HIV-1 associated myelopathy, metastatic cord compresssion and tropical spastic paraparesis (progressive non compressive myelopathy).

Other less common causes are cervical spondylosis, primary cord tumours and traverse myelitis, and infrequent causes are amyotrophic lateral sclerosis, subacute combined degeneration and fibrous band cord compression (Table 2).

Tuberculous spondylitis as the first common cause of spinal cord disease, affects frequently males and patients in the mid thirties. This observation corresponds with reports from India and Africa(2,5,6). Only one third of these patients had concomitantly detectable involvement of other system(1). The erythrocyte sedimentation rate was elevated in more than 90% of the cases. In contrast to the previous record, only 50% were having an elevated ESR level(1). The response to medical treatment alone was very good. 85.7% had shown significant improvement which is similar to the reports from Korea, Rhodesia and India(15). Unless indicated medical treatment alone would be sufficient for tuberculous spondylitis.

HIV-1 associated myelopathy was found to be second common cause of myelopathies. All of them showed a down hill course and two died. Acquired immuno-deficiency syndrome was first reported in 1986 in Ethiopia(17). Until 1989, neurological manifestation associated with HIV- infection and AIDS were not frequent. Now it has become one of the major complication in AIDS patients(9).

The development of spinal pain and neurological deficit produce a major deterioration in the quality of life of such patient who has malignancy elsewhere metastsizing to the spinal epidural space. The prevalence of this complication among spinal cord disorders is 15.4% and as in other studies, it frequently affect the elderly population with the mean age of 53 years(18). Hepatoma, lymphoma and multiple myeloma were found to be the common primary source, which is different from other reports where lung in male and breast in female are the common primaries(19,20). This difference may be due to the fact, these malignancies are seen commonly in Ethiopia(21-24). In 30% of the patients, the primary remained occult which is similar to other reports(25).

Tropical spastic paraparesis is seen in 13.8% in this series. The male to female ratio was 5:1 as compared to 1.5:1 for other myelopathies excluding TSP, which was different from other reports where females were affected more frequently(12,13). Majority of patients come from northern and western part of the country particularly from Gojam region. The cause of this chronic progressive myelopathy in Ethiopia remained obscure. HTLV-1 could not be attributed because of the low seroprevalence(14). Malnutrition too could not be entertained because of lack of clinical evidence of malnutrition. Neurolathyrism has been reported from other regions of the country(26,27). But history of excessive consumption of Lathyrus Sativus was negative. In addition, the clinical course of these patients was progressive; the mean duration of development of illness was 18 months. Konzo, an acute onset of isolated pyramidal signs without further progression which was associated with excessive consumption of cassava cyanogen was studied in Zaire, Tanzania, Mozambique and Central African Republic(28-30). However, since cassava is not a staple diet in Ethiopia it can not be incriminated as an aetiology.

Spinal cord tumours, cervical spondylosis and transverse myelitis are less common in this study. Other uncommon disorders are Amyotrophic lateral sclerosis, subacute combined degeneration of the spinal cord and fibrous band cord compression.

In neurological disease follow up to provide further

medical, psychological treatment and rehabilitation after establishing the diagnosis is indispensable. Only 38.8% were available for follow up after they have been given appointment according to their convenience and disease condition. This follow-up default obviously interfere in extending treatment and acquisition of knowledge. Even though transportation from remote area considered to be as one factor, only 51.6% of patient residing in Addis Ababa City were able to attend the follow-up.

CONCLUSION

Comprehensive and non-comprehensive myelopathies are one of the commonest cause of neurological admission at least in a teaching hospital. Tuberculosis, a preventable and treatable disease is the principal aetiology of myelopathies. Tuberculous spondylitis can be treated with antituberculous drugs and physiotherapy alone. HIV-1 associated myelopathy is the second common cause of spinal cord diseases in this series. Tropical spastic paraparesis or progressive non-compressive myelopathy is common. The aetiology in Ethiopia set up has to be searched in the future. Follow-up as an important strategy for extension of treatment for chronic neurological diseases the precise cause for its failure has to be identified and corrected.

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PARAPLEGIA AT THE TIKUR ANBESSA TEACHING HOSPITAL: A SEVEN YEAR RETROSPECTIVE STUDY OF 164 CASES

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ABSTRACT: *Admission analysis of adult non-traumatic paraplegia and paraparesis from 1981 to 1988 was carried out. Information was collected from charts of 223 consecutive admissions according to a pre-set protocol. Paraplegia or paraparesis was responsible for 164(13.4%) of all neurological admissions over the study period. The median age of the patients was 36 years with a male to female ratio of 1.7:1. Tuberculosis was the leading cause of paraplegia or paraparesis accounting for 47% of the cases. Tumours (20%), Landry-Guillain-Barre' syndrome (12.2%) and tropical spastic paraparesis (TSP) (9.8%) were important but less frequent causes in this series. Other causes like disc prolapse, transverse myelitis, spinal artery stroke and fluorosis were rarely encountered. Vertebral deformity (88.1%), vertebral tenderness (88.1%) and abnormal plain spinal X-ray (89%) were the most helpful findings in the diagnosis of tuberculous paraplegia. Nearly all cases of tuberculous paraplegia were treated medically alone. However, the outcome of treatment as judged by the treating physicians was good with a significant response recorded in 78%.*

INTRODUCTION

The relative importance, clinical manifestations, and causes of paraplegia or paraparesis in hospital practice in Ethiopia are not known. Like in several other developing countries tuberculosis is believed to play an important etiologic role (1,2). Therefore, the current analysis was undertaken to identify the relative importance of the disease, its causes, clinical manifestations and the outcome of treatment in patients admitted to the largest teaching hospital in Ethiopia.

MATERIALS AND METHODS

Charts of 223 consecutive patients admitted to the Department of Internal Medicine of the Addis Abeba University Teaching Hospital between 1981 and 1988 with the initial diagnosis of paraplegia or paraparesis were reviewed. Data were collected according to a pre-set protocol that contains information on clinical presentations, laboratory investigations, causes and response to therapy.

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The data on investigations included X-rays of the spines and the chest, myelography and histology. After discharge from the hospital all patients were referred to the neurology outpatient clinic for follow-up. Fifty-nine patients whose diagnoses of paraplegia or paraparesis were rejected on re-evaluation and follow-up by an experienced neurologist were excluded from the analysis. Data on the remaining 164 patients seen over the seven year period are presented.

A diagnosis of tuberculous paraplegia or paraparesis was made in those patients who had:

a. clinical and radiological evidences suggestive of tuberculosis of the spine,
b. tuberculosis elsewhere in the body simultaneously or preceding the spinal lesion and/or
c. significant response to antituberculous therapy.

RESULTS

A total of 164 adult paraplegic or paraparetic patients were seen over a seven year period. This accounted for 13.4% of all neurological admissions over the same period. The median age for the whole group was 36 years with a range of 15 to 70 years. Tuberculosis was the leading cause accounting for 77(47%) of the cases. Tumours, Landry-Guillain-Barre' syndrome and tropical spastic paraparesis were responsible for 20%, 12.2%, and 9.8% of the cases respectively (Table 1). Disc herniation, transverse myelitis, brucella spondylitis, and fluorosis, were rare causes (Table 1).

Important clinical and laboratory features of the patients of tuberculous paraplegia or paraparesis are given in Table 2. Sixty per cent of these patients were between the ages of 15 and 40 years. Males predominated over females with a ratio of 1.6:1. Gradual onset of weakness in the legs, vertebral deformity and vertebral tenderness occurring in 92.2%, 88.1% and 88.1% of the cases respectively were the main clinical features. Sudden onset of paraplegia occurred in only four of the cases (7.8%). Although spastic tone was more frequently noted, flaccid muscle tone occurred in nearly a quarter of the patients (23.3%). A third of the patients (N = 25) had associated tuberculosis elsewhere in the body. There was a delay of more than two months between onset of neurological symptoms and hospitalization in 59% of the patients. Plain X-ray of the spine could be traced in 64 of the 77 patients. Fifty seven (89%) of these were interpreted as suggestive of tuberculous spondylitis. X-ray findings interpreted as suggestive of tuberculosis of the spine were disc space narrowing and adjacent vertebral bone destruction. Myelography was done in 10 patients. There was partial block in four and changes suggestive of arachnoiditis in two while the examination was normal in the remaining four.

All patients suspected of having tuberculous paraplegia or paraparesis were treated with varying combinations of at least three anti-tuberculous drugs which consisted of isoniazid, streptomycin, thiacetazone, ethambutol or rifampicin. Complete or significant partial response was recorded in 60(78%) of the patients. Five patients died in the hospital. One died from septicemia related to urinary bladder catheterization and another from tuberculous meningitis. The cause of death in the remaining three patients was not documented.

Tumours were responsible for 33(20%) of paraparesis or paraplegia. Twenty-one (13%) of the paraplegia or paraparesis was

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caused by primary spinal cord tumours while 12(7%) had metastatic cord compression (Table 1).

The median age of patients with primary cord tumours was 37 years. All cases of primary tumours had either complete or partial block on myelography. Histology results were available for 14 of the 21 primary tumour patients who were subjected to surgery. Neurofibroma and meningioma were reported in seven and four cases respectively. The remaining three patients had intramedullary tumours. One patient had advanced disease and was found inoperable on exploratory laminectomy. There is no information on the remaining six patients.

Metastatic cord compression (N=12) affected predominantly males and relatively older patients (median age of 48 years). Hepatocellular carcinoma was a primary source for a third of the cases. Carcinoma of the lungs was a source in two of the cases. Other primaries were pancreatic adenocarcinoma, renal carcinoma and sarcoma of the buttock.

Twenty patients with the diagnosis of Landry-Guillain-Barre' syndrome had a median age of 35 years. Both sexes were equally affected. History of prior febrile illness was present in only five patients (20%). Flaccid paralysis was noted in both upper and lower extremities in 10(50%) of the patients. Bilateral facial palsy and bilateral papilloedema were recorded in two and one patients, respectively. Paraesthesia and numbness were frequent complaints but sensory deficit was objectively demonstrable in only one patient. Mild complaints of sphincter dysfunction were reported in two. Of the five patients who had respiratory failure, three died. Eleven (55%) patients had cerebrospinal fluid (CSF) protein of more than 45 mg/dl with cell count that ranged from 0-63/ml.

Tropical spastic paraparesis affected males much more frequently than females with a sex ratio of 3:1. These patients had slowly progressive weakness of the legs with a median duration of symptoms before presentation being three years. They exhibited spastic paraparesis with hyperreflexia and extensor plantar response. There was no sensory deficit on examination despite complaints of paraesthesia in the toes in six of them. Incontinence of the urine was recorded in two but frequency and urgency occurred in 20% of the patients. Cranial nerve lesion or cerebral dysfunction were absent. *Lathyrus sativus* ingestion in significant amount was not documented. Some of the patients reported consumption of small amounts of *L. sativus* for short periods. There was no clinical evidence of malnutrition or vitamin deficiency in any of the patients. Chest and plain spinal X-ray and myelography were normal in all of them.

DISCUSSION

Non-traumatic paraplegia or paraparesis was responsible for 13.4% of all neurological admissions during the study period. This was similar to admission analysis from Malawi (18%) (3) and Nigeria (12.4%) (4). As in several other developing countries tuberculosis was the leading etiology accounting for 47% of all the paraparetic or paraplegic cases (1,2,5).

Although tuberculous paraplegia or paraparesis occurred in a wide age range, as in the other reports majority of the patients were between the age of 15-40 years. In this and the other African series males were affected more frequently than females (6) while in an Indian report both sexes were equally affected (7). In most of

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the patients in this study the onset of paraplegia was gradual, but in a few (7.8%) it was sudden presenting like spinal shock, which may be due to ischaemic cord damage or spinal transection from pathological dislocation of the vertebrae (8). It is to be pointed out that weight loss and fever were not the presenting or associated symptoms in 50% of the patients. The absence of these symptoms did not thus exclude the diagnosis.

Kyphotic deformity (88.1%), tenderness of the spine (88.1%) and abnormal plain spine radiography (89.1%) were the most helpful findings for the diagnosis of tuberculous paraplegia. It is possible that patients without these findings had either tuberculous arachnoiditis or internal granuloma (7,9). Two of the patients suspected of having arachnoiditis had suggestive myelographic findings. Patients suspected of having internal granuloma had blockage on myelography. All the six patients with the diagnoses of tuberculous arachnoiditis or internal granuloma had complete or significant partial response after treatment.

All patients with tuberculous paraplegia/paraparesis were treated medically alone. A significant therapeutic response rate of 78% found in our series is slightly less than the results reported from Korea (85%), Rhodesia (86%) and India (87%) (10). The difference might be due to the mode of treatment and/or criteria used for assessment of improvement.

Tumours with relative frequency of 20% were the second largest group as causes of paraparesis or paraplegia similar to the series from Malawi (24.5%). Primary spinal cord tumours were more common in this group as compared to metastatic cord compression with a ratio of 1.8:1. The median age of patients with cord tumours was 37 years. As reported in other studies neurofibroma and meningioma were the commonest histological types encountered (11).

Hepatoma was the leading cause of metastatic cord compression probably reflecting its high prevalence in this country (12,13), which is in contrast to reports from the western countries where carcinoma of breast in females and carcinoma of the lungs in males are the commonest primary tumours which metastasize to the spine (14–16). Lungs, kidneys and pancreas were less common sources of metasis in this series.

Landry-Guillain-Barre' syndrome was found to be another common cause of paraplegia. The median age was found to be 33 years which is low as compared to 40 years of age in other studies (17). Cranial nerve involvement in Landry-Guillain-Barre' syndrome was not as frequent as shown in other reports (18). The mortality of 15% from respiratory failure however, was high compared to 3 to 5% in other studies (19). This was probably due to delayed diagnosis and inadequate respiratory support.

Tropical spastic paraparesis is relatively frequent in this series. The clinical features are similar to those described by Roman and Spencer (20). Although neurolathyrism is a prevalent disease in the north and northwestern part of Ethiopia (21), none of these patients admitted ingestion of *L. sativus* in appreciable quantity. The gradual onset of leg weakness over a period of three to four years is not a picture of lathyrism (22). Cassava is not consumed in Ethiopia. Most of the patients were described as an average built and there was no mention of clinical findings of malnutrition or vitamin deficiency to account for the occurrence of such a disease. Strong association between HTLV-1 infection and TSP is well

described elsewhere (23–25). In Ethiopia the association of tropical spastic paraparesis and HTLV-1 is unlikely because of a report of low prevalence of HTLV-1 in both patients and controls (26).

Other infrequent causes were disc herniation and transverse myelitis. Brucella spondylitis, hysterical paraplegia, anterior spinal artery stroke and fluorosis were rare causes.

In conclusion, non-traumatic paraplegia is a common neurological problem at least in a hospital practice. Tuberculosis, a preventable disease, is by far the leading etiology. The causes of non-traumatic paraplegia from this hospital is in general similar to reports from other African countries.

Table 1. Causes of paraplegia at Tikur Anbessa Teaching Hospital

Diagnosis	Cases No.(%)
Tuberculous spondylitis	77(47.0)
Spinal tumours	33(20.0)
Landry Guillain Barre' syndrome	20(12.2)
Tropical spastic paraparesis	16(9.8)
Others	18(11.0)
Disc herniation (7)	
Transverse myelitis (4)	
Hysterical paraparesis (2)	
Spinal artery stroke (2)	
Brucella spondylitis (2)	
Fluorosis (1)	
Total	164(100.0)

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Table 2. Clinical and laboratory features of tuberculous paraplegia

Variables	Cases No.(%)
Mode of onset:	
Gradual	47/51(92.2)
Sudden	4/51(7.8)
Fever	32/77(41.6)
Weight loss	34/77(44.2)
Vertebral deformity	52/59(88.1)
Vertebral tenderness	52/59(88.1)
Musole tone:	
Spastic	55/72(76.4)
Flaccid	17/72(23.6)
Sensory level	43/59(72.9)
Sphincter dysfunction	17/64(26.6)
Spine X-ray: abnormal	57/64(89.1)
Tuberculosis elsewhere	25/77(32.5)
Significant improvement from treatment	60/77(77.9)

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Case 2: A 35 year old Ethiopian-Somali who was reportedly healthy before July 1990 developed aphasia and quadriparesis following caesarean section in Djibouti Hospital. She was given supportive treatment in hospital for three months and stayed at home until the admission. Detailed information could not be extracted as the accompanying relative was not well versed about the course of the patient's illness.

She was admitted to Tikur Anbessa Hospital in January 1994 with a chief complaint of cough and fever of one week duration. Otherwise, the neurological deficit reportedly remained in the same state as was before the onset of cough and fever. Examination on admission revealed a chronically sick-looking patient with low-grade fever, in mild respiratory distress, and signs of consolidation on the right lower lobe of the lung. She had flexion contracture of the toes and both ankle joints (Figure 1).

On examination of the nervous system she appeared to be conscious and dysphasic. The optic fundi were normal. Pupils were normal in size and reactive to light. She had horizontal nystagmus bilaterally and was able to move her eyes in all directions spontaneously. Caloric-test was normal bilaterally. Corneal reflex was absent bilaterally and the jaw jerk was very brisk. She had loss of the nasolabial fold on the left side. There was no voluntary movement of the face, jaw, palate and tongue. The jaw was shut by tonic masseter contraction. She had spastic quadriplegia. Muscle stretch reflexes were exaggerated in all extremities. The plantar response was extensor bilaterally.

Complete blood count, erythrocyte sedimentation (ESR), urine analysis, liver function test, renal function test, fasting blood sugar, lipid profile and skull X-ray were normal. Chest X-ray showed right lower lobe non-homogeneous opacity with air bronchogram. Electroencephalogram and computed tomography (CT) scan of the cranium could not be performed, as these tests are currently unavailable here.

The diagnoses were LIS and pneumonia. She was treated with crystalline penicillin and was given supportive treatment with physiotherapy. Pneumonia resolved but the neurological findings remained the same. She was discharged after 26 days of hospital stay.

DISCUSSION

The term "locked-in syndrome" was first coined by Plum and Posner in 1966, to describe victims of brain stem stroke with limb and bulbar paralysis but unimpaired consciousness (5). Other terms such as "pseudocoma", "de-efferented state" and "ventral pontine syndrome" have been used to describe this unique clinical picture which occurs following infarction of the ventral portion of the pons (6). However, there are reports of LIS with pathological changes in the midbrain peduncles and a relatively intact ventral pons (5,7).

This disorder consists of quadriplegia and mutism with preserved consciousness. The only remaining voluntary movements are usually variable degrees of eye movements and eyelid blinking. In other words, patients are awake but selectively de-efferented i.e. have no means of producing speech, or limb, face or pharyngeal movements (8). This diagnosis is supported by a normal bilateral caloric test and with an EEG findings of posterior dominant alpha background activity that attenuate with alerting procedures (9).

The most common cause of LIS is basilar artery occlusion. Other causes include

pontine haemorrhage, trauma, tumours, vascular malformation of the basilar artery, acute inflammatory demyelinating polyneuropathy etc. (8).

The patients presented here have findings compatible with LIS. One has to be sure that the patient is conscious in order to differentiate this condition from vegetative state and akinetic mutism. Our patients were conscious because they blinked to visual threat, had accurate pursuit eye movements and responded to the call of their names and other verbal commands by eye signs.

We do not have adequate information on the first patient, regarding the circumstance at the onset of her illness, and so it is difficult to tell the exact cause of the locked-in state. Basilar artery thrombosis was the presumed cause, as the risk of ischemic stroke increases by four to six fold in the third trimester of pregnancy and peurprium (10). In the second patient compression of the brain stem by the tumour was found intraoperatively and this possibly complicated by vascular occlusion or trauma to the same area may have resulted in LIS.

In a review of the literature of 139 cases, the overall reported mortality was 60%. The prognosis was better in the group of patients whose syndrome was non-vascular in origin than those with a vascular etiology (11). Early, smooth, horizontal eye movement is said to be a favourable prognostic sign (12).

There are few reports of complete recovery. The second case reported here also showed partial recovery. Comprehensive and aggressive supportive treatment is recommended for all patients (13).

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Figure 1. Case 2 with decerebrate posture.

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Migraine, chronic tension-type headache, and cluster headache in an Ethiopian rural community

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Cephalalgia

Tekle Haimanot R, Seraw B, Forsgren L, Ekbom K, Ekstedt J. Migraine, chronic tension-type headache, and cluster headache in an Ethiopian rural community. Cephalalgia 1995;15:482–8. Oslo. ISSN 0333-1024

Fifteen-thousand-five-hundred adults (⩾20 years) in a rural district in Ethiopia with a population of 250 000 were studied for chronic headache. Door-to-door survey was performed by trained lay health workers using a questionnaire with a high degree or reliability and validity. The 1-year prevalence of migraine headache was 3.0% (4.2% for females and 1.7% for males) with the peak age specific rate in the fourth decade. Migraine headache was about three times more common in females than in males at any decade. Two-thirds of migraine sufferers had rather frequent attacks. The most frequent trigger factors were emotional stress (90%), changes of weather (78%), physical exhaustion (75%), and smell (70%). Migraine with aura was rare. Family occurrence of migraine in first-degree relatives was 30%. The 1-year prevalence of chronic tension-type headache was 1.7%, while cluster headache was found to be extremely rare. Compared to similarly performed surveys, the prevalence of migraine among rural Ethiopians was less than among Nigerian Africans. □ *Epidemiology, Ethiopia, headache, migraine, prevalence*

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The most extensive references to headache in Africans were collected by Spillane in his textbook on tropical neurology. Migraine was relatively uncommon in black Africans (1–4), except in Ghana (5).

In 1972, hemoglobin AS genotype (sickle cell trait) was found in 60% of Nigerians with migraine with aura compared to 20% of those with migraine without aura (6). Thereafter, little was written on migraine in Africans until Osuntokun et al. (7) published their findings that migraine was not uncommon in Nigerian Africans. The prevalence of migraine in the pilot study in rural Nigerians was 6.9%. A larger study in another rural community of southern Nigeria demonstrated a prevalence of 6.3% (6.8% in females and 5.7% in males) (8). Recently, a large study of urban Nigerians showed a prevalence of migraine to be 5.3% (5.6% in females and 5% in males) (9).

There are no community-based data on chronic headache in Ethiopia. This study was therefore carried out to determine the prevalence of migraine and other primary headaches.

Patients and methods

The rural district of Meskan and Marko of central Ethiopia with a population of 250 000 was selected for the survey of chronic headache. In this district, neuroepidemiologic studies were performed in 4 semi-urban dwellers' associations and 25 peasant associations randomly sampled from a pool of 82 peasant associations, to determine the prevalance of neurological disorders. For logistic reasons these epidemiological studies did not include headaches and low backache in the screening instrument (10).

For the headache survey 12 peasant associations were randomly selected from the 25 peasant associations previously covered by the neuroepidemiological survey. All four semi-urban dwellers associations of the district capital, Butajira, were included. This constituted a population of 35 700, of which 15 500 were ⩾20 years. The response rate among these adults was 96.8%.

A questionnaire (Appendix) with a high degree of reliability and validity developed by Ekbom (11, 12) was used in the survey. It was slightly modified to fit the criteria given below, and to accommodate the rural, predominantly illiterate, background of the surveyed population. The questionnaire was translated into Amharic, the official language of Ethiopia.

Enumerators were trained on the questionnaire until they were able to understand and translate the questions into the local dialects during the interview. Locally recruited from secondary school graduates, the enumerators had been working in the major neuroepidemiological surveys for at least 5 years (10), were quite familiar with the interview methodology, and had a good knowledge of neurological diseases. The study was carried out between December 1992 and November 1993. Confidence limits (95%) for prevalence rates were calculated in accordance with Colton (13). The clinical diagnoses of migraine, chronic tension-type headache, and cluster headache were established in accordance with the

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criteria of the International Headache Society (14). Persons identified by the enumerators to have chronic headaches were interviewed again by the internist (BS) or the neurologist (RTH) for confirmation of diagnosis and classification of headache. There was 90% agreement between the enumerators and the clinicians. The clinicians used a structured approach in the diagnosis and followed the criteria proposed by Ekbom to classify migraine, cluster and tension headaches based on the questionnaire (Appendix).

Results

The total sample size was 15 000 adults with a male to female sex ratio of 1:1.1. The mean age was 40.1 among males and 40.3 years among females. Seven-hundred-and-twelve (4.7%) out of 15 000 screened subjects were found to suffer from chronic headache. The male to female sex ratio was 1:2.7. The overall prevalence rate for migraine was 3% with a male to female ratio of 1:2.8. The peak age-specific prevalence rate for migraine occurred in the fourth decade for both males and females. The observed male and female peak age prevalence rates were 4.3% and 5.6%, respectively (Table 1).

Table 2 gives age-adjusted prevalence rates of the primary headaches. The five cases of cluster headache were not included in the table. Among migraineurs, females were observed to be affected two to four times more than males (Table 2).

Migraine with aura and migraine without aura were found in 0.3% and 2.7%, respectively. Migraine was more common in the major town (prevalence = 4.0%) than in the areas of peasants associations (prevalence = 2.6%). Of the migraine sufferers, 7.3% had attacks once or a few times per year; 26.4% had attacks on some occasions every month; 66.3% had attacks several times a month.

The most common precipitating or trigger factors in the migraine sufferers were emotional stress (406 cases, 90%), changes in the weather (353 cases, 78%), physical strain (exhaustion) (342 cases, 75%), and smell (316 cases, 70%). The following alcoholic beverages were reported by patients to precipitate migraine attacks: beer (23%), spirits (12.8%), wine (7.3%), and honey mead (2.5%). Chocolate was not consumed in the community and cheese was not an important factor in migraine attacks. Khat (*Catha edulis*), an amphetamine-like stimulant whose wet leaves are chewed on social occasions, was found to be an aggravating factor of migraine in 12%. 35.7% of migrainous subjects experienced attacks during the weekend. Nine percent of females had their attacks during menstrual periods. Only one of 333 female sufferers was found to have used the contraceptive pill. The occurrence of migraine in the first-degree relatives was 30% among migraineurs. Chronic tension-type headache occurred in 1.7%, and cluster headache in 0.03% of the surveyed population (Table 2).

Discussion

Table 3 surveys different studies on the prevalence of migraine in Africa and other representative countries of the world. The present study shows that migraine is not uncommon in Ethiopians, contrary to what has been claimed to be the case in Africans (1–4). The overall prevalence of chronic headache in this study (4.7%) should be regarded in the light of a specific search for repeated headache episodes. This is unlike the life-time occurrence of episodes of headache, which was shown in a Nigerian study to be as high as 51% (9).

The prevalence of migraine in our study was less than that for Nigerians; 3% versus 6.3% in rural (8) and 5.3% in urban Nigeria (9) and urban Zimbabwe (4.2%) (15). This might in part be explained by the exclusion of persons below 20 years in this study. The prevalence of migraine headache in our rural population was less than in a number of recent reports from Western countries (Table 3, refs 16–21; for reviews see refs 20 and 21), but much higher than in China (0.69%) (22).

Table 1. One-year prevalence of migraine by age and sex and 95% confidence intervals (95% CI) in a population of 15 000

Age (years)	Males				Females				Males + females			
	Sample	No.	Prev	95% CI	Sample	No.	Prev	95% CI	Sample	No.	Prev	95% CI
20–29	2458	27	1.10	0.69–1.51	2358	114	4.83	3.96–5.70	4816	141	2.93	2.45–3.41
30–39	1266	55	4.34	3.22–5.46	1993	111	5.57	4.56–6.58	3259	166	5.09	4.34–5.84
40–49	1394	20	1.43	0.81–2.05	1641	62	3.78	2.86–4.70	3035	82	2.70	2.12–3.28
50–59	904	14	1.55	0.70–2.36	962	33	3.43	2.28–4.58	1866	47	2.52	1.81–3.23
60–69	541	3	0.55	0.00–1.17	568	11	1.94	0.81–3.07	1109	14	1.26	0.60–1.92
70–79	323	2	0.62	0.00–1.48	359	2	0.56	0.00–1.33	682	4	0.59	0.02–1.16
80–89	114	0	0.00	—	119	0	0.00	—	233	0	0.00	—
Total	7000	121	1.73	1.42–2.04	8000	333	4.16	3.72–4.60	15000	454	3.03	2.76–3.30

Sample = sample size; No. = number of cases with migraine; Prev = prevalence in %.

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Table 2. One-year prevalence of primary chronic headaches by age and sex and 95% confidence intervals (95% CI) in a population of 15 000.

Age (years)	Migraine without aura						Migraine with aura						Chronic tension-type headache					
	Males			Females			Males			Females			Males			Females		
	No.	Prev	95% CI	No.	Prev	95% CI	No.	Prev	95% CI	No.	Prev	95% CI	No.	Prev	95% CI	No.	Prev	95% CI
20–29	21	0.85	0.49–1.21	110	4.66	3.81–5.51	6	0.24	0.05–0.43	4	0.17	0.00–0.34	10	0.41	0.16–0.66	0	0.00	—
30–39	44	3.48	2.47–4.49	106	5.32	4.33–6.31	11	0.87	0.36–1.38	5	0.25	0.03–0.47	5	0.39	0.05–0.73	13	0.65	0.30–1.00
40–49	18	1.29	0.70–1.88	60	3.66	2.75–4.57	2	0.14	0.00–0.34	2	0.12	0.00–0.29	13	0.93	0.43–1.43	71	4.33	3.35–5.31
50–59	12	1.33	0.53–2.08	24	2.49	1.51–3.47	2	0.22	0.00–0.53	9	0.94	0.33–1.55	18	1.99	1.06–2.90	78	8.11	6.38–9.84
60–69	3	0.55	0.00–1.17	9	1.58	0.55–2.61	0	0.00	—	2	0.35	0.00–0.84	15	2.77	1.39–4.15	22	3.87	2.28–5.46
70–79	2	0.62	0.00–1.48	2	0.56	0.00–1.33	0	0.00	—	0	0.00	—	6	1.86	0.39–3.33	0	0.00	—
80–89	0	0.00	—	0	0.00	—	0	0.00	—	0	0.00	—	0	0.00	—	2	1.68	0.03–3.33
Total	100	1.43	1.15–1.71	311	3.89	3.47–4.31	21	0.3	0.17–0.43	22	0.28	0.16–0.40	67	0.96	0.73–1.19	186	2.33	2.00–2.66

No. = number of cases; Prev = prevalence in %.

The peak age-specific prevalence rate was found to be in the fourth decade with a steady decrease after the age of 39 years in both sexes like that of the pilot study in rural Nigerians (7). In Nigerians, however, more sufferers were observed after the fourth decade in the larger study.

Migraine with aura has been said to be infrequent. In urban Zimbabwe (15) not one person interviewed (out of 5028 people) had the features of migraine with aura and the rarity was also seen in rural Nigeria (0.4%) (8). Our findings concur with these studies. On the other hand, Rasmussen and Breslau (23) stated that in America and Western Europe the 1-year prevalence of migraine with aura is around 4%.

Sixty-six per cent of our patients had attacks several times a month. Thus, many of them obviously had a fairly severe form of migraine. This frequency of attacks was similar to reports from China (20) and Thailand (24). On the other hand, studies from the USA and Europe (25) showed a much lower frequency among migraineurs. The available African studies (15, 26) do not allow similar comparisons.

The high frequency of attacks among migraineurs in the study population remains unexplained. Khat, found to precipitate migraine attacks in 12%, might be a contributing factor in the high frequency of attacks. Response to closed-end questions on precipitating and aggravating factors revealed that changes in the weather, physical and emotional strains were the major trigger factors in our migraine sufferers of the rural community. Food items, on the other hand, were not important precipitating factors. These findings were similar to the observations made by Ogunyemi among Nigerian university students (27).

Khat is widely used in Ethiopia among various social groups. It is commonly consumed during social recreation gatherings, it has medicinal uses, and it is consumed during ritual and religious ceremonies. Long-distance drivers and students during examination periods chew khat to keep awake (28, 29). The active substance in khat is cathinone, which closely resembles amphetamine. Cathinone has a fourfold affinity for serotonin receptors compared with amphetamine (30), but its effect on the release of serotonin is much less than amphetamine. Cathionine has also been shown to increase the release of central noradrenaline (31). In a study of 66 khat users, Mekasha found that 25% suffer from frequent headaches (32). It is therefore not surprising that 12% of the migraine sufferers in the present study reported khat as a precipitating factor of their headaches.

Family occurrence of migraine in our study was similar to the 31.7% rate in Zimbabwe (15) and 33.7% in a rural community in Bangkok, Thailand (24), and unlike the 68% and 80% rates reported in

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Appendix: Questionnaire for classification of headache

1. Do you have recurrent headache? No/Yes

As regards questions 2–5 put a cross against only one alternative. Have you had headache
2. during at least the last year? No/Yes
3. during at least the last 2 years? No/Yes
4. during at least the last 5 years? No/Yes
5. during at least the last 10 years? No/Yes

As regards questions 6–10 put a cross against only one alternative. Do you have headache
6. once or a few times per year? No/Yes
7. on some occasions every month? No/Yes
8. several times a month? No/Yes
9. several times a week? No/Yes
10. every day or the week? No/Yes

As regards questions 11–15 answer only one alternative. Does each attack of headache usually last
11. less than 3 hours? No/Yes
12. between 3 and 4 hours? No/Yes
13. between 4 and 6 hours? No/Yes
14. between 6 and 12 hours? No/Yes
15. between 12 and 24 hours? No/Yes

Table 3. Prevalence (%) of migraine in various countries.

Country 1st author, year (reference)	Population	Migr defin	No.	Age (yr)	Prevalence period	Migraine (± aura)	Classical (+ aura)	Common (− aura)
China								
Zhao, 1988 (20)	comm, rural	AHC	246,812	all	1-year	0.7	0.3	0.4
Denmark								
Rasmussen, 1991 (18)	comm	IHS	740	25–64	1-year	10.0		
Rasmussen, 1992 (19)	comm	IHS	740	25–64	1-year		3	5
Ecuador								
Sachs, 1985 (37)	comm, rural	AHC	1,113	all	1-year	3.7	2.3	1.4
Ethiopia								
The present study	comm, rural	IHS	15,000	⩾20	1-year	3.0	0.3	2.7
France								
Henry, 1992 (16)	comm	IHS	4,204	5–65	lifetime	5.5	—	—
Nigeria								
Osuntokun, 1982 (7)	comm, rural	AHC	906	all	?	6.9	—	—
Ogunyemi, 1984 (27)	students	AHC	1,756	16–42	?	16.7	3.9	12.9
Longe, 1986 (8)	comm, rural	?	2,925	all	?	6.3	0.4	5.9
Osuntokun, 1992 (9)	comm, urban	AHC	18,954	all	?	5.3	—	—
Saudi Arabia								
Al-Rajeh, 1990 (36)	clinic 222 headache cases (13% of referrals)	?	all	?	?	28.0	—	—
Sierra Leone								
Lisk 1987 (35)	clinic 250 headache cases (1/4 of referrals)	?	all	?	?	42.4	10.0	32.4
Tanzania								
Matuja 1991 (26)	clinic 139 headache cases	?	675	5–59	2-year	33.8		4X the classical
Thailand								
Phanthumchinda 1989 (24)	comm	AHC	540	⩾10	1-year	29.1	—	—
USA								
Stewart, 1992 (17)	comm	IHS	20,334	12–80	1-year	F:17.6 M:5.7	—	—
Zimbabwe								
Levy, 1983 (15)	comm, urban	AHC	5,028	⩾5	1-year	4.2	0	4.2

No. = sample size; yr = year; comm = community; migr defin = migraine definition; AHC = Ad Hoc Committee Criteria (38); IHS = International Headache Society (14); F = female; M = male.

the Nigerian studies (7, 8). There may have been an under-reporting of family occurrences of migraine in our study, which was based on reports from probands. Such reports may underestimate the true frequency (33).

As with the observation elsewhere, chronic tension-type headache was the second most prevalent headache in this study. Our figure (1.7%) is not far from that of Rasmussen et al. (3%) for a Danish population aged 25–64 years (18). Cluster headache was extremely rare. Only case reports have appeared from other African authors (27, 34, 35).

In conclusion, this study showed that migraine is not uncommon in Ethiopians although the figure is less than those reported in other African studies. The difference in migraine prevalence between countries may partly be due to differences in methodology and definition. We found in line with clinical outpatient experience in Ethiopia that there are more headache sufferers in the cities and bigger towns than among the rural populations. It is conceivable that the urban population may express the symptomatology of migraine headache more so than the rural population. This hypothesis needs to be tested in large comparative surveys of urban and rural communities.

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16. between 24 and 72 hours?
17. more than 72 hours?

As regards questions 18–20 answer only one alternative:

18. Does your headache come only in the day time? No/Yes
19. Does your headache come only in the night time? No/Yes
20. Do you have headache both in day time and night time? No/Yes
21. Are you ever awakened by headache in the middle of the night? No/Yes

N.B. You should first listen to questions 22–29 before answering them.

As regards questions 22–24 answer only one alternative:

22. Is the headache sometimes on one side of the head? No/Yes
23. Is the headache usually on one side of the head? No/Yes
24. Is the headache always on one side of the head? No/Yes

If question 23 or 24 is answered in the affirmative:

25. Is the headache always on the same side of the head? No/Yes
26. Is the headache sometimes on the right and sometimes on the left side of the head? No/Yes

As regards questions 27–29 put a cross against only one alternative:

27. Is the headache sometimes on both sides of the head? No/Yes
28. Is the headache usually on both sides of the head? No/Yes
29. Is the headache always on both sides of the head? No/Yes
30. Is the headache worse on one side than the other? No/Yes
31. Is the headache in the region of one eye? No/Yes
32. Is the headache in the region of both eyes? No/Yes
33. —in the forehead? No/Yes
34. —in the temple? No/Yes
35. —in the top of the head? No/Yes
36. —in the back of the head? No/Yes
37. —in the upper jaw? No/Yes
38. —in the lower jaw? No/Yes
39. —Does the headache involve shooting pain? No/Yes
40. —splitting pain? No/Yes
41. —throbbing pain? No/Yes
42. —dull pain? No/Yes
43. Does the headache consist of a feeling of pressure rather than of ache proper? No/Yes
44. Is the headache usually accompanied by nausea or vomiting? No/Yes
45. Is the headache usually accompanied by reddening of the eyes? No/Yes
46. —by a flow of tears? No/Yes
47. —by stuffiness of the nostrils? No/Yes
48. —by sensitivity to light? No/Yes
49. —by sensitivity to sound? No/Yes
50. —by being disturbed? No/Yes
51. —by diarrhoea? No/Yes
52. —by abnormally large quantities of urine? No/Yes

As regards questions 53–56 choose the reply you think best fits your case and put a cross against only one alternative:

53. Does the headache usually cause mild discomfort? No/Yes
54. Is the headache usually fairly severe but not so troublesome that it hinders your work? No/Yes
55. Is the headache usually so severe that you must stop work until it passes over? No/Yes
56. Is the headache usually almost unbearable? No/Yes

As regards questions 57–59 put a cross against only one alternative:

57. Do you prefer to lie down and rest when you have a headache? No/Yes
58. Do you prefer to sit up until the headache has passed? No/Yes
59. Do you prefer to walk around the room or go for a walk when you have a headache? No/Yes
60. Is the headache aggravated by walking stairs or comparable physical activity? No/Yes
61. —Do you prefer to be by the side of the fire? No/Yes
62. —Do you apply *butter* on your head? No/Yes
63. —Do you wash your head when you have a headache? No/Yes
64. Do you generally see flickering or flashes of light for about 20 min before the headache starts? No/Yes
65. Is the headache usually preceded by a period of numbness in one side of the face and one arm? No/Yes
66. Before you get a headache, do you know that one is coming? No/Yes
67. Has any member of your family recurrent headache accompanied by nausea or vomiting? No/Yes
68. Father? No/Yes
69. Mother? No/Yes
70. Brother or sister? No/Yes
71. Among your children? No/Yes
72. Among your relatives? No/Yes
73. Have you had attacks of very severe headache in the region of one eye, always on the same side and lasting at least 15 minutes and at most 3 hours? No/Yes
74. Do these attacks come once or more per day during shorter or longer periods? (if the above, 73 is responded to in the affirmative)? No/Yes

Are the headaches usually caused by

75. —exhaustion?

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76. —stress or anxiety?
77. —cheese?
78. —chocolate?
79. —during/after chewing khat?
80. "Teg" (Honey mead)?
81. "Tella" (local beer)?
82. —Beer?
83. —Red wine?
84. —'Araki' (spirit)?
85. —Didn't smoke a cigarette?
86. —Smell of tobacco?
87. —Good or bad smell?
88. —Change of weather?
89. —Do the headaches often come on Saturdays-Sundays?
90. Do you take headache tablets daily or almost daily? No/Yes
91. What kind of tablet is it?
92. Have you received any tablet containing ergot against the pains? e.g. Cafergot, Cafergot comp? No/Yes
93. Have you earlier visited a doctor because of headache? No/Yes
94. —When?
95. —Whom?
96. Have you been hospitalized for treatment of headache? No/Yes
97. —When?
98. —Where?

The following questions should be answered only be female patients:

99. Is your headache usually aggravated by menstruation? No/Yes
100. Does the headache come only in conjunction with menstruation? No/Yes

This question should be answered only if you have been pregnant:

101. Has your headache been much better during pregnancy (pregnancies)? No/Yes
102. Do you use contraceptive pills? No/Yes

If the answer is no:

103. Have you earlier used contraceptive pills? No/Yes
104. Have contraceptive pills improved your headache? No/Yes

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Hepatitis C virus infection and chronic liver disease in Ethiopia where hepatitis B infection is hyperendemic

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Abstract

To assess the prevalence and possible aetiological association of hepatitis C virus (HCV) with chronic liver disease and hepatocellular carcinoma (HCC), antibodies to HCV (anti-HCV) were determined by enzyme-linked immunosorbent and recombinant immunoblot assays in 500 healthy volunteer blood donors, 14 patients with chronic hepatitis, 156 cirrhotics and 68 cases of hepatocellular carcinoma (HCC) in Ethiopia. The prevalences of anti-HCV were 1·4%, 21%, 36% and 46%, respectively. There was no apparent risk factor to suggest the mode of transmission of HCV. Of the 238 patients, 65 (27%) had circulating hepatitis B surface antigen (HBsAg) (denoting current infection), 131 (55%) had antibodies to hepatitis B surface (anti-HBs) and/or core (anti-HBc) antigens (past infection) and 42 (18%) had no hepatitis B virus (HBV) marker. Anti-HCV antibodies were present in only one patient with HBsAg, in 54% with past infection and in 68% of those without HBV markers. Thus, HCV infection was uncommon in HBsAg-positive patients but significantly more common in patients with chronic liver disease and HCC who had evidence of past HBV infection or no marker for HBV infection. HCV infection appeared to be a more common cause of chronic liver disease and HCC than HBV infection in this population. However, considering the high prevalence of overall exposure to HBV infection (68% in healthy blood donors and 82% in those with chronic liver disease, including HCC), HBV is significant in terms of national preventive strategies.

Keywords: hepatitis C, hepatitis B, chronic liver disease, Ethiopia

Introduction

The overall prevalence of hepatitis B virus (HBV) markers among the general adult population of Ethiopia is about 80%, the carrier state of hepatitis B surface antigen (HBsAg) being 11–12% (Tsega *et al.*, 1986, 1987). Acute and chronic viral hepatitis, cirrhosis of the liver and hepatocellular carcinoma (HCC) accounted for 12% of hospital admissions and 31% of medical ward mortality (Tsega, 1977a). Hepatocellular carcinoma is the commonest tumor in medical in-patients, over 95% occurring on a background of cirrhosis (Pavlica & Samuel, 1970; Tsega, 1977b) and 21–50% in association with HBsAg (Tsega *et al.*, 1992). Although the association between HBV infection and chronic liver disease is high, there remains a significant number of patients with evidence of only past exposure to, or without any serological marker of, HBV infection (Tsega *et al.*, 1992). Recent studies in Italy (Colombo *et al.*, 1989), Spain (Bruix *et al.*, 1989), Japan (Saito *et al.*, 1990), Taiwan (Chen *et al.*, 1990) and South Africa (Kew *et al.*, 1990) have shown an association between hepatitis C virus (HCV) infection, chronic liver disease and HCC. The purpose of this study was to investigate the association between HBV and HCV infections in Ethiopian patients with chronic hepatitis, cirrhosis and HCC.

Patients and Methods

A total of 170 men and 68 women with chronic hepatitis, cirrhosis and HCC were studied consecutively between 1992 and 1994 (Table 1). After documentation of clinical and basic investigative data, including repeated ultrasonographic liver scans and upper gastrointestinal endoscopic examination, liver biopsy was performed with Menginhi needles percutaneously in 64 patients and laparoscopically in 174 patients. Biopsy specimens were stained with haematoxylin and eosin. Only biopsy proven cases were included in the study. There were 14 patients with chronic hepatitis (1 chronic persistent hepatitis and 13 chronic active hepatitis, 6 of whom showed early changes of cirrhosis), 156 cirrhotics (1 with chronic persistent hepatitis, 13 with chronic active hepatitis and 3 with atypical hepatocytes), and 68 cases with HCC (37 with advanced cirrhosis). From all cases of HCC diagnosed by laparoscopy, biopsies were taken from tumour masses only, although macronodular cirrhosis was universally detected.

Markers for HBV (HBsAg, antibodies to the core antigen (anti-HBc), antibodies to HBsAg (anti-HBs) and antibodies to hepatitis D virus (anti-HDV)) were determined in 459 healthy, volunteer blood donors (409 men and 50 women; Table 1) and in the 238 patients with chronic liver disease and HCC, using commercial radioimmunoassay kits (Abbott Laboratories). Antibodies to HCV (anti-HCV) were determined by enzyme-linked immunosorbent assay (ELISA-2®; Ortho Diagnostics, Raritan, New Jersey, USA) and confirmed by the recombinant immunoblot assay (RIBA-2®; Chiron Corporation, Emeryville, California, USA). As the sera from the 459 blood donors were over 8 years old, a fresh collection of sera was made from 500 healthy, volunteer blood donors (Table 1) and stored at −20°C until tested (within 2 months of collection) as a control in the anti-HCV study in order to avoid false positive results (Ellis *et al.*, 1990). Serum alanine transaminase (ALT) was determined in those patients who were RIBA-2 positive and those who gave indeterminate results.

Results

Only 24 (10%) patients had had a blood transfusion 6 months or more before the most recent hospital visit (Table 1) and most of these were cirrhotics given blood for variceal bleeding. A high prevalence of ascites, splenomegaly, mental changes and haematemesis and/or melaena among the patients with cirrhosis and HCC indicated advanced hepatic decompensation and the frequent association between these 2 conditions.

Table 1. Characteristics of patients with chronic liver diseases or hepatocellular carcinoma, and of healthy blood donors

Characteristics	Blood donors	Chronic hepatitis	Cirrhosis	HCC[a]
No. studied	459	14	156	68
Mean age[b]	30±11·6	35±13·1	42±13·8	49±13·1
Male/female ratio	8/1	4/1	3/1	3/1
No. who had received blood transfusion(s)	3	1	19	4
No. positive for HBsAg	50 (11%)	7 (50%)	45 (29%)	13 (19%)
Anti-HDV	1 (2%)	0	7 (16%)	3 (23%)
Anti-HBs±anti-HBc	311 (68%)	6 (43%)	87 (56%)	38 (56%)
Anti-HCV	7 (1·4)[c]	3 (21%)	56 (36%)	32 (46%)
No. HBV marker negative	98 (21%)	1 (7%)	24 (15%)	17 (25%)

[a]Hepatocellular carcinoma.
[b]±Standard deviation.
[c]Anti-HCV was determined in 500 recently collected sera from volunteer blood donors (mean age 29 years; range 18–75 years).

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The prevalences of HBV, HDV and HCV markers are shown in Table 1. The HBsAg carrier state in each type of chronic liver disease was about twice that in healthy adult Ethiopians. Among the HBsAg carriers, only 18 (27%) had HBeAg and 15 (23%) had anti-HDV, the latter rate being significantly higher than the 2% observed in the healthy blood donors.

None of the 7 RIBA-2 positive blood donors or the 14 with indeterminate results had an abnormal serum ALT level.

The prevalence of anti-HCV in the patients with chronic liver disease (38%) was significantly higher than that in the normal subjects (1·4%) (χ^2 with Yates's correction = 186·8; $P<0·001$). There was no significant difference in the prevalences of anti-HCV between the different types of chronic liver diseases. Thus, there was a strong correlation between HCV infection and chronic liver disease (relative risk (RR) = 27·3; 12·9<RR<58·0).

Only one of the patients (1·5%) with current HBV infection (HBsAg positive) was positive for anti-HCV while 71 (54%) of 131 patients with past HBV infection (anti-HBs and/or anti HBc positive) and 25 (60%) of 42 patients without HBV markers were anti-HCV positive (Table 2). The mean age of the patients with current HBV infection (HBsAg positive) was significantly less than that of those with past HBV infection or those who lacked all HBV markers ($P<0·05$). On the other hand, the mean age of the patients with anti-HCV was significantly higher than that of the patients with no anti-HCV ($P<0·05$) (Table 3), this difference being more marked in the patients with cirrhosis and HCC.

Table 2. Association of hepatitis B virus markers with hepatitis C virus infection in patients with chronic liver disease and hepatocellular carcinoma

Diagnosis	HBsAg		Anti-HBs plus/minus anti-HBc		No HBV marker		Total	
	No. studied	No. with anti-HCV	No. studied	No. with anti-HCV	No. studied	No. with anti-HCV	No. studied	No. with anti-HCV
Chronic hepatitis	7	0	6	2 (33%)	1	1 (100%)	14	3 (21%)
Cirrhosis	45	0	87	46 (53%)	24	10 (42%)	156	56 (36%)
HCC*	13	1 (6·7%)	38	23 (61%)	17	8 (47%)	68	32 (47%)
Total	65	1 (1·5%)	131	71 (54%)	42	25 (68%)	238	91 (38%)

*Hepatocellular carcinoma.

Table 3. Hepatitis B and C virus interaction and mean ages of patients with chronic liver diseases and hepatocellular carcinoma

Viral marker status	Chronic hepatitis		Cirrhosis		HCC*	
	No.†	Mean age (years)‡	No.†	Mean age (years)‡	No.†	Mean age (years)‡
Hepatitis B virus						
No. with						
HBsAg	7	28·67±12·61	43	34·05±11·82	13	38·77±14·75
Anti-HBS plus/minus anti-HBC	6	40·43±10·78	87	45·34±12·71	38	51·22±11·49
No HBV marker	1	–	23	42·58±10·76	17	52·41± 9·24
Hepatitis C virus						
No. with anti-HCV	3	45·67±12·39	55	49·35± 9·37	32	55·03± 7·61
No. without anti-HCV	10	31·80±11·44	88	37·53±13·99	30	41·97±15·34

*Hepatocellular carcinoma.
†Total number of subjects with/without the indicated viral marker.
‡±Standard deviation.

As summarized in Table 2, 27% of the 238 patients with chronic liver disease (including HCC) had HBV infection (were HBsAg positive) and 38% were anti-HCV positive (12 patients with HCC had evidence of HBV infection alone and 31 had evidence of HCV infection alone). Thus, there were more anti-HCV positive cases than those who were HBsAg positive (χ^2 with Yates's correction = 5·51; $P=0·02$). Neither HBsAg nor anti-HCV were detected in the remaining 35% of chronic liver disease and HCC cases.

Discussion

The prevalence of anti-HCV (1·4%) in healthy adult Ethiopian blood donors was about the same as that reported from Italy (FERRONI & SALVANESCHI, 1990), Norway (HETLAND *et al.*, 1990), South Africa (KEW *et al.*, 1990), Taiwan (CHEN *et al.*, 1990) and the USA (STEVENS *et al.*, 1990). On the other hand, the prevalences of anti-HCV positivity among patients with chronic hepatitis, cirrhosis of the liver and HCC (21%, 36% and 46%, respectively) were significantly higher than that in healthy blood donors, suggesting an aetiological association between HCV and these liver conditions. The prevalence of anti-HCV in chronic liver disease, including HCC, was less than that observed in Spain (BRUIX *et al.*, 1989) and Taiwan (CHEN *et al.*, 1990).

Screening using serum ALT levels would have been of no value since none of the anti-HCV RIBA-2 positive or indeterminate cases had elevated levels. This may have been partly due to the usual wide fluctuation of liver function test results in patients with HCV infection.

The mode of transmission of HCV in this population is not known. Exposure to blood and blood products is uncommon. Traditional practices like tattooing, circumcision at home, tonsillectomy, scarification, ear piercing and frequent injections with hypodermic needles in private clinics and homes for different illnesses are widely practised. However, the significance of these practices as vehicles of HCV transmission is difficult to evaluate (TSEGA *et al.*, 1988). Sexual transmission of HCV has been reported (ALTER *et al.*, 1989; EVERHART *et al.*, 1990; SANCHEZ-QUIJANO *et al.*, 1990), but its importance requires further investigation, especially in the light of a recent report (BRESTERS *et al.*, 1993). A report by OHTO and associates (1994) indicated that HCV infection can be transmitted from mothers to infants. Such vertical transmission has yet to be demonstrated in the population we studied. Thus, the mode of transmission of HCV remains an obvious and important area for future study.

As summarized in Tables 1 and 2, 65 patients (27%)

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with chronic liver disease and HCC were HBsAg-positive (current infection), 131 (55%) were positive for anti-HBs and/or anti-HBc (past infection), while 42 (18%) lacked all HBV markers. Of the group with current infection, only a single case (with HCC) had anti-HCV. On the other hand, 54% of those who had past HBV infection and 68% of those who lacked all HBV markers had anti-HCV. A low prevalence of anti-HCV among HBsAg-positive patients has also been reported by CHEN *et al.* (1990) and SAITO *et al.* (1990), but it was significantly lower in our study. The 2 viral infections did not overlap as causes of chronic liver disease in our population, but appeared in 2 separate groups. One possible explanation may have been that HBV infection occurred at an early age (TSEGA *et al.*, 1986, 1988), whereas HCV infection may have occurred later. The mean ages of the 2 groups with HBV and HCV infections (Table 3) supported this view. Another possibility is that the latency period before HCV infection manifests as clinical disease may be longer than that for HBV infection.

In terms of current or active infection, HCV (38%) was more common than HBV (28%) in this group of patients with chronic hepatitis, cirrhosis and HCC (χ^2 with Yates's correction=5·5; P=0·0189). Although the prevalence of chronic HBV infection in the general population was higher than that of HCV in blood donors (11% compared to 1·4%), HCV seemed to be the cause of more cases of chronic liver disease than HBV. One reason for this difference may have been that about 50% of acute HCV infections continue as chronic infections (approximately 20% of those with chronic hepatitis will have cirrhosis) (ALTER, 1989), while less than 10% of acute HBV infections may become chronic. Although these observations are well known, one should be aware of the fact that multiplication of HBV may occur in the absence of any conventional serological marker, since a high frequency of HBsAg-negative viral infections of the liver have been diagnosed by the detection of HBV deoxyribonucleic acid (BRECHOT *et al.*, 1985; FAGAN *et al.*, 1991). However, considering the high prevalence of past and present infections (68% in healthy blood donors and 82% in the chronic liver disease cases, including HCC), HBV is significant in terms of a nation-wide strategy for preventive measures.

Slow sequential progression from acute HCV infection through chronic hepatitis and cirrhosis to HCC has been reported by many investigators (RAKELA & REDDEKER, 1979; REALDI *et al.*, 1982; KORTEZ *et al.*, 1985; KIYOSAWA *et al.*, 1990a, 1990b). The histological overlap of chronic hepatitis, cirrhosis and HCC in a number of patients, the universal association of cirrhosis with HCC, the significantly higher prevalence of anti-HCV than that in normal blood donors, and the sequential increase in the prevalence of anti-HCV in patients with the 3 different liver conditions, suggest that HCV infection plays a role in the pathogenesis of chronic hepatitis, cirrhosis and HCC in this population.

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Announcement

Third Biennial Meeting of the Society for Tropical Veterinary Medicine
8–12 May 1995
San José, Costa Rica

The meeting will include two symposia, on "Vector-borne pathogens: challenges for the 21st century" and "International trade and animal diseases", as well as general sessions on tropical veterinary medicine.

Further information can be obtained from Dr James A. House, USDA APHIS FADDL, Box 848, Greenport, NY 11944, USA; telephone (+1) 516 323 2500, extension 350, fax (+1) 516 323 2798.

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CAUSES OF VISUAL IMPAIRMENT IN CENTRAL ETHIOPIA

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ABSTRACT: *A survey conducted on a stable, mainly rural population of 60,820 in Central Ethiopia revealed an overall blindness prevalence of 1.1%. A follow up study was carried out to accurately determine the etiologies and causes of visual loss and impairment. A detailed ophthalmic evaluation was done on 523 out of 872 individuals identified as being visually impaired. The results showed that 194 (37%) were blind (Categories 3,4, and 5 = maximum visual acuity less than 3/60 in the better eye). One hundred and seven (21%) (Categories 1 & 2 = maximum visual acuity better than 3/60 to less than 6/18 in the better eye using the WHO categories of visual impairment). The rest 222 (43%) were blind in one eye only. The commonest anatomical cause of blindness is corneal (32%). Cataract (25%), atrophied globe(s) (20%) and glaucoma (17%) follow as the other leading causes. Trachoma (35%), degenerative conditions (35%) and other infections (9%) were the major etiologies of blindness. Similar pattern of anatomical causation was observed in those classified under categories of visual impairment 1 and 2, referred to as "low vision". The most important etiologies of low vision were trachoma (30%), degenerative (24%), trauma (13%) and other infections (8%). Trauma was the most important etiology of monocular blindness (39%). Blindness was either preventable or curable in 74% of the cases.*

INTRODUCTION

Mass blindness is expected to double by the year 2,000; an insoluble problem in many developing countries (1). The current patterns and projections for the future indicate that blindness in Africa will remain a significant public health problem (2-4,6,7). Prevalence of blindness in African countries is the highest in the world, as demonstrated by many community-based studies (5,8,9,10). A prevalence rate as high as

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3.6% to 5.2% (11,12) has been reported.

In Ethiopia, the prevalence of blindness has been estimated to be 1.5% (13-16), with preventable or curable causes accounting for approximately 80% (13). These figures suggest that over 750,000 Ethiopians are blind.

Between 1986 and 1988, a survey was conducted on a stable rural population of 60,820 in central Ethiopia, to study the prevalence of neurological disorders and blindness. The survey showed an overall prevalence of blindness of 1.1% (17). This study is a follow up carried out over the period of 1988-1990 to accurately determine the causes and etiology of visual impairment in the visually impaired population identified by the survey.

METHODS

A 30% cluster sample of the peasant and urban dwellers' associations in the stable population (181,883) of Butajira District was made. This resulted in the selection of the entire population of 25 peasant associations and the three towns within the subdistrict giving a total population of 60,820 inhabitants in the study area.

All the communities within the peasant associations selected for the study were mapped by locally recruited enumerators. A house-to-house survey was carried out by the specially trained lay health workers who were familiar with the survey area and language.

As part of a neuroepidemiological survey, special questionnaires were designed and tested to identify neurological disorders and visual impairment. The age, sex and occupation of the patients were recorded as well as the age and manner of onset of the disease. In addition, any familial occurrence of the disorder identified, condition at the time of birth, history of trauma, diabetes and/or excess consumption of alcohol by the patient were registered. All such screened patients were then examined by neurologists. Those with visual impairment had gross examination to confirm the diagnosis. Six months later, these visually impaired patients were brought back for detailed examination by an ophthalmologist.

Each examination was carried out in a centrally located public place (usually the office of a peasant association or a rural clinic) according to a clinical protocol recommended by World Health Organization (WHO) for blindness survey (18). The survey team consisted of an ophthalmologist, a nurse, registrar and the locally hired enumerators.

In all cases of corneal scars or atrophy of the eye (phthisis bulbi), detailed history, including age of onset, presence or absence of concurrent illness or events at onset, such as use of traditional medications was enquired and recorded.

Using a focal hand-light, 2x binocular magnifying loupe, and an ophthalmoscope, the ophthalmologist examined the eyelids, conjunctiva, cornea and pupils of every participant after rechecking visual acuity.

In addition, for every participant with clear media, funduscopy was carried out using direct ophthalmoscope with dilated pupil when indicated. Schiotz tonometry was performed on all persons aged 30 and over and on anyone below that age when indicated. The results of examination were reviewed for accuracy and completeness at the end of the examination day by the field team.

Visual acuity was measured on all persons with illiterate 'E' opto-types. The procedure was carried out at 6 meters in outdoor light. If visual acuity was less than 6/18, it was rechecked with pinhole, and if

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there was improvement, both results were recorded with the latter being considered as the best visual acuity. The visual acuity of infants and children unable to be tested as well as adults with extremely poor vision (unable to count fingers in front of the eye) was measured by ability to fix centrally on a moving focal hand-light which was considered to be an adequate indication of normal vision.

As required by the protocol, a single major cause and etiology of visual impairment and/or loss in each eye was assigned. When conditions of multiple causation was encountered, the underlying or precipitation cause or the one which accounted for the major component of the visual loss was assigned.

The following diagnostic criteria were used:

Trauma: Definite history of trauma given by the individual himself/herself or a guardian. The cause and circumstance of injury was also enquired and recorded whenever possible.

Trachoma: This was assigned as a major cause of visual impairment in the following situations: (1) where there was simultaneous presence of corneal opacities and entropion/trichiasis; (2) the presence of easily visible scarring in the tarsal conjunctiva, corneal opacity or corneal ulcer where there were other signs of trachoma such as active inflammation, pannus or Herbert's pits.

Nutritional: Considered as a possible cause when highly suggestive history of malnutrition coupled with an attack of measles in childhood was obtained in the absence of history of trauma and signs of trachoma in those with corneal opacities.

Cataract: Opacity of the lens visible on anterior segment examination as well as ophthalmoscopy. The lens status was then recorded as no lens opacity, mature or immature cataract, aphakia, after cataract or other.

Refractive error: Retinoscopy was not done. However, refractive error was considered as a cause depending on ophthalmoscopic findings, i.e., lens power readings, fundus findings or observed improvement in acuity with pinhole examination.

Glaucoma: This diagnosis was made in the following:

1) Children with buphthalmos;
2) Adults with poor pupillary reaction to light, pathological optic disc (pallor or cupping with increased vertical diameter) in the presence of increased intraocular pressure (IOP > 21mmHg);
3) Marked rise in IOP ($\geq$ 35mmHg) even if funduscopy could not be performed due to hazy medium.

Optic nerve and retinal disorders: History and funduscopy with dilatation were used for the diagnosis of age-related macular degeneration, optic atrophy, retinal detachment, etc.

RESULTS

The neurological survey which was carried out between 1986 and 1988 covered 95% - 100% of the population in the selected peasant association and towns. A total of 872 visually impaired people were identified (17).

Of these, a detailed ophthalmic evaluation was possible on 523 (60%). Examination could not be performed on 116 (13%) and 43 (5%) of the identified people because of death and immigration from the study area, respectively. Death was ascertained by interviewing family members. The rest 174 (20%) failed to appear for examination.

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Evaluation of sub-sample of the non-responders was not possible because of logistic reasons. Excluding the dead, immigrated, the participant rate was 75%.

The age and sex distribution of the total population identified as having visual impairment and those examined by the ophthalmologist is shown in Table 1. The male to female ratio of the examined population was 1:1.3. This population was predominantly rural (83.5%). Increasing age tended to be directly associated with higher frequency of blindness in both sexes; becoming particularly evident after the age of 40 years. However, the frequency distribution in the unilaterally blind was rather even in the different age groups (Table 2).

As shown in Table 3, categories of visual impairment in 301 (57.6%) of the examined population revealed 194 blind in the better eye (64.6%) (maximum visual acuity less than finger counting at 3 meters, i.e., 3/60); severe impairment in 20 (6.6%) (maximum visual acuity less than 6/60); and visual impairment in 87 (28.9%) (maximum visual acuity less than 6/18) using the WHO Categories of Visual Impairment (18). The rate of blindness and low vision in females is almost two times higher than that of males in this population (1.8:1). Tables 4-6 summarize the etiological and anatomical classification of binocular blindness, low vision and monocular blindness,respectively.

As shown in Table 7, males were more often exposed (60.7%) to ocular trauma. In 52.6% of the injured population, the accident occurred, before the age of 15 years. The commonest cause of ocular injury in the age interval of birth to 6 years (32.6%) was due to injury inflicted to the eye by a fly-seeking hen and/or a hen attracted by eye movement or discharge 12/44 (27.3%). This injury usually occurred in infants less than one year of age. In those between the ages of 6 years to 15 years (20.0%) injury was as a result of trauma inflicted during play. In contrast, among those over the age of 15 years (46.7), injury was mainly sustained during domestic and occupational activities in this predominantly agricultural community. The agents of injury were mostly twigs, pieces of wood, thorns, and rarely, sharp instruments. Treatment by the traditional healer, including couching (six cases), was responsible for blindness in 10 cases.

Table 1. Age and sex distribution of the population identified as visually impaired and the examined

Age (yrs)	Identified				Examined			
	M	F	T	%	M	F	T	%
0-9	16	19	35	4.0	8	10	18	3.4
10-19	37	30	67	7.7	25	19	44	8.4
20-29	25	33	58	6.7	17	18	35	6.7
30-39	40	48	88	10.1	20	35	55	10.5
40-49	51	66	117	13.4	35	47	82	15.7
50-59	47	53	100	11.5	26	43	69	13.2
60-69	74	74	148	17.0	42	54	96	18.4
70+	111	138	249	28.6	51	65	116	22.2
Unknown	1	9	10	1.1	0	8	8	1.5
Total	402	470	872	100.0	224	299	523	100.0
%	46.1	53.9		100.0	42.8	57.2		100.0

Table 2. Age and sex distribution of monocular and binocular blindness

Age (yrs)	Binocular				Monocular			
	M	F	T	%	M	F	T	%
0-9	2	3	5	2.6	5	4	9	4.1
10-19	4	3	7	3.6	19	13	32	14.4
20-29	4	4	8	4.1	11	12	23	10.4
30-39	7	7	14	7.2	12	21	33	14.9
40-49	8	13	21	10.8	23	20	43	19.4
50-59	6	13	19	9.8	13	22	35	15.8
60-69	13	29	42	21.7	17	9	26	11.7
70+	26	45	71	36.6	16	4	17	7.7
Unknown	0	7	7	3.6	0	1	1	0.5
Total	70	124	194	100.0	116	106	222	100.0
%	36.1	63.9		100.0	52.3	47.8		100.0

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Table 3. Level of visual impairment by sex in the examined population (n=301)

Best vision	Visual impairment level	WHO category	Male	Female	Total	%
<3/60-NLP*	3 (blind)	3,4 & 5	70	124	194	64.5
<6/60-> =3/60	2 (low vision)	2	5	15	20	6.6
<6/18-> =6/60	1 (low vision)	1	33	54	87	28.9

*NLP = No light perception

Table 4. Etiological and anatomical classification of blindness

Etiology			Anatomical cause		
	No. of eyes	%		No. of eyes	%
Degenerative	135	34.8	Corneal	125	32.2
Trachoma	134	34.5	Cataract	96	24.7
Other infections	35	9.0	Atrophy of	78	20.1
Trauma	25	6.4	Globes		
Measles + Nutritional	13	3.4	Glaucoma	66	17.0
			Retinal	14	3.6
Developmental	12	3.1	Optic Atrophy	5	1.3
Small Pox	5	1.3	Others	4	1.1
Unknown + Unspecified	29	7.5			
Total	388	100.0		388	100.0

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Table 5. Etiology and anatomical causes of low vision*

Etiology	No. of eyes	%	Anatomical cause	No. of eyes	%
Trachoma	65	30.8	Corneal	79	36.5
Degenerative	51	23.8	Cataract	47	22.0
Trauma	27	12.6	Atrophy of Globes	39	18.2
Other infections	20	9.4	Glaucoma	13	6.1
Measles + Nutritional	9	4.2	Refractive Error	6	2.8
Small Pox	5	2.3	Chorio-retinal	3	1.4
Developmental	1	0.5	Strabismus	3	1.4
Unknown + Unspecified	35	16.8	Optic Atrophy	2	0.9
			Others + Unspecified	22	9.9
Total	214	100.0		214	100.0

*Low vision according to WHO definition of visual acuity in the best eye of < 6/18

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Table 6. Etiology and anatomical causes of monocular blindness

Etiology			Anatomical cause		
	No of eyes	%		No of eyes	%
Trachoma	65	30.8	Corneal	79	36.5
Degenerative	51	23.8	Cataract	47	22.0
Trauma	27	12.6	Atrophy of Globes	39	18.2
Other infections	20	9.4	Glaucoma	13	6.1
Measles + Nutritional	9	4.2	Refractive Error	6	2.8
Small Pox	5	2.3	Chorio-retinal	3	1.4
Developmental	1	0.5	Strabismus	3	1.4
Unknown + Unspecified	36	16.8	Optic Atrophy	2	0.9
			Others + Unspecified	22	9.9
Total	214	100.0		214	100.0

Table 7. Commonest causes of injury, age of onset and sex distribution of visual impairment and monocular blindness.

Age of onset	Sex		Total	%	Commonest Cause
	M	F			
Birth - < 2 Mths.	1	1	2	1.5	Attacked by a hen
2 Moths - 6 Yrs.	24	18	42	31.1	Attacked by a hen
6 Yrs. - 15 Yrs.	16	11	27	20.0	Accidental injury by another child
> 15 Yrs.	40	23	63	46.7	Agricultural and Domestic
Undetermined	1	0	1	0.7	Undetermined
Total	82	53	135	100.0	
%	60.7	39.3		100.0	

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DISCUSSION

This study indicates that trachoma and degenerative conditions are the leading etiologies of visual impairment in Ethiopia, as is the case in the rest of sub-Saharan Africa (4-12). Corneal opacities, cataract and glaucoma are the major anatomical causes of blindness. Trachoma was found to be the commonest etiology of blindness in our study population, as has been found in other community-based studies in Ethiopia (13,16) as well as other African countries such as Tanzania (5) and Egypt (19). Thus, in this rural population, trachoma and age-related changes with involvement of the cornea, lenses and disturbed aqueous dynamics account for most blindness and visual impairment. In contrast, traumatic atrophy of the globe and other infections involving the cornea account for most unilateral blindness. A comparison of the anatomical and etiological causes of blindness in the study villages with the highest (82%) and lowest (35%) participation rates revealed a similar pattern.

Hospital statistics reveal cataract as the commonest cause of blindness, demonstrating the selective nature of hospital-based populations (13,16,20,21,). There is a distinct and intriguing difference between our finding and that of a report from Malawi where no cases of blindness from classic trachomatous trichiasis were observed (22). The difference may be due to recent changes in the ecology of trachoma (22), as the Malawi report suggests, or due to a relative difference in the socio-economic and cultural pattern of hygiene of the two populations.

Cataract is the commonest cause of curable blindness in the adult population of Ethiopia (13-16, 20). Lack of trained manpower and facilities coupled with the difficult terrain of Ethiopia have resulted in this ever worsening problem.

Glaucoma is the other major cause of blindness. Close to 65% of the glaucoma patients coming to hospitals have been reported to be irreversibly blinded at diagnosis (20,23,24). Early diagnosis, which is critical in the management of these patients, is difficult because of inadequate medical services. Surgical treatment is currently available in only a few centres.

Trauma, with associated atrophy of the globe, corneal opacity and cataract, was the single most frequent cause of unilateral blindness. This is in agreement with reports from other developing nations (3,8,25) and previous studies conducted in this country (13,16,20).

Accidental ocular injury often occurred during chopping wood, as has been reported in Malawi (26). Flies play a dual role, both by transmitting infections and by attracting fly-seeking hens, in the causation of childhood blindness. Traditional healers and their unskilled practices constitute a major threat to eye health. The lack of prompt skilled care, and frequent secondary infection of eye injuries have undoubtedly further increased the likelihood of blinding consequences.

The alarmingly high mortality rate in those identified as visually impaired is noteworthy. The age specific annual death rate in our study population is much higher than that of the rural population of Ethiopia (27). Our study population has more older people, that is, 72% over 40 years compared with only 20% over 40 years in rural population of Ethiopia. However, the age adjusted death rate in the visually impaired was found to be two times more frequent than in the rural population of Ethiopia (18.6/1000 vs 9.1/1000) by direct adjustment of rates. An SMR (standardized

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mortality ratio) of 2.7 was found. Population-based longitudinal studies have demonstrated an increase in mortality associated with blindness (28,29,30). A future study designed to look into this very tragic situation is strongly indicated.

CONCLUSION

The blindness and low vision found in this population is largely preventable or curable. This study indicates that the major emphasis should be directed towards the control of trachoma. Ways and means of carrying out successful and inexpensive cataract surgery with appropriate technology should be developed. Studies on methods enabling early field diagnosis and treatment of glaucoma would be highly relevant.

Training health workers in primary eye care is of paramount importance. Increased public awareness through health education may also help to bring about reduction in the rates of visual loss. Promotion of behaviour change to prevent blindness is fraught with difficulties in this country, where the population has no easy access to water, the illiteracy rate is high and crowded living conditions prevail. However, future strategies designed to control this problem should give due consideration to the reported association between cattle and trachoma (31); the effectiveness of health education in primary schools (32); and the importance of face washing (33). The national program for prevention of blindness should be evaluated and strengthened in order to improve its effectiveness and achieve the goal of reducing the national blindness rate to less than 0.5% in accordance with the objectives of WHO (34).

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PARAPLEGIA AT THE TIKUR ANBESSA TEACHING HOSPITAL: A SEVEN YEAR RETROSPECTIVE STUDY OF 164 CASES

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ABSTRACT: *Admission analysis of adult non-traumatic paraplegia and paraparesis from 1981 to 1988 was carried out. Information was collected from charts of 223 consecutive admissions according to a pre-set protocol. Paraplegia or paraparesis was responsible for 164(13.4%) of all neurological admissions over the study period. The median age of the patients was 36 years with a male to female ratio of 1.7:1. Tuberculosis was the leading cause of paraplegia or paraparesis accounting for 47% of the cases. Tumours (20%), Landry-Guillain-Barre' syndrome (12.2%) and tropical spastic paraparesis (TSP) (9.8%) were important but less frequent causes in this series. Other causes like disc prolapse, transverse myelitis, spinal artery stroke and fluorosis were rarely encountered. Vertebral deformity (88.1%), vertebral tenderness (88.1%) and abnormal plain spinal X-ray (89%) were the most helpful findings in the diagnosis of tuberculous paraplegia. Nearly all cases of tuberculous paraplegia were treated medically alone. However, the outcome of treatment as judged by the treating physicians was good with a significant response recorded in 78%.*

INTRODUCTION

The relative importance, clinical manifestations, and causes of paraplegia or paraparesis in hospital practice in Ethiopia are not known. Like in several other developing countries tuberculosis is believed to play an important etiologic role (1,2). Therefore, the current analysis was undertaken to identify the relative importance of the disease, its causes, clinical manifestations and the outcome of treatment in patients admitted to the largest teaching hospital in Ethiopia.

MATERIALS AND METHODS

Charts of 223 consecutive patients admitted to the Department of Internal Medicine of the Addis Abeba University Teaching Hospital between 1981 and 1988 with the initial diagnosis of paraplegia or paraparesis were reviewed. Data were collected according to a pre-set protocol that contains information on clinical presentations, laboratory investigations, causes and response to therapy.

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The data on investigations included X-rays of the spines and the chest, myelography and histology. After discharge from the hospital all patients were referred to the neurology outpatient clinic for follow-up. Fifty-nine patients whose diagnoses of paraplegia or paraparesis were rejected on re-evaluation and follow-up by an experienced neurologist were excluded from the analysis. Data on the remaining 164 patients seen over the seven year period are presented.

A diagnosis of tuberculous paraplegia or paraparesis was made in those patients who had:

a. clinical and radiological evidences suggestive of tuberculosis of the spine,
b. tuberculosis elsewhere in the body simultaneously or preceding the spinal lesion and/or
c. significant response to antituberculous therapy.

RESULTS

A total of 164 adult paraplegic or paraparetic patients were seen over a seven year period. This accounted for 13.4% of all neurological admissions over the same period. The median age for the whole group was 36 years with a range of 15 to 70 years. Tuberculosis was the leading cause accounting for 77(47%) of the cases. Tumours, Landry-Guillain-Barre' syndrome and tropical spastic paraparesis were responsible for 20%, 12.2%, and 9.8% of the cases respectively (Table 1). Disc herniation, transverse myelitis, brucella spondylitis, and fluorosis, were rare causes (Table 1).

Important clinical and laboratory features of the patients of tuberculous paraplegia or paraparesis are given in Table 2. Sixty per cent of these patients were between the ages of 15 and 40 years. Males predominated over females with a ratio of 1.6:1. Gradual onset of weakness in the legs, vertebral deformity and vertebral tenderness occurring in 92.2%, 88.1% and 88.1% of the cases respectively were the main clinical features. Sudden onset of paraplegia occurred in only four of the cases (7.8%). Although spastic tone was more frequently noted, flaccid muscle tone occurred in nearly a quarter of the patients (23.3%). A third of the patients (N = 25) had associated tuberculosis elsewhere in the body. There was a delay of more than two months between onset of neurological symptoms and hospitalization in 59% of the patients. Plain X-ray of the spine could be traced in 64 of the 77 patients. Fifty seven (89%) of these were interpreted as suggestive of tuberculous spondylitis. X-ray findings interpreted as suggestive of tuberculosis of the spine were disc space narrowing and adjacent vertebral bone destruction. Myelography was done in 10 patients. There was partial block in four and changes suggestive of arachnoiditis in two while the examination was normal in the remaining four.

All patients suspected of having tuberculous paraplegia or paraparesis were treated with varying combinations of at least three anti-tuberculous drugs which consisted of isoniazid, streptomycin, thiacetazone, ethambutol or rifampicin. Complete or significant partial response was recorded in 60(78%) of the patients. Five patients died in the hospital. One died from septicemia related to urinary bladder catheterization and another from tuberculous meningitis. The cause of death in the remaining three patients was not documented.

Tumours were responsible for 33(20%) of paraparesis or paraplegia. Twenty-one (13%) of the paraplegia or paraparesis was

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the patients in this study the onset of paraplegia was gradual, but in a few (7.8%) it was sudden presenting like spinal shock, which may be due to ischaemic cord damage or spinal transection from pathological dislocation of the vertebrae (8). It is to be pointed out that weight loss and fever were not the presenting or associated symptoms in 50% of the patients. The absence of these symptoms did not thus exclude the diagnosis.

Kyphotic deformity (88.1%), tenderness of the spine (88.1%) and abnormal plain spine radiography (89.1%) were the most helpful findings for the diagnosis of tuberculous paraplegia. It is possible that patients without these findings had either tuberculous arachnoiditis or internal granuloma (7,9). Two of the patients suspected of having arachnoiditis had suggestive myelographic findings. Patients suspected of having internal granuloma had blockage on myelography. All the six patients with the diagnoses of tuberculous arachnoiditis or internal granuloma had complete or significant partial response after treatment.

All patients with tuberculous paraplegia/paraparesis were treated medically alone. A significant therapeutic response rate of 78% found in our series is slightly less than the results reported from Korea (85%), Rhodesia (86%) and India (87%) (10). The difference might be due to the mode of treatment and/or criteria used for assessment of improvement.

Tumours with relative frequency of 20% were the second largest group as causes of paraparesis or paraplegia similar to the series from Malawi (24.5%). Primary spinal cord tumours were more common in this group as compared to metastatic cord compression with a ratio of 1.8:1. The median age of patients with cord tumours was 37 years. As reported in other studies neurofibroma and meningioma were the commonest histological types encountered (11).

Hepatoma was the leading cause of metastatic cord compression probably reflecting its high prevalence in this country (12,13), which is in contrast to reports from the western countries where carcinoma of breast in females and carcinoma of the lungs in males are the commonest primary tumours which metastasize to the spine (14–16). Lungs, kidneys and pancreas were less common sources of metasis in this series.

Landry-Guillain-Barre' syndrome was found to be another common cause of paraplegia. The median age was found to be 33 years which is low as compared to 40 years of age in other studies (17). Cranial nerve involvement in Landry-Guillain-Barre' syndrome was not as frequent as shown in other reports (18). The mortality of 15% from respiratory failure however, was high compared to 3 to 5% in other studies (19). This was probably due to delayed diagnosis and inadequate respiratory support.

Tropical spastic paraparesis is relatively frequent in this series. The clinical features are similar to those described by Roman and Spencer (20). Although neurolathyrism is a prevalent disease in the north and northwestern part of Ethiopia (21), none of these patients admitted ingestion of *L. sativus* in appreciable quantity. The gradual onset of leg weakness over a period of three to four years is not a picture of lathyrism (22). Cassava is not consumed in Ethiopia. Most of the patients were described as an average built and there was no mention of clinical findings of malnutrition or vitamin deficiency to account for the occurrence of such a disease. Strong association between HTLV-1 infection and TSP is well

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described elsewhere (23–25). In Ethiopia the association of tropical spastic paraparesis and HTLV-1 is unlikely because of a report of low prevalence of HTLV-1 in both patients and controls (26).

Other infrequent causes were disc herniation and transverse myelitis. Brucella spondylitis, hysterical paraplegia, anterior spinal artery stroke and fluorosis were rare causes.

In conclusion, non-traumatic paraplegia is a common neurological problem at least in a hospital practice. Tuberculosis, a preventable disease, is by far the leading etiology. The causes of non-traumatic paraplegia from this hospital is in general similar to reports from other African countries.

Table 1. Causes of paraplegia at Tikur Anbessa Teaching Hospital

Diagnosis	Cases No.(%)
Tuberculous spondylitis	77(47.0)
Spinal tumours	33(20.0)
Landry Guillain Barre' syndrome	20(12.2)
Tropical spastic paraparesis	16(9.8)
Others	18(11.0)
Disc herniation (7)	
Transverse myelitis (4)	
Hysterical paraparesis (2)	
Spinal artery stroke (2)	
Brucella spondylitis (2)	
Fluorosis (1)	
Total	164(100.0)

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Table 2. Clinical and laboratory features of tuberculous paraplegia

Variables	Cases No.(%)
Mode of onset:	
Gradual	47/51(92.2)
Sudden	4/51(7.8)
Fever	32/77(41.6)
Weight loss	34/77(44.2)
Vertebral deformity	52/59(88.1)
Vertebral tenderness	52/59(88.1)
Muscle tone:	
Spastic	55/72(76.4)
Flaccid	17/72(23.6)
Sensory level	43/59(72.9)
Sphincter dysfunction	17/64(26.6)
Spine X-ray: abnormal	57/64(89.1)
Tuberculosis elsewhere	25/77(32.5)
Significant improvement from treatment	60/77(77.9)

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FLUOROSIS IN THE ETHIOPIAN RIFT VALLEY

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INTRODUCTION

Over 260 million people all over the world consume drinking water with a fluoride content of more than 1.0 ing/1. The majority of these people live in tropical countries (1). Fourteen countries in Africa, eight in Asia and the Middle East and six in the Americas face the problem of fluoride content above 1.5 mg/1 in drinking water (Figure 1)(2). Many of these countries are confronted with the problems of endemic dental and osteofluorosis.

Chronic fluorine intoxication has been documented to occur as a result of ingestion of large quantities of fluoride-rich waters over many years (3), as well as in occupational exposure in those engaged in aluminum production, magnesium foundries, fluorspar processing, and superphosphate plants (4).

Osteofluorosis and its complications, related to high-fluoride water consumption, have particularly gained attention in India (5-7). Similar reports, but mainly on endemic dental fluorosis, have appeared also from the African continent, the majority from East African Rift Valley regions (8-12).

The East African Rift valley which cuts through Ethiopia is geoniorphologically still an active volcanic region. The volcanic rocks particularly in the young basalt contain high concentrations of fluoride and fluorapatite. Large fault systems in the Valley create conditions that allow very deep percolation of infiltrating surface water. The floor of the Rift Valley which is characterized by a high hydrothermal activity accelerates the solubility of fluorite. There is therefore a high chance of striking water with high fluoride concentration in the faulted volcanic areas. The hot climate and high fluoride water bed of the Rift Valley therefore favour the development of endemic fluorosis.

The water supplies in the Ethiopian Rift Valley come mainly from boreholes with a depth of from 10 to 100 meters; the majority were deep boreholes. Fluoride levels from these boreholes ranged from 1.0mg/litre to 36 mg/litre (or parts per million, ppm). The sugar estates that had the highest population densities recorded high fluoride levels: Wonji-Shoa 3.7 ppin to 17.7 ppm, and Metahara 2.4 to 7.0 ppm (Table 1)(1 1).

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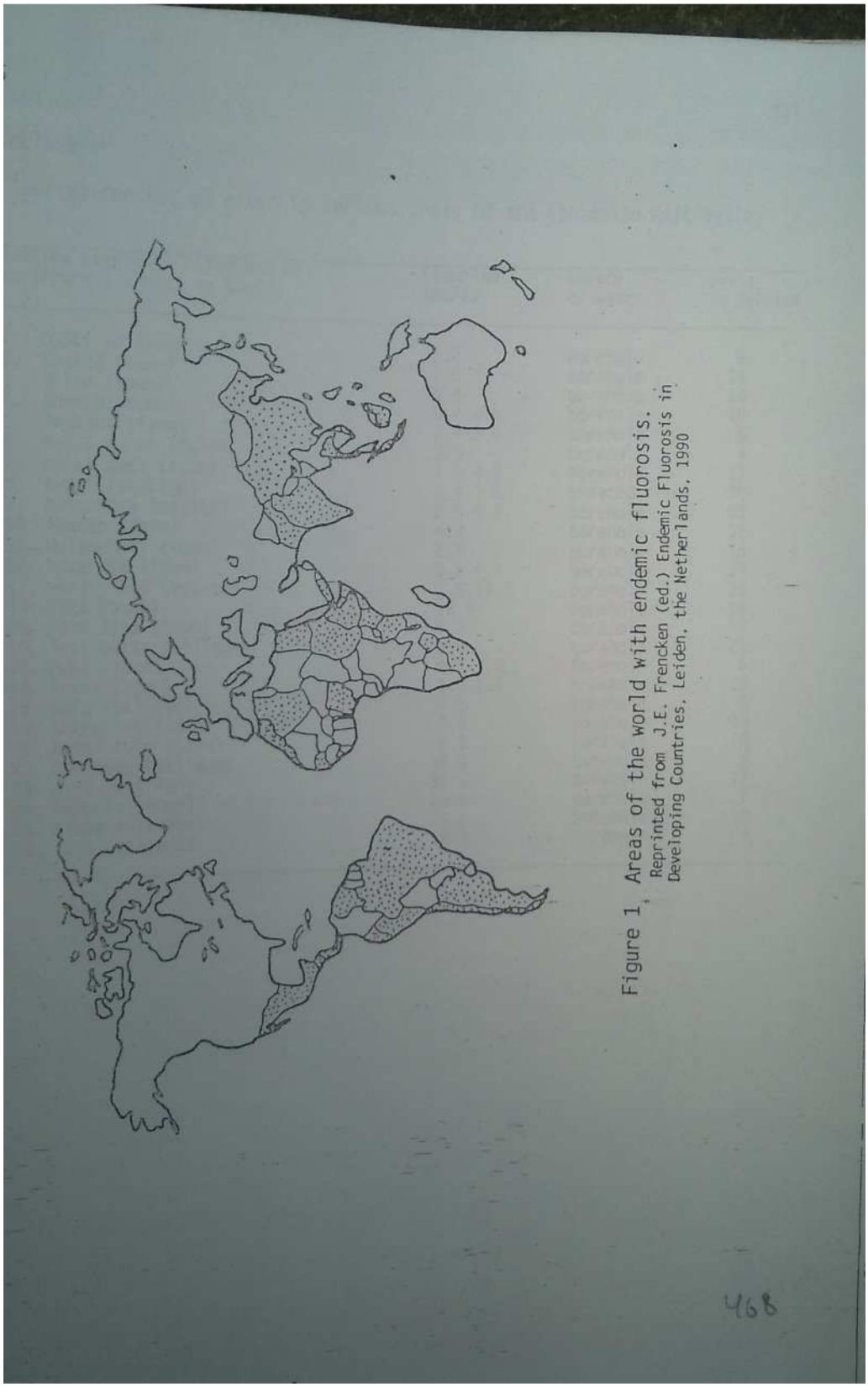


Figure 1, Areas of the world with endemic fluorosis.
Reprinted from J.E. Frencken (ed.) Endemic Fluorosis in Developing Countries, Leiden, the Netherlands, 1990

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Table 1

Flouride content of water in various areas of the Ethiopian Rift Valley

Samples site with reference No. to figure 1 (North to South)	Flouride (mg/1)	soruce of water	years in servic
1. Dubti (village)	1.2	borehole	9
2. Logiya (town)	1.0	borehole	10
3. Mille (town)	0.4	borehole	10
4. Gewane (town)	0.7-2.5	borehole	16
5. Amibara (farm)	2.4-3.0	borehole	5
6. Melka Warer (farm)	3.5	borehole	9
7. Melka sedi (farm)	1.5-4.3	borehole	13
8. Awash (station)	1.4-1.6	treated river	20
9. Meterhara (estate)	2.5-6.2	borehole	20
10. Abadir (farm)	4.0	borehole	12
11. Wolenchiti (town)	2.5	borehole	15
12. Nazareth (town)	0.8-4.3	borehole	20
13. Wonji-Shoa (estate)	2.5-14.0	borehole	30
14. Koka (town)	26.0	borehole	20
15. Alem Tena (town)	9.0	borehole	17
16. Sami berta (village)	9.0	borehole	23
17. Meki (town)	0.7-1.0	borehole	6
18. Zeway (town)	1.0-1.6	borehole	10
19. Waig (village)	3.5	borehole	8
20. Koshe (village)	3.0	borehole	15
21. Adami tulu (town)	5.1	borehole	10
22. Abernosa (village)	36.0	borehole	7
23. Jido (village)	33.6	borehole	12
24. Bulbula (town)	14.6	borehole	7
25. Alaba (village)	1.1	borehole	18
26. Togo (village)	4.9	borehole	4

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FLUORIDE BIOKINETICS AND METABOLISM IN HUMANS

Fluoride can enter the human body through ingestion, inhalation and absorption by the skin. The soluble form of fluoride is almost completely absorbed in the stomach and the intestine. Of the total amount of fluoride entering the body, 50% is excreted in the urine and a small part (5 - 1 0 %) in the faeces. Forty to 50 % of the remaining part is absorbed in the tissues, mainly in the bones. In the bones, fluoride is absorbed in the hydration shell around the apatite crystals, and in a second phase exchanged with the hydroxyl groups in the surface of these crystals. Very slowly the fluoride ions migrate to deeper layers of the bone. Once retained, only a small percentage of fluoride can be slowly released. Repeated or continuous exposure to fluoride sources will therefore cause accumulation of fluoride in the body (13,14).

SOURCES OF FLUORIDE

By far the single most important source of fluoride is drinking water. In a fluoride endemic regions, the per capita daily consumption of 2 to 5 liters of water with F-content of 4 mg/l results in the ingestion of 8-20 mg of fluoride per day/person. The high fluoride water used for cooking food also contributes to the excessive daily intake. This consumption of water and therefore fluoride could be as much as two folds in a hot environment like in the tropics where the majority of the endemic fluorosis problems exist. It is now well documented that tea leaves contain a relatively high fluoride content of 3.2400 mg/kg dry weight most of which eluted by brewing (15).

Other sources of fluoride include contamination and pollution of the atmosphere, soil and food from fluoride-containing fertilizers, pesticides, emissions from industries such as steel, aluminum and superphosphate plants, oil refineries, ceramic factories and brick and glass works.

BENEFICIAL AND TOXIC EFFECTS OF FLUORIDE

In minute quantities (± 0.2 mg/day) fluoride is an essential trace element starting the nucleation and formation of hydroxy-apatite crystals for the building of both bone and teeth. In slightly higher quantities (0.5-2.0 mg/day) it is an essential element, stimulating in growing teeth (thus before the eruption) the formation of a stronger enamel and after eruption stimulating and guiding the maturation of the enamel and the repair of initial caries lesions resulting in a still stronger enamel with a slightly increased fluoride content.

In still higher quantities, leading to fluoride plasma levels of > *0.* 15 ppm F, it starts to interfere with the normal formation of teeth (fluorosis of enamel) and bone (skeletal fluorosis), ending in older people in a non-functional continuing bone formation leading after 10-20 years of high fluoride exposure e.g. to a serious immobilization of joints and spine. In very high quantities, one to two gram/day, it may be lethal (14).

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CLINICAL MANIFESTATION OF EXCESS FLUORIDE INTAKE

If we consider the Ethiopian Rift Valley groundwater have very high fluoride levels, ranging from 1.5 ppm to 36 ppm. On the average, the water sources commonly used have fluoride contents of 3.5 ppm to 13.00 ppm. Studies from other countries (16,17) and our own experience in Ethiopia have shown that these levels readily cause dental fluorosis in children and over a prolonged period skeletal and crippling fluorosis.

The consumption pattern of drinking water differs individually and from area to area. In an extensive review of the literature on the epidemiology of endemic fluorosis Frencken (18) concluded that it is not possible to predict the prevalence and severity of dental and skeletal fluorosis from the consumption of fluoridated water alone because they are dependent of such risk factors as climatological condition, occupation (hard or light manual work), nutrition, frequency of food consumption, and amount of water, tea and other liquids drunk. However, among these risk factors fluoridated drinking water remains still as the most important

Dental fluorosis

The cause of dental fluorosis is a too high plasma fluoride level during the preeruptive mineralization of the enamel. A direct relationship exists between the prevalence and severity of dental fluorosis and fluoride content in drinking water (19).

In the Ethiopian Rift Valley dental mottling in a large section of the population has been recognized in a large section of the population areas with fluoride levels as low as 2 ppm. Dental fluorosis formed in early childhood (in incisors up to 5 years of age, molars and premolars up to 12 years of age) is a life long handicap. Apart from the cosmetic handicap, the severe forms of fluorosis may lead, in young adults, to a functional problem: a severe abrasion of the fluorotic, biting surfaces of molars (14).

In hot climates the values for the optional fluoride concentration in drinking-water may have been reduced to 0.6-0.8 mg/litre (10). This has been amply demonstrated by (20) who found milder forms of dental fluorosis in hot and dry regions of Senegal where the fluoride concentration in the drinkingwater was only 1.1 mg/liter.

Skeletal fluorosis

Unlike dental fluorosis skeletal fluorosis is not easy to recognize, as it becomes clinically obvious in far advanced stages. Early detection is based on roentgenological findings when the cancellous bones show accentuation of the trabecular structures due to thickening. In the advanced stage there is an increase in bone density where the bone appears chalky and structureless. There is irregular osteophytes periosteal growth (exostoses and marginal ripping of the vertebral bodies) and calcification of the ligaments (Figure 2).

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In the Ethiopian Rift Valley, with fluoride levels above 4 ppm, most of the inhabitants developed neurological complications after 15 years of exposure. Corresponding observations have also been reported by Singh and Jolly (21).

In our experience, high fluoride content in drinking water appears to play the most determinant role, as was observed by Reddy (22). However, men doing manual labour in hot environments appear to be more susceptible to advanced osteosclerosis with neurological complications. Similar observations have been recorded by Siddiqui (6)and Singh et al. (23).

The subjective symptomatology in persons with skeletal fluorosis is variable depending on the degree of affection. It may be asymptomatic osteofluorosis where the changes are apparent only on X-rays. The majority of the more advanced cases develops progressive bone pains and stiffness of the whole body. Squatting, particularly when defecating, becomes very troublesome. Standing up from a sitting position, and sitting up in bed, become increasingly difficult. Progressive kyphosis and limitation of movements become apparent (Figure 3 and 4). This clinical condition progressively worsens to the more severe debilitating state of crippling fluorosis.



Figure 2 X-Ray of the thoracolumbar spine of a patient with myelo-radiculopathy, showing increased bone density, osteophytosis and calcification of ligaments.

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Figure 3 Two elderly factory workers from Wonji Sugar Estate with different degrees of affection by skeletal fluorosis.

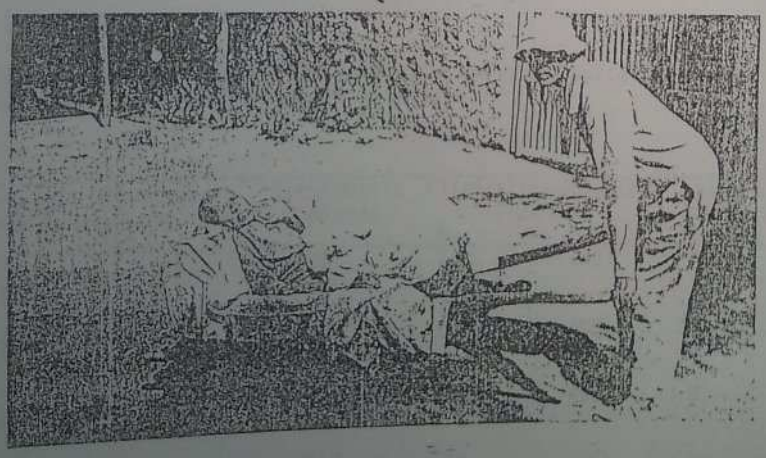


Figure 4 A 60 year old worker from Wonji Sugar Estate with crippling fluorosis brought for examination on a wheel barrow.

Crippling skeletal fluorosis

The underlying differences between the fluoride induced asymptomatic osteosclerosis and crippling fluorosis, are the nonfunctional calcifications at atypical places ultimately leading to serious invalidity.

In the tropics, fluoride concentrations in the drinking water of 4-6 ppm (or a daily fluoride absorption of > 10mg) may cause, under the hot and dry the conditions fasting plasma levels high enough to cause a skeletal fluorosis with serious complaints in a substantial part of the population over the age of 45 years (14).

At the stage when neurological symptoms and signs become manifested, the affected persons have marked kyphosis, with stiffness and restriction of movement of the whole body, which moves as a unit during postural changes. Flexion deformity of the hip and knees and fixation of the chest wall are typically seen.

Surveys carried out between 1976 and 1985 in the among 830 long time workers on a sugar estate with symptoms of osteofluorosis found that neurological manifestations (Table 2) in the forms of myelopathy with and without radiculopathy (respectively 72% and 28%) occurred after exposure to high fluoride(> 4 ppm) for longer than 10 years. In advanced stages of neurofluorosis, the clinical picture is rather uniform, with complete incapacitation and the bedridden state of severe spastic paraparesis, or quadriparesis with incontinence of urine and flexor spasms (Figure 4). Hyperreflexia, with absent abdominal reflexes and extensor plantar responses with or without patellar and ankle clonus confirm long tract involvement.

Table 2

Prevalence of advanced skeletal fluorosis and neurological complications in the Ethiopian Rift Valley

Survey area/year	Fluoride in drinking water (ppm)	Symptomatic persons	Clinical/radiological fluorosis		Neurological manifestations	
			No.	(%)	No.	(%)
Wonji/Shoa 1976-1983	3.7-17.7	530	244	(46)	3	(0.6)
Wonji/Shoa 1984	3.7-17.7	300	195	(65)	39	(13)
Alem Tena 1984	9.0	30	15	(50)	3	(10)
Sami Berta 1984	9.0	18	10	(56)	2	(11)

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The sensory symptoms tend to be patchy except when radicular pain in the upper limb is referred along a dermatome, or when cord compression is encountered. However, vibration sensation is reduced in about one third of those affected.

The pathogenesis of the neurological sequelae of osteofluorosis is fairly straight forward, as was shown by the postmortem study by Singh et al. (24) on a macerated skeleton, in which fluorotic changes resulted in considerable encroachment on the diameter of the intervertebral foramina and spinal canal. These changes tend to be most marked in the cervical region. This explains the clinical similarity of neurofluorosis to severe cervical spondylosis.

Decompressive larninectomies in osteofluorotic cord compression resulted in some initial improvement, which unfortunately is short-lived. Over time, develop recurrence of symptoms and advanced paraparesis, as they continued to live in the same endemic areas, consuming the high fluoride water.

Varying degrees of loss of hearing to high frequencies were found in 13 % of affected persons. This cochlear eighth nerve dysfunction, associated with skeletal fluorosis, has also been observed by Siddiqui (6). The pathogenesis is most probably related to sclerosis of auditory ossicles.

Kenhardt bone disease (juvenile osteosclerosis)

Some children and adolescents of fluoride endemic regions develop a spectrum of bony deformities in the form of genu valgum or 'knock knees' from an early age (25,26). Although the clinical signs and the radiographic findings appear serious the disease does not lead to the adult skeletal fluorosis. The high level of the remodelling of bone in children makes a repair possible. Indeed this has been our experience in Ethiopia.

Table 3

Fluoride contents in drinking water and possible effects

Concentration of fluoride	Possible effects
0.5 - 1.5 mg/l	Fluoride in water has no adverse effects, incidence of caries decrease
Above 1.5 mg/l	Mottling of teeth may occur to an objectionable degree= dental fluorosis incidence of caries decreases
3-6 mg/l	Association with skeletal fluorosis
Above 10 mg/l	Crippling skeletal fluorosis

Source: "Guidelines for drinking water quality", WHO, 1994.

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SAFE LEVELS OF FLUORIDE CONSUMPTION

The World Health Organization had set guide lines limits on fluoride as shown in Table 3. The guidelines, with 1.5 mg/1 as the upper limit of safe level are based on an average per capita daily water consumption of 2 liters. However it is abundantly clear that the daily consumption of water in hot tropical environments is much higher that the WHO propose average. It can be as high as 10 liters/day.

Based on their studies in Senegal Brouwer et al. (20) suggest that other guiding values would be more appropriate in tropical regions. They proposed that dental fluorosis will occur at F- levels above 0.6 mg/1 and crippling fluorosis above 7.0 mg/1.

In Argentina there are two standards operational: less than 1.5mg/1 for urban areas and less than 2.2mg/1 for rural areas for water supply systems covering a population of less than 3,000 (27). Furthermore, the governmnent of Tanzania on the basis of economical, practical and technical considerations has set the drinking water quality standard for fluoride at 8.0 mg/1 (28).

The controversial decisions are confronted also in Ethiopia when deep bore holes are being dug in the hot dry areas of the fluoride endemic Rift Valley. When alternatives are not available the Ethiopian Water Resource Commission has chosen the lesser of two evils: to make high fluoride water available to thirsty populations.

PREVENTIVE MEASURES

Prevention of high fluoride absorption is probably the only effective way of controlling the disease. Efforts and resources should be put by governments to find and provide drinking water with low concentration of fluoride especially in densely populated areas. Towards this end hydro-geological surveys and identification of lowfluoride surface water sources have to be made in an organized manner in fluoride endemic regions.

The supply of water from low fluoride sources through a piped supply system may be considered as an option. Although the capital investment may be high, maintenance cost may remain within acceptable limits, particularly when gravity fed system could be used. This alternative has not been entertained by the majority of the populations in fluoride endemic region.

Several water treatment technologies for the removal of excess fluoride in water, both for household and central level, are being used in rural settings. These technologies are often not really appropriate and sustainable considering the specific local technical and economic conditions.

There are several method of defluoridating drinking water. They include precipitation, adsorption, ion-exchange, osmosis and electrochemically stimulated coagulation and electrodialysis. Most of these methods are technically sophisticated and expensive to be applied

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in developing countries. The most applicable methods for developing countries at the household and/or community level include precipitation using lime and alum, gypsum and fluorite and polyaluminium chloride; adsorption and ion-exchange using clays granulated bone medium and bone char. These methods are of low cost and do not entail complicated technology. However the use of these methods in the fluoride endemic countries is not widespread because of unavailability of information based on field-tested conditions on cost, lifespan, and chemical and bacteriological quality of the treated water as well as its social acceptability by the community.

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Lathyrism in: Tropical Neurology (Ed. R. Bhatia, C.M. Poser, P.K. Newman) WB Saunders Co Ltd. pp 365-374 1995

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INTRODUCTION

The term 'lathyrismus' was coined by Carrani (1873) after the legume, *Lathyrus sativus*, the cause of the disabling disease. Lathyrism has been known since the time of Hippocrates (460–377 BC). In his work on epidemics Hippocrates wrote 'At Aimos, all men and women who ate peas continuously became impotent in the legs and that state persisted' (Selye, 1957). The description is consistent with human lathyrism as we now recognize it.

The toxic properties of *Lathyrus* flour were recognized in Europe as early as 1671 when Duke George of Wurtemberg issued an edict banning the sale of *Lathyrus* flour because of its paralysing effects on the legs (Buchanan, 1927). There is historical evidence that the disease was widespread with outbreaks and epidemics reported in parts of Europe, Russia, North Africa, the Middle East and Asia. Although living victims of lathyrism exist in Israel, Spain, Greece and France (Spencer *et al*., 1986), the disease is now endemic only in Ethiopia (Tekle-Haimanot, 1989), India (Dwivedi, 1989) and Bangladesh (Haque and Mannan, 1989). The prevalence of the disease in these endemic regions ranges between 0.1 and 3%. A great number of reports have appeared this century from India on the epidemiology and clinical characteristics of lathyrism. An earlier work was that of General Sleeman (1844) who, although not medically trained, gave an accurate description of lathyrism in his book *Rambles and Recollections of an Indian Official*. Acton (1922) presented a detailed scientific review of the disease including results of some of his animal experiments.

Subsequent careful and detailed epidemiological and clinical investigations performed in India (Dwivedi and Prasad, 1964; Kulkarni *et al*., 1977; Attal *et al*., 1978) have confirmed the observations of earlier workers that the crippling disease is caused by excessive consumption of *Lathyrus sativus* (chickling pea, vetch or grass pea). The disease occurs mainly among the poor who consume the legume in excess, as a staple or during times of food shortages. It affects predominantly young males. The peak months for disease onset are the

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rainy seasons (especially July) which is probably related to depletion of stored grain (Acton, 1922; Ganapathy and Dwivedi, 1961; Tekle-Haimanot *et al.*, 1990).

AETIOLOGY

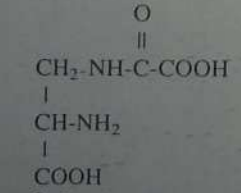
Lathyrus sativus (Chickling Pea, Grass Pea or Vetch)

This legume is a hardy crop which is drought and water-logging resistant and can withstand pest and weeds. It has rapid growth potential with a high per hectare yield and provides a nourishing diet of high-quality protein (about 25%) and carbohydrate (about 60%) and yields of 350 cal/100 g. With a low requirement for water, the pulse is a survival food during times of food shortages in lathyrism endemic areas. The disadvantage of this nutritious legume is its potential toxicity (Spencer *et al.*, 1986a). It is commonly consumed boiled or roasted and its flour is used to make bread. It may provide the entire diet during periods of food shortage. In times of plenty it is mixed with other cereals like wheat or rice. The seeds and fodder of grass pea are also used as animal feed.

Neurotoxicity

The most direct confirmation that *Lathyrus sativus* was responsible for human lathyrism came from the unfortunate experience of Romanian Jews interned in a German forced labour camp in the Ukraine. They developed the disease after being maintained on a daily diet of 400 g of grass pea cooked in salt water with bread made of barley and straw in a 4:1 proportion (Kessler, 1947). Prisoners who consumed less of the grass pea (200 g day^{-1}) did not develop the disease. The emergence of new cases ceased with the discontinuation of the grass pea diet in the camp. From the same camp there was also indirect evidence that malnutrition did not significantly contribute to the manifestation of the disease. It appears that excessive consumption plays a major role in toxicity.

Murti *et al.* (1964) and Rao *et al.* (1964) independently isolated the neurotoxic amino acid, β-*N*-oxalyl-α,β-diaminopropionic acid (ODAP) or β-*N*-oxalylamino-L-alanine (BOAA), the suspected culprit of neurolathyrism.



β-*N*-oxalyl-α, β-diaminopropionic acid (ODAP)
(β-oxalylamino-L-alanine (BOAA))

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There is experimental evidence from primate studies that β-ODAP is the neurotoxic amino acid involved in the aetiology and pathogenesis of lathyrism (Spencer and Schaumburg, 1983).

Epidemiological studies have shown that most people developed lathyrism after consuming grass pea consisting of over 30% of their daily diet for more than 3 months (Acton, 1922; Ganapathy and Dwivedi, 1964; Gebre-Ab *et al.*, 1978). There are reports of cases contracting the disease after consumption of the legume for less than one month (Ganapathy and Dwivedi, 1961; Attal *et al.*, 1978), but this may well be related to an increased intake, as observed by Kessler (1947), or to other factors such as nutritional deficiencies and individual susceptibility to the neurotoxin.

PATHOGENESIS AND PATHOLOGY

Knowledge of the neuropathology of lathyrism is rather limited. Very few postmortem examinations have been performed on cases of lathyrism because most patients are poor and die at home in remote regions and in endemic countries there are religious and cultural prohibitions on postmortems. The few published reports indicate that the neuropathological findings of human lathyrism are dominated by symmetrical axonal degeneration and crossed and uncrossed pyramidal tracts in the thoracic, lumbar and sacral spinal cord (Buzzard and Greenfield, 1921; Sachdev *et al.*, 1969; Streifler *et al.*, 1977). Additionally, loss of pyramidal cells in the region of the motor cortex controlling the leg is noted in an early study of the pathology of the brain in human lathyrism (Filimonoff, 1926). Primary neuronal degeneration, with secondary loss of cortical motor axons, is consistent with the neurotoxic action of ODAP, the culpable agent in grass pea.

Laboratory studies show that ODAP mimics the depolarizing action of the neurotransmitters glutamate and aspartate, and that micromolar concentrations rapidly trigger postsynaptic dendritic oedema followed by neuronal degeneration, in mouse cortical tissue in culture (Ross *et al.*, 1987). Since the primary molecular recognition site for ODAP (in rodent synaptic membranes) appears to be the quisqualate receptor (Ross *et al.*, 1989), it is possible that the dendritic arbor of pyramidal cells of the human motor cortex are endowed with a particularly heavy concentration of quisqualate receptors. Furthermore, if the dendritic expanse of Betz cells is proportional to axon length, those with projection to the lumbosacral cord might respond to the excitatory and excitotoxic (neuronotoxic) action of ODAP before motor neurones innervating the cervical cord. This hypothesis provides a possible molecular and cellular explanation for the clinical manifestations of lathyrism. Critical study of this hypothesis requires an animal model of human lathyrism.

There have been many failed attempts to induce irreversible spastic paraparesis in animals fed with *Lathyrus sativus* seed or its components (Spencer and Schaumberg, 1983). A recent study with carefully nourished macaques fed

L. sativus or ODAP reported the delayed onset of clinical (extensor posturing, increased tone and muscle cramping of hind limbs) and electrophysiological changes consistent with the initial, reversible signs of human lathyrism (Spencer *et al.*, 1986b). The primate neurological signs were also reversible, and neuropathological changes in cortex and cord were lacking. Further studies are therefore required to find a more complete animal model of human lathyrism, and to determine the role of malnutrition and other possible susceptibility factors (such as exercise) for the neurotoxic action of ODAP (Spencer *et al.*, 1988).

CLINICAL FEATURES

Mode of Onset

The widely accepted mode of presentation of lathyrism is that proposed by Ganapathy and Dwivedi (1961) who described three patterns. The most common is the *sudden onset* in which the affected individual complains of heavy, weakened legs after falling down or awakening from sleep. Acton (1921) quoted the description of a victim as follows: '. . . whilst ploughing I suddenly noticed that my legs were weak, there was no pain, but I had difficulties in sitting and getting up from a squatting position, I did not know I was paralyzed . . .'. In the *subacute onset* there are 10–15 days of prodromal symptoms of rheumatic pains, cramping and stiffness at the waist before the manifestation of the paralysis. In the very rare form of *insidious onset* the spastic paraparesis progresses over a period of months with associated dull aching pain in the lumbosacral region and back of the thigh. The patient may or may not give a history of myospasm and is invariably told by others about his ungainly gait.

In the very mild form the disability might not be obvious. The leg stiffness is detected only during running. Such cases have been referred to as 'latent lathyrism' (Dwivedi and Prasad, 1961). Recognized precipitating factors include such factors as manual labour, febrile illness and diarrhoea.

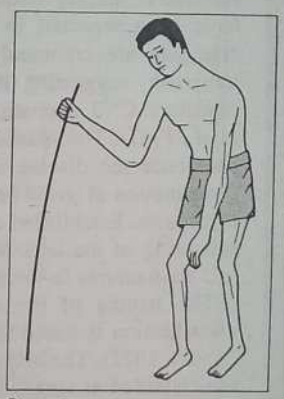
Age and Sex Distribution

All age groups are affected by lathyrism but around 80% are below the age of 40 when most are physically active. Males are affected more commonly (2.5:1) and more severely than females, although crude estimate of food intake suggested no substantial differences in *L. sativus* consumption. Contrary to the view of Acton (1921), who suggested that women eat less in order to save food for their husbands and children, there is evidence for other susceptibility factors, perhaps hormonal, to account for the gender difference in the levels of affliction. This view is consistent with the epidemiological findings that women of child-bearing

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Stage 1:
Mild spastic gait with no use of a stick; increased stiffness and exaggerated deep tendon reflexes (DTR); ankle clonus present; Babinski's sign absent.



Stage 2:
Spastic gait, with use of one stick; increased stiffness; mild rigidity; exaggerated DTR; ankle clonus present; Babinski's sign present



Stage 3:
Spastic gait; with use of two sticks; crossed adductor gait; exaggerated DTR; ankle clonus present; Babinski's sign present



Stage 4:
Crawling or bedridden state; loss of leg use, with contractures; arms strong; and pyramidal signs present.

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...representation of the stages of disability in human neurolathyrism.

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age are less severely affected by the disease (Dwivedi and Prasad, 1964; Tekle-Haimanot *et al.*, 1990).

More than one member of the same family may be affected by lathyrism. The extent of *Lathyrus* consumption, the sex and other susceptibility factors may be involved in determining the number of family members that exhibit the disease.

Clinical Signs

The picture of classical spastic paraparesis due to lathyrism is stereotypic. Mental status, speech and cranial nerve function are intact. Cerebellar signs are not detected. Spastic paraparesis of different degrees is manifested associated with adductor spasm in the worse affected cases, as well as exaggerated deep tendon reflexes, extensor plantar response and ankle clonus. Distal lower limb objective sensory deficits to pin-prick and light touch are uncommon. Reversible urinary frequency and urgency, nocturnal erection and ejaculation have been reported in victims of lathyrism. These symptoms and muscle cramping are commonly encountered early in the clinical manifestation of lathyrism, suggesting that *Lathyrus* consumption can result in diffuse and transitory CNS excitation of somatic motor and autonomic function (Ludoph *et al.*, 1987). The spastic paraparesis and the subsequent disabilities are permanent once the disease is manifested. The condition is reversible only if the consumption of grass pea is discontinued at the very early prodromal stage of myospasm. Established cases walk on their toes with an unsteady gait and show scissoring of the legs. With time, in those severely affected, muscle atrophies and contractures in the legs develop.

The staging of the resulting disability is presented in Figure 22.1. The classification is based on walking disability and the need for physical support (Acton, 1922). The majority (90%) of cases fall into stages 1 and 2. About 10% are classified as stages 3 and 4. Females tend to have milder involvement than males. Figure 22.2 shows Ethiopian lathyrism victims with stages 1, 2 and 3 of neurolathyrism.

Differential Diagnosis

Two important myelopathies come into the differential diagnosis of lathyrism. Tropical spastic paraparesis (TSP) is a slowly progressive spastic paraparesis with an insidious onset (see Chapter 3). Unlike lathyrism, cases of TSP commonly complain of sensory and autonomic disturbances including incontinence and impotence (Gessain and Gout, 1992). However, it may sometimes be difficult to differentiate between early TSP and lathyrism, particularly in localities where the two conditions coexist. The mode of onset, sensory symptoms and progression of the spastic paraparesis will assist in the differential

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Figure 22.2 Ethiopian lathyrism victims with stages 1, 2 and 3 of disability.

diagnosis. Lack of excessive grass pea consumption will rule out lathyrism in doubtful cases.

The other spastic paraparesis which has very similar clinical setting and manifestations is konzo, caused by excessive and exclusive consumption of insufficiently processed cassava (*Manihot esculenta*) (see Chapter 21). The dietary history helps differentiate between konzo and lathyrism and the two conditions exist in different geographical isolates. However, the clinical and pathogenetic similarities of the two diseases present an investigatory challenge in neurotoxicology.

Additional conditions to be considered in the differential diagnosis are motor neurone disease (amyotrophic lateral sclerosis), cord compression and other myelopathies including those caused by human immunodeficiency virus (HIV).

There are no specific investigations for lathyrism. A detailed dietary history and the exclusion of other conditions mentioned above are the hallmarks of the diagnosis.

TREATMENT

There are no known cures for lathyrism once it is established. Symptomatic treatments have not been successful in alleviating the disabling spasticity. The reported clinical improvement in a small percentage of those affected is presumably not related to traditional treatment or to low-dose vitamin supplements that the patients have received and probably represents a spontaneous feature of the disease, in which improvements have been reported in the early stages (Ludolph *et al.*, 1987).

PREVENTION

Lathyrism is a very serious social problem because it cripples the you productive age group. The following measures will be appropriate and feas the countries where the disease is endemic.

The public should be educated on the toxicity of grass pea, and instruc ways of processing it to help reduce the toxicity. It is now well documente soaking or boiling and discarding the excess water reduces the toxic OD the seed. Easy home-based methods of detoxifying the grass pea during preparation have been found to be effective (Mohan *et al.*, 1966; T Haimanot *et al.*, 1993). During poor harvest and famine situations commu in lathyrus-growing areas should receive external assistance. The banning sale and consumption of *L. sativus* has been found impractical if not impos

Recently, interests and hopes have been raised by a more effective and reaching approach to solving the lathyrism problem, involving the develop of low-ODAP varieties of grass pea. Extensive germplasm collections of pea with low-ODAP content exist and plant breeding programmes are under in endemic countries and elsewhere to develop a safe strain of *L. sativu* breeding out the neurotoxic element (Palmer *et al.*, 1989). These efforts ai give farmers a hardy, high-protein crop for home consumption and for us fodder. This is part of an international collaborative effort to improve *L. sat* and eradicate lathyrism.

Monitoring thiocyanate levels in populations at risk for neurotoxicity f consumption of bitter cassava has been successfully employed in the prevent of konzo in Mozambique (Casadei *et al.*, 1990). A comparable approach lathyrism would be to monitor blood or urine levels of ODAP.

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THE EFFICACY OF ISRADIPINE IN UNCONTROLLED HYPERTENSION IN ETHIOPIAN PATIENTS

Worku Zewdu, MD, Berhanu Habte, MD[1]

ABSTRACT: *The efficacy of isradipine, a new antihypertensive dihydropyridine calcium antagonist, was prospectively studied in Ethiopian patients with uncontrolled severe hypertension on multiple antihypertensive agents. Enrolled were 13 patients based on inclusion and exclusion criteria and 12 patients completed the study. The study design included a three-week wash-out period followed by eight weeks of active treatment. Eleven patients (92%) took diuretics in addition to isradipine. Patients were started on 2.5mg of isradipine twice daily and the dose was increased to 5mg twice daily in eight (67%) patients since the diastolic blood pressure (DBP) remained above 90mmHg four weeks after the initiation of therapy. The treatment resulted in a mean decrease of 42mmHg in systolic blood pressure (SBP) ($p < 0.0001$) and 34mmHg in DBP ($p < 0.0001$). Seven patients (58%) achieved normalization of DBP and in the remaining 5(42%) the DBP became less than 105mmHg. Almost all patients experienced mild and transient side effects resulting from vasodilation but all tolerated these except one who dropped out from the study. In conclusion, these results indicate that isradipine combined with a diuretic is a safe and effective antihypertensive agent in Ethiopian patients with uncontrolled hypertension.*

INTRODUCTION

Hypertension is a common health problem with a prevalence rate of about 10 to 20 per cent of the general adult population of the developed world and blacks are more affected than whites (1). There is an inverse relation between the level of blood pressure (BP) and life expectancy. Myocardial infarction, heart failure and stroke are the main causes of excess mortality in patients with poorly controlled hypertension.

The first report of the Veterans Administration Cooperative Study Group and several controlled trials on the treatment of hypertension since then, have made it clear that drug treatment indeed reduced the morbidity and mortality of severe as well as mild to moderate hypertension (2–4). Un-

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pleasant side effects, complex regimens and the large number of tablets necessary to control the high BP result in poor compliance and hence to very poor control of BP in some patients with severe hypertension. However with good compliance, about 5 to 18% of patients do have refractory hypertension, that is the BP which is not controlled with three or more appropriate agents given with maximal doses over an adequate period of time (5,6). Response to drug therapy is known to have racial differences. Beta-blockers are generally less effective in black subjects compared to white subjects (6,7). Angiotensin converting enzyme inhibitors are less effective in blacks than in whites (8). Although not universal, there are some observations that indicated efficacy of calcium channel blockers in black hypertensives (9-11). Isradipine is a new dehydropyridine calcium antagonist used in the treatment of hypertension. It has been shown that the drug is very effective as a first line monotherapy for mild to moderate hypertension while producing few side effects (12,15).

The purpose of the present study is to evaluate the efficacy of isradipine in severe hypertension that is poorly controlled by multiple currently available antihypertensive drugs.

PATIENTS AND METHODS

Among patients who are under follow-up in the Renal Clinics of the Department of Internal Medicine of Tikur Anbessa Hospital, Addis Abeba, 13 patients were selected for the study. The entry criteria were: patients with essential hypertension treated for over a year with a diuretic and one or more additional antihypertensive agents (methyldopa, clonidine, beta-blockers, hydralazine or prazosin) in maximal doses and yet having a mean diastolic BP $\geq$ 105mmHg. The mean BPs were derived from a minimum of four readings taken during the previous year. As very frequent and regular follow-up is required, only patients residing in the city were included in the study.

Pregnant and lactating women as well as patients with renal or hepatic insufficiency, congestive heart failure, malignant hypertension and concomitant diseases were excluded. Informed consent was obtained from each patient entering the trial.

All antihypertensive drugs were discontinued except for the diuretic for a wash out period of three weeks, which was followed by eight weeks of active therapy with isradipine, starting at a dose of 2.5mg twice daily. The dose was doubled to 5mg twice a day if the DBP remained above 95mmHg, at the end of four weeks of treatment. During the washout period patients were seen at the clinic every week and were told to inform the unit any time if anything unusual happened. During the active treatment period, they were clinically evaluated every two weeks for BP, heart rate and monitoring of side effects. At each visit, supine and erect BP was measured with a sphygmomanometer, using Korotkoff phase I for SBP and phase V for DBP. Blood test including a complete blood count, electrolytes, renal and liver function test and lipid profile were performed at the beginning and at the end of the study.

Results are reported as means $\pm$SD.

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Statistical analysis was performed using analysis of variance to compare the mean blood pressure values and the student paired t–test to compare the mean BP measured every two weeks.

RESULTS

Thirteen Ethiopian patients who fulfilled the criteria started the study. One withdrew because she could not tolerate the adverse effects of the drug mainly the headache and palpitation. Among the 12 patients who continued the trial, nine (75%) were men and three (25%) were women. The ages ranged from 34 to 56 years and the mean age was 44±9.92 years. All patients except one had severe hypertension (DBP ≥ 115mmHg) during the previous year of their follow-up. One patient had moderate hypertension (an average DBP of 108mm Hg) before the trial which increased to 117mmHg at the end of the washout period. Previously six patients received methyldopa and hydrochlorothiazide, four patients received Beta blockers, hydralazine and hydrochlorothiazide, whereas one patient received Enalapril and hydrochlorothiazide.

No problems were encountered during the washout period. The results obtained are shown in Table 1 and Figures 1–3.

The increment of the SBP and DBP from the previous record during the washout period were 9.5mmHg and 6.8mmHg respectively and the change was not significant ($p > 0.05$). By the end of the study both DPB and SBP were significantly reduced by 34.8mmHg ($p < 0.0001$) and 42.5mmHg ($p < 0.0001$) respectively.

Although the SBP continued to decrease till the end of the trial, the significant drop was observed only at the end of the second week of treatment. The DBP decreased continuously over the active treatment period and the decrement was significant between each two weeks time until the end of the sixth week. The drops of DBP between the sixth week and eighth week of active treatment was not significant.

The dose of isradipine had to be increased to 10mg daily in eight patients (67%) after four weeks of treatment. All but one took diuretics in addition to isradipine. Seven patients achieved normalization of DBP. The DBP in the rest became less than 105mmHg.

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Table 1. Mean Blood pressure and reduction: baseline and 2,4,6 and 8 weeks after initiation of isradipine therapy in 12 patients

	SBP(mmHg)	DBP(mmHg)
Baseline reading		
Before Study Mean ± SD		
Day 0 Mean ± SD	193.0 ± 23.4	122.0 ± 10.6
Active treatment	192.5 ± 30.2	128.8 ± 9.3
Two weeks		
Mean ± SD	167.0 ± 23.0	108.8 ± 14.5
Mean reduction between day 0-2 weeks	-25.5	-20
Four weeks		
Mean ± SD	163.0 ± 18.7	105.0 ± 13.6
Mean reduction between day 0-4 weeks	-29.5	-23.8
Six weeks		
Mean ± SD	152.3 ± 20.0	98.0 ± 8.6
Mean reduction between day 0-6 weeks	-40.2	-30.8
Eight weeks		
Mean ± SD	150.0 ± 11.8	94.1 ± 7.6
Mean reduction between day 0-8 weeks	-42.5	-34.8

SBP = Systolic blood pressure
DBP = Diastolic blood pressure

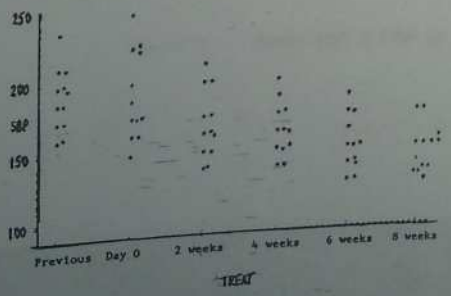
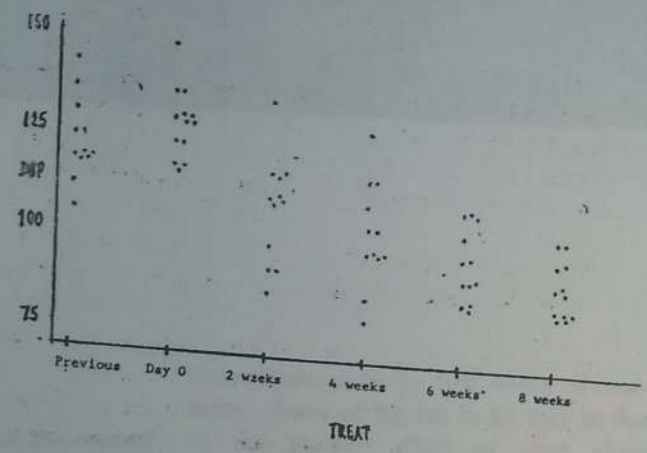


Figure 1. Systolic blood pressure records of 12 patients, the mean of the previous year, the record after the washout period and during the active eight weeks treatment period.

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igure 2. Diastolic blood pressure records of 12 patients. The mean of the previous year, the records after the washout period and during the active eight weeks treatment period.

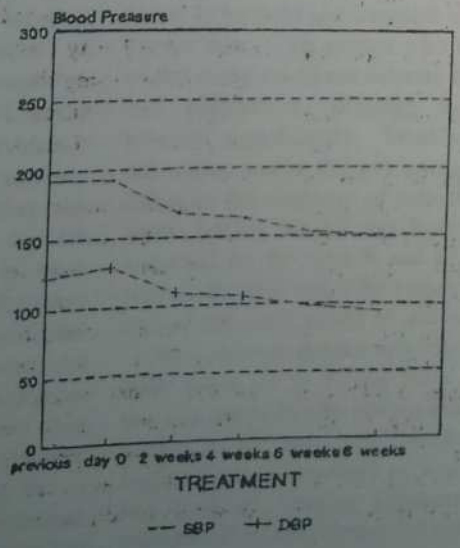


Figure 3. Mean SBP & DBP of 12 patients.

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DISCUSSION

It is our clinical experience that the control of BP in some patients with primary hypertension is very far from satisfactory with the available older antihypertensive agents. In these patients, the multiple drugs administered only added to the cost, inconvenience and adverse effects rather than lowering the BP. Based on the records of clinic attendance and assessment of their level of consciousness on the consequences of hypertension the patients were thought to have satisfactory compliance. The clinical assessment also did not reveal any evidence of secondary cause for the hypertension. The BP remained unchanged during the washout period. This may speak for the ineffectiveness of the drugs used in these particular patients. This study was designed to assess the efficiency of isradipine in these problem cases. As the use of calcium antagonists in hypertension has gained great interest, several studies have shown that isradipine, a new dihydropyridine calcium antagonist, is effective in lowering BP in patient with mild to moderate hypertension (12–15). To our knowledge, this drug has never been tested in patients with severe hypertension. In these patients, the drug was found to be safe and effective in lowering both the SBP and DBP. In seven patients (58.3%), the DBP became less than 90mmHg. This result is similar to the normalization rates observed in patient with mild to moderate hypertension (16,17). Even in the remaining five patients (41.7%), the DBP came down below 105mmHg. Sixty-nine per cent and 68.4% reduction of the SBP and DBP respectively were observed in the first weeks of treatment. Some of the fall in BP may be due to the placebo effect of close clinic follow-up and the phenomenon of regression to the mean. The decrements of both systolic and diastolic blood pressures were found to be clinically and statistically significant in all patients except one.

The side effects were mostly related to vasodilatory nature of the drug but were found to be mild and transient in all patients except one. The patient who dropped out of the study could not tolerate the headache and palpitation, although the BP was lowered significantly. Doubling the dose after four weeks did not intensify the side effect in the majority of patients but it did lower further the BP significantly. This is reflected by the 94.6% and 88.5% reduction of the SBP and DBP respectively at the end of the sixth weeks of active treatment.

As a dose–response relationship applies with doses up to 7.5mg twice daily (17), the five patients who did not attain normalization of BP may have benefitted from a higher dose (15mg/day) of isradipine. As the goal of treating hypertension is to change the natural history but not to provide symptom relief, the spur to compliance is less than satisfactory. Therefore, the simplicity of the regimen and the smaller number of tablets required is expected to improve compliance.

Therefore, isradipine combined with a diuretic is a safe and effective antihypertensive agent in Ethiopian patients with uncontrolled hypertension. A study over a longer period of time would be required to evaluate further response to doses of isradipine higher than 10mg daily

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and without the addition of diuretics.

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ORIGINAL ARTICLE

Treatment of Louse-borne Relapsing Fever with Low Dose Penicillin or Tetracycline: A Clinical Trial

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A clinical trial was conducted in order to evaluate the efficacy of procaine penicillin and tetracycline, respectively, in the treatment of louse-borne relapsing fever. 184 patients (160 men, 24 women) admitted to the Gondar hospital during the rainy season 1992 were assigned to 1 of 4 treatment groups: procaine penicillin 100,000 (PP100), 200,000 (PP200) or 400,000 (PP400) international units (IU) intramuscularly (i.m.), or tetracycline 250 mg per os (TTC, p.o.). All drugs were given as single doses. The overall case fatality rate was 3.3%. Frequency of relapses, Jarisch-Herxheimer-like reactions (JHR) and deaths were significantly different between patients treated with TTC and those treated with PP100. Relapses occurred most often in the group receiving the lowest dose of penicillin (46%), and decreased with increasing dosage of penicillin; none of the patients treated with TTC had a relapse. Occurrence of JHR showed the opposite pattern: whilst 2 (5%) patients treated with PP100 developed a JHR, 16 (29 %) in the PP200 group, 10 (31%) in the PP400 group, and 27 (47%) in the TTC group developed a JHR. As mortality is linked to severe JHR, and most relapses are clinically mild and easily treated, these results speak in favour of using low-dose penicillin to initiate the treatment of relapsing fever.

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INTRODUCTION

Louse-borne relapsing fever (LBRF) is an acute febrile disease caused by an infection with Borrelia recurrentis, a spirochetal organism that is transmitted to humans by the infected human body louse, Pedunculus humanus. Outbreaks of the disease are related to poor hygiene and crowding, and occur mainly during wars and periods of famine. The disease is endemic in Northeast Africa, South America and East Asia (1–7). In Ethiopia, more than 10,000 cases occur each year (4). If untreated, the case-fatality rate ranges from 30 to 70% (1). Antibiotic treatment has reduced mortality to 2–6% (3, 8, 9).

A variety of antibiotic drugs have been used in the treatment and have been proved to be efficient in removing spirochetes, for example tetracyclines including doxycycline, erythromycin, chloramphenicol, and penicillin. Clinicians favour a single dose or multiple doses of tetracyclines (8–11), low dose penicillins (3), or a combination of both (7) for treatment of adults. The clearance of borreliae is often accompanied by a Jarisch-Herxheimer-like reaction (JHR), characterized by a sudden rise in fever, blood pressure, and respiratory rate, being followed by a severe hypotonic phase. It has been shown that highly efficient drugs such as tetracyclines are associated with the highest rate of JHR. Drugs that are more slowly combatting the infection, for example slow-release penicillins, induce JHRs not only at a lower rate, but also less severely (11). Deaths during the shock phase of a JHR have been reported, with a case-fatality rate of up to 4% in patients treated with penicillins (5), and up to 6% in those receiving tetracyclines (1, 2, 7).

Clinical trials so far conducted have not resulted in a consensus as to the optimal drug, dose, and route of administration for the treatment of LBRF. Often, the trials included only low numbers of patients (5, 9, 11, 12), had a high percentage of lost-to-follow-ups (1, 8), and/or were not conducted as controlled clinical trials (8, 10).

The purpose of our study was to conduct a controlled clinical trial comparing single doses of the most commonly recommended drugs, tetracycline and penicillin, the latter one at different dose levels.

PATIENTS AND METHODS

During the rainy season (June–September) 1992, 255 patients with LBRF were admitted to the medical wards of the Gondar College of Medical Sciences in Gondar, Ethiopia. The diagnosis was verified microscopically by identifying the spirochetes in the patients peripheral blood smears. Patients in serious condition on admission (systolic blood pressure below 75 mmHg, coma, anuria, severe jaundice and/or acute heart failure with pulmonary edema), children below age 15 years, and those with a history of allergy to penicillin or tetracycline were not included in the study. All others were eligible for the study and consent was obtained from 184 patients, 160 men and 24 women. These were assigned to one of the following 4 treatment groups:

- procaine penicillin, 100,000 IU i.m. (PP100): 39 patients;
- procaine penicillin, 200,000 IU i.m. (PP200): 55 patients;
- procaine penicillin, 400,000 IU i.m. (PP400): 32 patients;
- tetracycline, 250 mg, p.o. (TTC): 58 patients.

The assignment of a patient's drug regimen was chosen by drawing a card labeled with the drug and dose to be given. Out of 300 cards prepared, 30% were labeled PP200, 30% TTC, and 20% each were prepared for PP100 and PP400. PP200 and TTC were the treatments of choice at the clinic, and were therefore overrepresentated. All drugs were given as a single dose after i.v. fluid installment. Both antibiotics were from Epharm Co., Addis Abeba, Ethiopia. Patients were monitored closely for one week for the development of signs of JHR and/or relapses. A JHR was defined

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as an increase in body temperature (>1°C) combined with tachycardia (pulse rate >100 min^{-1}), occurring within 4 h after treatment, followed by a drop in systolic and diastolic blood pressure greater than 10 mmHg. A relapse was recorded for those patients who suffered a further fever attack with positive blood smear at least 2 days after the first attack. The study was approved by the Ethics Committee in Gondar, Ethiopia.

Differences in the proportion of JHR and relapse among groups were tested using the Cochran-Mantel-Haenszel statistics, controlling for gender and age group. Age groups were set up as follows: 15–19, 20–29, 30–39, ≥40 years. Because of the low number of patients, all those above 30 years (n = 37) were included in 1 group when analyzing age as a risk factor for the development of JHRs and relapses. Logistic regression analysis was used to study the effect of clinical parameters on mortality, relapse and JHR incidence. Independent variables included in these models were: age, sex, drug, jaundice, cardiac gallop rhythm, blood pressure, and duration of symptoms before admission. All data analyses were performed using the SAS statistical analysis software (SAS Institute, Cary, NC).

RESULTS

Epidemiological characteristics

The patients' age ranged from 15 to 56 years with a mean of 23.4 years; 98 patients (53%) were in the age group from 20 to 30 years. The male:female ratio was 6.7:1. Of the male patients, 38 (23.8%) were soldiers or ex-soldiers, 30 (18.7%) students, 14 (8.8%) prisoners, 30 (18.7%) daily labourers or unemployed, and 12 (7.5%) farmers.

Clinical symptoms and signs

The average duration of symptoms before admission was 4.5 days (range 1–21 days). The most prominent symptoms reported were fever (100%), general malaise (82%), and headache (76%). Myalgia occurred in 104 patients (66%), arthralgia in 75 (41%), cough in 22 (12%), and diarrheoa in 21 patients (11%). On admission, all patients were febrile with a mean axillary temperature of 38.5°C. Jaundice was noticed in 45% of the patients, abdominal tenderness, hepatomegaly or splenomegaly or both were less common findings, occurring in 18.5%. The average blood pressure was 103/69 mmHg.

Fatalities

Out of the 184 patients 6 (3.3%) died after development of a JHR; no death occurred in the PP100 group, 1 in the PP200, 2 in the PP400, and 3 in the TTC group. The case fatality rate between PP100 and TTC was significantly different ($p = 0.03$). Mortality was significantly associated with the occurrence of a JHR ($p = 0.009$), but was unrelated to relapses, jaundice, cardiac gallop rhythm, age, gender, blood pressure, and length of symptoms prior to admission.

Relapses

Overall, 30 patients (16.3%) developed a relapse. Relapses occurred in nearly one-half ($n = 18$; 46.2%) of the patients in the PP100 group, and decreased in number with increasing dosage of penicillin. No relapse was noted in patients receiving TTC (Fig. 1). The differences between TTC and PP100 and PP200 were highly significant ($p = 0.001$). Relapses tended to occur at a higher rate in younger patients: 12 (26.7%) patients aged below 20 ys, 16 (16.3%) of those aged between 20 and 30 ys, and 2 patients (5.4%) aged above 30 years developed a relapse. When controlled for sex and drug, this trend was not significant (Table I).

Table I. *Adjusted odds ratios and 95% confidence intervals for the development of Jarisch-Herxheimer-like reactions and relapses in patients with louse-borne relapsing fever, Gondar, Ethiopia, 1992*

Age (years)	Number	JHR OR[a]	JHR 95% CI	Relapse OR[a]	Relapse 95% CI
15–19	49	1.00		1.00	
20–29	98	0.56	0.25–1.24	0.82	0.31–2.14
≥30	37	0.32	0.11–0.95	0.23	0.04–1.34

[a] adjusted for drug and gender

Jarisch-Herxheimer-like-reactions

In contrast to what was observed for relapses, JHR occurred in about half of the patients treated with tetracycline (46.6%), and in about one-third (31.3%) of those receiving PP400. The JHR-rate decreased with decreasing dosage of penicillin: 15 patients (27.8%) in the PP200 group and only 2 (5%) of the patients in the PP100 group developed a JHR (Fig. 1). When controlling for age and gender, the difference in this regard between TTC and PP100 treatment was significant ($p = 0.005$), but not between TTC and PP200 or PP400, respectively.

Development of a JHR was significantly less frequent in patients above 30 years than in those aged below 20 years (Table I). Gender was unrelated to the occurrence of JHR, and none of the other variables were associated with an increased rate of development of JHR at a significant level.

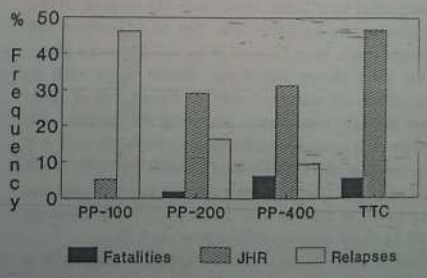


Fig. 1. Frequency of relapses, Jarisch-Herxheimer-like reaction (JHR), and fatalities in patients with louse-borne relapsing fever treated with penicillin or tetracycline, June–September 1992, Gondar, Ethiopia.

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DISCUSSION

We found an increasing rate of JHRs with increasing dose of penicillin, from 5.1% (PP100) to 31.1% (PP400). Penicillin clears the blood of spirochetes more slowly than do other relevant antibiotics, and accordingly induces JHRs later, at a lower rate and with less severity. Combined treatment using PP400, followed by 2 g of TTC a day later, has resulted in a JHR-rate of 13% (7). 47% of our patients receiving tetracycline developed a JHR. All but 1 (8) previous studies reported the development of JHR in all patients receiving tetracycline (1, 5, 9, 11, 12). These studies included severely ill patients – who in our study were excluded. Moreover, criteria for JHR were not clearly defined in those studies, so that a comparison with our results is hampered.

Low age was found to be a risk factor for the development of a JHR. A possible explanation is that younger individuals are likely to be of lower weight than older ones, thus receiving a higher drug dose per kg body mass. Unfortunately, the weight of patients was not recorded, and it can not be established if this association is spurious or real. More likely, the difference reflects a partial immunity to Borrelia and borrelia toxins in patients aged 30 years or more. When comparing our results to reports from other countries the high prevalence of malnutrition in our region has to be taken into consideration. Lack of data on body mass index unabled us to evaluate the effect that malnutrition could have on the incidence of JHR and/or relapses.

We noticed an overall case fatality rate of 3.3%. Deaths were significantly associated with the occurrence of JHRs. The different mortality rates between patients treated with PP100 and TTC are likely to reflect the different rates of JHRs.

The relapse rate in our study decreased with increasing dose of penicillin from 45.0% (PP100) over 16.7% (PP200) to 9.4% (PP400). Relapse rates of 1.2% have been reported for combined penicillin-tetracycline treatment (7), and 1.8% for PP400 administered twice (2). None of our patients treated with TTC showed a relapse, a finding consistent with previous reports (1, 5, 8, 11, 12).

In conclusion, it appears that treatment of LBRF should be initiated with low dose penicillin rather than the common use of tetracycline. A low dose of penicillin obviously reduces the rate of JHR, and thus mortality. Further clinical trials are needed to establish the optimal dose, or possibly combinations of doses or drugs for the treatment of this disease.

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BYSSINOSIS AND OTHER RESPIRATORY DISORDERS AMONG TEXTILE MILL WORKERS IN BAHR DAR NORTHWEST ETHIOPIA

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ABSTRACT: *The prevalence of byssinosis and other respiratory symptoms were studied among 433 workers who were occupationally exposed to cotton dust in Bahr Dar Textile Mill. One-hundred-one nonexposed workers living in the same geographical area were included as controls. All of the subjects completed the British Medical Research Council Questionnaire. Pulmonary function tests were administered on a vitalograph spirometer before starting the shift for all subjects, and after at least four hours of exposure for exposed subjects. Among the cotton dust exposed workers, byssinotics behaved distinctly and showed the maximum acute and chronic changes in pulmonary functions. The overall prevalence of byssinosis was 45.5%. The highest prevalence was found in carding (57.9%) and in ring frame (57.1%) operatives and the lowest in weaving preparatory section (32.1%). Unlike bronchial asthma, chronic cough and chronic bronchitis were significantly higher ($p < 0.01$) in cotton dust exposed subjects compared with controls. The mean measured values of ventilatory capacity (FEV_1 and FVC) are to a significant extent reduced in the exposed groups compared with controls ($p < 0.01$). In view of the above findings, preventive measures are of paramount importance in minimizing the prevalence of byssinosis and other respiratory disorders.*

INTRODUCTION

Many developing countries are aiming at industrialization and there is a growing concern for occupational safety and health issues. Ethiopia is experiencing some degree of industrialization and the textile industry is one of the major targets for promoting trade export.

Byssinosis and other respiratory symptoms have been reported as the major health threats to textile workers exposed to cotton dust (1-3). Byssinosis is diagnosed by a characteristic history of chest tightness and/or shortness of breath on the first day of the working week after a weekend break (4-6).

Chronic byssinosis is differentiated from the acute form by the severity and persistence of symptoms during the work week and away from the work environment (7,8). The acute symptoms are reversible and particularly evident on the first day of work after shift or holiday breaks, but gradually

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subside over a period of several days in the work environment or immediately when removed from vegetable dust exposure (7,9). These acute symptoms gradually develop into chronic irreversible symptoms which persist in a dust-free environment (3,10).

These symptoms are associated with changes in objective measurements of pulmonary function (2,11). Not all byssinotic patients show objective changes, but as a group they tend to have a greater reduction in forced expiratory volume (FEV_1) over the work shift than asymptomatic workers and those not exposed to cotton dust (12, 13).

In Ethiopia, the effect of cotton dust exposure among textile workers has not been investigated. This study is aimed at reporting the prevalence of byssinosis and other respiratory disorders among workers exposed to cotton dust in the Textile Mill in Bahr Dar northwestern Ethiopia.

MATERIALS AND METHODS

Four-hundred-thirty-three textile operatives, 233 male and 200 female, aged between 22 and 55 years and composing 35% of the study population were randomly selected. To minimize the selection bias, operatives were given numbers and a simple random sampling technique was applied using random number tables.

Operatives were interviewed to gather information on age, personal condition, smoking habits, duration of work, occupational history and experience.

Medical examination and lung function testing: Workers were interviewed and examined by one of the authors and completed the British Medical Research Council Questionnaire on respiratory symptoms (14). Byssinosis was diagnosed and graded according to the criteria laid down by Schilling et al as follows (15):

Grade 0 : No evidence of Monday cough, chest tightness or breathing difficulty (Monday is the first working day of the week).

Grade ½ : Occasional chest tightness or breathing difficulty every Monday.

Grade I : Chest tightness or breathing difficulty every Monday.

Grade II: Chest tightness or breathing difficulty on Monday and other days of the week.

Subjects suffering from chronic or recurrent cough or phlegmon for at least three months each year for not less than two successive years were diagnosed as chronic bronchitis. Subjects with past medical history of some chronic obstructive lung disease, such as "blue blooters", far advanced emphysema, acute respiratory infection such as pneumonia, TB and patients with cardiovascular disease were excluded.

Pulmonary function tests were carried out using one vitalograph respirometer. The instrument was calibrated as per the instruction given in the vitalograph manual.

The procedure for the spirometric maneuvers was explained carefully for the subjects.

Forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were measured in litres after a day's break at the beginning of the shift and after a minimum exposure of four hours. The readings were taken with the subjects standing. Five expiratory efforts were recorded and the highest two were averaged to estimate the FEV_1 and FVC in the standard way. All volumes were corrected to body

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temperature and pressure saturated (BTPS) with water vapour.

The control subjects living in the same geographical area were selected from the town hospital workers where there is absolutely no exposure to cotton dust. The management of the hospital provided lists of names of those on the payroll. Subjects with comparable socio-economic conditions such as marital status, family size, and income with textile workers were identified. Thus a total of 101 workers, 52 male and 49 female, were examined as the control group.

The predicted normal values of FEV_1 and FVC for each subject were obtained from normogram for healthy adults of African descent (16).

Environmental measurements: The concentration of the total particles (all size) and of the respirable fraction of the dust particles (less than seven micro equivalent diameter) is in range of 0.86-3.52 mg/m^3 and 1.03-3.83 mg/m^3, respectively (17).

Statistical analysis: KRUSKAL WALLIS test was run for the analysis of anthropometric data and for comparison of the mean FEV_1 and FVC difference among the different sections of textile workers and controls. T–test was used to compare the mean FEV_1 and FVC difference between textile workers and controls. Odds ratio with 95% confidence intervals were calculated to compare the prevalence of respiratory symptoms in cases and controls.

This study was conducted during the 1990/91 academic year at the Bahr Dar Textile Factory Clinic for exposed subjects and at Felege-Hiwot Hospital in Bahr Dar for controls.

RESULTS

Table 1 indicates the physical characteristics of exposed workers and controls by sex who were tested for pulmonary function. The questionnaire revealed that marital status, family size and monthly income were similar in all groups. Estimation of living standard for each subject was made on the basis of monthly income and family size. There was no statistically significant difference in height and weight, however, a significant age difference ($p < 0.05$) was found among the different sections of textile workers and controls.

In order to assess the contribution of age and height to the variability of pulmonary function measurements between the exposed and control groups, predicted values of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were obtained by applying the prediction formula of Mustafa (1977).

The predicted values of FEV_1 and FVC in the two groups were very close to each other. Hence, it was presumed that age and height would not contribute to the variability in measurements between the two groups and the actual values obtained in control subjects were used for comparison with those obtained in textile workers.

The observed and predicted mean values of FEV_1 and FVC of all groups are summarized in Table 2 (a,b). The observed values of FEV_1 and FVC were significantly different ($p < 0.01$) among the groups. The mean FEV_1 values of male controls compared with textile workers of the same sex were 2.75 and 2.33 l/s, respectively. The difference was statistically significant ($p < 0.01$). The mean FVC of male controls and textile workers were 3.39 and 3.12 litres, respectively. The difference was also statistically significant ($p < 0.05$).

The same situation was observed in female controls and mill workers. The mean FEV_1 of controls and cases were 2.24

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l/s and 1.87 l/s, respectively. The difference was statistically significant ($p < 0.01$). The mean FVC values were 2.72 and 2.43 litres in controls and textile workers, respectively. The difference was significant ($p < 0.05$).

There were no significant differences between sexes of both control and exposed subjects in the rate of prevalence of respiratory symptoms.

Acute pulmonary changes estimated from the percentage of across-shift decline of FEV_1 divided by FEV_1 before shift (FEV_1%) was seen among cotton workers. The total number of workers with across shift decrement beyond 5% was 73.2%.

Chronic pulmonary changes expressed by observed FEV_1 divided by predicted FEV_1 (%) below 80% was found in 55.9% workers.

The definition of acute and chronic changes in lung function are based on the recommendation by the World Health Organization (18). Tables 3 and 4 are based on this classification.

Table 3 shows the classification of acute change of lung function as no effect, mild effect, moderate effect and severe effect. The number and percentage of byssinotic and non-byssinotic workers are shown in each group. The percentage of byssinotic workers are higher in mild, moderate and severe effect categories as compared to the non-byssinotic workers.

The classification of byssinotic and non-byssinotic workers for chronic change is shown in Table 4. The proportion of byssinotic workers in the severe effect category is higher than non-byssinotic workers.

From the analysis of respiratory symptoms, it was found that the prevalence of chronic cough was significantly higher ($p < 0.01$) among textile workers compared to control subjects (Table 5). The highest prevalence occurred among the carders (21.1%), blowers (15.0%) and waste room workers (14.3%) compared with workers in other sections.

The highest prevalence of chronic bronchitis was found in the ring frame (48.4%) and the lowest in the weaving preparatory (2.5%) section. As there were no chronic bronchitis cases in controls, the odds of having chronic bronchitis among the different sections of textile workers and controls was undefined or infinitely large. Fisher's exact test showed significant association ($p < 0.001$) for all groups of textile workers except for those in weaving preparatory section. There was no significant difference in the prevalence of bronchial asthma among the different sections of textile workers and controls.

The overall prevalence of byssinosis in the textile workers was 45.5% (Table 6). The prevalence of severe byssinosis increased with increasing duration of exposure. Grades I (18%) and Grade II (20.6%) were more prevalent among subjects with over 20 years exposure. The highest prevalence of byssinosis was recorded among individuals in carding (57.9%), ring frame (57.1%), blowers (55%) and simplex (50%) of the spinning department compared to weaving preparatory (32.1%) and weaving (36.7%) sections of the weaving department.

DISCUSSION

In this investigation an attempt has been made to study the prevalence of byssinosis and other respiratory disorders among textile workers in Bahr Dar.

The results of the study indicate a very high prevalence of byssinotics (45.5%) compared to other reports (4,6,11,12,19).

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The byssinotics in this study are classified as recommended by Shilling et al (15). As the labour "turn over" is low, most byssinotic workers have the advanced types. This suggests that the progress of the disease certainly manifests as acute and chronic impairment of lung function. The acute changes tend to occur less with increase in the number of exposed years (Table 3). On the other hand, chronic changes tend to occur more with the increase in the number of exposed years (Table 4).

The nature of the cotton dust to which the workers are exposed is variable. For export finished products, the cotton used is imported mainly from the Sudan. This type is supposed to be good quality cotton with long fibers and less dust. The rest is hand picked usually fresh domestic product around the region with all possible source of contamination.

The dust concentrations measured by Mentesinot (17) in different sections of the mill was higher than in other studies. This might explain the reason for the high prevalence of byssinosis in these textile workers. The results also indicate that there is an inconsistent relationship between dust levels and the prevalence of byssinosis. We found lower dust concentration in ring frame but a higher prevalence of byssinosis. This may be due to the fact that just a minimum amount of dust is required to elicit symptoms and pulmonary function changes. However, once this level has been reached, the composition of the dust may be more important than its amount in the air. Similar results were reported by other investigations (3,11).

In the present study, the acute effect of cotton dust was observed very clearly. Higher percentage of byssinotic workers than non-byssinotic workers were found in the mild, moderate or severe effect categories (Table 3). However, a clear trend for chronic effect and effect of duration of exposure is not found. This might be due to a cross-sectional study design used. A clear picture of pure effects may be determined by a longitudinal study.

A high prevalence of chronic bronchitis was observed among textile workers in contrast to the control group. Previous studies have also suggested that exposure to cotton dust may produce or be involved in the development of bronchitis (4,6,10,13). At the same time, as this group of workers were aged, one could argue that the findings might be due to more advanced age. However, the difference in the prevalence of bronchitis between the various exposed groups coincided well with that of byssinosis among the same groups.

Although the sample size in each section is small the prevalence of chronic cough was relatively high in all exposed groups in line with previous reports (7,12,20).

The high prevalence of bronchial asthma among controls was an interesting observation; the prevalence was comparable between the exposed groups and controls. The reasons for this finding could only be speculated upon. Firstly, there is a relatively high prevalence of bronchial asthma in this administrative area of Ethiopia compared to other adjacent regions (unpublished observation). Secondly, since the control subjects were hospital workers, they might have had a high index of suspicion as to their respiratory illness.

The mean reduced values of ventilatory capacity (FEV_1 and FVC) in the present study are significantly low among the textile workers. Such impairment of ventilatory capacity due to cotton dust exposure was reported in a follow up studies (8,20,21) and by others (7,9-11) in cross-sectional studies.

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On the basis of the findings in our study, the following recommendations are made. Dust sampling in textile mills should be done at regular intervals so that one can obtain a record of the trends in dust levels over the years. Technical conditions in the mills are subject to changes such as the replacement of the old machines by new high speed ones. The new machines produce more dust and remove more trash from the raw cotton than the older machines which run at lower speeds. Therefore, air-conditioning and dust removing equipment which should correspondingly be improved. Dust respirators which provide personal protection to workers exposed to high dust loads may also be used.

Physiological studies are needed to establish the responses of workers exposed to given dust concentration. Fortunately, it is relatively simple to determine whether or not a group of workers inhale sufficient amount of active dust by determining their FEV_1 before and after work on the first following a break. Thus it is not necessary or desirable to rely only on determination of air borne dust concentration in order to assess the ventilatory impairment risk in any given set of conditions.

Medical aspects of prevention include periodic examination of employees and pre-employment check ups to exclude workers with pre-existing lung diseases from working in risky area of textile mills.

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Table 1. Physical characteristics of cotton textile workers and controls by sex, mean ± SD

Section	Sex	Number examined	Age (yrs)	Height (m)	Weight (kg)
Blowing	M	17	47.2± 4.60	1.7±0.09	60.8± 9.1
	F	3	42.0± 3.46	1.7±0.09	72.0±13.1
Carding	M	18	45.1± 4.18	1.7±0.09	59.3± 7.9
	F	1	45.0	1.5	59.0
Simplex	M	28	39.4± 9.46	1.7±1.00	61.4± 8.9
	F	28	42.0± 4.81	1.6±0.06	56.0±10.5
Ring frame	M	27	44.6± 6.57	1.7±0.07	58.1±10.3
	F	99	39.2± 5.69	1.6±0.06	54.5± 8.8
Waste	M	5	46.4± 8.91	1.7±0.09	60.6±11.3
	F	9	41.0± 3.57	1.6±0.04	51.7± 3.9
Weaving preparatory	M	30	40.3± 7.51	1.7±0.07	59.4± 9.8
	F	48	40.0± 6.01	1.6±0.60	55.3±10.6
Weaving	M	108	41.8± 6.95	1.7±0.06	60.1± 8.9
	F	12	42.1± 3.96	1.6±0.12	57.6±10.6
Control	M	52	38.8±91.18	1.7±0.07	59.9± 8.0
	F	49	31.2± 7.11	1.6±0.06	57.7±10.1

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Table 2. Pulmonary function data, observed and predicted forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) of all groups, mean ± SD

2(a) Male: n = 233 (study), n = 52 (control)

		Observed		Predicted	
Section	No.	FEV_1 (l/s)	FVC (l)	FEV_1(l/s)	FVC (l)
Blowing	17	2.5±0.62	3.2±0.63	2.8±0.42	3.2±0.54
Carding	18	2.3±0.55	3.1±0.37	2.9±0.27	3.3±0.33
Simplex frame	28	2.2±0.72	2.9±0.77	3.1±0.42	3.5±0.51
Ring frame	27	2.4±0.61	3.2±0.70	2.9±0.32	3.4±0.41
Waste	5	2.2±0.52	2.8±0.54	2.8±0.47	3.3±0.58
Weaving preparatory	30	2.2±0.83	3.0±0.80	2.8±0.37	3.2±0.42
Weaving	108	2.4±0.69	3.2±0.68	2.9±0.33	3.3±0.50
Control	52	2.7±0.60	3.3±0.60	3.0±0.43	3.3±0.50

Kruskal Wallis H = 23.595, $p < 0.01$ (FEV_1)
Kruskal Wallis H = 11.84 , $p > 0.05$ (FVC)
Degree of Freedom = 7

2(b) Female: n = 200 (study), n = 49 (control)

		Observed		Predicted	
Section	No.	FEV_1 (l/s)	FVC (l)	FEV_1(l/s)	FVC (l)
Blowing	3	2.3±0.62	2.7±0.27	3.0±0.4	3.4±0.5
Carding	1	1.4	2.6	2.2	2.4
Simplex	28	1.9±0.47	2.5±0.29	2.0±0.29	2.7±0.35
Ring frame	99	1.9±0.54	2.4±0.54	2.5±0.32	2.7±0.37
Waste	9	1.8±0.68	2.4±0.85	2.4±0.23	2.6±0.27
Weaving preparatory	48	1.7±0.67	2.4±0.69	2.4±0.33	2.6±0.38
Weaving	12	1.9±0.57	2.6±0.78	2.7±0.35	3.0±0.46
Control	49	2.2±0.40	2.7±0.38	2.6±0.29	2.8±0.32

Kruskal Wallis H = 36.063, $p < 0.001$ (FEV_1)
Kruskal Wallis H = 18.517, $p > 0.01$ (FVC)
Degree of freedom = 7

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Table 3: Acute change in lung function in exposed workers

Expo-sure in yrs	Category	No. of subjects	No effect No.(%)	Mild effect No.(%)	Moderate effect No.(%)	Severe effect No.(%)
0-10	Byssinotic	11	1(9.1)	1(9.1)	4(36.4)	5(45.5)
	Non-byssinotic	17	7(41.2)	3(17.6)	3(17.6)	4(23.5)
11-20	Byssinotic	61	8(13.1)	13(21.3)	14(23.0)	26(47.6)
	Non-byssinotic	53	23(43.4)	4(7.5)	9(17.0)	17(32.1)
≥21	Byssinotic	143	40(28.0)	10(7.0)	31(21.7)	62(43.4)
	Non-byssinotic	148	54(36.5)	19(12.8)	34(23.0)	41(27.7)

Table 4. Chronic change in lung function in exposed workers

Exposed group (yrs.)	Category	No. of subjects	No effect No.(%)	Mild to moderate effect No.(%)	Severe effect No.(%)
0-10	Byssinotic	11	5(45.5)	1(9.1)	5(45.5)
	Non-byssinotic	17	9(52.9)	3(17.6)	5(29.4)
11-20	Byssinotic	61	19(31.2)	15(24.6)	27(44.3)
	Non-byssinotic	53	25(47.2)	18(34.0)	10(18.9)
≥21	Byssinotic	143	31(21.7)	51(35.7)	61(42.7)
	Non-byssinotic	148	69(46.6)	48(32.4)	31(21.0)

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Table 5. The prevalence of respiratory symptoms in the investigate subjects

Section	No. of subjects	Chronic bronchitis No.(%)	OR	95% CI	Chronic bronchitis No.(%)	Bronchial asthma No.(%)	OR	95% CI
Blowing	20	3(15.0)	17.65	1.25- 935.11	7(35.0)	2(10.0)	0.82	0.08- 4.22
Carding	19	4(21.1)	26.67	2.32-1325.40	7(36.8)	2(10.5)	0.87	0.09- 4.50
Simplex	56	3(5.4)	5.88	0.73- 267.70	12(21.4)	5(8.9)	1.00	0.41- 2.48
Ring frame	126	7(5.6)	5.66	0.44- 300.05	61(48.4)	15(11.9)	0.73	0.19- 2.38
Waste	14	2(14.3)	16.66	0.77- 992.40	5(35.7)	4(28.6)	2.97	0.58-12.41
Weaving preperatory	78	3(3.8)	4.00	0.31- 212.04	2(2.5)	13(16.6)	1.48	0.88-3.80
Weaving	120	17(14.1)	16.50	0.25- 698.50	6(5.0)	13(10.8)	0.90	0.36-2.28
Control	101	1(0.9)*	-	-	-	-	-	-

*Referent OD = Odds ratio CI = Confidence interval

Table 6. Prevalence of byssinosis and mean duration of exposure in years of all sections

Section	No. of subjects	Grades of byssinosis No. (%)					Mean duration of exposure (yrs.)
		G0	Affected				
			G ½	GI	GII	Total affected	
Blowing	20	9(45.0)	2(10.0)	6(30.0)	3(15.0)	11(55.0)	22.8±7.00
Carding	19	8(42.1)	2(10.5)	4(21.1)	5(26.3)	11(57.9)	21.7±4.65
Simplex	56	28(50.0)	2(3.6)	12(21.4)	14(25.0)	28(50.0)	20.5±7.12
Ring frame	126	54(42.9)	11(8.7)	32(25.4)	29(23.0)	72(57.1)	22.0±6.08
Waste	14	8(57.1)	1(7.1)	2(14.3)	3(21.4)	6(42.9)	21.9±6.73
Weaving preparatory	78	53(67.9)	2(2.5)	10(12.8)	13(16.7)	25(32.1)	22.1±6.36
Weaving	120	76(63.3)	10(8.3)	12(10.0)	22(18.3)	44(36.7)	21.5±7.44
Total	433(100%)	236(54.6)	30(6.9)	78(18.0)	89(20.6)	197(45.5)	21.72(6.65)

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