WILLIAM P. HOWLETT

NEUROLOGICAL DISORDERS IN TANZANIA

Studies on HIV-1, Guillain-Barré Syndrome and Konzo

Centre for International Health and Department of Neurology, University of Bergen, Bergen, Norway 1994
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ABSTRACT

This thesis is the result of clinical studies carried out in Northern Tanzania from 1984-1992 and reports on a number of new clinical entities. These are HIV related neurological disorders, konzo and new forms of existing diseases such as Guillain-Barrè Syndrome (GBS). The first and second papers report that neurological disorders were amongst the most common (70%) disorder in AIDS. The Snout and Palmomental reflexes were the most common abnormal neurological finding and increased incrementally with advancing HIV stage and associated neurological disorders. The third paper investigates a consecutive series of GBS cases admitted to Kilimanjaro Christian Medical Centre (KCMC) and to Haukeland University hospital Western Norway and demonstrated that the incidence rate, epidemiological and main clinical findings apart from minor differences were similar in the two series. The increased mortality rate (15%) seen in the Tanzanian series is explained mainly by the lack of resources for adequate intensive care. An association between HIV infection and GBS was seen in the Tanzanian but not the Norwegian series and HIV positive GBS patients tended to have more severe neurological disease and increased mortality. The fourth and fifth papers are reports on field surveys in Tarime district in Northern Tanzania investigating an epidemic of unexplained spastic paraparesis which occurred in 1985. The studies showed that the disease is a distinct entity manifested by spastic paraparesis and characterized by a disorder which always affects the distal upper motor neurones to a greater extent than the proximal ones. The disease was named konzo, a local name from the first reported outbreak in Zaire (Trolli 1938). The prevalence of konzo in 15 villages studied ranged from zero cases in the lake shore villages to 14/1000 in the inland villages only 5 km away. All patients gave a history of almost complete reliance on bitter cassava as a staple food in the months prior to and during the epidemic. This arose because of the widespread failure of other crops as a result of the severe drought in 1984. In addition the traditional processing methods used for removal of cyanogenic compounds from the roots of bitter cassava appeared to have been shortened. A resulting high cyanide exposure was supported by high serum thiocyanate levels, the mean SCN in May 1985 in 20 cases and 9 controls were 368 and 303 μmoles/l respectively. The geographic and temporal distribution of konzo was also shown to be compatible with cyanide exposure from insufficiently processed cassava roots and there was no evidence of an infectious aetiology. The sixth paper reports on specialized neurological investigations of two patients with konzo who were brought to Sweden which suggests that the site of the pathology in konzo is most probably situated centrally in the motor cortex rather than in the spinal cord.

Keywords: Africa; Tanzania; Norway; Sweden; HIV; AIDS; Neurological disorders; Snout; Palmomental; Reflexes; Guillain Barré syndrome; Konzo; Spastic paraparesis: upper motor neurone disorder; Cyanide; Thiocyanate; Cassava; Motor cortex.
1. ACKNOWLEDGEMENTS

The choice of neurological disorders as the subject of this thesis was determined by the authors special interest in neurology and the appearance of a number of new neurological disorders in Tanzania. However it is the authors considered opinion that other fields in clinical medicine would have proved equally fruitful to research during that same time. Anyone who has worked in Africa will know that the research in this thesis was made possible with the help and support of a great number of persons, including patients, individuals, staff, institutions and organizations. I therefore wish to express my sincere thanks to:

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- Juliet, my wife, and Patrick, our son, for love and happiness together.
2. LIST OF PAPERS


3. **ABBREVIATIONS**

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<th>Abbreviation</th>
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<tr>
<td>ADC</td>
<td>AIDS dementia complex</td>
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<td>ARC</td>
<td>AIDS related complex</td>
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<td>CIH</td>
<td>Centre for International Health</td>
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<td>CMV</td>
<td>Cytomegalovirus</td>
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<td>CNS</td>
<td>Central nervous system</td>
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<td>CT</td>
<td>Computerized tomography</td>
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<td>EEG</td>
<td>Electroencephalography</td>
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<td>EMG</td>
<td>Electromyography</td>
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<td>FLRS</td>
<td>Frontal lobe release signs</td>
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<td>HAM</td>
<td>HTLV-1 associated myelopathy</td>
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<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<td>HTLV-I</td>
<td>Human T-cell lymphotropic virus type I</td>
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<tr>
<td>ICH</td>
<td>International Child Health Unit, Uppsala University</td>
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<td>KCMC</td>
<td>Kilimanjaro Christian Medical Center</td>
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<tr>
<td>MoH</td>
<td>Ministry of Health</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<td>OR</td>
<td>Odds ratio</td>
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<td>PMR</td>
<td>Palmomental reflex</td>
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<td>PNS</td>
<td>Peripheral nervous system</td>
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<td>SCN</td>
<td>Thiocyanate</td>
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<td>SR</td>
<td>Snout reflex</td>
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<tr>
<td>TB</td>
<td>Mycobacterium tuberculosis</td>
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<td>TAN</td>
<td>Tropical ataxic neuropathy</td>
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<td>UoB</td>
<td>University of Bergen</td>
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4. INTRODUCTION

Neurological disorders are an important cause of morbidity and mortality in sub-Saharan Africa but a large percentage of patients with such disorders never get to hospital (Tekle-Haimanot 1990). In spite of this, neurological disorders may account for up to 10% of medical admissions to referral hospitals (Billinghurst 1987). However, they are frequently under-diagnosed or misdiagnosed because of inadequate clinical training and the unavailability of diagnostic resources. Only a few specialized centers in Africa have access to modern diagnostic facilities. In the vast majority of African hospitals neurological diagnoses remain a matter of clinical judgment alone.

While a large part of neurological diseases in Africa are similar to those in the West there are some striking differences which are due to special environmental, genetic, and socioeconomic factors (Spillane 1973). In this thesis I use the term Africa to mean sub-Saharan Africa and the West as a handy designation for the most affluent or industrialized countries. Infections of the nervous system like cerebral malaria, sleeping sickness, tetanus and meningococcal meningitis are all common in African countries whereas they do not occur at all or are relatively uncommon in developed countries. Paralysis of the legs is several times more common in Africa because of leprosy, polio, tuberculosis and trauma. In contrast, neurodegenerative disorders such as Alzheimers dementia, Parkinsons disease, as well as multiple sclerosis are all uncommon or may not occur at all in African countries.

The African pattern of neurological disorders is also changing over time. During the last decades infections such as syphilis, sleeping sickness, polio and leprosy have decreased. In the same period new neurological disorders have been identified in Africa. These include human immunodeficiency viruses (HIV-1 and HIV-2) associated neurological disorders (Mukuyandela and Mweindapole 1987, Clavel et al, 1987, Amayo et al, 1988, Belec et al, 1989, Klemm et al, 1988, Kayembe et al, 1989), Human T cell-Lymphotropic Virus type 1 (HTLV-I) associated myelopathy also known as HAM (Gessain et al, 1985, 1986) and also an epidemic form of spastic paraparesis associated with consumption of insufficiently processed cassava (Ministry of Health Mozambique 1984a). The most alarming new development in African neurology is without doubt the neurological disorders resulting from the rapid dissemination of HIV. WHO estimates that there are now more than 10 million persons infected in sub-Saharan Africa.

Tanzania is among the worst HIV affected countries in Africa with an estimated one million persons HIV infected out of a total population of 27 millions. The life expectancy in Tanzania is approximately 54 years and adult literacy rates approach 90%. Tanzania has a gross national product in the order of 160 US dollars per person which is among the lowest in the world. In spite of this it has a national comprehensive health service although its function is hampered by severe economic constraints. There are only two specialized neurologists for the entire country both of whom are based at Muhimbili Medical Center in Dar es Salaam. There are no facilities for computerized tomography (CT) or magnetic resonance imaging (MRI) and Tanzania has only one functioning electroencephalograph machine.

From 1984 to 1992 it was my privilege to work for the Ministry of Health (MoH) of Tanzania in Kilimanjaro Christian Medical Center (KCMC) Moshi in the northern zone of this country.
KCMC is one of the four consultant hospitals in Tanzania and serves as a referral center for over 6 million people. The hospital is situated in the beautiful setting of the foot hills of Mount Kilimanjaro ("see cover").

The present thesis is based on 8 years work as a general physician in the medical department at KCMC. Among my tasks was to be consultant neurologist for northern Tanzania from 1984 to 1992 during which time I examined over 2000 referred neurological patients. This thesis reports on three neurological disorders which appeared for the first time or in a new form during this period (Fig 1). The first two papers are reports on neurological findings in a large series of HIV positive and negative patients from the catchment area of KCMC. The third paper is a comparative study based on a consecutive series of GBS cases admitted to KCMC and to Haukeland hospital, University of Bergen, Western Norway. The fourth and fifth papers are reports on field surveys in Northern Tanzania investigating an epidemic of unexplained spastic paraparesis which occurred in 1985. This upper motor neurone disorder was identified as a distinct disease entity and named konzo, a local name from the first reported outbreak in Zaire (Trolli 1938). The sixth paper reports specialized neurological investigations of two patients with konzo. The background information for these three clinical conditions is reviewed in the following sections.

4.1. Neurological disorders in HIV disease

Retroviruses were known to be pathogenic to animals but infections in man were not recognized until 1980 when HTLV-1 was isolated from a patient with cutaneous T-cell lymphoma (Poiesz et al, 1980) and later in patients with T-cell leukaemia (Hinuma et al, 1981, Miyoshi et al, 1981). Although a new form of immunodeficiency was first recognized as a clinical entity in the United States in 1981 (Gottlieb et al, 1981) the link between immunodeficiency, AIDS and retrovirus infection was not made until 1983 when human immunodeficiency virus type 1 (HIV-1) was isolated from a patient with generalized lymphadenopathy (Barré-Sinoussi et al, 1983). In 1985 evidence of a second human immunodeficiency virus (HIV-2) was identified from West Africa (Barin et al, 1985).


Neurological disorders in HIV infection can be categorized into three main groups, A) disorders of the central nervous system caused by primary HIV infection, B) disorders caused by secondary mainly opportunistic processes and C) disorders affecting the peripheral nervous system and muscle. These disorders may occur at seroconversion, in the long asymptomatic stage, or more commonly during the symptomatic stages of AIDS related complex (ARC) and AIDS.
Neurological disorders occurring at seroconversion include encephalopathy, meningitis, myelopathy and neuropathy, (Carne et al, 1985, Piette et al, 1986, Denning et al, 1987, Wiselka et al, 1987, McArthur and Johnson 1988). These neurological manifestations associated with primary HIV infection are relatively uncommon and usually self limiting and tend to go unrecognized in Africa despite the high incidence of HIV infection there. Inflammatory neuropathies, including Guillain-Barré syndrome and Bells palsy were among the first HIV related neurological disorders to be reported in Africa (Conlon 1989, Thornton et al, 1991) occurring mainly in the asymptomatic stage. Herpes zoster infection also occurs mainly in asymptomatic HIV infection and often provides the first clinical clue as to the presence of underlying HIV infection in this continent (Kestelyn et al, 1987, Colebunders et al, 1988, Van de Perre et al, 1988, Katabira et al, 1989, Nkya et al, 1989, Thornton and Latif 1989). Major focal and non focal neurological disorders tend to occur in ARC or in AIDS and are the group most frequently reported in clinical studies on AIDS from Africa (Mukuyandela and Mweindapole 1987, Amayo et al, 1988, Belec et al, 1989, Kayembe et al, 1989, Thornton et al, 1989). Most major neurological disorders occur as a result of opportunistic processes but definitive microbial and pathological confirmation is mostly missing in Africa.

4.1.1. AIDS dementia complex

AIDS dementia complex is amongst the most frequently reported neurological disorders encountered in AIDS in the West affecting one to two thirds of patients (Navia et al, 1986, Gabusda et al, 1987, Price et al, 1988, 1992) although recent studies suggest a somewhat lower overall prevalence rate (Portegies et al 1993). In contrast ADC is frequently not reported at all in the African continent or at a much lower rate (Belec et al, 1989, Kayembe et al, 1989). ADC is characterized by disturbances of cognition, motor performance and behaviour and usually becomes clinically apparent in late AIDS. The pathogenesis of ADC has not been established but there is evidence that ADC may be the result of direct HIV infection of the brain via infected macrophage and microglial cells. The staging of ADC is based on clinical findings (Price et al, 1992). However, the diagnosis is also heavily dependent on the exclusion of opportunistic processes by neuroimaging. A mild elevation in protein and mononuclear cells in the CSF seen in some patients is non diagnostic. The neuroimaging features of ADC include widened cortical sulci, enlargement of the ventricals and subcortical white matter abnormalities. The main histopathological abnormalities comprise of subcortical HIV specific encephalitis characterized by widespread multiple foci of multinucleated giant cells and diffuse white matter changes called leukoencephalopathy (Budka 1991). A substantial loss of cortical neurons and synapses (Ketzler et al, 1990, Everall et al, 1991) particularly in the frontal lobes has also been reported in AIDS and ADC. Associated abnormal neurological findings include tremor, ataxia, pyramidal tract signs, distal neuropathy and frontal lobe release signs (FLRS) (Price et al, 1992). At the start of the present study there were no reports of ADC in AIDS in Africa.

4.1.2. Frontal lobe release signs

The snout reflex (SR) and palmomental (PMR) reflexes belong to a group that are called primitive, developmental or foetal reflexes (Kugelberg 1952, Paulson and Gottlieb 1968). They
may also be classified as frontal lobe release signs (FLRS). They include other well known reflexes such as the grasp reflex, glabellar tap, sucking reflex and the jaw jerk. FLRS are normally present during the development of the foetal nervous system but are suppressed as the brain matures. They may reappear when the higher centers in the central nervous system (CNS) cease to function or have been altered by disease or old age. They are found more commonly in advanced bilateral diffuse cortical disease than in corresponding unilateral disease states (Tweedy et al, 1982, De Renzi and Barberri 1992) and particularly in frontal lobe disease as the name implies. The choice of any one of these reflexes in a study is somewhat arbitrary as there are interrelationships and clinical overlap between the individual reflexes.

The SR was first observed in children in 1898 while investigating the Chvostek phenomenon (Escherich 1898) and in adults in 1903 (Bechterew 1903). It was defined more clearly in 1903 (Toulouse and Vurpas 1903). The PMR was first described in 1920 in a patient with extensive corticobulbar disease due to amyotrophic lateral sclerosis (Marinesco and Radovici 1920). The SR and PMR are the earliest foetal developmental reflexes (Bieber 1940, Paulson and Gottlieb 1968) and the SR has in the past been considered to be the labial component of the sucking reflex. The SR and PMR have been described mainly in association with specific CNS diseases. These include dementia, Parkinson's disease, frontal lobe disease, cerebral arteriosclerosis, stroke, amyotrophic lateral sclerosis, pseudobulbar palsy, hydrocephalus and other conditions (Blake and Knukle 1951, Ekbom et al, 1952, Bracha 1958, Reis 1961, Ansink 1962, Paulson & Gottlieb 1968, Jenkyn et al, 1977, Gossman and Jacobs 1980, Jacobs and Gossman 1980, Marx and Reschop 1980, Tweedy et al, 1982, de Noordhout and Delwaide 1988). Very rarely these reflexes are unobtainable because of a break in the reflex arc, i.e. in Bell's palsy.

The SR and PMR are generally regarded as soft neurological signs because of their lack of specificity in the absence of other localizing neurological signs and the fact that they can be found in the normal subjects, with a higher frequency in infancy and in old age (Kugelberg 1952, Ekbom 1952, Jacobs and Gossman 1980, Whittle and Millar 1987, de Noordhout and Delwaide 1988). Indeed many neurologists doubt their clinical usefulness particularly in the face of widespread availability of modern neuroradiological facilities (Whittle and Millar 1987).

FLRS were first described in association with AIDS in 1986. (Navia et al, 1986). In that report they were reported to be present in 38% of patients with advanced ADC. Since that report the SR and grasp reflexes have been described as common in ADC (Gabuzda et al, 1987, Navia et al, 1987, Price et al, 1988, Price et al, 1992). At the time of the present study there were no published studies of FLRS in African patients with HIV disease and no detailed study of their frequency in the different stages of the disease.

4.1.3. Opportunistic processes

Opportunistic infections and tumours in the CNS are known to be the main cause of major focal and non focal neurological disorders in HIV disease (Dix et al, 1988, Pons et al, 1988, So et al, 1988). Their diagnosis in Africa relies mainly on inference from advanced clinical and autopsy studies carried out in the West and more recently a few similar studies in Africa (Lucas et al, 1988). Toxoplasmosis, tuberculosis and cryptococcal meningitis were recognized early on as

Toxoplasma gondii is an intracellular protozoan parasite frequently found in humans. Serological evidence suggests that more than 20% of adults in African populations have been exposed to primary infection with Toxoplasma (WHO 1984, Clercq et al, 1986). It is the main opportunistic infection in the brain affecting between 20 to 40% of AIDS in the West (Navia et al, 1986, Luft and Hafner, 1990). The first report of this infection from Africa came from a postmortem series in Uganda where 23% of AIDS cases had cerebral toxoplasmosis (Lucas et al, 1988). Features strongly suggestive of cerebral toxoplasmosis were also present in early clinical studies from Africa (Thimossat 1987, Belec et al, 1989). Cerebral toxoplasmosis presents mainly as headache and fever, usually in combination with the onset of a focal neurological disorder occurring over weeks but occasionally within days. Confusion and coma may also occur, particularly in late cases.

The laboratory diagnosis of active toxoplasmosis infection is considered unreliable (Grant et al, 1990). The CSF may only show a nonspecific increase in lymphocytes and protein although occasionally serological studies may disclose a diagnostic high antibody titre, or a rise in titre. Neuroimaging is the most sensitive investigation, however, other opportunistic processes such as tumours can give an appearance similar to toxoplasmosis. A definitive diagnosis can only be obtained by brain biopsy but in practice the diagnosis mostly relies on clinical suspicion and a therapeutic response to empirical treatment (Cohn et al, 1989).

Mycobacterium tuberculosis (TB) and Mycobacterium avium-intracellulare (MAI) both cause CNS infection in AIDS. In Africa TB is the main opportunistic infection in AIDS, affecting more than 50% of terminal cases (Colebunders et al, 1989, Nelson 1990). Reactivation of latent mycobacteria, thought to exist in as many as 60% of adult Africans is considered to be the main mechanism of TB infection in HIV disease. In the West TB affecting the CNS in HIV infection has been described mainly in immigrants and IV drug users. In one series of 14 HIV positive patients with CNS tuberculosis the main clinical presentations were multiple brain abscesses, meningitis, grand mal seizures, headaches, meningism and alteration in mental state (Levy et al, 1988). Despite the high prevalence of TB there were no clinical reports of TB affecting the CNS in AIDS in Africa at the time when this study was initiated.

Cryptococcal meningitis was one of the first CNS opportunistic infections to be reported in AIDS in Africans (Clumeck et al, 1984, Desmet et al, 1989, Belec et al, 1989, Testa et al, 1989). These early studies suggested geographical variation in the prevalence of cryptococcal meningitis. The prevalence was highest in Central Africa where environmental exposure to the causative organism seems to be high (Desmet et al, 1989). Clinical features of cryptococcal meningitis include slow onset of fever, headache, photophobia and malaise, often over a period of several weeks. Vomiting, neck stiffness and confusion are usually late manifestations (Chuck and Sande, 1989). The diagnosis is often prompted by the presence of meningeal symptoms and signs, but they may also be absent. A definitive diagnosis can be made in 70 to 80% of AIDS patients by examining the CSF with India ink and demonstrating the presence of capsular yeasts. The CSF lymphocytes counts and protein levels may be slightly elevated and glucose levels normal or decreased. Cryptococcal antigen can be demonstrated in 95% of cases (Desmet et al, 1989).
Herpes zoster occurs in HIV infection due to reactivation of latent varicella-zoster infection. The HIV epidemic in Africa has resulted in a 20-fold increase in zoster incidence rates in some hospitals in Africa (Colebunders et al, 1988, Van de Perre et al, 1988, Katabira et al, 1989). Herpes zoster affects between 5 to 10% of HIV infected persons and is one of the earliest and distinctive clinical disorders seen in HIV infection in Africa. It is typically multi-dermatomal, locally aggressive and leaves a very characteristic residual hyperpigmented scar occasionally with keloid formation. Complications include post herpetic corneal scarring and neuralgia and rarely encephalitis, stroke and radiculitis (Kestelyn et al, 1987, Thornton and Latif 1990).

Cytomegalovirus (CMV) infection is common worldwide. High rates of infection are also reported in Tanzania where most adult persons seem to have corresponding antibodies (Mhalu and Haukenes 1990). Chorioretinitis is the most common ocular opportunistic infection in AIDS in the West (Holland and Kreiger 1988). Neurological manifestations related to CMV infection include encephalitis and radiculitis, but these are uncommon. At the time of the present studies there were no reports of CMV infection in HIV disease in Africa.

In the West other viral, bacterial and protozoal infections are known to affect the nervous system in HIV disease. These include progressive multifocal leukoencephalopathy (PML) due to human papovavirus and encephalitis due to herpes simplex viruses, but at the time of this study there were no reports from Africa for comparison. Infection with Treponema pallidum is relatively common in Africa but the overall prevalence of neurosyphilis is low, probably due to the widespread use of penicillin. Apparently the natural history of neurosyphilis can be altered by co-infection with HIV (Johns et al, 1987). However there are few reports on neurosyphilis and HIV infection (Hook 1989) including only one from Africa (Thornton et al, 1989). Also there are only isolated reports in Africa of bacterial meningitis in HIV infection (Gilks et al, 1990). It should be noted that several infectious diseases in Africa affect the nervous system apparently without any definite association with HIV infection. This is the case with malaria, leprosy, trypanosomiasis, schistosomiasis and many others.

Tumours in the CNS may be associated with HIV infection. These include primary lymphoma, systemic non-Hodgkins lymphoma and metastatic Kaposi’s sarcoma (Bayley, 1988, So et al, 1988). These tumours are relatively uncommon and in Africa are mostly reported as incidental postmortem findings (Lucas et al, 1988). The clinical presentation is typically one of progressive focal neurological deficits similar to toxoplasmosis, but the symptomatic evolution is slower. Their accurate diagnosis depends mostly on neuroimaging.

4.1.4. Peripheral nerve disorders

HIV is associated with a wide range of complications affecting the peripheral nerves, nerve roots and muscles. These complications are amongst the most frequent neurological disorders in HIV infection and vary in nature and frequency with the stage of the disease (Cornblath et al, 1987, de la Monte et al, 1988, Leger et al, 1989, Millar et al, 1988, Parry 1988). The most common neuropathy is a distal sensory polyneuropathy which may affect as many as a third of terminal AIDS patients (Cornblath 1988). Inflammatory polyneuropathies and mononeuropathies, may also occur during or soon after seroconversion and also in the asymptomatic stage of HIV infection (Przedborski et al, 1988, Cornblath et al, 1987). They
include Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDR) and mononeuritis, most commonly Bells palsy. Disorders of muscle range from polymyositis, occurring mainly in HIV infection, to a myopathy in symptomatic HIV disease and in AIDS. At the start of the present study there were few reports on neurological disorders in HIV disease in Africa and none on peripheral nerve disorders.

4.2. Guillain-Barré Syndrome

Guillain-Barré Syndrome (GBS) is an illness causing progressive weakness of the limbs with diminished or absent reflexes due to polyradiculoneuropathy in the absence of a recognized cause. Such an illness was first described by Landry in 1859. In 1916, Guillain, Barré and Strohl described the albumin-cytological dissociation which is characteristic of GBS and they gave the disease its name (Hughes 1990a). The pathological basis of GBS is now regarded to be an immune mediated inflammatory polyneuropathy (Hartung HP 1993).

GBS is known to occur worldwide with average yearly incidence rates in the range of 1-2 cases per 100,000 population (Alter 1990, Hughes 1990b). GBS was once considered to be rare in persons of African origin (Haymaker and Kernohan 1949) and the incidence rate in adults in sub-Saharan Africa is still not known. There are few detailed descriptions of GBS from sub-Saharan Africa apart from studies in Nigeria (Osuntokun and Agbebi 1973) and in Kenya (Bahemuka 1988). Those studies suggest that the frequency and clinical findings in GBS in Africa are generally similar to those found in the West. The onset of GBS is in most cases associated with an antecedent triggering event, most commonly infection, but it may also be associated with a recent vaccination or trauma.

An association between primary and latent HIV infection and inflammatory polyneuropathies was found early on in the epidemic in the West (Piette et al, 1986, Berger et al, 1987, Cornblath et al, 1987, Dalakas and Pezeshkpour 1988). In those studies inflammatory polyneuropathies were described at or around the time of seroconversion, in asymptomatic HIV infection as well as occasionally in AIDS. The clinical presentation was similar to non HIV associated inflammatory polyneuropathies but a distinguishing feature was presence of increased lymphocyte count in the CSF in the HIV seropositives. This was reported as a mean 23 cells/ml in one series (Cornblath et al, 1987). The outcome was favourable in most cases although a variable and fulminating course has also been reported (Dalakas and Pezeshkpour 1988). At the time of the present study there were no published reports of GBS in HIV in Africa and no information on GBS in Tanzania.
4.3. Tropical Myeloneuropathies

The term "tropical myeloneuropathies" was used to describe a group of obscure paraparesis of unknown aetiology by Roman et al, (1985). They distinguish two main clinical groups. First tropical spastic paraparesis, a mainly spastic paraplegia with minimal or no sensory signs, and second tropical ataxic neuropathy (TAN) which is a mainly sensory form of ataxia combined with peripheral neuropathy. The causes of many forms of paraparesis in the tropics were obscure for decades but gradually several distinct etiological and clinical entities have been distinguished from this group of tropical myeloneuropathies.

4.3.1. Lathyrism

Lathyrism is an epidemic form of acute spastic paraparesis found exclusively in parts of India, Bangladesh, Ethiopia and nowadays South East Asia where large quantities of the chick pea (Lathyrus sativus) a drought resistant crop are grown and consumed (Ludolph et al, 1987). It has been causally linked to a neuroexcitatory amino acid in the chick pea, beta-N-oxalylamino-L-alanine (Spencer et al, 1986). The association with chick pea was already recognized in ancient Greece (Acton 1922) and the same cause was claimed earlier this century in Southern Europe (Gardner and Sakiewicz 1963). The reports of lathyrism to date in Africa have all been confined to areas of Ethiopia which seems to be the only part of that continent where chick pea is presently grown and consumed (Tekle-Haimanot 1990).

4.3.2. HAM

HTLV-I associated myelopathy (HAM) was distinguished as a separate entity following the discovery in 1985 of HTLV-I antibodies in two patients with spastic paraparesis in Martinique (Gessain et al, 1985). This was quickly followed by the discovery of HTLV-I antibodies in patients with the same type of spastic paraparesis throughout the Caribbean (Rodgers-Johnson et al, 1988), South America, (Zaninovic et al, 1988), the Seychelles (Roman et al, 1987) as well as in West Indian born UK residents (Newton et al, 1987). In Japan Osame et al (1987) used the term HAM for the first time to describe a chronic progressive myelopathy in six patients who had high serum and CSF HTLV-I antibody titres. This disorder which affects mainly older or middle aged persons, is characterized by a gradual onset of a progressive form of spastic paraparesis associated with sphincteric disturbances and usually some sensory loss. A causal relationship between HTLV-I and HAM was definitely established in 1990 when a cardiac transplantation recipient developed HAM within a year of receiving HTLV-I infected blood (Gout et al, 1990).

The first reports of HTLV-I associated myelopathy (HAM) in Africans were made in expatriates living in Europe. (Gessain et al, 1986, 1993, Ryberg et al, 1987, Gout et al, 1989). In one of the first studies in Africa, 3 out of 26 cases of spastic paraparesis reported from the Ivory Coast were clinically and immunologically identical to HAM (de The' et al, 1989). Since then a number of reports of HAM have come from Africa. An endemic cluster of 23 cases out of a total of 32 patients with spastic paraparesis was reported from a village in Northern Zaire (Kayembe et al, 1990). Another report involved 24 cases of HAM out of 36 cases of
unexplained myelopathy in a referral hospital in the province of Natal in South Africa (Bhigjee et al, 1990). Similarly, in Zimbabwe three out of 5 cases of spastic paraparesis were diagnosed as HAM (Houston et al, 1994). While the identification of HTLV-I antibodies in a number of patients with unexplained tropical myeloneuropathies in Africa represents a major advance in our understanding of these disorders, HTLV-I still accounts for only a relatively small proportion of myeloneuropathy cases seen in Africa (Tyleskär 1994).

4.3.3. Konzo

An epidemic form of acute spastic paraparesis was first described by Trolli (1938), an Italian physician working in the Bundundu region in the former Belgian Congo (Trolli 1938). His report describes over 1000 cases occurring in 1936-37 in this cassava growing region of modern day Zaire. He also mentioned similar epidemics in the same region in 1932 and 1928 and possibly even earlier. He used the local name for the disease "konzo" in his report. The clinical similarity to lathyrism was noted at the time, but as no Lathyrus sativus was grown or consumed in the area an infectious cause or a toxico-nutritional effect related to cyanide intoxication from insufficiently processed cassava was proposed. Fourteen years later Lucasse reported the same cases (Lucasse 1952) unaware of Trolli’s publication. New epidemics occurred again in Zaire in 1978 and 1983 (CEPLANUT 1982, WHO 1982, Kasela 1983).

In 1981 an epidemic of over 1000 cases of spastic paraparesis occurred apparently for the first time in East Africa in a cassava growing region in Mozambique (Ministry of Health Mozambique 1984a, 1984b). The clinical description was of a symmetrical spastic paraparesis with an abrupt onset affecting mainly children and young adults. That epidemic was attributed to a high dietary cyanide intake from insufficiently processed cassava and also a dietary deficiency of sulphur containing amino acids (Cliff et al, 1985). At the time of the present studies there were limited clinical descriptions of this epidemic form of spastic paraparesis and it was unclear if it was to be regarded as a separate entity. There was no information as to the site of the lesion in the CNS and the theories on aetiology were conflicting. In 1986 Carton described a similar disease in the Bundundu Region of Zaire (Carton et al, 1986). He found it to be identical to the epidemic spastic paraparesis from Mozambique but he suggested an infectious cause rather than the cyanide hypothesis put forward from the Mozambique studies.

4.3.4. TAN

Tropical ataxic neuropathy (TAN) is another form of tropical myeloneuropathy which occurs in Africa. An epidemic form of ataxic polyneuropathy or peripheral neuritis was first described in sugar cane workers in the West Indies at the end of the last century and early in this century (Strachan 1888, 1897, Scott 1918). The main clinical features were painful sensory symptoms in the feet, areflexia, ataxia, optic neuritis and skin signs of avitaminosis. A similar pellagra-like disease was reported from Africa (Stannus 1936) and in Europe where residual upper motor signs were first noted in some prisoners of war (Fisher 1955). The occurrence of these disorders were linked to malnutrition, as patients responded to vitamin B supplementation or a change in diet. In 1930 Moore reported an association between optic neuritis, avitaminosis and a high cassava diet in boarding school boys in Nigeria. Their symptoms improved with a change in
diet. The term tropical ataxic neuropathy (TAN) was first used in Nigeria (Osuntokun 1968) to describe an almost similar disease in a cassava eating population. The clinical picture was characterized by a gradual onset of ataxia in older adults in combination with peripheral neuropathy, optic atrophy, nerve deafness and sometimes spastic paraparesis. The presence of any two of these clinical features was sufficient to establish a clinical diagnosis. Similar clinical features were described in patients in Tanzania (Haddock et al., 1962, Makene and Wilson 1972). TAN was also attributed to CN exposure from cassava although it is clinically and epidemiologically different from epidemic spastic paraparesis. Other possible dietary factors including vitamin B deficiency were considered to play a role in the disease. Since that time no further cases of TAN have been reported in Nigeria or Tanzania.
5. **AIMS OF THE PRESENT STUDY**

1. To describe the main neurological findings in AIDS and HIV disease and the natural history of Frontal lobe release signs in HIV disease in Northern Tanzania (papers I, II).

2. To describe the clinical and epidemiological findings in Guillain Barré syndrome in Northern Tanzania in comparison to such cases in Western Norway with special emphasis on the role of HIV (paper III).

3. To describe the clinical, epidemiological and laboratory findings in an epidemic of unexplained spastic paraparesis which was named konzo (paper IV), and to determine its temporal and geographic distribution (paper V) and the site and character of the neurological lesion in this disease (paper VI).
6. REVIEW OF PAPERS

Paper I. Neurological findings in HIV infected persons in Tanzania.

To study the occurrence of AIDS associated neurological disorders in Tanzania a total of 200 consecutive cases of AIDS admitted to the medical department at KCMC from March 1985 to June 1988 were examined by the author. History was obtained in English or Kiswahili or by translation when appropriate from the local languages, Kichagga, Kimeru, Kipare, Kimasai and others. The results showed that 21 out of 200 (10.5%) had an obvious focal neurological disorder. These included cranial nerve palsies (5), involuntary movements (4), hemiparesis (3), paraparesis (3), seizures (3), hemianopia (1), cerebellar ataxia (1) and hemianesthesia (1). A detailed neurological examination was carried out on the last 135 AIDS patients and on 53 HIV seronegative controls. The controls comprised of inpatients hospitalized for a variety of chronic non neurological conditions and were comparable in age, sex and tribe. Ninety-seven out of 135 (72%) had less obviously detectable neurological abnormalities, versus 36% of controls (p<0.005). The most frequent abnormal neurological findings in AIDS were ADC (54%), retinopathy (23%), areflexia (21%), pyramidal tract signs (19%) and ataxia (19%).

On examination for the presence of FLRS, the SR and PMR were found to be present in 76% of AIDS patients versus 36% in controls (p<0.005). AIDS patients with advanced and terminal disease were more likely to have neurological disorders than were AIDS patients in the earlier stage. A further study on 87 patients presenting only with acute neurological disorders showed 10 out of 87 (11.5%) to be HIV positive, (three case studies are presented). These HIV related disorders included Guillain Barre syndrome (5), hemiplegia (1), encephalitis (1), space occupying lesion (1), epilepsy (1) and Bells palsy 1. The results of this paper suggest that in Tanzania, neurological disorders are common in AIDS. They are also associated with otherwise asymptomatic HIV infection.

Paper II. FLRS in HIV infected persons in Tanzania.

The aim was to study the relationship of the SR and PMR in HIV infected persons. Between 1987-92 the presence of these reflexes were recorded by the author in a series of 1127 adults, 649 HIV seropositive and 478 HIV seronegative, from 4 groups in Northern Tanzania at different risk for HIV infection. The respective prevalences were analyzed in a model controlling for sex, age and stage by multiregression analysis. In the total series the prevalences of SR was 65% and PMR 49% in the HIV seropositives, versus SR 19% and PMR 15% in the HIV seronegative reference group. Similar associations were observed, although somewhat weaker in each of the groups (II-IV) which were assumed to be less exposed to HIV infection. In the HIV seropositive group there was a clear increase in the prevalence FLRS with advancing HIV stage. The results ranged from SR 39% and PMR 23% in asymptomatic HIV infection to SR 87% and PMR 69% in terminal AIDS. The prevalence of SR and PMR increased significantly with age in HIV seronegatives, but not in seropositives. The SR and PMR were also independently associated with ADC, distal polyneuritis and pyramidal tract signs independent of HIV stage, but not with herpes zoster and retinopathy. FLRS in advanced and terminal AIDS were the most obvious and easiest to elicit. This study showed a strong
association between the SR and PMR and HIV disease and associated neurological disorders in Tanzania.

Paper III. GBS in Northern Tanzania and Western Norway.

The aims of this paper were to compare the clinical and epidemiological findings in GBS patients in Tanzania and Norway. The patients were selected from consecutive neurological admissions to the medical wards at KCMC from 1984 to 1992 and similarly from the neurological department of Haukeland hospital, Bergen, from 1980 to 1992. The records of patients with a diagnosis of GBS aged 12 or older were retrospectively evaluated. Using the NINCDS criteria (Asbury 1990) a consecutive series of 59 patients in Northern Tanzania and 56 in Western Norway were identified as cases of GBS. A total of 45 out of the 59 patients in the Tanzanian series came from the Kilimanjaro region and here the average annual incidence rate was found to be 0.83 cases per 100,000. In Western Norway the corresponding incidence rate in an earlier study was 1.2 cases per 100,000 (Larson et al, 1985). The results of HIV testing was available for 36 out of the 59 GBS patients in the Tanzanian series, eleven of whom (31%) were HIV seropositive. None of the patients in the Norwegian series were HIV seropositive. None of the patients in the Norwegian series were HIV seropositive.

A significantly greater number of GBS in the Tanzanian series occurred in the second 4 year period of the study. There was a seasonal preference for the coldest months of the year in the Norwegian but not in the Tanzanian series. Comparing the two series, GBS patients in the Tanzanian series had less antecedent infection 41% vs 66% (p<0.001), and there was a longer time interval from onset of neurological symptoms to hospital admission, 19 vs 8 days (p<0.001), and a longer duration in hospital 76 vs 42 days (p< 0.01). On neurological examination the GBS patients in the Tanzanian series compared to the Norwegian series presented with, less upper extremity involvement, less motor weakness 49% vs 75% (p<0.01) and less sensory disturbance 19% vs 45% (p<0.01). On the other hand urinary retention, 15% vs 4% (p<0.05) and elevated CSF protein, 204 versus 112 mg% (P<0.05), were more frequent in the Tanzanian series. The overall mortality was significantly greater in the Tanzanian than in the Norwegian series, 15% versus 2% (p<0.01).

HIV infection was significantly more frequent in the Tanzanian GBS patients (11/36, 31%) as compared to (161/4687, 3.4%) (p<0.001) found in blood donors from Northern Tanzania. The HIV seropositive GBS patients in comparison with the seronegative GBS patients presented with more, upper limb involvement 82% vs 40% (p<0.05), and cranial nerve paralysis 64% vs 12% (p<0.01). They also had a higher mortality 46% vs 16% (p= 0.07). In conclusion, although the main findings were generally similar there were some differences in clinical presentation and mortality rate between the two series. HIV infection was associated with GBS in the Tanzanian series and led to a poorer prognosis.
Paper IV. Konzo epidemic.

The main aim was to elucidate the character and cause of an outbreak of unexplained paraparesis which had occurred for the first time in early 1985 in some villages in the Tarime district located in the Western part of the Mara region of Northern Tanzania. Following a request from the local authorities in the Mara region, a survey was carried out by the author in April, May, and June in three villages known to be most affected. The staff at the local hospital, village leaders and health care workers identified the patients who had developed paralysis of the legs during the previous year. The criterion for inclusion as a case, was onset of difficulty in walking during the previous year due to paralysis of the legs in the absence of any other well defined neurological disease. A total of 39 cases (30 males and 9 females) were identified and these formed the study group. The case histories were obtained through interviews in the local Luo language by a medical assistant. Dietary information was obtained by observations and open interviews with family heads and village leaders. A blood sample was taken for serum thiocyanate SCN and HTLV-I analysis from each patient and 9 of his/her non affected family members. Follow up examinations were carried out on 20 patients in May and June 1985, on 15 patients in March 1986 and again on 10 patients in May 1988.

The overall prevalence in the three villages surveyed was 3.8/1000. No case was reported from nearby fishing villages along Lake Victoria or in the district capital or the adjacent highlands. The patients were primarily males in the age group 3-19 years and also women in the childbearing years. Eleven out of 39 cases gave a history of a previous attack of the same disease prior to 1984. Many families had more than one affected member with almost half the cases coming from 6 families. A total of 73% of the onsets occurred between February and April 1985. The uniform history in all cases was of an abrupt onset of a symmetrical spastic paraparesis usually first noticed on waking or walking. Progression to peak weakness occurred over an average of 2-3 days. Clinical investigation also showed evidence of hyperreflexia in the upper limbs in 56% of cases. Functional involvement of the upper limbs was generally absent or limited to the dorsal extensors, except in the most severely affected cases when it was more generalized. Optic neuritis was found in 6/8 patients with difficulties seeing, and impaired gag reflex in 2 patients with dysarthria. Examinations after 3 years confirmed that all persons with konzo remained with the same degree of spastic paraparesis in flexion and a scissors gait.

All patients gave a history of a drought induced almost complete reliance on bitter cassava as a staple food in the months prior to and during the epidemic. In addition the traditional processing methods used for removal of cyanogenic compounds from the roots of bitter cassava appeared to have been shortened. A resulting high cyanide exposure was supported by high serum thiocyanate levels. Mean SCN in May 1985 in 20 cases and 9 controls were 368 and 303 mmol/L respectively. In June and July 1985 the levels had decreased to 256 and 184 mmol/L respectively.

The clinical findings and associations with cassava toxicity were almost identical to outbreaks in Mozambique (Ministry of Health 1984a), and the so called "konzo" outbreak in Zaire (Trolli 1938). It is concluded that konzo constitutes a distinct upper motor neuron disease entity probably caused by a toxic effect from insufficiently processed cassava under adverse dietary conditions.
Paper V. Konzo distribution

The aim was to study the temporal and geographic distribution of konzo with reference to the proposed toxico-nutritional or infectious aetiology. In April 1989 using the same methods as in the previous study a total of 15 villages in the northern part of Tarime district were surveyed over a 2 week period. All subjects with a neurological cause of locomotor difficulties were examined and a clinical neurological diagnosis was made. The criteria used for a diagnosis of konzo were: (1) The presence of a visible symmetrical spastic abnormality of gait and/or running; (2) a history of distinct onset in time in a previously healthy person; (3) non progression; and (4) the presence of bilaterally exaggerated tendon reflexes in the legs. A total of 116 cases of konzo were identified. In addition 91 cases of neurological disorders other than konzo were identified and clinical findings presented.

The prevalence of konzo in the 15 villages ranged from zero cases in the lake shore villages to 14/1000 in the inland villages, only 5 km away, confirming the observations in the earlier study in 1985. The first cases of konzo in 1979 coincided with the introduction of new drought tolerant high yielding bitter cassava varieties. A total of 62% of cases occurred in 1985 during the main epidemic but a low endemicity was present each year since 1985 despite normal rainfall. All cases had a uniform clinical picture of isolated, non progressive, spastic paraparesis identical to findings in earlier studies. Of the 116 konzo patients examined 14% had a visible spastic gait only on running, 53% had a clear spastic gait, but did not require sticks, 19% required one stick to walk, 9% used 2 sticks and a further 5% were unable to stand. The main outcome of the study was that the geographic and temporal distribution of konzo were compatible with the proposed dietary aetiology of cyanide exposure from insufficiently processed cassava roots. Other toxico-nutritional factors may be involved. The possibility of HTLV-infection had been excluded in an earlier study, and the complete absence of cases from the fishing villages close by the high prevalence villages makes an infectious aetiology less likely.

Paper VI. Site and character of the lesion in konzo.

The aim was to localize the site and neurological character of the lesion in konzo. With the approval of the ethical committees of the Ministry of Health of Tanzania and of the Uppsala University two male patients with moderately severe konzo were invited to Sweden in October 1991 for advanced investigations. They had onset of konzo in 1985 during the epidemic in the Tarime district when both had high serum SCN levels indicating high dietary cyanide exposure. Histories and detailed neurological examinations were repeated in Sweden. Magnetic Resonance Imaging of the brain and spinal cord was performed with a Philips T5 MR scanner without use of intravenous contrast. The following neurophysiological investigations were carried out: electroencephalography, electromyography at rest and during contraction, motor and sensory peripheral nerve conduction studies, somatosensory, visual and brain stem evoked potentials, transcranial magnetic stimulation of the motor cortex and cervical cord, pure-tone audiometry and conventional caloric tests and electroneystagmography and conventional ophthalmological investigations. Hematological, serological and CSF investigations were also carried out including attempts to isolate retroviruses.
MRI imaging, peripheral nerve conduction studies and EMG were completely normal in both patients. However motor evoked potentials on magnetic brain stimulation were abnormal. Surprisingly there was a complete absence of response not only in the legs in both patients and also in the arms which were only slightly clinically affected. There were also signs of central visual field defects in one patient who had a history of optic neuritis. The results of the laboratory investigations showed no evidence of an infectious agent. It is concluded that konzo is a distinct disease entity with a very selective type of upper motor neuron damage that is compatible with a toxico-nutritional etiology.
7. DISCUSSION

The main scientific contribution of this thesis is the detailed clinical description of a number of apparently new clinical entities in northern Tanzania. These include HIV related neurological disorders, konzo and new forms of GBS. These disorders are a reflection of the recent dramatic change in the pattern of neurological disease not only in Tanzania, but throughout sub-Saharan Africa. The work presented is primarily based on the clinical observations of one physician and therefore must reflect the inherent weaknesses of this type of research. The individual investigations are reasonably representative of the respective study populations particularly with regard to gender, age and ethnic group. The studies involved both hospital and community based approaches, both of which are needed in modern clinical research in Africa. Access to patients was probably not a major determinant in any of the studies as health services in Tanzania are free. KCMC itself is a large teaching hospital and is supported by the excellent laboratory facilities at the Northern Zonal Reference Center for Parasitic and Infectious Diseases. The Kilimanjaro region is fairly densely populated and is renowned for its good infrastructure, health services and communication network. Another important factor in the studies was the stability of political, social and health services in Tanzania relative to several other countries in Africa. In particular the well structured administrative divisions allowed ready and long term access to patients and the relevant census data.

7.1. Neurological findings in HIV Disease.

Neurological disorders had previously been considered to be uncommon in AIDS in Africa, or at most only about 10% of patients (Amayo et al, 1988, Beloc et al, 1989, Mukuyandela and Mweindapole 1987). Our results from Tanzania shows that at least in this part of Africa the burden of abnormal neurological findings is generally similar to findings in AIDS in the West (Levy et al, 1988, Rowen and Carne 1991). This conclusion is supported by recent similarly detailed studies from Central and West Africa (Perries et al, 1992, Kouassi et al, 1993) where neurological disorders were found in over 40% of AIDS patients. An association between neurological disorders and otherwise asymptomatic HIV infection in Tanzania (Paper I) was also shown in West Africa (Kouassi et al, 1993). In the present as well as previous studies in Africa major neurological disorders were found in over 10% of AIDS patients. In contrast the less obvious but more common abnormal neurological findings in AIDS (paper I, Perries et al, 1992, Kouassi et al, 1993) appears to have been overlooked in most other studies in Africa.

In the West most major neurological disorders in AIDS occur as a result of opportunistic processes (Rowen and Carne 1991, Koppel 1992). The results of the present study and other reports suggest a similar pattern in Africa (Beloc et al, 1989, 1993, Girdano et al, 1990, Perries et al, 1992). However the lack of neuroimaging, biopsy and autopsies in Africa has up to now precluded precise correlation of neurological findings with underlying opportunistic processes. Despite this obvious limitation a working diagnosis may frequently be possible allowing some patients to be treated empirically.

Autopsies were fundamental to the early clinical descriptions of AIDS in the West (Reichert et al, 1983, Moskowitz et al, 1983). The early autopsy studies in Uganda (Lucas et al, 1988), in Cote d'Ivoire (Abouya et al, 1992), and Zaire (Nelson 1990), reported selected patients and,
except for the study by Lucas et al, without commenting on the brain. However the publication of a recent major autopsy series of HIV positive deaths from Abijan, Cote d'Ivoire provided missing vital information on the role of opportunistic disease in AIDS on the African continent (Lucas et al, 1993). In that series opportunistic infections accounted for 85% of the main clinical manifestations with two or more opportunistic infections being present in over half of the cases. Toxoplasmosis, tuberculosis and cryptococcal meningitis were the main opportunistic processes in the CNS.

Toxoplasmosis.
Clinical features suggestive of cerebral toxoplasmosis were present, but not etiologically confirmed in about 10% of the cases in the present as well as in other main clinical studies in Africa. More recently, a study from Cote d'Ivoire using modern neuroinvestigative techniques confirmed cerebral toxoplasmosis to be the major opportunistic CNS infection in AIDS, affecting 37% of 78 AIDS neurological patients (Kouassi et al, 1993). In the major autopsy series from Cote d'Ivoire cerebral toxoplasmosis was shown to be present in 15% of AIDS patients, and to be the third most common cause of death after tuberculosis and bacteremia (Lucas et al, 1993). In that same study cerebral toxoplasmosis was also shown to correlate closely with a defined cerebral lesion before death. These studies suggest that toxoplasmosis may also be a major opportunistic infection in other parts of Africa. However the differing seroprevalence rates of Toxoplasma infection reported from Africa (WHO 1984, Thimossat 1985, Clercq et al, 1986) shows that there may be variations in the prevalence of cerebral toxoplasmosis within the continent.

Tuberculosis (TB).
In the present study definite evidence of TB was found in only 11% of our AIDS patients and evidence involving the CNS was found only in 0.5% of these cases. It is likely however that TB was considerably under-diagnosed, mainly because of lack of Xray equipment. TB involving the CNS in HIV disease has been rarely reported in Africa despite the fact that the prevalence of TB of the lungs in such groups may range from 11-40% (Colebunders et al, 1991, De Cock et al 1992). Clinical presentations include meningitis and brain abscess (Thornton et al, 1989, Colebunders et al, 1989, Gilks et al, 90, Nelson et al, 90). TB of the lungs was confirmed in 38% of all cases, and in 54% of those dying with AIDS in the autopsy series in Cote d'Ivoire (Lucas et al, 1993). In the same study evidence of tuberculous meningitis was reported in 11% cases of terminal AIDS and in 20% of all patients with proven TB. Patients diagnosed as tuberculous meningitis had a significantly higher median CD4+ T-lymphocyte count than those without meningitis but with TB. This report from Cote d'Ivoire suggests that patients with tuberculous meningitis may present at an earlier stage of HIV disease. This was the first study to report a high incidence of CNS related TB in HIV infection in Africa. A similar high frequency of TB meningitis has also been reported in Spain (Berenguer 1992), but not elsewhere. Tuberculomas were found in only 1% of autopsy cases in Cote d'Ivoire suggesting that mass lesions due to TB may be uncommon in that part of Africa. Similarly, although the spinal cords were not examined, clinically suspected spinal compression due to tuberculosis was present in only one patient in that series. Tuberculous involvement of the CNS in HIV disease, in particular meningitis, appears to have been underestimated in Africa up to now, but its diagnosis clearly depends on a high degree of clinical suspicion.
Cryptococcoses.
Clinical evidence suggestive of cryptococcal meningitis was present in a small number of patients in the present study. Although laboratory evidence of cryptococcal infection was not looked for at the time, serological investigations carried out later on stored sera suggest an overall prevalence rate of 2 to 3% (non published observation). A similar low prevalence rate (3%) was seen in the autopsy series from Cote d'Ivoire (Lucas et al, 1993). Other clinical and autopsy studies from this region have reported prevalence rates of cryptococcal meningitis in HIV infected patients between 3 and 13% (Clercq et al, 1986, Desmet et al, 1989, Pierriens et al, 1992, Belec et al, 1993) which probably reflect regional variation of prevalence of this infection.

Varicella-zoster.
Herpes zoster (HZ) scarring was present in 6.5% of our AIDS patients in this study. This agrees with the rate of 6% recorded previously in a HIV positive high risk group in Northern Tanzania (Nkya et al, 1989), but is higher than a rate of 4% reported at autopsy in Cote d'Ivoire (Lucas et al, 1993) and lower than the 11% observed in symptomatic outpatients in Uganda (Katabira et al, 1989). Thus, as may be expected there appears to be some regional variation in the prevalence of HZ in HIV disease within Africa. There were no neurological complications in the present study apart from post herpetic neuralgia which occurred in about 10% of cases.

AIDS dementia complex.
AIDS dementia complex was reported in 54% of the AIDS patients in this study. A similar high frequency of ADC had been reported in the West (Navia et al, 1986, Price et al, 1988), although recent studies suggest that the true figure may be somewhat lower (Portegies et al, 1993). The overall frequency of ADC reported in Africa varies from only 1% in Cote d'Ivoire (Kouassi et al, 1993), 3.3% in Central African Republic (Belec et al, 1989), and 12.5% in Zaire (Perries et al, 1992). It has been suggested that the prevalence of ADC in HIV disease is particularly low in Africa because of shortened survival, also the finding of HIV specific neuropathological findings in only 2% of autopsied cases in Cote d'Ivoire would seem to support this (Lucas et al, 1993). However this suggestion has not been confirmed by the findings in the present study or the study from Zaire (Perries et al 1992).

The high frequency of ADC, reported in our study may be related to diagnostic criteria. Evidence for this can be seen from the high prevalence of psychomotor retardation (24%) reported in our study. Psychomotor retardation is the very earliest stage of ADC (Price et al 1992) and is not mentioned in the other studies on ADC from Africa, apart from Zaire (Perries et al 1992). In that study psychomotor retardation was present in 20% of AIDS patients but was always in association with cognitive impairment. Evidence of cognitive impairment was present in 19% of AIDS patients in our study, a result which compares favorably with the frequency in Zaire and a recent study in the West (Portegies et al, 1993).

Another major factor in ADC in Africa is the inability to distinguish between cognitive changes caused by direct HIV encephalopathy from those resulting from secondary opportunistic processes. This is likely to contribute to a false positive diagnosis and suggests that the true prevalence of ADC in AIDS in Africa may be lower than that presently reported.
Abnormal motor findings frequently accompany ADC (Price et al, 1988). In our study almost three out of four AIDS patients had abnormal neurological findings on detailed examination. These included FLRS, tremor, ataxia, hyperreflexia, and extensor plantar response, distal neuropathy, and retinopathy. These findings were more common in advanced than in the early AIDS cases and generally agree with the results from Zaire (Perries et al, 1992). In that study the frequency of pyramidal tract signs were 19% and tremor 32%. The frequency of distal polynueuritis was, however, only 3% as compared to 21% in our study. However the presence of decreased or absent reflexes were not commented on in the Zairian study. Similarly signs of retinopathy were not commented on in the Zairian study although they were reported in 23% of the AIDS patients in our study. Only 2% of our patients had typical features of cytomegalovirus (CMV) retinitis. A similar frequency was reported at autopsy in Cote d'Ivoire (Lucas 1993), suggesting that disseminated CMV infection may be less frequent in AIDS in Africa.

7.2. FLRS in HIV disease.

Although FLRS in HIV disease are known to be associated with advanced AIDS and ADC in the West (Price et al, 1988), this is the first study from Africa to show that the SR and PMR were strongly associated with progressive HIV disease and its related neurological disorders. Recently a positive SR has been included as a criteria for the earliest stage of ADC (Price et al 1992). FLRS, the grasp reflex (5%), SR (2%), and PMR (38%) were also reported in a study involving 42 patients with advanced AIDS from West Africa (Perries et al 1992). However there was no information concerning the methodology, patient population, HIV stage or controls in this or the other studies on FLRS in HIV infection. Thus, the present study is the first to give these details in HIV infection.

Differences in methodology for eliciting, grading and recording FLRS was considered to be the major reason for the wide variation in prevalence rates seen in similar CNS disease states in the past (Blake and Knukle 1951, Reis 1961, Ansink 1962, Paulson & Gottlieb 1968, Jenkyn et al 1977, Jacobs and Gossman 1980, Marx and Reschop 1980, Whittle and Millar 1986). This may also explain the differences reported in HIV disease. These methodological problems are in turn related to the techniques, instruments, sites, strength and type of stimulus used, and in particular testing for habituation or repeatability. Other non neurological factors apart from age may influence the SR and PMR. The state of an individual's excitement (Marx and Reschop 1980), as well as the use of drugs such as phenothiazine, alcohol and anoxia may transiently increase the frequency of positive reflexes (Bracha 1958). Clearance of positive FLRS with improvement in the underlying CNS disease state has also been known to occur (Whittle and Millar 1987). These associations may be important to control for in future studies in HIV disease. FLRS may be demonstrated electrophysiologically in 100% of normal people depending on the type and strength of stimulus used (Ekborn et al, 1952, Kugelberg 1952, Girlanda et al, 1986, Caccia et al, 1991) but the corresponding rates of clinical detection are usually much lower.

The importance of FLRS in HIV disease appears to have been underestimated up to now. Quite apart from their role in understanding the pathophysiology of HIV related CNS disorders they provide a physical sign which may be useful in monitoring HIV disease. Although the
pathophysiology of FLRS is not understood they are probably related to the widespread cortical and subcortical damage in the brain which occurs as a result of direct HIV infection (Dunlop et al, 1993, Jernigan et al, 1993, Masliah et al, 1992, Ketzler et al, 1990, Everall et al, 1991, McArthur et al, 1990). Recommended criteria for standardizing examining techniques in any future studies on FLRS in HIV disease should include, 1) the methodologies outlined in paper II, 2) screening for habituation or repeatability of positive FLRS five times before considering a reflex to be positive, 3) the use of an independent observer and or modern electrophysiological methods to confirm results, 4) the use of laboratory methods eg CD4 counts, in addition to the clinical staging of HIV infection.

7.3. GBS.

The main epidemiological and clinical features of GBS in Tanzania and Norway were remarkably similar, allowing for the differences in age distribution and in resources between the two countries. The incidence rate in the Kilimanjaro region also agrees with the world wide figure of one or two cases per 100,000 population (Hughes 1990b, Alter 1990). This is the first report on GBS incidence rate in adults in sub-Saharan Africa, although similar a similar rate has been reported before in North Africa (Radhakrishnan et al, 1987) and in children in South Africa (Kibel 1983). It is reasonable to suppose that most clinical cases of this acute or subacute disease occurring during the study period in the Kilimanjaro region were referred to KCMC. The compiled evidence then suggests that GBS in Africa is similar to other parts of the world. The role of antecedent events was apparent in both series, and seasonality was seen in the Norwegian but not the Tanzanian series. A similar slight increase in the frequency of GBS during the colder months of the year has already been reported in an earlier study from Hordaland county (Larsen et al, 1985) and is most likely explained by an increased incidence of mainly viral infections predisposing to GBS. However seasonality alone is not considered sufficient to significantly affect overall incidence rates of GBS (Alter 1990).

The main clinical features of GBS in the Tanzanian series were similar to the other main studies in Africa (Osuntokun and Agbebi 1973, Bahemuka 1988). By comparison with the Norwegian series there were delays from onset to hospital admission and a prolongation of hospital stay in the African studies. This is hardly surprising given the obvious lack of resources for admission and discharge which exist in most hospitals in developing countries. There were also some differences in clinical findings including a tendency for more sphincter and lower limb involvement and less sensory involvement in the Tanzanian series. Whether these differences are real or a function of other factors such as methodology or case selection is not known but similar findings have been reported in the other main studies on GBS in Africa.

The mortality rate in GBS in our study was increased by comparison with the Norwegian series and is higher than corresponding rates reported from Nigeria (6%), and Kenya (11%). It is likely that these reported rates from Africa are an underestimate, as deaths occurring during the period prior to hospitalization are likely to have been missed. Mortality rates similar to that reported in the Tanzanian series were frequent in the West before the introduction of intensive respiratory and cardiac care (Haymaker and Kernohan 1949). The much lower rate (2%) seen in the Norwegian series agrees with the best data from other specialized centers in the West (Loffel et
al, 1977) and has been attributed to early intervention with intensive care and plasmapheresis (Hughes 1990c, McKhann 1990).

HIV infection was associated with GBS in the Tanzanian series and this agrees with the results of a similar study from Zimbabwe (Thorton et al, 1991). GBS is amongst the earliest neurological disorders encountered in HIV disease in Africa (Conlon 1989, Thornton et al, 1991, Chinyanga and Dunha 1992). In the West descriptions of GBS in HIV disease have been mainly in association with seroconversion after primary infection (Cornblath et al, 1987, Millar et al, 1988). It is unlikely, however, that studies in Africa will reveal an association with seroconversion as primary HIV infection is only rarely reported there, despite the pandemic. There was no evidence of an association between HIV infection and GBS in Norway, where the overall seroprevalence of HIV infection is particularly low.

In our study the clinical features and course of GBS were more severe in the HIV seropositives than in the HIV seronegatives. This was evidenced by the shortened duration of onset, increased neurological involvement, higher CSF protein levels and the higher complication and mortality rate in the HIV seropositives. These findings are in contrast to those reported in Zimbabwe where no major clinical differences between HIV seropositives and seronegatives were found (Thornton et al, 1991). While the findings in the Zimbabwian study agrees with what is generally the case concerning GBS in HIV disease a more rapid and fulminating course has also been reported in the West (Dalakas and Pezeshkpour 1988) and in some cases in Africa (Conlon 1989, Chinyanga and Dunha 92). Although the level of immunodeficiency is likely to be critical for the clinical course further research is needed in order to assess the presentation and natural history of GBS in HIV disease.

7.4. Konzo.

The present studies on konzo in Tanzania provide detailed clinical, epidemiological and neurophysiological information on this dramatic disease. Several other epidemics of konzo have been reported from countries in Africa during the last decade. These include Mozambique (Ministry of Health Mozambique 1984a, 1984b, Essers et al, 1992, Davis and Howarth 1993), Zaire, (Tylleskär et al, 1991, Banea et al, 1992), Southern Tanzania (Mlingi et al, 1991) and Central African Republic (Tylleskär et al, 1994a). The combined evidence from Tanzanian and the other studies in Africa is now sufficiently strong to confirm that konzo represents a new and distinct human disease entity.

**Epidemiology.**

The most striking feature of all studies on konzo is the uniformity of epidemiological and clinical findings. The prevalence of konzo in the Tanzanian villages ranged from 1-14 per 1000 (paper V), as compared to 1-30/1000 in Zaire (Tylleskär et al, 1991) and 0.1-29/1000 in Mozambique (Ministry of Health 1984a). The highest dry season incidence rate in an epidemic of konzo to date 29/1000 was recorded in Mozambique. It is noteworthy that in all affected communities konzo causes more paralysis than all other neurological disorders including polio (paper V). The mean age of patients with konzo in Tanzania (paper IV) was 13 years (range 4-46 years) and this agrees with other studies. There was sparing of breast fed children and adults
greater than 50 years in all studies. The male to female ratio was increased in Tanzania and Mozambique, but this was reversed in Zaire, suggesting that local factors can influence the sex ratio (Ministry of Health Mozambique 1984a, Tylleskär et al, 1991). There was a pronounced tendency for family clustering in the Tanzanian and all other studies which could be explained by shared environmental exposure, genetic predisposition or, alternately, by an infectious aetiology. However there was no evidence of infection in the in any studies to date. A history of recurrence of aggravating episodes, in this and other studies may also be related to environmental factors.

The temporal distribution of konzo in Tanzania also follows a characteristic pattern seen in other epidemics with the major outbreaks following drought. In the case of Zaire the epidemic did not coincide with drought but appeared to occur in conjunction with a chain of recurring stressful agroeconomic events resulting in the same type of food insecurity (Tylleskär et al, 1991). In that study, the building of a main road in the area allowed access to new markets which in turn led to intensive sales and a shortening of the processing method. The start of the epidemic in Tanzania was heralded by the occurrence of cases during the dry months. This was then followed by a dramatic increase over a 2-3 month period extending into the rainy season and then followed by a steep decline and cessation of cases (Papers IV, V). A similar pattern was reported in Mozambique except that the epidemic there occurred exclusively in the dry season. In Zaire the epidemic occurred over a greater number of months during the dry season and the first part of the rainy season. Endemicity is seen in all studies with a small number of cases occurring during the non epidemic years. Endemic cases also follow a seasonal pattern similar to that of the epidemics. The pronounced geographic limitation of konzo was also the same in every epidemic. Konzo only affects poor rural populations in cassava growing areas of Africa whose diet during the preceding months consists almost exclusively bitter cassava roots. To date, no case of konzo has been reported from the nearby urban populations and similar to Mozambique the epidemic in Tanzania completely spared the mainly cassava eating populations in adjacent fishing villages.

**Clinical features.**

The clinical findings in konzo are also similar in all studies. (Trolli 1938, Lucasse 1952, Ministry of Health Mozambique 1984b, Carton et al, 1986, Papers IV, V). There are no prodromata or triggering illnesses reported in konzo. In Tanzania the onset was characterized by an abrupt isolated paraparesis occurring within minutes or hours. A typical history was of sudden onset of weakness in the legs after prolonged exercise or on waking in the morning. A slower onset with progression over 2-3 days occurred in some cases or more rarely over a week. This was also reported in Mozambique (Ministry of Health 1984a). The main symptoms at onset were heaviness, trembling or weakness of the legs associated with difficulty or inability to stand. Other complaints at onset in more severe cases included generalized body weakness, weakness in the arms and hands, difficulty in articulating speech and blurring of vision and sensory symptoms including radicular low back pain and paraesthesia in the legs. These symptoms tended to clear during the first weeks or months in all but the most severely affected cases (Banea 1992). There was no evidence of autonomic or sphincteric involvement in this or other studies.

On neurological examination the characteristic finding in every patient was of symmetrical spastic paraparesis which varied in severity from isolated hyperreflexia in mild cases to almost
complete paralysis of the legs in severe cases. The muscle weakness invariably affected the extensor muscle groups to a greater degree than the corresponding flexors (paper IV). The arms in konzo may be similarly involved but always to a much lesser extent than the legs. Hyperreflexia in the arms was present in over half the cases in Tanzania and Mozambique (Ministry of Health Mozambique 1984a). Any associated loss of power in the arms was generally mild and limited mainly to the extensors of the wrist, except in severe cases when it was more extensive. A postural thoracolumbar kyphosis related to weakness of the lower trunk muscles was evident in about a third of the patients in the Tanzania study.

There were some minor clinical differences between the Tanzanian and the other main studies. Extensor plantar responses were not found in the Mozambique (Ministry of Health 1984b) and the original Zairian study (Trolli 1936), but were present in 85% in the Tanzanian study. This was most probably a correct finding as they were shown to be present in most konzo patients in subsequent studies (Papers V, VI and Carton et al, 1986). This difference may have been caused by technical difficulties in eliciting reflexes in heavily calloused feet as it was found necessary in the Tanzanian study to lie the patients flat and relax the legs muscles during the neurological examination in order to elicit a clear response. Sensation appears to be normal in konzo in this and other studies. Slight sensory impairment was found in a few patients in Mozambique, but this cleared later on (Ministry of Health Mozambique 1984b) and detailed peripheral nerve conduction studies showed no evidence of any peripheral neuropathy in the Tanzanian study (paper VI). There was no evidence of cerebellar involvement in konzo in the Tanzanian or any other study. The finding of impaired rapid alternating hand and eye movements in some patients in the Tanzanian study may be explained by associated muscle weakness. Isolated nystagmus was reported in two patients in Zaire (Tyleskær et al, 1991) but may have another origin as it has not been reported in other studies.

The cranial nerves may be involved in a small number of konzo patients. Symptoms and signs suggestive of optic neuritis, occurred in about 10% of acute cases in the Tanzanian study (paper IV), however, all patients were able to count fingers at one meter and symptoms cleared in the first few months in all patients. Persistent optic pallor was noted in two severe cases. Visual acuity was also normal in two Tanzanian patients with severe konzo when tested in Sweden, despite persistent signs of optic neuritis in one with a past history of visual problems (paper VI). Hearing difficulties are probably not a feature of konzo, or may be relatively rare. Although they were present in 1 out of 53 Mozambique cases (Ministry of Health 1984b) and in 2 out of 20 Zairian cases (Carton et al, 1986) they were absent altogether in the Tanzanian studies. Difficulty in speaking or persistent nasal voice is common in the acute phase in all studies but persists in only the most severe cases. The origin of this is unclear, although it is generally considered to be most likely suprabulbar in origin. The finding of an impaired gag reflex in two dysarthric patients in Tanzania (paper IV) would appear to contradict this, but this finding was present in only 5% of cases examined under field conditions. Intellectual and mental capacity appear to be normal in konzo.

Konzo is therefore characterized by isolated, symmetrical, permanent but non progressive damage to the upper motor neurones varying only in severity and always bilaterally affecting the distal order neurones to a greater extent than the proximal ones. The permanent clinical features are spastic paraparesis, scissors gait, flexion and adduction deformities at the hips and knees, valgus ankle deformity with plantar flexion and inversion of the feet and abduction of the
forefoot and toes. Functional involvement of the arms and cranial nerves occurs in the more severe cases.

**Course and prognosis.**
There was an improvement in the level of disability in konzo in Tanzania during the first weeks or months after the onset of the disease (paper IV). Most patients were then able to stand or crawl or walk with assistance. This is also reported in other studies. Very mild cases may appear clinically normal at this stage except for the presence of disability visible only on running, or the finding of hyperreflexia on neurological examination. However, in all other cases the underlying spastic paraparesis remains unchanged for life. This impression was confirmed in Tanzania (paper V) where 96% of patients reviewed 4 years after onset reported no long term improvement.

Konzo typically presents in sharply limited geographical foci in Africa. During the epidemic in Tanzania only the first two patients were referred to the local mission hospital after which all patients were cared for at home by their extended families. These were then involved in locally initiated rehabilitation programs lasting many months with traditional healers and using home made walking aids and sticks. Children with mild or moderate disabilities subsequently continued to attend school while some of those with more severe disabilities developed a sedentary trade eg, shoemaker. The majority of konzo patients continue to live a relatively normal life despite their disabilities that put a considerable extra burden on their families. Some konzo patients of both sexes are known to marry and have healthy children.

The most serious long term consequence of konzo is an increased mortality rate. This has been observed in all study areas, including Tanzania. In Zaire, a mortality rate of over 20% was recorded 1-7 years after onset occurring particularly in severe cases and in males (Tylleskär et al, 1991). Individual konzo deaths have been attributed to malnutrition and infection. Flexion contractures around the ankle and knee are also long term complications (paper V). There was a dramatic improvement in mobility after surgery in two konzo patients who were operated on by an Italian surgeon for contractures (Tylleskär et al, 1994). This suggests that increased muscle spasm and secondary contractures may contribute significantly to the disability in konzo.

**Differential diagnosis.**
The use of simple diagnostic criteria (Tylleskär et al, 1991, paper V) suggests that in its epidemic form konzo can be easily diagnosed by medical and lay persons alike. While the uniform findings in konzo also help distinguish it from the other main causes of paraplegia, a more detailed neurological evaluation by a physician may be necessary in order to distinguish it from the other types of tropical myeloneuropathies. These differences are summarized in Table 1.

Lathyrism is the paraparesis which is most similar to konzo and if the two diseases were to occur in the same geographic area it would be clinically almost impossible to distinguish one from another. It is possible, however, to distinguish konzo from lathyrism simply because there is no chick pea grown or consumed in areas affected by konzo. Hence, konzo and lathyrism have not yet been reported in the same populations. There are however some minor clinical
differences between lathyrism and konzo (Ludolph et al, 1987). Firstly, the onset of lathyrism is mainly in the second and third decade, an older age than konzo. Secondly, sphincteric disturbance, although rare in lathyrism, are absent in konzo and, thirdly, there is no optic neuritis in lathyrism whereas it can occur in konzo.

Konzo and HTLV-1 associated myelopathy (HAM) can also be distinguished clinically from one another. The onset of HAM is typically slow and its course progressive over months or years whereas the onset of konzo is acute and its course non progressive. HAM is endemic worldwide with relatively low prevalence rates of around 0.1% and also occurs in urban areas whereas konzo is epidemic, restricted to cassava growing areas in rural Africa and has much higher prevalence rates, up to 3%. The mean age at onset of HAM is the fourth and fifth decade, whereas konzo affects mainly children above the age of three. There are also some clinical differences. Peripheral neuropathy, sensory dysesthesia on the trunk and sphincteric disturbances are all clinical features of HAM, but these are all absent in konzo. The cranial nerves are usually normal in HAM but may be involved in konzo. Finally HAM is caused by a chronic neurotropic virus, HTLV-1 infection whereas evidence of HTLV-1 infection is absent in konzo.

Tropical ataxic neuropathy (TAN) is the tropical myeloneuropathy (Osuntokun 1981) which is most often confused with konzo. The main reason is that they both have been attributed to dietary cyanide exposure from the consumption of insufficiently processed cassava. There are, however, a number of epidemiological and clinical features which distinguish TAN from konzo. TAN occurs endemically whereas konzo is mainly epidemic. Also interestingly they have not been reported occurring together in the same population. The onset of TAN is typically gradual, over months or years and its course is progressive. This is in sharp contrast to konzo whose onset is abrupt, within minutes or hours, and its course non progressive. The mean age group affected in TAN is greater than forty years, whereas konzo has a predilection for children and females in the fertile age group. However the major difference between these two disorders is clinical. Ataxia, sensory neuropathy and deafness which are the clinical features of TAN are absent in konzo. Optic neuritis is common in TAN whereas in konzo it is relatively uncommon. Spastic paraparesis only affects only about 20% of patients with TAN whereas it is present in all konzo cases.

The dietary observations in this study support the hypothesis that the etiology of konzo is linked with exclusive consumption of insufficiently processed cassava. A clear temporal relationship was seen between the first occurrence of konzo in Tarime district and the introduction in 1979 of the more high yielding toxic varieties of cassava (paper V). The cassava processing method reported in Tarime (paper IV) had not been described before, and may be ineffective in removing cyanogenic substances since root disintegration is incomplete (Essers et al, 1992). The removal of cyanogens may have been still more ineffective because of shortening of processing due to food shortages (Lancaster et al, 1982). The association between exposure to a dietary cyanide and konzo is supported by the high serum thiocyanate level found in cases in Tanzania that correspond to levels in konzo reported from Mozambique and Zaire (Ministry of Health 1984a, Tylleskär et al, 1991). These levels are in fact amongst the highest recorded in cassava eating populations and are up to eight times higher than in a reference population (Lundquist 1982). There was also a pronounced seasonal variation of cyanide exposure in the
konzo affected populations in Tanzania and Mozambique. This was measured as decreasing thiocyanate levels which coincided with the end of the epidemic.

Konzo completely spared the cassava consuming lake shore villages in Tanzania where they had greater fish consumption, and also the adjacent town where they had other commercially available food. In contrast there was almost a complete absence of supplementary food and dietary protein in the konzo affected inland villages (paper V). This pattern was identical to that seen in Mozambique where a high dietary cyanide in combination with low protein, in particular sulphur based amino acids, has been postulated as a possible mechanism for konzo (Cliff et al., 1985). An attempt was made to exclude other possible dietary causes in Tanzania. Lathyrus sativus was not grown in the area and there was no evidence of widespread consumption of wild plants or use of pesticides.

An infectious agent was initially suspected in the Tanzanian and the other konzo epidemics (Carton et al., 1985) but no laboratory evidence of HTLV1 or any other infectious agent was found in this or any of the other studies. The results of extensive laboratory and neurophysiological investigations carried out in Sweden on two Tanzanian konzo patients were essentially normal (paper VI) with the exception of the magnetic brain stimulation. This result, however, was highly abnormal showing no visible contraction in the legs or in the less affected arms in response to maximum stimulation. This finding suggests that the site of pathology in konzo is situated centrally in the motor cortex rather than in the spinal cord. A similar pattern of response has been reported in other neurological diseases with known central sites of pathology including motor neurone disease (Hugon et al., 1987). The lack of response in the arms was a somewhat surprising result given the relatively small amount of clinical involvement as compared to the legs. This suggests subclinical damage to a subpopulation of central motor neurones serving arm function. Evidence to support subclinical involvement in konzo comes from the finding of isolated increased ankle reflexes in asymptomatic healthy school children in affected communities (Cliff et al., 1986, personal observation).

Possible pathogenic mechanisms.
Cyanide exposure can result in damage to the nervous system, but the type of damage attributed to cyanide appears to depend on dosage, duration and possibly other associated dietary factors. Acute, fatal cyanide intoxications are uncommon, but well known in cassava eating populations worldwide, and have also been reported in Tanzania (Mlingi et al., 1992). Basal ganglia damage with subsequent parkinsonian features can result from sublethal acute cyanide exposure (Carella 1988). Central and peripheral nervous system damage has been associated with moderate cyanide exposure over years possibly in combination with vitamin deficiency as occurs in TAN (Osuntokun 1981). There is also laboratory evidence that chronic high dose cyanate, a cyanide metabolite, exposure in primates can induce a konzo like disease, and of particular interest is the fact that only minor histological changes were noted in the cortico-spinal tracts of those primates (Shaw et al., 1974). The pathogenic mechanism of konzo is not known and the causal role for cyanide is not proven beyond doubt. However the evidence is sufficiently strong to assume that konzo results from abrupt irreversible selective upper motor neurone cell damage or cell death arising after weeks or months of uninterrupted exposure to dietary cyanide without adequate protein or other factors necessary for cyanide metabolism. Verification of the etiology of konzo is probably possible with animal models.
While understanding the pathogenic mechanisms of konzo is clearly of much importance in itself and may also help in elucidating the mechanism of cell damage in other forms of upper motor neurone disease, the public health aspects are more important. There is now enough evidence to prevent konzo by promoting effective processing methods and ensuring adequate supplies of supplementary foods.

CONCLUSIONS

HIV: Focal neurological disorders (10%), cognitive impairment (19%) and associated abnormal neurological findings (70%) were major clinical findings in patients with mainly advanced AIDS from northern Tanzania. The neurological findings were generally similar to those reported in AIDS in the West. The SR and PMR were the most frequent abnormal neurological finding occurring terminally in three out of every four AIDS patients. The frequency of SR and PMR increased incrementally with advancing HIV stage and associated neurological findings, from asymptomatic HIV infection to terminal AIDS.

GBS: Comparing a series of GBS patients from northern Tanzania with GBS patients in Western Norway, the incidence rate, epidemiological and main findings, apart from some minor clinical differences, were similar in the two series. The significantly increased mortality rate (15%) seen in the Tanzanian series is probably explained by the lack of resources for adequate intensive medical care. An association between HIV infection and GBS was seen in the Tanzanian, but not the Norwegian series. HIV positive GBS patients tended to have more severe neurological disease and increased mortality.

Konzo: Konzo represents a new disease entity which can be distinguished clinically from the other main forms of tropical myeloneuropathies. In its epidemic form it is the single most important cause of paralysis in affected communities. The aetiology of konzo is most probably a toxic effect arising from some months of ingestion of cyanogenic compounds from insufficiently processed cassava under adverse dietary conditions. The site of the pathology in konzo is most probably in the motor cortex rather than in the spinal cord.
Fig 2. Family of five children who developed konzo within one week.

Table 1. Characteristic features of four tropical myeloneuropathies.

<table>
<thead>
<tr>
<th></th>
<th>Konzo</th>
<th>Tropical ataxic neuropathy</th>
<th>Lathyism</th>
<th>HTLV-1 associated myelopathy</th>
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**MAIN NEUROLOGICAL FINDINGS:**

- **Gait abnormality**: Spastic paraparesis, Ataxia, Spastic paraparesis, Spastic paraparesis
- **Peripheral neuropathy**: No, Yes, No, Common
- **Sphincter involvement**: No, No, Yes, No
- **Optic atrophy**: Rare, Yes, No, No
- **Deafness**: No, Common, No, No

**AETIOLOGY:**

- Attributed to weeks of high cyanide exposure from cassava
- Attributed to years of varying cyanide exposure from cassava
- Caused by weeks of high lathyrus consumption
- Caused by chronic HTLV-1 infection
Figure 1. Map of Tanzania with the study sites indicated.
REFERENCES


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