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Lathyrism in Rural Northwestern Ethiopia: A Highly Prevalent Neurotoxic Disorder

REDDA TEKLE HAIMANOT*, YEMANE KIDANE**, ELIZABETH WUHIB**, ANGELINA KALISSA**, TADESSE ALEMU*, ZEIN AHMED ZEIN† AND PETER S SPENCER‡

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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.

* Faculty of Medicine, PO Box 4147, Addis Ababa University, Addis Ababa, Ethiopia.
** Ethiopian Nutrition Institute, Addis Ababa, Ethiopia.
† Gondar College of Medical Sciences, Addis Ababa University, Gondar, Ethiopia.
‡ Center for Research on Occupational and Environmental Toxicology, Oregon Health Sciences University, Portland, Oregon 97201, USA.

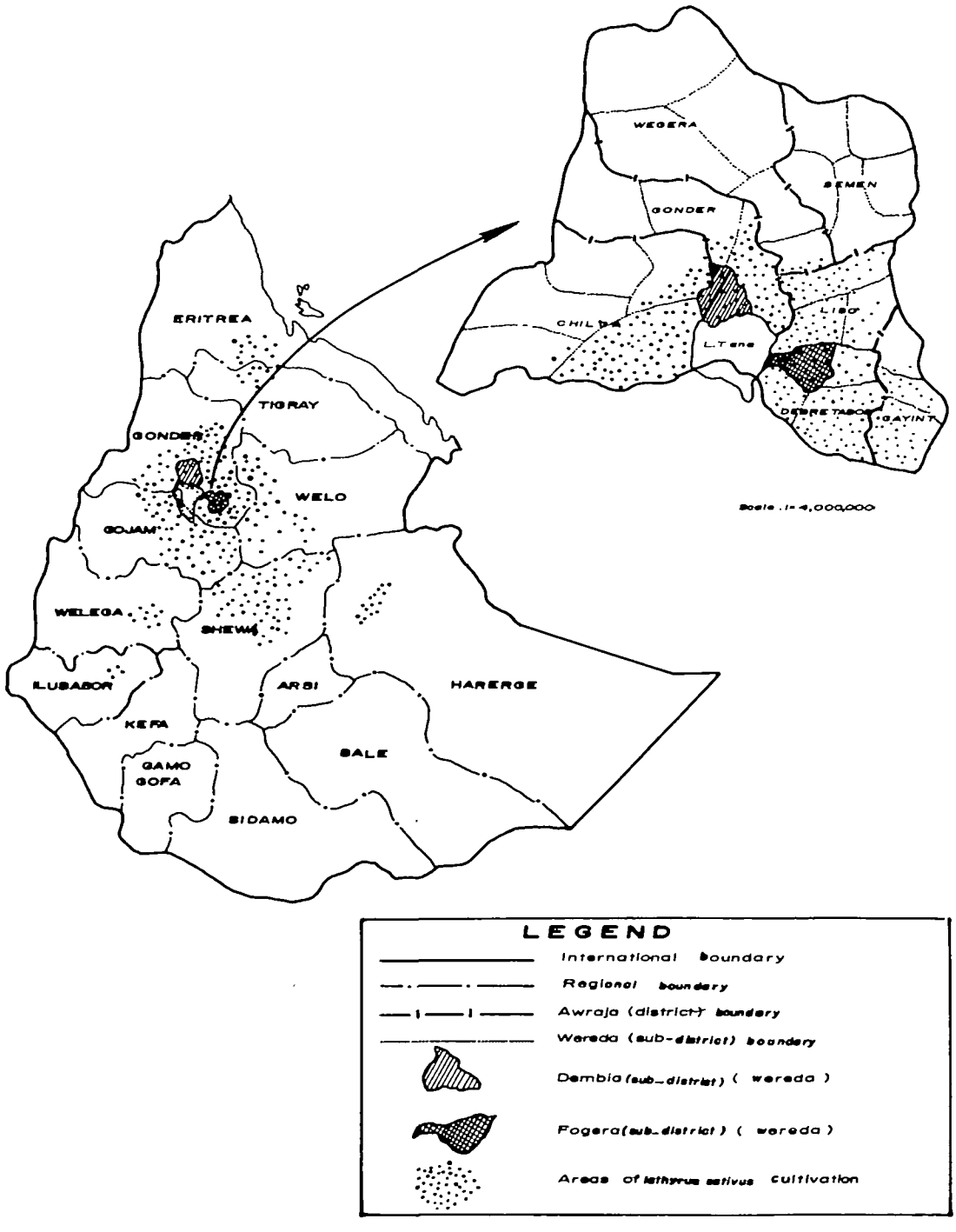

FIGURE 1 *Map of Ethiopia and Gonder administrative region showing the survey sites and areas of* Lathyrus sativus *cultivations.*

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[4] 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 1 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

beliefs were that the steam from boiling, the smoke from roasting or the dust from harvesting of the grass-pea were responsible for the disease. The pancake and raw forms of the pulse were considered to be the most poisonous when consumed with milk. Although they were aware of the toxic properties of grass-pea, community elders stated that consumption of it was preferable to starvation at times of severe shortage.

The grass-pea is an inexpensive, nourishing and tasty legume. In markets located within the survey areas, the seed sold for 20 US dollars per 100 kg during harvest, and for 40 dollars at other times. Thirty per cent of a family's production was brought to the market, and the rest was consumed at home. It was commonly 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 food shortage. Grass-pea was also used as a fodder crop 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.[13]

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) ($p<0.001$). 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	

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 (%)	Age at onset Female (%)	Age at onset Total (%)	Population Ethiopia* 1986 (%)
0–10	49	32	81	154	103	257	
	(3.8)	(6.3)	(4.5)	(22.0)	(37 3)	(26.4)	33.9
11–20	341	166	507	175	88	263	
	(26.6)	(32 7)	(28.3)	(25 1)	(31.9)	(27.0)	20.7
21–30	267	139	406	120	33	153	
	(20.8)	(27.4)	(22.7)	(17.2)	(12.0)	(15.7)	14.6
31–40	168	64	232	117	32	149	
	(13 1)	(12 6)	(12.9)	(16.8)	(11.6)	(15 3)	12.2
41–50	183	50	233	65	12	77	
	(14.2)	(9.8)	(13.0)	(9 3)	(4.3)	(7 9)	8.2
51–60	152	31	183	67	8	75	
	(11.8)	(6.1)	(10.2)	(9.6)	(2.9)	(7.7)	6.0
61≥	124	26	150	—	—	—	
	(9.7)	(5.1)	(8.4)	—	—	—	4 4
Total	1284	508	1792	698	276	974	
	(100)	(100)	(100)	(100)	(100)	(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

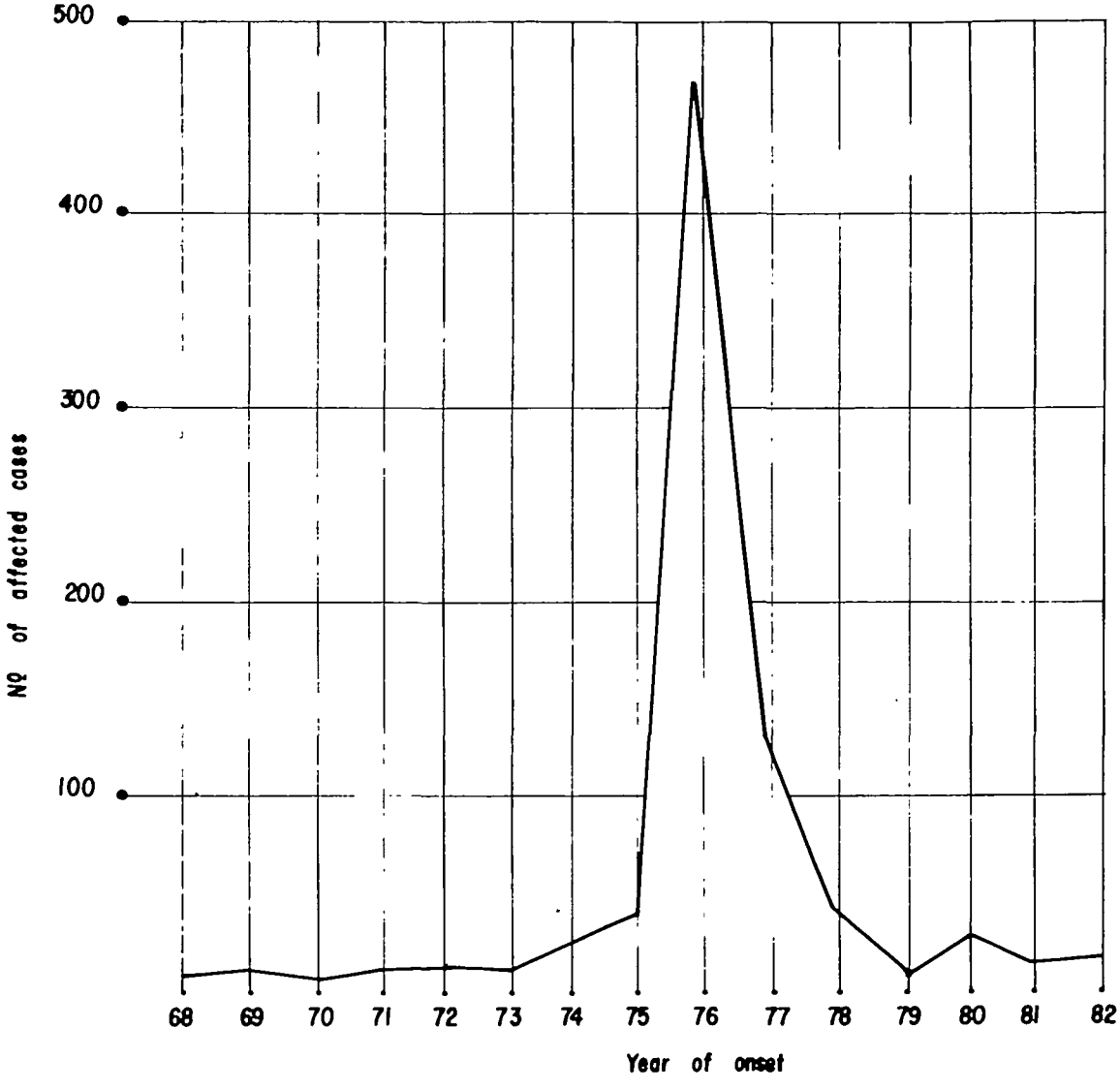

FIGURE 2 *Cases of Lathyrism by year of onset (1968–1982).*

stations. Eleven per cent of the patients reported some degree of improvement after the onset of the paralysis, mainly in the initial phases of the disease.

DISCUSSION

Lathyrus sativus is cultivated mainly in the central highlands of Ethiopia. It is grown both as a double crop or an intercrop. Farmers also make use of its fertilizing properties in crop rotation, particularly with teff. Although an 'unpopular' crop its national production has increased from 313 thousand quintals in 1980/81 to 376 thousand quintals in 1986/87, an increase of 20% over a period of six years.[14] Recent predictions by experts from the Ethiopian Ministry of Agriculture anticipate an even sharper increase in production, particularly in northern regions of the country. The increase of grass-pea cultivation as a profitable cash crop in our study area is also alarming. Much of the produce finds it way into central parts of the country where this cheap pulse crop is used as an adulterant of other legumes in the preparation of the flour form shiro. The prevalence of lathyrism across Ethiopia is unknown. Scattered cases have come from different parts of the country, mainly the highland regions. However, many cases go unrecognized.

As the majority of identified patients contracted the

disease in the 1976/77 epidemic, for this survey they were between 11 and 12 years older. Therefore, only a small percentage (4.5%) of those affected in our series were in the zero to ten year age group, as compared to 26.6% during the 1976/77 epidemic.[11] The age and sex distribution in our study is similar to that reported elsewhere.[4–6,16] However, what is interesting is that lathyrism has continued to manifest itself in the community at an estimated incidence rate of 1.7/10 000. This presents a real public health problem, particularly because the disease cripples the productive young members of society. While village elders and community heads recognized lathyrism as a significant health problem, there was considerable misunderstanding of the mechanism by which *Lathyrism sativus* caused the disease.

Peak months for disease onset were during the rainy season. This was probably related to food shortages and depletion of stored grain. This is comparable to the experience in India as reported by Acton[4] and Attal *et al.*[15] Additional possible precipitating factors and prodromal symptoms, such as manual labour, febrile illness, and cramping, were also similar to the Indian experiences.

We also observed that females were less commonly and less severely affected than males, although crude estimate of food intake suggested no substantial differences in *L. sativus* consumption. Contrary to the view of Acton,[4] who suggested that women eat less in order to save food for their husbands and children, we agree with Dwivedi and Prasad[5] that there may be other susceptibility factors, perhaps hormonal, to account for the sex difference. This view is consistent with our finding that women of child-bearing age are less severely affected by the disease (Table 2).

The picture of classical spastic paraparesis due to lathyrism is stereotypic, and the clinical features of the disease in Ethiopians are consistent with those in other reports.[16,17] In non-endemic areas of the country, it may be difficult to distinguish between the insidiously developing form of lathyrism from the so-called tropical spastic paraparesis associated with HTLV Type-1.[18,19] However, lathyrism lacks the sensory deficits seen in HTLV-1-associated spastic paraparesis. Additionally, evidence of HTLV-1 infection was lacking in control and affected subjects. Patients and controls also lacked antibodies to HIV-2 and HIV-1.

The majority of our patients developed lathyrism after consuming grass-pea for over three months although 12% reported consumption for less than one month before contracting the disease. This may well be related to an increased intake, as observed by Kessler,[20] or to other factors such as nutritional deficiencies and individual susceptibility to the BOAA toxin.

The reported clinical improvement of 18% of those affected is presumably not related to traditional treatment or to the low-dose vitamin supplements that our patients received. It probably represents a spontaneous feature of the disease, in which improvements have been reported in the initial period of the disease.[17]

There are no autopsy reports from cases of lathyrism in Ethiopia, and there is a dearth of morbid anatomy on this disease. Most patients are poor and die at home in remote regions. The few published reports indicate that the neuropathological signs of human lathyrism are dominated by symmetrical axonal degeneration of crossed and uncrossed pyramidal tracts in the thoracic, lumbar and sacral spinal cord.[21–23] Additionally, loss of pyramidal cells in the region of the motor cortex controlling the leg is noted in one study of the pathology of the brain in human lathyrism.[24] Primary neuronal degeneration, with secondary loss of cortical motor axons, is consistent with the neurotoxic action of BOAA, the culpable agent in the grass-pea. Laboratory studies show that BOAA 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.[25] Since the primary molecular recognition site for BOAA (in rodent synaptic membranes) appears to be the quisqualate receptor,[26] 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 BOAA prior to motor neurons innervating the cervical cord. This hypothesis provides a molecular and cellular explanation for the clinical involvement of the legs prior to the arms. The latter show pyramidal signs only in advanced (crawler) stages of lathyrism.

Critical study of this hypothesis requires the availability of a complete 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.[2] A recent study with carefully nourished macaques fed *L. sativus* or BOAA 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.[7,27] 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 BOAA.

Monitoring blood or urine levels of BOAA might provide another approach to disease prevention in populations consuming the native neurotoxic species of *Lathyrus sativus*. A comparable rationale has been successfully employed in Mozambique to monitor thiocyanate levels in populations at risk for neurotoxicity from consumption of bitter cassava.[28]

Extensive germplasm collections of grass-pea with low BOAA content exist and plant breeding programmes are under way both in Ethiopia and elsewhere to develop a safe strain of *L. sativus* by breeding out the neurotoxic element.[10] These efforts aim to give farmers a hardy, high protein crop for home consumption and for use as fodder. Concurrently, nutritional studies are being carried out to find easy home-based methods of detoxifying the grass-pea during food preparation, as reported from India.[29] These approaches are necessary, because banning sale and consumption of *L. sativus*, at least in the Ethiopian situation, is impractical if not impossible.

Of 143 victims of the 1976/77 lathyrism epidemic from 12 Peasant Associations, 121 could be traced and re-evaluated. Twelve (10%) had died from different causes not directly related to lathyrism. The 109 survivors were found to be leading the lives of the phsyically disabled in a difficult rural environment, without medical and social rehabilitatory services.

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