The Causation of Konzo

Studies on a Paralytic Disease in Africa

BY

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ABSTRACT


Epidemics of a permanent, non-progressive spastic paraparesis with sudden onset has been reported from several rural areas of sub-Saharan Africa. Studies in East Africa suggested an association with dietary cyanide intake from unprocessed cassava. In Zaire the disease was attributed to an infectious cause as the cyanogenic glucosides in the cassava consumed were known to be removed by traditional soaking. The aims of the thesis were to define the disease entity and elucidate its etiology. A community-based survey in rural Zaire identified 110 live and 24 dead cases among 6764 inhabitants (16/1000). The clinical findings were identical to earlier studies and it was decided to name the disease konzo as in the first known report. Annual and monthly incidence of konzo was associated with almost exclusive consumption of short-soaked bitter cassava roots. The appearance of konzo coincided with the completion of a tarmac road from the capital, which turned cassava into the main cash crop, and induced short-cuts in the processing. A processing experiment showed that flour from short-soaked roots was high in cyanogens. A higher cyanide intake in affected compared to un-affected populations was confirmed by much higher urinary thiocyanate levels, the main metabolite. A low urinary sulphate indicated low availability of sulphur, the substrate for detoxification. All three konzo patients examined at onset had blood cyanide levels above 4 μmol/l, versus only 2 out of 23 controls (p<0.01). This supports an etiological role for cyanide. An odds ratio of 11 was found for short-soaking of cassava, in a multivariate logistic regression analysis of a case referent study in Zaire, with a dose-response curve indicating higher risk of konzo with frequent consumption of short-soaked cassava. Serological investigations of 33 cases in Zaire excluded retrovirus etiology for konzo. Konzo was also identified in low prevalence in the Central African Republic, again associated with consumption of insufficiently processed cassava. Investigation in Sweden of two severely disabled Tanzanian patients revealed normal magnetic resonance imaging but neurophysiology showed isolated upper motor neuron dysfunction. This is consistent with clinical findings and identifies konzo as a distinct disease entity. The evidence for an etiological role of high cyanide and low sulphur intake in konzo is now strong enough to urge for prevention by promotion of efficient processing of cassava roots.

Key words: Spastic paraparesis, konzo, cassava, cyanide, thiocyanate, inorganic sulphate, HTLV-I.

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The obstacle to discovery is the illusion of knowledge
Daniel Boorstin 1986

To Karin
and
Anna, Ida & Erik
PAPERS INCLUDED IN THE THESIS

The present thesis is based on the following papers which will be referred to in the text by their Roman numerals:


IV Tylleskär T, Banea M, Böttiger B, Thorstensson, R, Biberfeld G, Rosling H. Konzo, a newly defined spastic paraparesis in Africa, is not associated with antibodies to HTLV-I, HIV or HIV 'core' proteins. Submitted for publication.


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### ABBREVIATIONS

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<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>CAR</td>
<td>Central African Republic</td>
</tr>
<tr>
<td>CEPLANUT</td>
<td>Centre National de Planification de Nutrition Humaine, the national nutrition institute in Zaire</td>
</tr>
<tr>
<td>CN</td>
<td>cyanide</td>
</tr>
<tr>
<td>CNS</td>
<td>the central nervous system</td>
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<td>EEG</td>
<td>electroencephalography</td>
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<tr>
<td>EMG</td>
<td>electromyography</td>
</tr>
<tr>
<td>ICH</td>
<td>International Child Health, Uppsala University</td>
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<tr>
<td>MoH</td>
<td>Ministry of Health</td>
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<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>HTLV-I</td>
<td>human T-lymphotropic virus type I</td>
</tr>
<tr>
<td>IDD</td>
<td>iodine deficiency disorders</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>OCN</td>
<td>cyanate</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio, an estimate of the relative risk.</td>
</tr>
<tr>
<td>SCN</td>
<td>thiocyanate</td>
</tr>
<tr>
<td>TAN</td>
<td>tropical ataxic (poly-) neuropathy</td>
</tr>
<tr>
<td>TFNC</td>
<td>Tanzania Food and Nutrition Centre, Dar-es-Salaam.</td>
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<tr>
<td>TSP</td>
<td>tropical spastic paraparesis</td>
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**Terminology explained:**

- **ecological study**: a study in which the units of analysis are populations or groups of people, rather than individuals, a study on the aggregated level.
- **etiology**: the causes of disease.
- **incident case**: a patient at onset of a disease.
- **paraparesis**: paresis of both legs.
- **prevalent case**: a patient having a disease.
- **referents**: the reference individuals with which the cases are compared, often called "controls".
- **retrovirus**: a group of viruses including HIV and HTLV-I.
- **soaking**: to leave in cold a liquid to make soft or completely wet.
  
  In Zaire, cassava roots are usually soaked in water.
- **spastic, spasticity**: increased muscle tone, a tendency for the muscles to go into spasmic contractions.
PREFACE

At the age of twenty I went to work one year in Bandundu region in Zaire as a youth leader volunteer. My background as a scout leader in Sweden was most useful in the work with the youth of "Communauté Baptiste de Bandundu", in the northern part of Bandundu region. I came to love Zaire. I learned Lingala, the lingua franca of the area, and understood that whatever profession one has, the effort put in learning the local language is crucial not only for your work but also for the way you feel at home in a foreign country.

During my medical studies, I went to Paris to study African Linguistics. Together with my wife Karin I returned to Zaire for a field study of Kisakata, a formerly poorly documented local language of northern Bandundu. We lived for nine months with the 500 inhabitants in Ikoko village, as the only Europeans who have ever lived there. We learned the language (Tylleskär 1987), how people live in such a rural village, how to survive and how to behave. We learned how to cultivate, process and eat "bèçwè", Kisakata for "cassava", and we understood the virtues of this crop.

In 1986 my wife and I were sent back to Zaire on a minor field study to find out if konzo existed in northern Bandundu. A short report in Weekly Epidemiological Records had convinced our supervisor Hans Rosling that the disease did exist in Bandundu, though in northern Bandundu, we did not find it. During a brief visit to Vanga and Djuma hospitals in Bulungu zone, just south of the Kasai river, we faced this human tragedy for the first time. We examined some of the hundreds of women and children disabled by konzo in Bulungu zone. In the Djuma hospital archives we found a report from the epidemic in 1983 by Dr Kasela (Kasela 1983). He was the sub-regional medical officer and had examined 111 cases. He wrote:

"I had the sad privilege to recognize the disease, through clinical signs, that I earlier had fought in the Masi-Manimba zone: the famous Kwango spastic paraparesis. The situation is alarming if one considers the number of victims I have counted in the villages. My humble opinion is that the political and medical authorities have to engage as soon as possible specialised teams to study the disease. Yesterday (1978-79) it was Feshi and Masi-Manimba, today it is Bulungu. Today the disease is gaining ground and leaves invalids in the whole sub-region and perhaps tomorrow in the whole region and the whole country."

Dr Kasela’s report was what encouraged me personally to undertake the studies presented in this thesis. I hope they will help to prevent outbreaks of konzo in other parts of Zaire and Africa.

L'existence d'une paraparésie spastique non-progressive permanente, débutant de manière soudaine a été rapportée dans plusieurs aires rurales d'Afrique Sub-Saharienne, souvent sous la forme d'épidémies. Des études en Afrique de l'Est ont suggéré une association avec la consommation de manioc non-traité, contenant un taux élevé de cyanure. Au Zaïre cependant la maladie était considérée d'origine infectieuse étant donné que les glucosides cyanogéniques du manioc consommé ont été enlevés avec le traitement traditionnel. Les buts de cette thèse a été de définir l'entité clinique et éclaircir son étiologie. Une enquête menée au sein de communautés rurales zaïroises a pu identifier 110 individus vivants et 24 individus décédés affectés par le konzo, sur un total de 6764 habitants (16/1000). Les signes cliniques sont identiques à ceux des études précédentes et il a été décidé de nommer la maladie konzo d'après le premier rapport connu, provenant du Zaïre. L'incidence annuelle et mensuelle fut associée à la mono-consommation de racines de manioc insuffisamment traitées. L'apparition du konzo coïncida avec l'achèvement d'une route goudronnée assurant la liaison avec la capitale. Ceci amena le manioc à devenir la principale culture commerciale, et induisit l'adoption d'une méthode abrégée de traitement du manioc.

Une expérience de traitement du manioc confirma le fait que le manioc traité selon la méthode abrégée contenait une quantité importante de cyanohydrines. La teneur élevée en cyanure du régime alimentaire des populations affectées fut confirmée par des concentrations urinaires importantes de thyocyanate, le principal métabolite de détoxication. De même, une faible concentration urinaire de sulfate indiqua une carence alimentaire en acides aminées souffrées, le substrat de détoxication. Trois patients souffrant du konzo, examinés lors du début de leur maladie, avaient des concentrations sanguines de cyanure supérieures à 4 µmole/L, ce qui n'était le cas que chez 2 des 23 cas-témoins (p<0.01), ce qui supporte l'hypothèse du rôle étiologique du cyanure. Une analyse à régression logistique à multivariable d'une étude cas-témoins, menée dans une autre partie du Zaïre, donna un risque relatif égal à 11.0 pour la méthode abrégée de traitement du manioc, indiquant un risque plus important pour les consommateurs fréquents. Des études sérologiques purent exclure l'hypothèse d'une étiologie rétrovirale du konzo. Finalement, des cas de konzo furent identifiés en faible prévalence en République Centrafricaine, ceux-là aussi associés à la consommation de manioc insuffisamment traité. Une investigation menée en Suède, portant sur deux patients tanzaniens sévèrement handicapés, a donné des images par résonance magnétique nucléaire normales, mais une analyse neurophysiologique a pu montrer une dysfonction isolée des motoneurones supérieurs. Ceci est bien en corrélation avec les données cliniques et identifie le konzo comme une entité clinique. L'évidence du rôle étiologique d'un régime alimentaire riche en cyanure et pauvre en acides aminés souffrés dans le développement du konzo est suffisamment forte pour exhorrer la prévention par la promotion d'un traitement efficace du manioc.
INTRODUCTION

In the last century, medical science has successfully revealed the causation of several neurological disorders that have occurred in localized epidemics or in endemic foci. Diseases such as beri-beri, pellagra, kuru and polio have thereby already been, or are being, eradicated (Cruickshank 1976, Gajdusek 1977, Paul 1971, Robertson et al. 1990, Victor 1984). The success has been achieved by a combination of epidemiological, clinical and molecular studies. The distinct variations in disease occurrence over time and space, as well as variations in age groups and between the sexes have facilitated both the hypothesis generation and the testing in epidemiological studies. High prevalence in geographical foci has enabled local populations to contribute with their own ideas in the investigations and in the terminology.

Beri-beri, the Singhalese word for “I cannot”, is used as name for the clinical syndrome resulting from thiamine deficiency. The main symptoms are cardiac insufficiency, peripheral polyneuropathy and edema tendency. In the latter part of the last century, epidemics of beri-beri resulted in southern Asia from the introduction of steam-powered rice mills providing polished rice with a low thiamine content.

Pellagra, named after the Italian word for “rough skin”, is caused by niacin deficiency with the classical triad of “diarrhea, dermatitis and dementia”. The early accounts of the disease are from Spain and Italy. Epidemics still occurred in the United States in the beginning of this century, in populations eating a monotonous maize diet with low niacin content (Terris 1964).

There are, however, still a number of obscure neurological disorders occurring in localized epidemics or in endemic foci in tropical countries. Most of these syndromes consist of various combinations of peripheral polyneuropathy and signs of spinal cord involvement. The term “tropical myeloneuropathies” has been used to group these disorders of unknown etiology (Román et al. 1985). To reduce the confused nosology and clinical terminology of tropical myeloneuropathies, Román distinguishes two clinical groups which he calls: tropical ataxic neuropathy (TAN), with prominent sensory ataxia, and tropical spastic paraparesis (TSP), with predominantly spastic paraplegia with minimal sensory deficit.

SYNDROMES OF ATAXIC POLYNEUROPATHY

The first extensive report of an epidemic ataxic polyneuropathy was published by Strachan (Strachan 1888, 1897). He reported 510 cases of
“a form of multiple neuritis prevalent in the West Indies”. The main symptoms were severe burning pain of the soles of the feet, dimness of vision, ataxia and increased pigmentation of the skin. In 1918 Scott reported an outbreak of polyneuropathy on a sugar estate in Jamaica (Scott 1918). The symptoms were numbness, tingling and burning of the feet and in a few days the patients were unable to stand due to loss of co-ordination. These reports led to the recognition of a tropical neurologic syndrome characterized by painful polyneuropathy, orogenital dermatitis and amblyopia, known as Strachan’s syndrome (Victor 1984). It was linked with malnutrition and reported also from Africa (Stannus 1936). During the Second World War, prisoners of war in tropical and subtropical regions suffered from similar syndromes with “burning feet”, numbness and loss of vision with pallor of the temporal border of the optic disks. Spastic paraplegia was also seen (Fisher 1955) in these highly variable conditions. Since the Second World War, ataxic polyneuropathies have been reported from many tropical and subtropical areas (Román et al. 1985). Up to the 1960s, deficiencies in B-group vitamins have been thought to be a major cause of ataxic neuropathies in the tropics and it was shown that a majority of the patients improves on vitamin B complex treatment (Collomb et al. 1967).

In the 1930’s, Moore described, in an institution in Nigeria, a syndrome of visual loss, sore tongue, stomatitis and eczema of the scrotum in adolescent boys (Moore 1930, 1937a, 1937b). Their cassava-based diet was suggested to be the cause, as the students improved during holidays. The cyanide-yielding capacity of bitter cassava and its toxic effects were described at that time (Clark 1936). This syndrome of painful polyneuropathy, ataxia and blurred vision has been subjected to extensive studies in Nigeria by Osuntokun (1981). The diagnostic criteria used for this tropical ataxic neuropathy (TAN) were the presence of two of the following four (Osuntokun 1968): myelopathy, bilateral optic atrophy, bilateral sensorineural deafness, and symmetrical peripheral polyneuropathy. Men and women were equally affected, with a peak incidence in the fifth and sixth decades of life. The prevalence in certain areas of Nigeria ranged from 1.8 to 2.6% in the general population (Money 1958, Osuntokun 1971). When discussing the neurological syndromes resembling Nigerian ataxic neuropathy described from different parts of the world, Osuntokun (1973) pointed out that it is unlikely that the same specific etiological factor is involved in all places. In Nigeria, TAN was associated with cyanide intake from cassava, as will be presented later (Osuntokun 1981).
SYNDROMES OF SPASTIC PARAPARESIS

The second clinical group of tropical myeloneuropathies proposed by Román (1985) is comprised of syndromes with spastic paraparesis as the main feature. Besides paraparesis as a sequel of poliomyelitis, leprosy or extrinsic cord compression due to trauma or tuberculosis, several syndromes with spastic paraparesis have been reported in epidemics or endemic foci throughout the world.

The classic form of locally occurring spastic paraparesis, mentioned already by Hippocrate, is lathyrisn (Acton 1922), caused by excessive consumption of grass pea, *Lathyrus sativus* (Spencer et al. 1986). The clinical picture is an acute or sub-acute onset of an isolated spastic paraparesis, with increased muscle tone, brisk reflexes, extensor plantar responses and no sensory signs. It has been known since ancient times and has occurred in Europe (Gardner & Sakiewicz 1963) and North Africa but is today only known as a public health problem in Bangladesh, India (Dwivedi & Prasad 1964) and Ethiopia (Haimanot et al. 1990). An excitotoxic amino acid in the grass pea, beta-N-oxalylamino-L-alanine (BOAA) is held responsible for the disease (Spencer et al. 1986).

A second form of spastic paraparesis, called tropical spastic paraparesis, has been found in geographical isolates in different parts of the world (Román et al. 1985). Up to the mid-1980s it too was thought to be a neurotoxic disease. It was therefore a major breakthrough in neuroscience when human T-lymphotropic virus type I (HTLV–I) was identified as a causative factor of this chronic, progressive myelopathy (Gessain et al. 1985). This condition is now defined as a paraparesis or a paraplegia with gradual onset and varying degrees of sensory loss, where amyotrophic lateral sclerosis, spinal cord compression, and multiple sclerosis have been excluded (Gessain & Gout 1992). It is now called HTLV-I associated myelopathy (HAM) or sometimes still tropical spastic paraparesis (TSP) or both together, HAM/TSP (WHO 1989). HTLV-I is a retrovirus and this myeloencephalopathy demonstrates some similarities to the HIV-induced encephalopathy, although HAM shows a peculiar predilection for the motor system. Recently, HTLV-II has been demonstrated to cause similar neurological disorders (Harrington et al. 1993, Jacobson et al. 1993).

The discovery of the association of HTLV-I and the chronic progressive myelopathy was initially made by Dr Gessain when investigating HTLV-I and blood malignancies in a hospital in the French West Indies and because neurological patients were used as controls. None of the cases – but 2 of the controls – were HTLV-I positive, both with spastic paraparesis, which enabled Guy de Thé’s group to identify the association. Their later case report on a man who developed HAM
within a year of being infected by HTLV-I during a successful cardiac transplantation, established the causal relationship (Gout et al. 1990). The huge infective dose and the drug-induced immunosuppression are thought to have increased the speed of progress in this case. HAM has been reported in high HTLV-I endemic areas throughout the world and sporadic cases have also been described in non-endemic HTLV-I areas such as the United States and Europe, mainly among immigrants from HTLV-I endemic areas (Blattner 1989, Gessain & Gout 1992, Montgomery 1993).

A third form of spastic paraparesis with abrupt onset has been reported in epidemic outbreaks in Africa. Clinically and epidemiologically it is similar to lathyrism but without any association with consumption of Lathyrus. This disease is now called konzo and is the subject of this thesis.

THE DISCOVERY OF KONZO

To the best of my knowledge, konzo was first described in 1938 by the Italian doctor Trolli, head of the Belgian medical support to Belgian Congo in a report called: “Résumé des observations réunies, au Kwango, au sujet de deux affections d’origine indéterminée. 1) Paralplégie spastique épidémique, ‘konzo’ des indigènes du Kwango 2) Syndrome edématieux, cutané et dyschromique” (Trolli 1938). The report describes two disorders of unknown etiology. He was not the first to describe the dyschromic syndrome with cutaneous edema that today is known as kwashiorkor, named after the local designation in Ghana meaning “disease of the weanling” (Williams 1933).

Trolli’s extensive description of konzo was based on reports from seven district medical officers working in southern Bandundu region. Dr Tessitori was the first to recognize the disease in Kahemba in 1936 (figure 6). A large epidemic occurred in 1936-37 with more than 1,000 cases but earlier outbreaks in 1928 and in 1932 with a total of 140 affected persons were also reported. In two of the affected areas, Kahemba and Feshi, old cases with onset 30-50 years back were reported by Trolli and konzo was said to be endemic with epidemic outbreaks. The etiology was believed by most of the doctors to be of infectious origin, but Dr Georgiades points out the clinical similarities to lathyrism that was known to be a toxico-nutritional disease. He was also the first to suggest that konzo might be an intoxication of cyanide from insufficiently processed cassava.

The second description of konzo is also from Bandundu region, by Lucasse 14 years later (Lucasse 1952). All the cases described had had their onset during the epidemic of 1936-37. After 30 years without any known reports a team from CEPLANUT, the Zairian national
The causation of konzo

nutritional planning centre, headed by Dr Kabamba (CEPLANUT 1982) reported several hundreds of cases of spastic paraparesis in central Bandundu. This outbreak starting in 1978 was reported in the Weekly Epidemiological Records as a “peripheral neuropathy” (WHO 1982).

In 1983, an outbreak of konzo occurred further north in Bulungu zone, between Djuma and Vanga hospitals. About 200 cases were reported and Dr Kasela, the sub-regional medical officer, examined 111 cases and reported (Kasela 1983): "The disease, described in 1938 in Kwango has not varied in its symptomatology, ... I had the sad privilege to recognize the disease, through clinical signs, that I earlier had fought in the Masi-Manimba zone: the famous Kwango spastic paraparesis". The disease was completely new to both the medical staff and the population in Bulungu zone and Dr Kasela was the only one to recognize it, as he had prior knowledge of the disease.

In 1981 an outbreak of more than 1,000 cases of a spastic paraparesis occurred in an area in northern Mozambique, formerly unknown in the area. When Dr Julie Cliff, Dr Hans Rosling and others investigated the new disease they were unaware of the reports from Zaire and the disease was not formerly reported from Mozambique. The studies in Mozambique attributed the disease to a high dietary cyanide intake from insufficiently processed cassava roots, independently of former studies (Ministry of Health Mozambique 1984a, Ministry of Health Mozambique 1984b, Cliff et al. 1985).

In 1986 a Zairo-Belgian team of neurologists, headed by Dr Carton and Dr Kazadi published a detailed clinical investigation of 20 konzo cases in southern and central Bandundu region in Zaire (Carton et al. 1986). They concluded that the disease was identical to the one described by Trolli and the one reported from Mozambique. They refuted the toxico-nutritional etiology suggested in the studies from Mozambique and advanced an infectious etiology, also suggested by (Trolli 1938). Observations of familiar clustering and “events of transmission” were the main arguments in favor of an infectious etiology.

At the beginning of the present studies there were thus two conflicting hypotheses on the etiology of konzo. The toxico-nutritional hypothesis relates to cassava and its potential toxicity that will be presented briefly in the following.
CASSAVA - THE WONDER CROP

Konzo is a paralytic disease unknown to most medical scientists and therefore "exotic". It is associated with cassava, a strictly tropical crop that also is perceived as "exotic" by some readers, although it is a daily staple food for 400 millions (FAO 1990). Some fast readers might conclude that cassava should not be eaten. To avoid such an erroneous conclusion a presentation of the virtues of cassava is pertinent.

Cassava (Manihot esculenta), is a 2-4 meter high tropical shrub (figure 1). It is also known as "manioc" in American English and French, "mandioca" in Portugese and "yuca" in Spanish. The starch from cassava is often called tapioca. It is widely grown throughout the tropical parts of Latin America, Africa, Asia and Oceania (Carter et al. 1992). It ranks fourth on the list of major food crops in developing countries after rice, wheat and maize. In sub-Saharan Africa, cassava is cultivated mainly by small-scale farmers. Zaire is the country with the highest per capita consumption of cassava in the world, about 60% of total daily energy intake is provided by this crop (FAO 1990).

Cassava was introduced into Africa by Portuguese traders and it was cultivated by Portuguese settlers as early as 1558 in the area around the mouth of the Zaire River. Two-hundred and fifty years later it was successfully incorporated into many farming systems in Central Africa (Carter et al. 1992).

Cassava has been widely adopted by African peasants due to its numerous agricultural advantages (table 1). As all root crops, potential yields per area are higher than those of cereals. The introduction and importance of cassava in Africa have many parallels to the role of potatoes in Europe. Both were introduced from Latin America in the 16th to 18th centuries and they were both adopted largely due to their high yields.

Figure 1. The cassava plant.
Cassava has a potential yield of 75 tons per hectare (Okigbo 1980), which is equal to 25 tons per hectare of dry weight matter, roughly twice as much as for wheat. In different terms, yields can be 250,000 kilo-calories/ha/day.

In many areas of Africa where cassava is the most important staple, e.g. Central Africa and parts of Nigeria, the attitude to cassava is very positive and cassava forms part of the culture. This can be illustrated by a recent poem praising the virtues of cassava, see box. This is in sharp contrast to many expatriates’ negative attitudes towards cassava. In East Africa the attitude to cassava is often negative, cassava is seen as “poor man’s food”, only eaten when there is nothing else to eat.

Table 1. Advantages of cassava.

<table>
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<tr>
<td>The most efficient converter of solar energy into dietary carbohydrates</td>
</tr>
<tr>
<td>Higher yields per area and hour than cereals under similar conditions</td>
</tr>
<tr>
<td>Grows on poor soils where no other staple can be cultivated</td>
</tr>
<tr>
<td>No critical planting or harvest time</td>
</tr>
<tr>
<td>Non-edible stem cuttings are used for planting</td>
</tr>
<tr>
<td>Weeding is only necessary in the first year.</td>
</tr>
<tr>
<td>Drought tolerant</td>
</tr>
<tr>
<td>Stored on root → minimal storage losses, harvested when required</td>
</tr>
<tr>
<td>Roots in the ground → not easily destroyed in warfare</td>
</tr>
<tr>
<td>Perennial → possible to compensate for one bad agricultural year</td>
</tr>
<tr>
<td>Contains cyanogens → pest resistant</td>
</tr>
<tr>
<td>→ keeps away both animals and humans</td>
</tr>
</tbody>
</table>


CASSAVA CYANOGENSES

About 2,000 species of higher plants are equipped with defence substances, which can liberate hydrogen cyanide (HCN), a phenomenon called cyanogenesis (Montgomery 1980). The structure of these cyanogenic substances has been identified in about 300 species and they are all glycosides. At least 75 cyanogenic glycosides are known and the most common are amygdalin, found in bitter almonds and other fruit kernels; dhurrin, found in sorghum and other grasses; and linamarin and lotaustralin, found in cassava, linseed and various other plants. Bamboo shoots and cassava are the food plants with the highest recorded...
content of cyanogenic glucosides.

The formulas for the two cyanogenic glucosides in cassava, linamarin and lotaustralin are shown in figure 2. The former constitutes up to 90-95% of the total amount. Cassava also produces an enzyme, linamarase, that is capable of breaking down these cyanogenic glucosides. It is stored in a separate compartment of the plant cells. When the structure integrity of the cells is destroyed the enzyme is brought in contact with the glucosides, resulting in rapid formation of the corresponding cyanohydrins. In a second reaction, cyanohydrins yield hydrogen cyanide (Halkier et al. 1988). The hydrogen cyanide, once produced, will dissolve in water or evaporate into the air (O'Brien et al. 1992). The glucosides, cyanohydrins and hydrogen cyanide are collectively known as cyanogens.

<table>
<thead>
<tr>
<th>Cassava Song</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flora Nwapa, Nigeria</td>
</tr>
<tr>
<td>We thank the almighty God,</td>
</tr>
<tr>
<td>For giving us cassava.</td>
</tr>
<tr>
<td>We hail thee, cassava</td>
</tr>
<tr>
<td>The great cassava.</td>
</tr>
<tr>
<td>You grow in poor soils</td>
</tr>
<tr>
<td>You grow in rich soils</td>
</tr>
<tr>
<td>You grow in gardens,</td>
</tr>
<tr>
<td>You grow in farms.</td>
</tr>
<tr>
<td>You are easy to grow</td>
</tr>
<tr>
<td>Children can plant you</td>
</tr>
<tr>
<td>Women can plant you</td>
</tr>
<tr>
<td>Everybody can plant you.</td>
</tr>
<tr>
<td>We must sing for you</td>
</tr>
<tr>
<td>Great cassava, we must sing</td>
</tr>
<tr>
<td>We must not forget</td>
</tr>
<tr>
<td>Thee, the great one.</td>
</tr>
<tr>
<td>As children, you fed us</td>
</tr>
<tr>
<td>You were like a mother</td>
</tr>
<tr>
<td>You fed us fat</td>
</tr>
<tr>
<td>But we easily forget</td>
</tr>
</tbody>
</table>

The level of cyanogenic glucosides is controlled by the genetic characteristics of each cassava variety and several environmental factors such as soil, humidity, rainfall, degree of shading and type of fertiliser used (de Bruijn 1973). The concentration of glucosides correlates to the
taste of the fresh roots. It is higher in the bitter varieties of cassava than in the sweet varieties (Sundareshan et al. 1987, Bokanga 1993). However, a variety that is sweet if grown in one area may become bitter in another (Pereira et al. 1981).

Figure 2. The transformation of linamarin into cyanohydrin and hydrogen cyanide. Linamarin constitutes 90% of the cyanogenic glucosides in cassava and the remainder is lotaustral, which has an additional methyl group on the carbon with asterisk.

Fresh cassava roots deteriorate within 3-4 days after harvest if they are left unprocessed and transport of fresh cassava is therefore both difficult and expensive. Roots from bitter varieties contain levels of cyanogenic glucosides that must be removed before consumption. Thus, the main reasons for processing cassava are to increase shelf-life, to facilitate transport and to remove cyanogens (Hahn 1989).

Many types of processing methods are used for bitter cassava in Africa. Most methods are based on one of the following steps: soaking in water, moist fermentation of grated fresh roots or sun-drying of fresh roots. In Central Africa the cassava processing is based on soaking, usually in a small stream close to the fields or the village.

**METABOLISM OF CYANIDE IN MAN**

The cyanide ion (CN⁻) is made up of two of the most common atoms in organic matter that are joined by a triple bond. It may seem surprising that this simple ion is one of the compounds most toxic to man. Hydrogen cyanide (HCN) is a colorless liquid that boils at 25.7°C. Cyanide was discovered by the Swedish chemist Scheele in 1782 (Scheele 1782). It smells like bitter almond. Two mmol is lethal if inhaled. The cyanide ion is reactive and readily forms complexes with metal ions – which is the basis for its toxicity.

Humans may be exposed to cyanide from consumption of cyanogenic plants, from fire when nitrogen-containing materials are burning, and from tobacco smoke. Occupational exposure to cyanide may occur either from alkyl-cyanides used as solvents or from cyanide
Thorkild Tylleskær

salts used industrially for metal cleaning and polishing. Some drugs are also cyanogenic, the most widely known being the intravenous anti-hypertensive drug sodium nitroprusside, consisting of 44% cyanide. Studies on the pharmacokinetics of this drug and its cyanide metabolites have expanded our knowledge of cyanide detoxification in humans (Schulz 1984)

\[
\begin{align*}
R-S^- & \leftrightarrow R-S-S^- \\
\text{Enz-S-S^-} & \text{Enz-S^-} \\
CN^- & \rightarrow SCN^- \\
\end{align*}
\]

Figure 3. The conversion of cyanide to thiosulfate. Rhodanese is the catalysing enzyme and a sulphane sulphur donor is needed. R can be a number of different radicals being carriers of sulphane sulphur.

The human body has a two-fold defence against cyanide, an immediate trapping of cyanide and a subsequent enzymatic detoxification. Cyanide that enters into the blood stream, from either the lung or the upper gastro-intestinal tract, is trapped by the methemoglobin fraction that normally constitutes less than 1% of all hemoglobin in the red blood cells. The cyanide is reversibly bound as cyanomethemoglobin and is passively released and detoxified. The most important detoxification mechanism is the conversion of cyanide to thiocyanate (figure 3), catalysed by the enzyme rhodanese, also called thiosulphate sulphur transferase (EC 2.8.1.1). It was crystallized by Sörbo in 1953 (Sörbo 1953). The conversion can similarly be catalysed by mercaptoppyruvate sulphurtransferase (EC 2.8.1.2) (Sörbo 1975). The endogenous maximum detoxification rate of hydrogen cyanide in well-nourished humans has been estimated to be about 1 μg (0.04 μmol)/kg and minute (Schulz et al. 1982). This corresponds to 3-4 mmol/24 h, which is a lethal dose in an adult. Continuous cyanide exposures, such as nitroprusside infusion, that does not exceed the maximum cyanide conversion rate, will result in blood cyanide levels less than 4 μmol/l (accumulation level) (Schulz et al. 1982). For the enzymatic cyanide to thiocyanate conversion a sulphane sulphur substrate is needed. sulphane sulphur is a divalent sulphur (-S-) covalently bonded only to other sulphur atoms. The sulphur donor is the rate-limiting factor for cyanide to thiocyanate conversion. An infusion of thiosulphate will increase the conversion rate several-fold. The principal dietary source of sulphur is the sulphur containing amino
acids, cysteine and methionine (Bingham 1977). Cyanide is also converted into other metabolites but they are quantitatively of minor importance. It can form cyanate or cyanohydrin, or react with cysteine in proteins to form 2-aminothiazoline-4-carboxylic acid (Osuntokun 1973), or with hydroxycobalamine (vitamin B₁₂).

Acute cyanide intoxication occurs when exposure rates are greater than the conversion rate and cyanide saturates the methemoglobin pool. Cyanide then rapidly accumulates in plasma (Lundquist et al. 1985) and attacks target organs, such as the brain. The cyanide ion readily forms complexes with metal ions, a “metal poison”, and can react with the prosthetic group of any metalloenzyme (Lindahl et al. 1993). The fatal toxicity of cyanide is believed to cause energy failure in the cell by inhibiting of the two heme groups, α and α₃, of the cytochrome c oxidase, the terminal enzyme (complex IV) of the mitochondrial electron transport chain which blocks the oxidative phosphorylation (Nicholls 1983, Palmer 1993, Pettersen & Cohen 1993). The central nervous system is considered particularly sensitive to cyanide because of its limited anaerobic metabolism, low energy reserves and high energy demands and high respiratory rate. Cyanide seems to act directly on the neuronal energy metabolism (Isom & Way 1976). The main clinical symptoms and signs of acute sub-lethal doses of cyanide are light-headedness, headache, drowsiness, dizziness, tremor and coma. Acute inhalation of 2 mmol (50 mg) HCN can be lethal. Ingestion of 200 mg NaCN or 300 mg KCN can be lethal, which on a molar basis is twice as much as when inhaled. Lethal blood levels of cyanide in man are estimated to be 180 µmol/l in whole blood and 20-30 µmol/l in plasma.

Specific antidotal treatments include direct chelation or indirect binding of cyanide, enhanced conversion as well as antagonizing systemic effects (Hall & Rumack 1986, Kulling 1992). Direct cyanide chelation therapy, i.e. dicobalt EDTA, is associated with frequent side effects, especially in patients without actual cyanide poisoning. Hydroxycobalamine (vitamin B₁₂) is another direct chelator, non-toxic but expensive. The classical treatment of cyanide intoxication is indirect binding of cyanide, by increasing the pool of methemoglobin up to 25% with sodium nitrite or DMAP (4-Dimethylaminophenol). The problem is that too much methemoglobin will impede oxygen transport, which might be dangerous (Hall et al. 1981). Enhanced conversion of cyanide to thiocyanate can be achieved by administering sodium thiosulphate (NaS₂O₃), a non-toxic sulphane sulphur donor. The cyanide antidotes with low intrinsic toxicity, sodium thiosulphate and hydroxycobalamin, are warranted in situations where cyanide intoxication is suspected but not yet verified (Kulling 1992).

The main cyanide detoxification product, 60-100% in well-nourished humans, is thiocyanate (SCN⁻) (Baumann et al. 1933, Smith &
Malcolm 1930), with low toxicity. Thiocyanate is a pseudo-halide which is processed as chloride by the kidney. It is rapidly filtered by the glomerulus and efficiently reabsorbed by the tubule. The elimination half-life of thiocyanate was estimated to be 2.7 days in healthy subjects at physiological levels (Schulz 1984). At serum concentrations above 250-450 μmol/l, thiocyanate is rapidly excreted into the urine as the reabsorption in tubuli becomes saturated. In the thyroid gland it interferes with iodine transport and metabolism. Toxic symptoms such as bone marrow depression, hypothyroidism, fatigue, anorexia and nausea occur at serum levels above 1,300 μmol/l. Some foods, such as cabbage, milk and cheese are known to contain thiocyanate, which can increase serum levels. As tobacco smoking result in cyanide exposure, serum and urine thiocyanate levels have been extensively used to assess smoking (Hauth et al. 1984, Foss & Lund-Larsen 1986, Pré & Vassy 1991).

Per Lundquist and colleagues at the Department of Clinical Chemistry at Linköping University have developed a number of methods for the determination of cyanide and its metabolites and of sulphur metabolites, also useful in samples from field surveys (Lundquist et al. 1979, 1980, 1983, 1985, 1987). He has also made an extensive review of cyanide metabolism in his thesis (Lundquist 1992).

THE CYANIDE HYPOTHESIS FOR KONZO

The hypothesis that konzo is caused by high cyanide exposure from exclusive consumption of insufficiently processed cassava, was already suggested in the first report (Trolli 1938). The studies of konzo in Mozambique advocated this hypothesis and suggested that a low sulphur intake, decreasing cyanide to thiocyanate conversion, enhanced cyanide exposure (Cliff et al. 1985). Objections have been raised against a cyanide etiology. One is that no similar damage to the nervous system has been documented following exposure to cyanide from sources other than cassava. A second argument, forwarded by Carton et al. (1986) is that konzo was not associated with drought, food shortage or ineffective cassava processing in Zaire. Third, the serum thiocyanate was equally high in both cases and controls, which also questions a causal relationship (Lancet 1984). Fourth, a clinically different neurological syndrome, tropical atactic neuropathy, has also been linked to cyanide exposure from cassava.
AIMS OF THE PRESENT STUDIES

The aims of the present studies were to define konzo as a disease entity, to test the cyanide hypothesis and to elucidate underlying social causes.

The specific objectives were:

- to ascertain whether if the geographical, temporal and social distributions of konzo in a high prevalence area of Bandundu region, Zaire, are associated with high consumption of inadequately processed bitter cassava (paper I).

- to measure cyanogen levels in flour from short-soaked cassava, the intakes of cyanide and sulphur in konzo-affected and unaffected populations and to assess blood cyanide at onset of konzo as well as in control subjects in Bandundu region, Zaire (paper II).

- to assess in a case-referent study the association between insufficient cassava processing and konzo in individuals, taking a number of potential confounders into account (paper III).

- to investigate the possible association between konzo and retroviral infection (paper VI).

- to determine the site and character of the lesion in the nervous system in konzo (paper V).

- to establish whether if konzo occurs in the Central African Republic and if it is associated with dietary cyanide exposure from short-cuts in cassava processing (paper VI).
MATERIAL & METHODS

Four of the present studies (I-IV) are based on data from two field surveys in Zaire in 1988 and 1990. Study V is based on findings from investigations in 2 konzo patients from Tanzania who were invited to Uppsala in 1991 for detailed neurological investigations in a well-equipped university hospital. The last study was made in the Central African Republic in 1992. Table 2 presents a summary of the study areas, the principal methods used for data collection and where the results are published. The geographical locations of the different studies are shown in figure 4.

Table 2. Overview of study areas and investigations in the different papers.

<table>
<thead>
<tr>
<th>Country</th>
<th>Zaire</th>
<th>Zaire</th>
<th>Tanzania</th>
<th>Central African Republic</th>
</tr>
</thead>
<tbody>
<tr>
<td>District</td>
<td>Masi-Manimba</td>
<td>Pay-Kongila</td>
<td>Tarime</td>
<td>Nana-Mambéré</td>
</tr>
<tr>
<td>Survey of incident konzo cases (= at onset)</td>
<td>II, IV</td>
<td>II, IV</td>
<td>V</td>
<td>VI</td>
</tr>
<tr>
<td>Dietary investigations</td>
<td>II, III, V, VI</td>
<td>II, III, V, VI</td>
<td>II, IV, V, VI</td>
<td>II, IV, V, VI</td>
</tr>
<tr>
<td>Biomarkers of cyanide exposure</td>
<td>II, III, V, VI</td>
<td>II, III, V, VI</td>
<td>II, IV, V, VI</td>
<td>II, IV, V, VI</td>
</tr>
<tr>
<td>Cassava processing experiments</td>
<td>II, IV</td>
<td>II, IV</td>
<td>V</td>
<td>VI</td>
</tr>
<tr>
<td>Retrovirus investigations</td>
<td>II, IV</td>
<td>II, IV</td>
<td>V</td>
<td>VI</td>
</tr>
<tr>
<td>Advanced neurological investigations</td>
<td></td>
<td></td>
<td>V</td>
<td></td>
</tr>
</tbody>
</table>

* reported by Banea et al. 1992a
** reported by Howlett et al. 1992
The causation of konzo

Figure 4. Reported occurrence of konzo in Africa with year of first known outbreak. The present studies are indicated.

Survey of prevalent konzo cases (papers I, VI)

The same survey methodology was used in all areas studied in Zaire and the Central African Republic (papers I, VI). The community survey of konzo in the second area in Zaire and the one in Tanzania are not part of this thesis (Banea et al. 1992a, Howlett et al. 1992).

To find and identify the konzo cases a community-based survey of the population in a geographically well-defined area was done. With informed consent and assistance from village leaders, a demographic census was performed in all villages in each area. The inhabitants were registered according to ethnic affiliation, sex, and age group (children
<15 years, adults ≥15 years). In paper I a total population of 6,764 were registered and in paper VI a total of 4,500. The screening for konzo was done by examining all persons with locomotor disabilities identified by village leaders and local health staff. The following criteria for konzo were applied:

1. a visible symmetrically spastic abnormality of gait when walking or running;
2. a history of onset in less than one week followed by a non-progressive course in a formerly healthy person;
3. bilaterally exaggerated knee or ankle jerks without signs of disease of the spine.

In none of the areas was *Lathyrus sativus* consumed, thus excluding the possibility of finding cases of lathyrism meeting the above criteria. Those fulfilling the criteria were interviewed in the local language according to a standardized questionnaire regarding the time of onset and the diet at onset. Information on year of onset was cross-checked with date of birth certificates available for neighboring children born around the onset. Month of onset was determined by using a local events calendar. Konzo-affected persons who had died were traced and characterized through interviews with village leaders, neighbors, and relatives. Consistent information on onset, course and gait abnormality was required to establish the diagnosis of konzo.

Ethical clearance was obtained from the ministries of health concerned. These ministries also took an active part in the surveys. The aims and the methods of the study were clearly stated at public meetings in each of the villages before the field work commenced. Informed consent was obtained from each family involved. Health care and transport for sick persons were also provided during the study.

**Study of incident konzo cases (paper II)**

To study the association between the combined effect of high cyanide and low sulphur intake and konzo it was necessary to measure blood cyanide at the abrupt onset of the disease. Since no konzo patients were present at hospitals at the time of the studies, it was necessary to actively seek cases at onset or within the first days thereafter. This was done by asking the population through village leaders and churches to bring suspected new konzo patients for immediate examination during the period while the survey team was living in the villages. There was no epidemic during the surveys and despite considerable effort, only 3 patients were identified. They were interviewed, examined and had blood specimens collected 18–90 hours of onset. They were immediately treated with one week of cassava-free and protein-rich food and vitamin B complex. The patient identified in 1990 was also treated with intravenous thiosulphate, an innocuous cyanide antidote.
Dietary investigations (papers I, II, III)

The diet and the traditional cassava processing as well as possible occurrence of short-cuts were studied by the qualitative methods, i.e. focus group interviews and participant observations. Quantitative aspects of the diet were studied through dietary interviews. In papers I and II diet was assessed by 24-hour recalls and in paper III by food frequency interviews.

Focus group interviews (Dawson et al. 1992, Khan & Manderson 1992) with about six adult participants of mixed ages were performed in each village. The participants were selected by the local health staff at an announced information meeting in each village. Village leaders and others in positions of power were not included in the groups. The 2-3 hour discussions were held in privacy, gently guided by a well-trained national nutritionist and a translator. A set of open questions was introduced about the village, seasonal and annual variations in agriculture, cassava processing, cassava marketing, diet and konzo, a well-known disease in the affected areas in Zaire. As almost all food crops, especially cassava, are cultivated by women in the study areas, mainly women were selected in the groups. One or two men were included in each group since pilot activities showed that this resulted in more open discussions.

Participant observations (Scrimshaw & Gleason 1992) on general life conditions, agriculture, cassava cultivation, processing and marketing were also made. The survey team lived in the villages, in a health center, a school or ordinary dwellings. During these periods we participated in common events, such as hunting by bush fire and cassava processing. This gave an understanding of the people and valuable opportunities to check the consistency between word and deed.

Twenty-four hour recalls (Cameron & Van Staveren 1988) were performed in 40 randomly selected households in the affected villages and among all 167 first-form schoolchildren in the unaffected villages (I, II).

A food-frequency questionnaire (Cameron & Van Staveren 1988) was used in a case-referent study, also called case-control study (III). It was carried out in five of the most konzo-affected savanna villages and to control for age, sex and other possible confounding “neighborhood factors” a matched study design was used. For each of the 57 cases a referent, matched for sex, age at onset and village at onset was randomly selected from the population census. The focus-group interview data permitted the identification of the key questions to be addressed and the adaptation of a structured questionnaire for the individual interviews.

The study subjects, their parents, or other close relatives caring for
the patients were interviewed according to a structured questionnaire with a local interpreter in the privacy of their homes. The questionnaire covered social structure, household economy and socio-economic difficulties, cassava processing and a food-frequency questionnaire relating to the entire household. Food-frequencies were registered as daily, weekly, monthly or never during the current dry season, corresponding to the last 3 months. For the cases this dietary information was collected both for the current dry season and the situation as it was during the 3 months preceding the onset of the disease.

In a matched bivariate analysis, odds ratios and 95% confidence limits were calculated for the different variables. A selection of variables was then included in multivariate logistic regression models using the conditional maximum likelihood method (Breslow & Day 1980) with EGRET statistical package for PC (Statistics and Epidemiology Research Corporation, Seattle, USA). The analysis was done both by comparing cases at onset with referents at interview and comparing cases at interview with referents at interview.

**Biomarkers of cyanide exposure (papers II, V, VI)**

Collection of blood and urine samples under field conditions poses ethical and logistical problems. Informed consent both on community level and family level preceded collection of all samples. Venous blood samples were obtained with Vacutainer® equipment. For serum separation we used an ordinary laboratory swing-out centrifuge connected to a portable electric generator. In 1988, the samples were frozen in a kerosene-freezer. In the subsequent surveys all samples were frozen in cryovials in liquid nitrogen in a 35 liter cryovessel which is a flexible and reliable way to obtain long-lasting freezing capacity in rural surveys.

The sample collection was carried out in the same households as the dietary interviews. All eligible members of the interviewed households were then asked to contribute a morning urine specimen during a sample collection session. The adult household members were further asked to contribute a blood sample. The contact established during interviews permitted us to explain the need for the sample collection and we thereby got almost all eligible persons to participate.

Determination of cyanide in blood was done in three konzo cases at onset and 23 randomly selected controls (II) with a method enabling transport of frozen specimens (Lundquist et al. 1985). Thiocyanate, the main end product of cyanide metabolism, was determined in urine and serum as a biomarker for cyanide intake (Lundquist et al. 1983). Urinary inorganic sulphate, the main end product of sulphur metabolism, was determined (Lundquist et al. 1980) as biomarker of
dietary intake of sulphur amino acids (Sabry et al. 1965).

**Cassava processing experiments (paper II)**

On the basis of the information from the focus group interviews and participant observations on traditional and short-cut cassava processing, a controlled processing experiment was designed in an affected village. Cassava flours were prepared by local women using their own utensils and soaking ponds. Two roots were harvested from each of 20 plants of the most bitter cassava variety grown. The first set of 20 roots was processed traditionally: soaked for 70 h, peeled, pounded into a mash, squeezed by hand into balls, sun-dried for 2 days and finally pounded into flour. The second set of 20 roots was processed according to the short-cut method used since the mid-1970s when konzo first occurred: peeled, soaked for 30 h and sun-dried as whole roots for 4 days. Each of the dried roots was divided longitudinally and one-half was immediately pounded into flour, while the other half was kept at ambient temperature for one month before milling, as done in urban areas. Flour specimens were immediately collected after pounding, sealed in double polyethene plastic bags and frozen. Along with this experiment, a third set of 20 short-processed roots was selected from those sold at the market in a konzo-affected village. Each root was split longitudinally into two pieces and treated as described above. Flour specimens were also collected from 40 randomly selected households in the affected villages.

Determination of cyanogens was done with a modified enzyme assay (O’Brien et al. 1991) that permits separate quantification of cyanogenic glucosides, cyanohydrins and hydrogen cyanide.

**Retrovirus investigations (papers II, IV, V, VI)**

In paper IV, blood was obtained with informed consent from 13 male and 20 female konzo patients aged 10-56 years and 109 healthy controls (53 males and 56 females) aged 4-68. The 3 incident konzo patients in Zaire (II) and the 2 Tanzanian cases investigated in Uppsala (V) and 13 of the 16 konzo patients seen in the Central African Republic (VI) were also tested.

Serum samples were tested for the presence of HIV-1 antibodies with two different ELISA kits, Wellcozyme HIV-1 (Wellcome Diagnostics, Dartford, England) and Abbott anti-HIV-1 (North Chicago, IL, USA) (area A) or Enzygnost anti-HIV 1+2, (Behring, Marburg, Germany) (area B). All samples were further tested by HIV-1 Western blot (WB) kit (Dupont, Wilmington, USA). The WHO criteria for HIV-1 WB seropositivity were used, requiring reactivity with at least two envelope bands (WHO 1989). Screening for antibodies to HTLV-I was performed with Abbott Anti-HTLV-I ELISA and reactive sera were
further tested by an HTLV-I WB assay including recombinant glycoproteins, rgp46 and rgp21 (Diagnostics Biotechnology, Singapore). Reactivity with one envelope protein and one gag-encoded protein was required to confirm HTLV-I WB seropositivity.

Due to the rapid evolution of the retrovirus field, tests have changed over time. The 2 patients in paper V were tested with HIV-1+2 (Enzygnost AntiHIV1+2 EIA, Wellcosyme Recombinant HIV-1 EIA, PCR HIV-1), HTLV-I (Abbott HTLV-I EIA, PCR HTLV-I). Characterization of lymphocyte sub-populations by immuno-fluorescence and flow cytometry as well as an attempt to isolate HIV-1 and HTLV-I from blood specimens were also performed.

**Advanced neurological examinations (paper V)**

Two male konzo patients aged 25 and 19 years were invited to Sweden in October 1991. They had been diagnosed in 1985 during an epidemic in Tarime district (Howlett et al. 1990, Howlett et al. 1992), situated east of Lake Victoria in the northern part of Tanzania.

The study was prepared for one year with the approval of the Ministry of Health of Tanzania and the Research Ethics Committee of Uppsala University. Local civil and health authorities informed the patients and their families about the aim and procedures to be undertaken and obtained written consent from the patients to participate. A local health worker accompanied the patients to Sweden and acted as interpreter. The patients were provided adequate walking aids in collaboration with Gábor Tiroler, physiotherapist.

Histories were taken and neurological examinations were carried out in both patients during visits to their homes in May 1985 and repeated in 1986, 1988 and in Sweden in 1991.

Magnetic Resonance Imaging (spin echo) of the brain and spinal cord was performed with a Philips T5 MR-scanner (0.5 Tesla unit) without use of intravenous contrast. T1-weighted, proton density and T2-weighted images were obtained in sagittal, coronal and axial planes of the brain and in the sagittal plane of the whole spinal cord. Axial proton density and T2-weighted images over the conus medullaris were also obtained.

Neurophysiological investigations were performed with conventional techniques including: motor and sensory nerve conduction, small fiber tests such as respiratory-dependent heart rate variation (Stålberg & Nogues 1989), thermal perception thresholds for warmth and cold and pain thresholds for heat and cold; concentric electromyography (EMG) both at rest, at slight voluntary contraction and during maximal contraction (automatic turn/amplitude analysis (Stålberg et al. 1983), single fibre EMG, fibre density measurement, jitter analysis, blink reflexes, electroencephalography (EEG), somatosensory evoked
potentials (SEP), full-field visually evoked potentials (VEP) and brain stem evoked response audiometry (BERA). Transcranial stimulation of the motor cortex was performed with a magnetic stimulator to elicit motor-evoked potentials (MEP). Stimulation was also performed over the C7 vertebra. Pure-tone audiometry and caloric stimulation of the vestibularis were studied in conventional ways. Electro-nystagmography (ENG) in a dark room supervised by an infrared camera was used for the registration of spontaneous nystagmus, head shake nystagmus, positional nystagmus, and gaze nystagmus at 30° eye deviation. Smooth pursuit movements of 60° with a fixed velocity of 20°/s, 10 movements to the right and 10 to the left were recorded with ENG and analysed by computer for velocity, accuracy and superimposed saccades according to standardized procedure (Bergenius 1984). Voluntary saccades (i.e. rapid eye movements) of 60° were performed 20 times to the right and 20 times to the left analyzed by computer for start latency, accuracy and velocity (Bergenius 1984).

Conventional ophthalmological investigations included: visual acuity, eye pressure, direct/consensual pupillary reflex, corneal sensitivity, color vision, dark adaptation and binocularity. Visual fields were examined with Goldmann perimetry. The ocular fundi were photographed and scrutinized for defects in the nerve fiber layer.

The cerebrospinal fluid was screened for syphilis and examined for cells, protein, glucose and lactate. A protein electrophoresis and an isoelectric focusing were done.

Figure 5. Konzo patients in a severely affected village in Zaire. The adolescent boys all had their onset of konzo in childhood.
SUMMARY OF RESULTS

Paper I

In this community-based survey in the catchment area of Lumbi Health Center in collectivité de Masi-Manimba in Bandundu Region, Zaire (figure 6), 110 live and 24 dead konzo-affected persons among 6,764 inhabitants were identified, a prevalence of 16/1000 (figure 5). All cases had occurred after 1974 with peak incidences in 1978 and 1982. The appearance of annual konzo outbreaks in the dry season coincided with the following chain of events: completion of the tarmac road, increased market pressure turning cassava into the main cash crop from 1974-75 and onwards, which considerably changed and shortened the cassava processing method in the area. The cyclical variation in the number of annual konzo cases correlates to the 4.5-year-long cycles of deflated price of cossettes in Kinshasa. The coherence between the new road, price and konzo incidence suggests that marketing pressure induced short-cuts in cassava processing practices in the chain of factors generating konzo in Bandundu. The link between intensive trade and short-cuts in processing was independently recognized in the focus groups. The konzo onsets during the dry season correlate with the worst dietary situation of the year, with a supplementary-food shortage and a monotonous cassava diet. The seasonal occurrence also correlates with an intensive cassava selling season, when short-processing and high cyanide exposure are most likely to appear.

The age and sex distribution of the konzo cases in the two surveys in Zaire (paper I and Banea et al. 1992a) is presented in figure 7 together with the age and sex specific occurrence of konzo.

Paper II

This paper contains three studies done in the same area in Zaire as paper I. First, dietary interviews and determination of urinary thiocyanate and urinary sulphate as indicators of cyanide and sulphur intakes were compared between the affected area and a previously surveyed unaffected area in Bandundu region only 200 km north, areas A and C in figure 6. In both areas more than 95% of meals were cassava based. In the unaffected area, traditional safe cassava processing was adhered to without any short-cuts and urinary thiocyanate was low (figure 8 and 9). In the affected area short-cuts in processing were frequent and urinary thiocyanate very high.
Figure 6. Map of Bandundu region showing the survey areas A (papers I, II, IV), B (Banaa et al. 1992a) and papers II, III, IV) and the unaffected reference area C (paper II). Hatching indicates the areas with reported konzo.
Figure 7. Age and sex distribution of the 197 konzo patients still living at onset in a total population of 14,231 persons (pooled data from 2 surveys, in paper I and (Banea et al. 1992a). The deceased patients were not included. (Top) The absolute numbers of live subjects in different age groups. (Middle) The age and sex specific konzo occurrence. In the enumerators are the numbers of konzo cases at onset in each stratum and in the denominators the numbers of persons in each stratum. (Bottom) The population data, obtained in a demographic census of a sample of 1,341 persons in the first survey (I). There were 89 males to 100 females.
Unaffected area

<table>
<thead>
<tr>
<th>1st night</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
<th>5th</th>
<th>6th</th>
<th>7th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chikwange</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Affected area:

<table>
<thead>
<tr>
<th>Balls</th>
<th>Cossettes</th>
<th>Short-cut cossettes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Legend

- Soaking
- Wet pounding
- Sun-drying
- Dry pounding to flour

Figure 8. The cassava processing methods identified in the areas unaffected and affected by konzo.

Second, a cassava processing experiment compared cyanogen content in flour from traditionally and short-cut processed roots. The short-cut flour had a high content of remaining cyanohydrins, the acid-stable intermediate breakdown products. It was found that 71-91% of the cyanohydrins remained after cooking. The amounts found in the flour correspond roughly to the urinary thiocyanate excretion in the population.

Third, 3 konzo patients with onset within the last 90 h were found and examined. All 3, but only 2 of 23 controls, had blood cyanide concentrations above 4 μmol/l (p<0.01), although serum thiocyanate concentrations were similar.

Paper III

In this case-referent study performed in Pay-Kongila in Zaire in 1990 with 57 matched sets of cases and referents we devised multivariate logistic regression models to test the association between insufficient cassava processing and konzo in individuals, taking a number of potential confounders into account. We compared the situation of the cases at onset with the referents at interview.
All cases and controls ate cassava daily. A significant odds ratio of 11 (95% Confidence interval 1.7–73) for short-processing of cassava was found with a dose-response curve indicating greater risk for frequent users. This supports a causal relationship between insufficient processing of bitter cassava and konzo.

**Paper IV**

In this study we tested sera from 33 konzo cases and 109 healthy controls from both konzo areas in Zaire. All were negative for HIV-1 and HTLV-I antibodies. Further, we found no relation between konzo and gag-encoded protein reactivity in Western Blot.

**Paper V**

In this study we examined two Tanzanian patients in Uppsala by magnetic resonance imaging (MRI) and neurophysiological investigations. The main findings are presented in table 3. They had their onset of konzo in March 1985 while eating short-processed cassava. Dietary cyanide exposure was verified in May 1985 by high serum thiocyanate levels. They were severely disabled by a spastic paraparesis. MRI of brain and spinal cord was normal but motor evoked
The cause of konzo

potentials on magnetic brain stimulation were absent in both patients, even in the very slightly affected upper limbs. Other neurophysiological investigations were largely normal but the more affected patient had central visual field defects.

Table 3. Main findings of the investigations in 2 konzo patients, (V).

<table>
<thead>
<tr>
<th>Test</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnetic Resonance Imaging</td>
<td>normal</td>
</tr>
<tr>
<td>Nerve conduction</td>
<td>= normal</td>
</tr>
<tr>
<td>EMG</td>
<td>normal</td>
</tr>
<tr>
<td>Evoked potentials:</td>
<td></td>
</tr>
<tr>
<td>SEP, VEP, BERA</td>
<td>normal</td>
</tr>
<tr>
<td>EEG</td>
<td>= normal</td>
</tr>
<tr>
<td>Transcranial magnetic stimulation</td>
<td>no response</td>
</tr>
<tr>
<td>Oculomotor test</td>
<td>abnormal</td>
</tr>
<tr>
<td>Perimetry</td>
<td>cecocentral scotoma</td>
</tr>
<tr>
<td>Ocular fundus</td>
<td>loss of nerve fiber layer</td>
</tr>
<tr>
<td>Cerebrospinal fluid</td>
<td>= normal</td>
</tr>
</tbody>
</table>

Paper VI

A Swedish missionary doctor (S-A. Silfverdahl) had heard about konzo during a course in Uppsala. In the Central African Republic he saw some children at a rehabilitation center reminding him of konzo and he sent a letter to my supervisor. A further letter, from an American nurse (P. Stecker), with photographs and clinical histories of these children prompted us try to verify if these children really had konzo.

This survey identified a new focus of konzo in an area of the western Central African Republic. Here was a non-epidemic or pre-epidemic situation with a few cases scattered over a wide area. The prevalence was less than 0.5%. The individual patients had been treated by the medical staff but they did not recognize it as a distinct disease. The population in the most affected village recognized the disease as new. The interviews and the high serum levels of thiocyanate implicate cyanide exposure from insufficiently processed cassava as the cause of konzo.
DISCUSSION

These studies have been carried out among konzo-affected populations that are struggling for survival under very difficult circumstances. The studied savanna areas in Zaire have a poor sandy soil, unsuitable for agriculture. On the slopes of the river valleys much of the forest has been cut down for subsistence agriculture and it is easy to see how much of the top soil has been flushed away from the naked slopes. The population has quadrupled since 1950 and the traditional livelihoods of hunting and fishing have become impossible. The people now have to rely on agriculture or migrate. The traditional small-scale shifting cultivation requires long fallow periods to maintain fertility. Although fallow periods are shortened, many villages no longer have any land available for the young generation. Therefore cassava has been a “saviour” because it is the only staple crop that can be cultivated in this deteriorating agro-ecological system (Fresco 1986).

In this desperate life situation we have studied a disease that is most certainly induced by the hardship people are facing. Hardship and poverty are often shameful and there is always a tendency to hide it for outside observers. Divergence from traditionally established cassava processing methods has been particularly difficult to disclose and can easily be missed in conventional quantitative structured interviews. These studies have therefore required creative and flexible selection of research methods in the search for the causation of konzo. Food practices were explored by biomedical investigators using anthropological methods such as focus group interviews and participant observations when living in affected communities. The findings were directly confirmed through quantitative interview surveys and biochemical studies. This approach has been called “molecular anthropology” by Hans Rosling. The approach is not new. It has proved useful in studies of diseases related to marginal life conditions, e.g. by Gajdusek on kuru (Gajdusek & Zigas 1957, 1959), and by Goldberger on pellagra (Terris 1964).

THE OCCURRENCE OF KONZO

So far, konzo has been found in Mozambique, Tanzania, Zaire and the Central African Republic (figure 4). The total number of konzo cases that have been confirmed in studies and reports exceeds 3,700 (table 4). One-third of these cases had onset in the 1930’s in Zaire, and the remainder from 1975 and onwards. Carton (1986) says that cases occur also in Angola which is very plausible. Konzo is not yet a major
African public health problem, but locally it might be one of the biggest health issues. An alarming aspect is the risk of konzo epidemics occurring in other parts of Africa, where a development similar to that experienced in Bandundu is likely.

Table 4. Total number of konzo cases reported up to 1993.

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of konzo cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaire</td>
<td>2,156</td>
</tr>
<tr>
<td>Mozambique</td>
<td>1,420</td>
</tr>
<tr>
<td>Tanzania</td>
<td>119</td>
</tr>
<tr>
<td>Central African Republic</td>
<td>16</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>3,711</strong></td>
</tr>
</tbody>
</table>

**Konzo in Zaire**

Zaire is the country with the largest reported number of konzo cases. Two adjacent administrative regions are confirmed to be affected, Bandundu with 2,043 reported cases and Kasai Occidental, east of Bandundu, with 113 reported cases with onset during the years 1981-84 (Wilson 1985). Half of the cases in Bandundu have occurred in the last 20 years. The epidemics have "spread" from south to north (figure 6). The total number of cases in Zaire is undoubtedly underestimated, since careful case-detection has only been performed in some villages in the affected parts of Bandundu. There may be at least twice as many cases as reported. In the rest of the country konzo may occur with a low prevalence in pockets as in the Central African Republic.

In Bandundu, 88% of konzo onsets occurred during the dry season, mid-May to August, and at the very beginning of the rainy season, September, which is in accordance with the seasonal distribution in East Africa.

**The age and sex distribution**

The age and sex distribution of konzo shows a distinct pattern, with few variations (figure 7). No breast-fed child, or child under the age of 2.5 years, has ever been found to contract konzo. Women of child-bearing age and children 3-13 years of age run the highest risk of becoming paralysed by konzo; men are rarely affected. There is a tendency in the different studies of more boys than girls to become affected. The cases who have died have a similar age and sex distribution as the survivors. The age and sex specific occurrences
Thorkild Tylleskær

reveals a relatively increased risk for women, whereas the risk for children is somewhat attenuated. In field situations, the absolute numbers of konzo onsets in the different age and sex groups point out the vulnerable groups in a population. In the studied population there were 89 males to 100 females, most probably reflecting the “rural exodus”, i.e. the trend to move to town, presumably most pronounced in young males, but this skewed distribution is not enough to explain the incidence differences between the sexes.

**Konzo is both “epidemic” and “endemic”**

It should be emphasized that although konzo has been reported in several large epidemics, there are repeated reports of endemic konzo or sporadic cases of konzo. Up to recently this was the case only in areas where there have also been epidemics. The survey in the Central African Republic demonstrated, however, that konzo might appear with a low prevalence without any epidemic outbreak. This makes konzo important in the differential diagnosis of any form of spastic paraparesis of unknown etiology. This should be considered in future textbook descriptions of the disease, i.e. calling konzo “epidemic tropical spastic paraparesis” (Rodgers-Johnson et al. 1988) in contrast to “endemic tropical spastic paraparesis” (= HTLV-I-associated myelopathy) is pointless.

**KONZO – A DISTINCT CLINICAL ENTITY**

An important conclusion from these studies is that konzo is a distinct clinical disease entity. The findings fully support Carton’s statement that the clinical picture of konzo is “conspicuously uniform” (Carton et al. 1986). It is dominated by the acute onset of symmetric spastic paraparesis with increased knee and ankle reflexes and ankle clonus. If konzo is known to the doctor, the diagnosis is straightforward and the diagnostic criteria for konzo used in these studies are applicable at large: (1) a visible symmetrically spastic abnormality of gait while walking or running, (2) a history of onset in less than one week followed by a non-progressive course in a formerly healthy person, (3) bilaterally exaggerated knee or ankle jerks without signs of disease of the spine. The first and third criteria will be fulfilled by many types of spastic paraparesis, but the history of a rapid onset and non-progressive course will leave very few diagnostic alternatives. One is lathyrism and it is necessary to exclude consumption of *Lathyrus sativus*. Beside the similarity with lathyrism, konzo can be distinguished from other tropical myeloneuropathies on clinical and epidemiological ground, independently of the etiological linkage to cassava that will be discussed later.
Many classifications of tropical myeloneuropathies have mixed clinical, anatomical and etiological criteria, especially in the names. Bruyn (1991) has pointed out that the diagnostic management of spastic para/tetraplegia ideally runs a three-stage course that will be followed in this discussion:

1) **functional diagnosis**, establishing the nature of dysfunction, i.e.
   if the spastic paraplegia is isolated or associated with sensory, coordinative, autonomic, cranial nerve, and higher nervous system dysfunctions;
2) **anatomical diagnosis**, establishing the site of the lesions;
3) **etiological diagnosis**, defining the cause of the lesion.

**FUNCTIONAL DIAGNOSIS OF KONZO**

The functional diagnosis can now be summarized based on seven case series with clinical and neurological descriptions of konzo patients from Mozambique, Tanzania and Zaire (Trolli 1938, Lucasse 1952, Ministry of Health Mozambique 1984, Carton et al. 1986, Howlett et al. 1990) and papers I and V. The coherent findings in these 250 cases will be summarized in the following.

**The onset**

The onset of konzo is sudden, without prodromata. In 90% of the cases the duration of onset is less than one day. In general there is no fever or other symptoms before or at onset. Sometimes a long walk or hard work seems to precipitate the onset. The initial symptoms are described as trembling or "cramping" in the legs, heaviness or weakness of the legs, a tendency to fall or an inability to stand. Symptoms such as low back pain and paresthesias in the legs are occasionally present at the onset but clear during the first month. During the first few days most patients experience generalized weakness and are usually in bed for some days or even weeks before trying to walk. Some 10–20% of the patients complain of blurred vision initially and some of them have persistent problems. About one-third of the patients (Banea et al. 1992) has initial speech difficulties which typically clear during the first month except in severely affected patients who may remain with a spastic dysarthria. In 3 cases we have been able to examine the patients on the day of onset or the day after (II) and apparently the spasticity is present immediately, without any initial phase of flaccidity as seen in injuries of the spinal cord. After the initial weeks of functional improvement the disability remains unchanged over the years, and the clinical history and picture are unchanged (I). Both patients history and clinical examinations after 14 years confirm that the symptoms are no different from those in patients with a more recent onset.
Once the symptoms and signs of konzo are present, the clinical picture is stable. The exception is that about 10% of the patients examined (paper I), had suffered a second, aggravating episode, which is a sudden and permanent deterioration of the spastic paraparesis, the character of which is identical to the first onset. These aggravating episodes show the same seasonal distribution as the first onsets. I have interpreted these aggravating episodes as new "onsets". The konzo patients run a tenfold increased risk of contracting such a new onset compared with the risk for the general population of having a first onset of the disease.

Neurological findings

On detailed neurological examination, higher intellectual functions show no apparent deficit. In the field setting (papers I, VI) with obvious communication obstacles this has been tested by carefully asking the family members of a konzo patient whether he or she has changed in character or intellectual capacity after the onset.

Cranial or bulbar symptoms are only seen in severe cases and they are of three reported types: disturbances of vision, of eye movements and of speech. Paper V demonstrates that the visual disturbances reported by patients may be due to bilateral central visual field defects and a corresponding atrophy of the papillomacular nerve fiber layer with temporal pallor of the optic discs. When eye movements are examined in field studies, a lack of speed and finesse can be demonstrated in severe cases. This is done by asking the patient to fix his gaze alternately upon two different objects, one to the left and one to the right, usually the patient's own fingers. Nystagmography demonstrated saccadic eye movements as a confirmation of the lack of speed and finesse in the ocular movements (V). Hearing loss is not part of the syndrome, although one of the patients examined by Carton (1986) had unilateral deafness, and two mothers of konzo children complained about hearing impairment (Ministry of Health Mozambique 1984). The 2 severe cases in paper V had normal hearing and normal auditory evoked potentials. The dysarthria seen in severe cases is of a spastic or pseudobulbar type. Cranial nerve functions are reported normal as confirmed in study V.

Moving to the motor system, there is a general increase in muscle tone in the lower limbs, especially in the hip and knee flexors, sometimes leading to contractures in flexion (papers I, V, VI). The striking finding is the symmetric spastic paraparesis, ranging from hyperreflexia in the legs to severe spastic paraparesis with associated weakness of the trunk. Severe cases have a tetraparesis with spasticity, hyperreflexia and occasionally also clonus in the arms. In moderately affected patients, the arms are apparently unaffected, but an impaired
rapid-alternating movements in the arms can often be found as a sign of an affection of the cortico-spinal tracts, as reported in paper V. Although the severity varies from patient to patient the longest upper motor neurons are always more affected than the shorter ones (Howlett et al. 1990). Thus a konzo patient never has dysarthria without severe symptoms in the legs and symptoms in the arms.

The reflexes of the lower limbs are exaggerated in all cases, but due to contractures they might be impossible to elicit in patients with severe and long-standing disability. Extensor plantar responses can be elicited in most moderate and severe cases if done with the patient in recumbent position. Co-ordination is intact and there are no ataxia or other signs of cerebellar dysfunction (V).

Konzo patients have generally no sensory deficits, which was confirmed in paper V by normal sensory evoked potentials and normal conduction velocity. There is no urinary, bowel or sexual dysfunction.

Table 5. The distribution of severity in konzo patients according to the suggested functional grading scale.

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Mild form Unaided walking (%)</th>
<th>Moderate form Regularly using stick(s)/crutches not walking (%)</th>
<th>Severe form Bedridden/ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tylleskär 1991</td>
<td>110</td>
<td>64</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>Banea 1992</td>
<td>87</td>
<td>66</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>Tylleskär 1993</td>
<td>16</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

**Functional grading**

Konzo constitutes a range of neurological deficits, from slightly increased reflexes in the lower limbs to a severely disabled, bedridden patient with an associated weakness of the trunk and arms, impaired eye movements, dysarthria and possibly visual impairment. Lucasse (1952) therefore classified konzo cases into three groups: a *mild form* where the patients are not regularly using any walking aids, a *moderate form* where the patients are regularly using one or two stick(s) or crutches and a *severe form* where the patients are bedridden or unable to walk without living support. A similar grading was suggested for lathyrism by Acton (1922), but he made a distinction as to whether one or two sticks were needed for the moderate cases. This will complicate grading, as exemplified by rehabilitated cases in Central African Republic (VI),
who had exchanged their single stick for two arm crutches. A functional grading is useful for the assessment of the rehabilitation needs and I propose the use of the three-point functional grading scale suggested by Lucasse (table 5). This grading has the advantage of being easy to use for paramedics not familiar with neurological examination. It will directly indicate the need for rehabilitation and walking aids. The same grading has been used for HTLV-I associated myelopathy (Gessain & Gout 1992) and a similar one for hereditary spastic paraparesis (Behan & Maia 1974).

To compare the disability of konzo patients with other neurological disorders we have used the Expanded Disability Status Scale, initially devised by Kurtzke for multiple sclerosis (Kurtzke 1983). This scale includes several dimensions of disability that can be seen in multiple sclerosis, whereas for konzo the functional impairment is fairly one-dimensional.

The major diagnostic difficulty in konzo is to distinguish slightly affected individuals from non-affected. In the high prevalence communities many persons report a mild attack of konzo but on examination they can walk and run without any visible sign of spasticity (paper I). In most persons with such history the knee or ankle jerks are exaggerated as a sign of possible sub-clinical konzo. In Mozambique a high frequency of ankle clonus was found after the epidemic in clinically unaffected children. These are probably subclinical cases (Cliff et al. 1986) and the one's with manifest konzo may only be the tip of the iceberg.

The name

In Trolli's presentation (1938) he tells that hunters in the affected communities use a fetish to catch animals in the trap. It is a powder given by a magician to each hunter and kept scrupulously in their houses. If one of the hunters dies, the fetish will not be used by his children. If they breach the oath they will get konzo, i.e. “tied legs”. During our investigations in Bandundu, some elderly persons recognized the word “konzo” as the name of a fetish which “tied legs” of animals in the trap so they were unable to escape. The name konzo thus evokes the rigidity of the tightly crossed spastic legs that makes it impossible to walk.

In the beginning of my studies, it was not clear whether the reports from different countries were describing the same syndrome and the descriptive name “epidemic spastic paraparesis” was still used for the observed condition. With the article in 1986 by Carton it became clear that the disease found in Mozambique was the same as the one in Zaire, first described by Trolli in 1938. The use of “epidemic spastic paraparesis” was cumbersome in the medical literature and useless for
public health use. When found that the results in paper I were consistent with earlier publications and with findings under compilation in Tanzania (Howlett et al. 1990) it was decided to give the designation konzo to the new disease entity. This give credit to the first publication by Trolli. There has been full agreement among involved researchers on the use of konzo as the scientific designation. The name has proved effective to use in preventive efforts in both Tanzania and Zaire. I suggest the name konzo be written without capitalization or quotation marks, just like pneumonia, diabetes, beri-beri and kwashiorkor.

It has been suggested (P. Spencer, personal communication) that konzo should be named after cassava in analogy with lathyrism but there are three good reasons for not doing so.

First, the etiology is not yet confirmed and well-processed cassava do definitely not cause konzo, even if eaten as the sole staple.

Second, etiology can be attributed at the wrong level. Analogously, beri-beri could have been termed “ricism” during the epidemics in south-east Asia in the last century. Fortunately, this was not done because far from all rice consumption implies a risk of beri-beri. This is only the case with exclusive consumption of polished rice. Further we know today that rice is not at all necessary to induce beri-beri; in Europe alcoholism is a more frequent cause. When the molecular cause of beri-beri was understood an etiological name was introduced: “thiamine deficiency”. It is recommended to use the same strategy for konzo. Our studies show a strong association with high cyanide and low sulphur intake from exclusive consumption of cassava. If this is the cause it is quite conceivable that konzo can be induced by the same direct toxico-metabolic circumstances without cassava. When the etiological mechanisms are known, an etiological name can be applied, whatever it might be.

Third, beside konzo there are at least 3 other health effects attributed to consumption of insufficiently processed and still toxic cassava: 1) acute intoxications with vomiting, dizziness and possibly death after ingestion of a toxic meal (Cheok 1978, Essers et al. 1992, Mlingi et al. 1992); 2) aggravation of iodine deficiency disorders (IDD) in areas with low iodine intake (Bourdoux et al. 1978, 1980); and 3) the clinically different ataxic polyneuropathy (Osuntokun 1981). Evoking cassava in the name for konzo would create confusion since it is unclear which of the above effects are included in this term. Especially the distinction between konzo and the TAN would be difficult. This confusion is already evident in several reviews, e.g. (Agency for toxic substances and disease registry 1993).

It can be questioned whether it is the onset, the lesion or the disability that should be named konzo. This is parallel to diabetes and polio, both of which have an abrupt onset when a cell population stops
functioning normally and where a life-long disability ensues due to this loss of function. In the case of poliomyelitis, where the etiology is sufficiently elucidated, the name designs the acute illness, whereas the disability is called a sequel. In the case of diabetes, where the cause and character of the cell damage is relatively unknown, the name designs the sequel, "he has diabetes". I suggest, in analogy with diabetes, the use of konzo as the name of the disability, "he has konzo".

**Differential diagnosis**

The clinical history can distinguish konzo from HTLV-I-associated myelopathy. An insidious onset of a progressive spastic paraparesis is characteristic for HAM. The progression is usually slow, taking several years; 10 years after onset, 30% are bedridden and 45% cannot walk unaided. In contrast to konzo, sensory and urinary symptoms and impotence are common complaints in HAM whereas optic nerves are rarely affected (Gessain & Gout 1992). It will be demanding but possible to differentiate the two diseases even when occurring in the same community. Two endemic areas of HTLV-I associated myelopathy have already been identified in central Africa (Goubau et al. 1990, Kayembe et al. 1990, Jeannel et al. 1993). They are located between the konzo-affected areas in Zaire and the Central African Republic described in this thesis (I, IV, VI). The diagnostic situation resembles the one presented by Kitze et al. (1992) in the differential diagnosis of HAM and multiple sclerosis in Iranian patients. The two diseases may resemble each other and it is foreseeable to find a HTLV-I positive patient with unrelated multiple sclerosis or konzo. Seropositivity to HTLV-I is not sufficient to conclude that a patient with spastic paraparesis has HAM.

**ANATOMICAL DIAGNOSIS OF KONZO**

An anatomical diagnosis is best based on autopsies. To my knowledge, only two autopsies have been done on konzo patients (Trolli 1938). The first was a 6-year old child from Feshi with konzo for 2 months, who died in September 1937. A part of the spine with the spinal cord was sent to Dr van Bogaert in Léopoldville (Kinshasa) for histological examination and he found the spinal cord to be normal without signs of poliomyelitis. The second case was a 6–year-old boy with konzo who died in November 1937 in a clinical picture of kwashiorkor with severe tibial edema and swollen face. On autopsy, severe cerebral edema was found. The laboratory in Léopoldville reported negative findings but it was not stated what has been examined. The non-existence of recent autopsies in konzo had been well explained by Carton (1986): "...the rareness of fatal outcome, the remoteness of
The causation of konzo

The regions involved, the local customs and the Zaire law all make the chances of ever obtaining suitable necropsy material remote." Overcoming these difficulties is a challenge for future research.

Some ideas on the site of the lesion have, however, been raised from these studies. The konzo patients present with selective upper motor dysfunction. The cognitive function, cerebellar function, autonomic function, peripheral nerve function and auditory function are unaffected. Besides the upper motor neurons only the optic nerves are involved, which will be discussed under pathogenesis. The selective character of clinical impairment points to a focal lesion at cellular level and this is supported by normal MRI in konzo.

There are four possible locations for the focal lesion in konzo (figure 10). The first possibility is a pre-synaptic cortical lesion. Experimental lesions in the pre-motor area can cause spasticity and increased tonus (Davidoff 1990). The transcranial magnetic stimulation is known to act pre-synaptically (Barker et al. 1987) and the fact that this stimulation failed completely in the two severe konzo cases investigated (V) favors a cortical location.

The second possibility is a lesion of cell bodies of the upper motor neurons or a sub-population of such cells in the motor cortex. The third possibility is a conduction block in the motor axons of the motor neurons. The fourth possibility is a synaptic failure in the spinal cord.

The konzo patients (V) presented with spasticity, increased muscle tone, impairment of skilled voluntary movements, increased tendon reflexes, and extensor plantar reflexes, which is considered to be an upper motor neuron lesion in clinical neurology. The simplistic presentation of the "pyramidal tract" as the sole neuronal system mediating voluntary movements, originating from the Betz cells of the motor cortex and terminating on the alpha-motor neurons in the spinal cord, is an oversimplification (Davidoff 1990). The pyramidal tract is a heterogeneous structure arising from functionally different cortical areas and consisting of different types of fibres distributed to a variety of spinal and supraspinal locations. From experimental sections of the pyramidal tract in primates it is clear that the tract is not needed to provide "voluntary" movements, but it is necessary for speed and agility during these movements. Nor does such a lesion cause increased muscle tone, spasticity and paresis. In these experimental situations the cortical motor neuron cell bodies are still intact and can act via other pathways in the brain (Davidoff 1990). The disability demonstrated in the apparently normal upper limbs of the konzo patients is very similar to the experimental disability mentioned above, with loss of speed and agility but preserved voluntary control. This analogy between the two findings points to a focalized lesion of the upper motor neurons.
Patients with Strümpell’s hereditary ‘pure’ spastic paraparesis (Harding 1981, Bruyn et al. 1993, Polo et al. 1993), develop a stereotyped clinical picture, constituted exclusively of an increasingly spastic gait, similar to konzo. Motor-evoked potentials have been reported abnormal (Pelosi et al. 1991) or largely normal (Polo et al. 1993). The histological abnormalities in these patients consist of axon degeneration mainly involving the longest, large-diameter spinal cord fibre systems and the degeneration is consistently most severe in the most distal portion of these systems. Spinal roots and peripheral nerves are normal (Behan & Maia 1974). The distal axon degeneration may still be due to a preferential loss of long-axon-motor neurons in the motor cortex. It is conceivable that the lesion in konzo, similar to the hereditary spastic paraparesis, is a selective upper motor neuron death preferentially striking long-axon-motor neurons in the motor cortex. A certain proportion of upper motor neurons might be lost at all levels (bulbar, short-axon and long-axon) but the loss in the longer tracts is clinically most important.

Whether konzo is histopathologically related to hereditary spastic paraparesis is still an open question, as is the issue of the site of the lesion. This uncertainty regarding the site of the lesion precludes the use of the term “myelopathy” for konzo. Further neurophysiological studies, “neuroimaging” and possibly autopsies of konzo patients may elucidate the site of the lesion.
ETIOLOGICAL DIAGNOSIS OF KONZO

Etiological epidemiology has a wider objective than just to show an association between exposure and disease. The aim is to understand both disease determinants and mechanisms of the disease process, having prevention as the ultimate goal. Causal inference is the process of determining whether observed associations are likely to be causal. An association is first assessed for the possibility that it is a result of chance, bias or confounding. Hill (1965) elaborated a systematic approach for causal inference based on the studies on smoking and lung cancer (United States Public Health Service 1964). This has further been elaborated by Evans (1978), Rothman (1988) and Susser (1991). A more recent textbook version is presented in table 6. One important non-epidemiological aspect is the experimental evidence. In most cases this is achieved in animal models, which have the additional advantage of making studies of the pathogenetic mechanisms possible.

Table 6. Guidelines for causation (Adopted after Beaglehole et al. (1993) and Hill (1965)).

<table>
<thead>
<tr>
<th>Temporal relationship</th>
<th>Does cause precede effect?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength</td>
<td>How strong is the association?</td>
</tr>
<tr>
<td>Consistency</td>
<td>Are the results similar to other studies?</td>
</tr>
<tr>
<td>Dose–response relationship</td>
<td>Does greater exposure increase effect?</td>
</tr>
<tr>
<td>Plausibility</td>
<td>Is the association biologically plausible?</td>
</tr>
<tr>
<td>Reversibility</td>
<td>Does removal of exposure reduce risk?</td>
</tr>
<tr>
<td>Study design</td>
<td>Is the study design weak or strong?</td>
</tr>
<tr>
<td>Judging the evidence</td>
<td>How many lines of evidence lead to the conclusion?</td>
</tr>
<tr>
<td>Experimental</td>
<td>Can the disease be reproduced in animals?</td>
</tr>
</tbody>
</table>

A cause of a disease can be defined as an event, condition, characteristic or a combination of these factors which plays an important role in producing the disease (Beaglehole et al. 1993). A cause is termed sufficient when it inevitably produces or initiates a disease and is termed necessary if a disease cannot develop in its absence. Each sufficient cause has a necessary cause as a component (Rothman 1976, 1986). Epidemiology encompasses a whole set of relationships from more remote environmental causes, sometimes called “underlying factors” or “basic causes”, such as low income, poor nutrition, bad housing, to “predisposing factors”, such as age, sex, previous illness or genetic susceptibility and finally “precipitating
factors", such as exposure to a specific noxious agent. Such "chain of events" or can be presented graphically in a "conceptual framework" to show the causes at different explanatory levels. Frameworks are useful for public health & nutrition, a widely known example is the causes of child malnutrition elaborated by Jonsson (Jonsson 1981, UNICEF 1990). With increasing understanding of different factors' biological role in the disease process and the use of biomarkers in molecular epidemiology similar frameworks are also developed for etiological studies of disease mechanisms (Hulka 1990). The studies on konzo have generated a conceptual framework for both the social and the biomedical causation of konzo (figure 11). Before discussing this framework, based on the cyanide hypothesis, the transmission hypothesis need to be scrutinized.

The transmission hypothesis

Two hypotheses on the causation of konzo had been suggested when these studies were initiated, one of a transmissible agent, the other toxico-nutritional. Two arguments were advanced in favor of an infectious etiology – the familial clustering and the evidence of transmission (table 7). Familial clustering is a weak argument since almost all nutritional diseases also occur in familial clusters. The events adduced as evidence of transmission by Carton (1986) are of greater relevance. On a few occasions a person joined a konzo-affected household and after some time also acquired the disease. In one case, a person fell ill one week after returning from the konzo-affected household to her own home. These events are, however, compatible with a toxico-nutritional etiology of the disorder, as both host and guest shared the same food.

There are several arguments against the transmission hypothesis. Some are inductive, i.e. drawn from experience, such as the fact that attempts to isolate virus have failed. The other arguments are deductive, i.e. they contradict the concept of an infectious agent, regardless of all attempts to find one. There are no symptoms or signs of infection in konzo and the cerebrospinal fluid is normal. To explain the epidemiological pattern, the agent must be persistent in the patient over the decades, in spite of the acute onset and the epidemic occurrence. All konzo cases occur in limited remote rural areas, without spreading to neighboring urban or semiurban areas. Not a single case of onset of konzo has been reported among all those who migrate from konzo-affected areas to the cities where different diets are available. None of the health staff with better diet, examining or caring for the patients have ever contracted the disease, even if they shared occasional meals. The distinct age and sex distribution is difficult to explain by transmission but it fits with the toxico-nutritional hypothesis. A strong
The causation of konzo

argument against the transmission hypothesis is the tenfold risk of an aggravating attack among those already affected with the same seasonal pattern as the first onsets, yet no viral disease is known to behave in this way.

Table 7. Arguments for and against a transmissible agent as the cause of konzo.

Arguments in favor of transmission:
1. Familial clustering (Carton et al. 1986)
2. Evidence of transmission (Carton et al. 1986)

Arguments against the transmission hypothesis:
1. No virus found and all isolations negative (Carton et al. 1986)
2. No signs of infection (Carton et al. 1986)
3. Must be virus with acute effect, persistent over decades (Carton 1986)
4. Outbreaks in remote rural areas, not in townships or along roads
5. No secondary cases at distance
6. The distinct age and sex distribution
7. Increased risk of second attack, with the same seasonal pattern, in those already affected

The conclusion drawn from this discussion on the transmission hypothesis is that konzo is not caused by any known type of infectious agent and definitely not by any known retrovirus (IV). In view of the list of arguments against this hypothesis it is also unlikely that konzo is caused by an unknown type of infectious agent.

The cyanide hypothesis

The arguments in favor of the cyanide hypothesis can be grouped in five clusters (table 8). The first is the very strong association between konzo and the chain of events leading to a high cyanide and low sulphur intake (figure 10): intensive cultivation of bitter cassava varieties, the cassava dominated diet, the insufficient cassava processing, the high cyanide intake indicated by high urinary thiocyanate levels, the low intake of protein-rich food providing sulphur for cyanide detoxification as indicated by the low urinary sulphate excretion. The second argument, equally strong, is the consistent association with the same dietary factors in five geographically widely separated and ecologically different areas: Nampula province, Mozambique, Mtwara and Mara regions in Tanzania, Bandundu region in Zaire and Nana-Mambéré province in Central African Republic (figure 4). The number of clusters and the distances between the affected areas are strong factors
favorising this argument (Alexander & Cuzick 1992). The consistency is not only geographical but also temporal. At the time of konzo outbreaks

Table 8. Arguments for and against the cyanide hypothesis.

**Arguments in favor of the cyanide hypothesis:**

1. **Strong association** on the aggregated level of:
   - Cassava dominated diet and konzo (I, II, VI)
   - Insufficient cassava processing and konzo (I, II, VI)
   - Very high urinary thiocyanate levels and konzo (II)
   - Supplementary food shortage and konzo (I, III)
   - Low sulphur intake and konzo (II)

2. **Consistent** association found:
   - In geographically widely separated areas
   - In different study periods (I, II, III, VI)
   - With different methods for exposure measurement

3. **Strong association on individual level** between:
   - Very high cyanide levels and onset of konzo (II)
   - Short-processing of cassava and onset of konzo, Odds Ratio = 11 (III)

4. A **dose–response relationship** demonstrated between:
   - short-processing and onset of konzo (III)

5. **Plausible** chain of pathogenetic events and underlying environmental and social factors.

**Arguments against the cyanide hypothesis:**

1. Serum thiocyanate equally high in cases and controls (Lancet 1984)

2. Sudden selective upper motor neuron lesions not caused by cyanide exposure from other sources.

3. A different disease, TAN, is attributed to the same cause

4. No mechanism has been identified.

5. **Cassava use is safe in Bandundu** (Carton et al. 1986)
   - Short-processing denied
   - Soaking effectively removes cyanogens from cassava
   - No food shortage in Bandundu
   - No konzo among cassava consumers in Kinshasa

6. The peculiar age and sex distribution is unexplained

7. The association is found mainly in studies on the aggregated level

8. Prevention not demonstratively successful (no attempts made)

9. Disease could not be induced in animals (no attempts made)

the exposure has been shown to be higher than before and after (Casadei et al. 1990, Essers et al. 1992, Mlingi et al. 1991, 1992, 1993). There has also been agreement in dietary findings between all methods used,
qualitative and quantitative interviews, food chemistry studies and biochemical studies of humans. An additional support is that the underlying causes have been shown to be different in the different areas, either commercialization of cassava or drought, yet the final diet is close to identical at time of onset in all affected populations.

Third, a very strong association has been found on the individual level between high blood cyanide and konzo (II). At onset 3 patients had very high blood cyanide levels, exceeding the accumulation level, (II:Fig 2). Also among the 23 controls, blood cyanide levels were elevated, but only 2 exceeded the accumulation level of 4 μmol/l. The thiocyanate levels were equal in cases and controls. This has been an argument against a cyanide etiology, but the differing blood cyanide and equal thiocyanate levels in cases versus controls, can be attributed to a decreased cyanide to thiocyanate conversion rate as being an important causative factor. The thiocyanate levels depend on both the cyanide intake and the conversion rate, which can be reduced if the intake of sulphur amino acids is low. This makes thiocyanate less valid as a quantitative biomarker for cyanide intake in nutritionally compromised subjects. Thiocyanate may therefore only be a useful biomarker in studies on the aggregated level. The combined effect of high cyanide intake and decreased conversion rate, i.e. the biologically effective dose of cyanide, can be measured as the blood cyanide concentration.

Another strong association on the individual level is between insufficient cassava processing and konzo (III) with an odds ratio of 11 (95% Confidence interval 1.7-73). Moreover, the case-referent study also demonstrated a dose–response relationship which further strengthens the argument. It is plausible that the association found in paper III was even stronger in reality because, as recently pointed out (Hiller & McMichael 1991), an association found in ecological studies can be attenuated in studies on the individual level by the homogeneity of exposure among individuals within the study population. The resulting narrow gradients of exposure may further reduce the power of a case-referent study to detect an increased risk. Had referents in this study been selected from a wider area, a higher relative risk of konzo when exposed to short-soaked cassava might have been found.

The plausibility of the chain of events is also an argument in favor of the cyanide hypothesis. There are plausible explanations for each link in the chain – agricultural, socio-economic and biological (figure 11).

The macro-geographical agro-ecology of cassava in Africa has recently been presented by Carter & Jones (1993). They devised a multivariate model for the distribution of cassava in Africa and identified, on a continental scale, six areas where more cassava is cultivated than predicted by the model, when controlling for population density, altitude, dry season length and soil features. From the time
trends of cassava cultivation they further predict an increase of cassava's importance in six areas. All five known konzo areas are among the 12 areas identified on these two lists.

The objections to a cyanide hypothesis

The first objection, that thiocyanate levels are equal in cases and controls, may be an effect of insufficient exposure measurements as discussed above.

The second objection, that cyanide exposure from other sources has not caused konzo, is very relevant. High single-dose exposure to cyanide is reported to produce a parkinsonian-like syndrome (Carella et al. 1988, Messing & Storch 1988, Uitti et al. 1985). This apparent paradox may be explained by the special pattern of blood cyanide levels that result from weeks of high cyanide and low sulphur intake. A similar blood cyanide pattern does not result from other types of cyanide exposure. Ingestion of porridge rich in cyanogenic glucosides and cyanohydrin will result in a gradual release of cyanide in the gut, lasting for many hours. When the detoxification rate is simultaneously reduced due to low sulphur availability, the blood cyanide level will rise and fall slowly. These two factors can be expected to yield a continuously high but sub-lethal blood cyanide level rarely sufficient to produce clinical symptoms, nor falling to physiological levels.

Tropical ataxic neuropathy (TAN) is a clinically different syndrome with progressive polyneuropathy dominated by sensory deficits deriving from a number of modalities and not from the acute onset of an isolated spastic paraparesis. The commonest signs of tropical ataxic neuropathies are defective perception of sensory modalities of the lower limbs, bilateral optic atrophy, ataxic gait, impaired muscular coordination, bilateral perceptive deafness, weakness and wasting of the muscles. The tendon reflexes are absent in the lower limbs in about 50% and exaggerated in about 20%. Several case series from other countries, reporting similar symptoms and signs are grouped under the same heading of TAN but the proportion of the different signs varies between studies. It is therefore still unclear to what extent they share a common etiology and pathophysiology (Román et al. 1985).

In Nigeria TAN has been attributed to chronic cyanide intoxication from cassava consumption based on increased serum thiocyanate levels. The normal thiocyanate level varies with the diet but the upper reference limit was found to be 77 µmol/l in non-smokers in populations lacking any known specific source of cyanide or thiocyanate exposure (Lundquist et al. 1979). The mean (±SD) serum thiocyanate concentrations found in TAN are 126±58 µmol/l (n=20) (Monekosso & Wilson 1966) and 114±39 µmol/l (n=375) (Osuntokun 1973). This is slightly higher than in smokers but considerably lower than in both
cases and controls in konzo-affected populations (307±67μmol/l in paper II). The blood cyanide levels found in TAN cases were 1.0±0.4 μmol/l (n=108) (Osuntokun 1973), which is comparable to that of smokers and of the control subjects in a konzo-affected population (II) but the levels found in konzo at onset are more than 20 times higher. One would expect TAN to appear in konzo-affected populations but this has not been verified. TAN cases are thus exposed to much lower cyanide levels, but over longer periods. The contradiction could be explained if different dose-rates were to cause the different neurodamage patterns. Possible mechanisms will be discussed below.

The fifth argument, that cassava use is safe in Bandundu, has been repudiated by the present and related studies (Banea 1992a+b). Soaking of cassava proved insufficient in konzo-affected areas both in Zaire and in the Central African Republic; short-processing was revealed by our methodology of focus groups and participant observation (I, II, VI). The present studies also demonstrated a supplementary food shortage in the affected communities (I, III).

Large differences in the diet over short distances correlate well with differences in konzo incidence and provide a sound explanation to the localized occurrence of konzo (Banea et al. 1992a). The peculiar age and sex distribution, with higher incidence among women and children, apart from those breast-fed, has two possible explanations. Either it suggests that the high-risk groups are biochemically more vulnerable due to the greater demand on metabolism from growth and pregnancies, or else they are the ones most exposed, for social and cultural reasons, i.e. underprivileged in food access or a heavy work load, or a combination of the two. The fact that breast-fed children are spared supports this hypothesis, since they eat the least cassava and have the highest sulphur amino acid intake in the community.

The processing experiment (II) demonstrated that the remaining cyanogens in cassava flour obtained immediately after short-soaked roots disappear if root pieces are stored 2 weeks at ambient temperature, which would explain why no distant cases occur in Kinshasa where the cassava is sold.

The fact that the association is found mostly in ecological studies or studies on the aggregated level can be justified by the helpful distinction between “causes of cases” and “causes of incidence” done by Rose (1985). The traditional individual-centred approach in clinical medicine has also shaped the thinking in modern epidemiology. Analytical epidemiology has been restricted to the identification of individual risk factors and judging if these risk factors are causal. This assumes a heterogeneity of exposure within the study population: “If everyone smoked 20 cigarettes a day in the study population, then clinical, case-control and cohort studies alike should lead us to conclude that lung
cancer was a genetic disease.” Or differently stated, “the hardest cause to identify is the one that is universally present in the study populations, for then it has no influence on the distribution of disease.” Rose therefore distinguishes two kinds of etiological question: “Why do some individuals have hypertension?” and “Why do some populations have much hypertension, whilst in others it is rare?” These questions require different kinds of study design and they will yield different answers. To find the determinants of incidence, the characteristics of populations, rather than the characteristics of individuals, should be studied. Comparisons can be temporal or geographical. When the entire population in an area, such as in figure 9, shows very high urinary thiocyanate levels, with the median above +20 standard deviations of the reference value, it is a situation where “the cause of incidence” may be verified with an analytical ecological study design.

The last two arguments about lack of animal model and lack of successful prevention are valid criticisms and challenges for the future.

Figure 11. A conceptual framework of the present understanding of the causation of konzo.

The conceptual framework
These studies have generated a conceptual framework for both social and biomedical causation of konzo (figure 11). It explains why konzo is not easily induced. A number of factors are needed
The causation of konzo

simultaneously to pass the bottlenecks in the causational chain. First a
number of underlying factors, such as agro-ecological crisis with
decreasing yields, population pressure on the land, a high workload for women and insufficient household food
security will lead to a farming system dominated by bitter cassava. This
will lead to very cassava-dominated diets. In a second step, a heavy
workload for women and insufficient household food security together
with commercialization of the staple crop, cassava and adverse climatic
events such as drought, might induce short-cuts in processing of the
bitter cassava roots. This second bottleneck has to be passed if konzo is
to result. So far this has not happened in areas where the dominant
processing method is “unshortcuttable”, e.g. chikwangue, which cannot
be made from insufficiently processed cassava. The poor access to
supplementary food results in inadequate sulphur amino acid intake. All
those three bottlenecks must be passed for konzo to occur. If one is
missing, the disease does not arise. There may obviously be further
genetic or acquired factors that increase susceptibility.

Judging the evidence

Assessment of the evidence should be made regarding the cyanide
hypothesis (table 6). First, the timing is not a problem, as cyanide
exposure is known to precede the onset of konzo. The association is
strong and the results are very consistent irrespective of place, time and
methods used for the investigation. A dose–response relationship has
been demonstrated. There are a number of biologically plausible
explanations for the association. No systematic attempts to prevent the
disease have so far been made. Although most studies had an ecological
design they are relevant for testing the hypothesis. The cyanide
hypothesis has not been tested in an animal model. From this discussion
it is concluded that there are very strong reasons to believe that konzo is
caused by a high cyanide and low sulphur intake.

The present hypothesis is that the subjects affected by konzo have
invariably had a very monotonous diet based almost exclusively on
insufficiently processed cassava roots resulting in a high cyanide and
low sulphur intake, which leads to uninterrupted high levels of blood
cyanide lasting several weeks. It may be the absence of “cyanide-free
intervals” that allow blood cyanide to return to physiological levels, that
creates the pathogenetic metabolic insult. After several weeks of
 uninterrupted cyanide toxicity, a metabolic threshold is suddenly passed,
resulting in an abrupt and permanent cell damage. Konzo was seen in
Mozambique in a pre-famine situation but it is not associated with
famines. It seems that a certain supply of food is necessary for konzo to
arise, just as in beri-beri and pellagra (Victor 1984). There are two
possible explanations for this: either the toxic load is less due to
Thorkild Tylleskär

decreased food intake, or the body is in a catabolic state that produces sulphur amino acids from the protein catabolism, thereby increasing the detoxification capacity.

Definite confirmation of an etiological role of cyanide in konzo, from prophylactic trials or from an animal model, is a challenge for the future. It must not be forgotten, however, that this hypothesis is still an hypothesis. The may be some wild toxic plant, vitamin deficiency, another toxin in cassava, and/or some other contributory factor, strongly associated to cyanide exposure, that causes konzo.

THE PATHOGENETIC MECHANISMS

The pathogenetic mechanisms of konzo have not been part of the present investigations, but four different pathogenetic mechanisms for neuron damage have been suggested for konzo.

The first is the possibility of an over-excitation of the neurons. This is an analogue to lathyrism that has been attributed to an excitatory amino acid in the pea called \(\beta\)-N-oxalylamino-L-alanine (BOAA or \(\beta\)-ODAP) (Spencer et al. 1986). This compound is sterically similar to glutamate and might thus be able to interact with the excitatory glutamate receptors on the neurons. Recent research in neuroscience has focused on excitatory receptors of the neurons and excitotoxic amino acids. It has been hypothesized that such overexcitation is the cause of several neurodegenerative disorders (Spencer et al. 1987, Barinaga 1990, Krogsgaard-Larsen & Hansen 1992). In konzo, however, no excitatory compound has been identified.

The second possible mechanism, a direct cyanide effect, is attractive but cyanide exposure from other sources has not caused paralysis of this kind. Nor does it explain the pattern of selective neuron damage. In a recent review it is suggested that mitochondrial energy metabolism underlies the pathology of neurodegenerative diseases and that such defects result secondarily in excitotoxic neuronal degeneration (Beal et al. 1993). It has been shown that incubation of chicken retina with potassium cyanide produced histological lesions similar to those found with N-methyl-D-aspartate (NMDA) or kainate, both of which are potent inhibitors of one of the subclasses of glutamate receptors (Zeevalk & Nicklas 1990). 3-Nitropropionic acid is another inhibitor of the oxidative phosphorylation that selectively damages the striatal parts of the brain (Ludolph et al. 1991). Recently it has also been found that BOAA is a potent inhibitor of the NADH-dehydrogenase (complex I) in the mitochondrial oxidative phosphorylation (Pai & Ravindranath 1993). This opens up a new possibility of finding a final common toxicological mechanism in lathyrism and konzo.

The third suggested mechanism is that the specific toxicity in konzo
The causation of konzo arises from a cyanide to cyanate conversion due to decreased cyanide to thiocyanate conversion. Cyanate (OCN) is a carbamylating agent (Carreras et al. 1976) that was a promising drug for sickle cell anemia 20 years ago but its neurotoxicity stopped its use. High-dose cyanate led to spasticity of the hind limbs in rats (Alter et al. 1974, Toskes et al. 1973) and to leg weakness in dogs (Cerami et al. 1973). Primates given continuous high dose cyanate abruptly produced a very konzo-like syndrome after 42 days (Shaw et al. 1974), possibly due to carbamylation of a neuronal protein. This mechanism would explain why 6-8 weeks of exposure are needed, as the proteins are gradually carbamylated.

Finally, a specific lack of an essential sulphur compound may be the pathogenetic mechanism. No sulphur deficiency syndrome has been described; it is claimed that the general protein deficiency develops earlier (Whitney et al. 1991). In situations with high cyanide exposure week after week it is conceivable that a preferential use of sulphane sulphur for cyanide conversion ultimately makes sulphur availability drop to levels that could selectively impair the neuronal function of the motor cortex. It is noteworthy that spastic paraparesis is often one of the clinical signs of hereditary metabolic disorders with enzyme defects in the sulphur amino acid metabolism, such as homocystinuria (Bremer et al. 1981, Hagberg et al. 1970). Children in konzo-affected communities excrete more than half of their sulphur in the form of thiocyanate at a time when their intake of sulphur amino acids is below the daily requirement.

Optic nerve involvement is very common in neurotoxic syndromes and it has also been associated with cyanide exposure in the so called tobacco amblyopia (Freeman 1988). It is an argument for a neuro-toxic etiology but is a rather unspecific clue in the pathogenetic discussion.

ECOSYSTEM HEALTH & THE PREVENTION OF KONZO

Accumulating evidence that konzo is caused by consumption of insufficiently processed bitter cassava in combination with a low protein intake is now sufficient to warrant preventive measures. The increasing number of konzo epidemics during the last decade in several areas of Africa and the potential threat of further epidemics appears to be consequences of agro-ecological deterioration and rapidly increasing populations. Konzo can therefore be regarded as an ecosystem effect on human health, an environmentally induced disease and an "alarm bell" indicating the ecosystem collapse. There are a number of areas in Africa with similar agro-ecological crisis where high-yielding bitter cassava varieties are very important as a staple food, as mentioned in the etiological discussion (Carter & Jones 1993). Additional pressure on
such communities, such as changing marketing patterns through urbanization and improved transport as well as food shortage, may change cassava utilization practices and precipitate further konzo epidemics. Therefore konzo prevention should not be limited to already affected communities but also include identification of communities at risk.

Konzo must become part of the general medical teaching in Africa so that nurses and doctors can recognize it. Konzo outbreaks have previously been invariably misdiagnosed as outbreaks of poliomyelitis. Polio surveillance should distinguish between polio and konzo. There is a need to explicitly mention konzo in the WHO guidelines for polio surveillance (WHO/EPI 1991). This can help to diagnose konzo in low prevalence areas, where konzo patients can easily be mis-classified in a disability survey as other upper motor neuron diseases, e.g. cerebral palsy or post-encephalitis, as found in Central Africa (VI). In areas where konzo is a major disabling factor the disease is well known and readily distinguished from other gait difficulties. An important aspect in any preventive program is the rehabilitation of already affected persons and the combination of rehabilitation and prevention may well be an efficient approach.

The most important and a preventable factor seems to be insufficient cassava processing. Minor improvements of processing can substantially reduce the risk for dietary cyanide exposure (Banea 1992b, 1993). This can be highlighted by health education programmes promoting safe processing and providing the necessary utensils for populations at risk. Monitoring of the effects may be done by urinary thiocyanate determinations (figure 9).

In the longer perspective, preventive measures must tackle the underlying factors contributing to the deteriorating ecosystem. The promotion of sustainable agricultural ecosystems in Africa calls for much human creativity, skill and resolution (McMichael 1993).
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