

Working together to eliminate cyanide poisoning, konzo, tropical ataxic neuropathy (TAN) and  
neurolethyrism



# CCDN News

Cassava Cyanide Diseases & Neurolethyrism Network

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an Ethiopian boy adopted in an American family <sup>2</sup>. Some 'recycled' reports on cases that occurred decades ago in India or Ethiopia were also published. In the present issue professor Mishra reports on a survey in an area of India that is supposed to be prone to neurolethyrism, but found no new cases. The local diet consisted of a mixture of rice and grass pea seasoned with onion. This confirms the findings of dr Getahun in Ethiopia who identified addition of cereals and onion as protective factors in the epidemiology of neurolethyrism <sup>3</sup>. When dr Gopalan visited the Rewa district he noted that rice was cheaper than grass pea and that market effects may be responsible for the absence of new cases of neurolethyrism. Also in Bangladesh no recent cases are reported in the literature, and the price of rice seems to be lower than the price of grass pea. Poverty and food insufficiency during drought are often reported as risk factors, when the poorest and often illiterate only can afford the cheapest food available, which after a drought is grass pea. The absence of new cases in Ethiopia may be explained by the rapid economic development (up to +10% GNP/year). In the multi-pronged approach to prevent neurolethyrism, increasing the market value may be a valid tactic. Toxicity and nutritional value of grass pea remain a matter of controversy. While much research is focusing on physiological effects of ODAP in animal systems and its level in the plant, others herald the positive effects of grass pea on the ecology and on human health.<sup>4</sup>

In 2017, research on *Lathyrus sativus* and its neuroactive metabolite has also produced remarkable results. Metabolomic studies on the biosynthesis of  $\beta$ -ODAP have shown a link with primary metabolism.<sup>5</sup> This explains the difficulty to lower the content of  $\beta$ -ODAP by classical breeding, especially to develop varieties with zero ODAP. However, as the opposition against the use of GMO-technology in food seems to be waning <sup>6</sup>, there is hope that such technologies may circumvent the

## Editorial

The year 2017 seems to have given hope for the prevention of neurolethyrism, but new cases of konzo and new areas afflicted by konzo give a very different picture.

In the recent literature on neurolethyrism, we found the description of some older cases that have emigrated from Ethiopia to Israël <sup>1</sup> and the story of

metabolic obstacles.

The picture of konzo in several African countries is grimmer, although the interest for konzo is increasing. A recent issue of *The Lancet* carried a picture of a severe konzo case (see below) among prize-winning photographs.<sup>7</sup> The first epidemic of konzo has now been published as a case study for teaching purposes.<sup>8</sup> This may give rise to further epidemiological surveys like the one in this issue on a previously un-surveyed part of Mozambique. Even more alarming is the article by professor Boivin et al. on the effect of cassava on cognitive performance of small children in D.R. Congo.<sup>9</sup> This can have long-term effect on the development of the children and hence on the development of populations depending on cassava as staple food. In his comment, Charles Newton pointed out the often occurring limitation of sulphur donors in malnutrition. The deficiency of essential sulphur amino acids methionine and cysteine in cassava and grass pea is well documented and can be countered by addition of cereals or onions to the diet.

The low incidence of neurolathyrism in grass pea consuming regions, and the persistence of the high incidence of konzo in cassava depending populations might be linked to differences in economic development in the regions that influenced the availability of foodstuffs added in the diet to the grass pea or cassava staple, giving a better balance of essential amino acids and micronutrients. The recent low incidence or even absence of new cases of neurolathyrism is excellent news, but new periods of drought-triggered famine could dramatically change this, especially in view of the progressing change in climate.

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## Articles

### Hans Rosling – edutainer and konzo researcher

Hans Rosling, figure 1, died 7 February 2017. (1-3) He was a professor at the Karolinska Institutet in Stockholm, Sweden who became a well-known edutainer in 2006 after a TED talk. His message was that we need to base our worldview on facts and not on prejudices. He founded the foundation Gapminder ([www.gapminder.org](http://www.gapminder.org)) together with his son Ola Rosling and his daughter-in-law Anna R Rönnlund. The moving bubbles of the “Gapminder world” has been a success factor. (4) In 2018 a book will be published “Factfulness” which all three gapminder founding members have authored together. Hans continuously underlined the need to have an updated view of the world. Many of his presentations are available on YouTube. One of the most well-known is perhaps his 200 countries, 200 years in 4 minutes (5).

For most of the CCDN readers, Hans Rosling, may also be known as a prominent researcher on konzo. In November 2017 his autobiography “How I learnt to understand the world” was published, written in Swedish by him and an assisting journalist (6). In this autobiography, he describes how this came about. In the following, I will summarise some of the key events. You should know, however, that the original version is more elaborated and contains many hilarious memories.

The starting point was when he as an active member of the socio-democrat students' association was organising a meeting in November 1967 with a

Mozambican professor of anthropology from the University of Syracuse in the United States, Eduardo Mondlane, who at the time was the leader of the Mozambican independence movement FRELIMO. After the meeting, which was very poorly attended, Eduardo Mondlane said goodbye individually to each of the attendees by asking each of them:

“What are you studying? When do you get your exam?”

Hans, as a 19-year old first-year student in statistics, had not yet thought of any exam and answered:

“I start my studies in medicine next year and will graduate as a doctor in ... 1975.”

“Great! We will most likely be independent by then! Promise me to come to Mozambique and serve as doctor when you have finished! You will be needed!” Eduardo Mondlane said and smiled.

Hans kept his promise and on the 23 October 1979 he went together with his wife Agneta and the two first children Anna and Ola, to Mozambique to work as a doctor in the public health service for 2 years. He was appointed to the hospital of Nacala in Northern Mozambique where he worked together with a local doctor.

In August 1981, towards the end of his contract, he got a message written on a piece of paper:

“To the doctor in Nacala. Come immediately. Over the last days, we have admitted 30 children and women with paralysed legs. Is it polio? Sister Lucia,

Cava Health Centre.”

Cava, located over 100 km Northwest of Nacala, had a small catholic mission with a health centre, the most remote in the district of Nacala. Sister Lucia was an Italian nun and nurse who had worked there for over 20 years. She was highly appreciated in the area, known to ride a 250 cubic motorbike and never ask for help.

After a 1-day ride in a jeep, Sister Lucia welcomed them warmly. Hans noticed she was called “Mama Lucia” by the locals. Sister Lucia took the command and showed them to simple but clean guest rooms. Next morning after breakfast and prayer, it was time to examine the patients. Hans noticed that they all had the same history: Suddenly both their legs had become paralysed. No pain, no fever or other symptoms. All had become ill over the last weeks and many in the last week. They could feel touch in the legs and feet. Some were able to stand supported but this created spastic jerking. This was not polio. But which illness was it? The observations did not fit with any disease in his sizeable neurology book. Suddenly he was struck by a thought: this can be contagious! He became full of fear: “Can I become infected?” Or, “am I already infected?” And later: “why am I here? Someone more knowledgeable should be called to come and check this out.” He knew that a South African submarine had been sighted outside Cava. Had the desperate South African apartheid regime started using biological weapons? Hans describes how the thoughts of “Flee!” and “Professional duty” were fighting in his mind as he continued examining the patients.

In the middle of the examinations, sister Lucia invited him for lunch. “No time for lunch”, said Hans impolitely. “Of course there is time for lunch!”, said Mama Lucia. “Whatever happens we pray and eat at noon here in Cava. Without this, we could never had managed to stay on here for 20 years. How long have you worked in Mozambique?

“Soon two years”, Hans stuttered.

“So you are a newcomer and you should follow my advice.”

Hans followed her order and came for lunch. During Mama Lucia’s long prayer, Hans’s sense of professional duty overcame the fear and when she said “Amen”, Hans decided to be a researcher until the cause of this nasty disease was revealed.

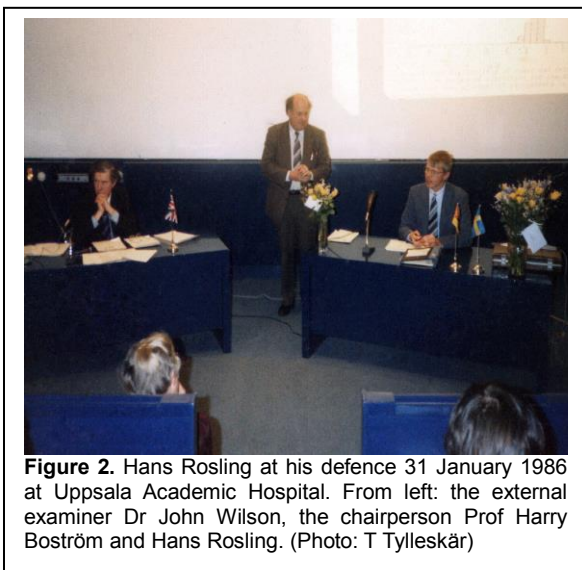
During the next two days, the patients continued to come. When looking at the overview of the patients, Hans noticed that the number of new cases doubled every week. It was not necessarily biological warfare. There had also been a severe drought in 1981. There was severe food shortage. People had started to eat wild plants. Could it be that any of



**Figure 1.** Hans Rosling by the end of the 1980's in his office at International Child Health (ICH) at Uppsala University where Hans worked from 1981 to 1996. (Photo: T Tylleskär

these wild plants was toxic and causing this disease? Back in Nacala, Hans and Agneta decided to evacuate Agneta and the children to Nampula town and that Hans should take the lead of the investigations of the outbreak.

Hans states that it is very straightforward to investigate an outbreak. Once you have defined the symptoms of the disease, a brief investigation is enough to decide if the patient has the disease or not. In this case, it was simple: a sudden onset of a spastic paraparesis (paralysis of the legs) and when you hit the tendon under the patella you get exaggerated knee jerks and when you hit the tendon of the Achilles, the foot starts jerking. Normal senses in the legs and no symptoms of tuberculosis



**Figure 2.** Hans Rosling at his defence 31 January 1986 at Uppsala Academic Hospital. From left: the external examiner Dr John Wilson, the chairperson Prof Harry Boström and Hans Rosling. (Photo: T Tylleskär)

of the spine.

The next step was to investigate half a million people in one of the poorest areas of the world. They visited all the village headmen in the area and assessed all 500 or so households where somebody had developed walking difficulties since the last rain. The best local nurses speaking the local language Makua were trained to conduct the neurological assessments. They filled out a form and each day they reported the cases to one of the doctors. The biggest challenges were to determine the age of the person and which day he or she fell ill in a population living without a calendar. The nurses the local calendar of events.

After six weeks, half a million people had been examined and a total of 1102 cases of the paralytic disorder, locally called “mantakassa” had been identified. There were three prominent patterns. The temporal distribution showed that the number of cases peaked by the end of August, going down in September and in October there were almost no new cases. The age and sex distribution showed that the large majority were children but nobody

below the age of two years and among the adults the large majority were women. The geographical distribution showed that the outbreak was limited to the agricultural areas located 10-40 km away from the coast. This was an area with normally little rain but this year had had a drought that had killed crops like maize, groundnuts and beans. The only crop that survived and saved the people from starvation was cassava.

An important part of an outbreak investigation is to determine whether the disease is contagious or not. Large efforts were invested in finding cases in the city of Nacala but in spite of intensive contacts between the countryside and in the city, there was not a single case in the city. So after three weeks they concluded that the disease does not transmit from person to person. That was a very crucial conclusion. Now Agneta and the children could come back to Nacala and the fear of personally getting the disease subsided.

Instead, their main suspicion was that the outbreak was linked to the drought. The outbreak coincided both in time and space with the drought. The main food crop in this area was the bitter type of cassava with a natural content of cyanide-yielding compounds, cyanogenic glucosides. Under usual circumstances the toxin was removed by slow sun-drying over weeks before making a stiff dough. The toxin was like an invisible lock on the crops that kept away the three most common thieves: monkeys, warthogs and hungry men.

Hans and Agneta turned to anthropology to better understand what was happening. They stayed with some rural families and a gentle translator for some time. Over and over they heard the same story: “we know the roots are bitter and the drought has made them even more bitter. We left them in ground for as long as possible hoping that the rains would come and make them grow bigger. In the end, I had to dig up the roots and try to speed-process the roots by beating the roots thinly and quickly sun-drying them.”

Based on these observations, they concluded that the paralysis was most likely caused by a combination of undernutrition and intoxication. The scientific publications with the results from the studies in Nacala were published in the Bulletin of the WHO and the Lancet (7-9) and formed the basis for Hans Rosling’s PhD dissertation, which he defended in January 1986.

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### **Survey of grass pea consumption in Gazipur, Uttar Pradesh, India**

“Excess of anything is toxic”, is a well-known quotation and the same was in the case of khesari dal. Khesari dal which was banned in 1961 due to its high degree of Beta-N-Oxalylaminoalanine (or  $\beta$ -N-oxalyl- $\alpha,\beta$ -diaminopropionic acid or ODAP), a neurotoxic amino-acid in the legume, which may be responsible for neurolathyrisms.

Khesari dal also known as the “Pulse of poor” is the crop which has the property to best withstand the adverse climatic and soil condition. *Lathyrus sativus* is a legume which is extensively cultivated in Madhya Pradesh, Bihar and to some extent in Uttar Pradesh; Bengal, Andhra Pradesh and Maharashtra. It is known locally as Khesari, Teora

Metra, lakh, lankalu, etc.

A survey was conducted on 9,345 subjects from the district of Gazipur (Uttar Pradesh) where the people were enquired about Khesari dal and its toxic effect. These people were found to be consuming Khesari dal on regular basis from past 4 years. This survey was carried out by the team of 4 trained volunteers and 2 neurologists from Institute of Medical Sciences, Banaras Hindu University and it took about almost 4 months to be completed.

It was found that of the total screened population, 97% were reported to be totally dependent on khesari pulse as the major source of food and even a single case of primary walking difficulty was not reported. Khesari is commonly consumed as a dal and mixed with rice, made into an edible handful ball and seasoned with salt and red chili. Mashed potatoes and onion are taken together with the khesari/rice balls adding flavour to the food intake. Those in middle to higher socioeconomic group consumed also other green vegetables.

In the screened group, 58% were non vegetarian having intake of meat with khesari dal, rice and vegetables.

In an another survey carried out on 500 peoples belonging to the state of Uttar Pradesh and Bihar it was found that a total of 20 subjects out of 500 respondents had prolonged history of Lathyrus intake (>7 years) but none has been reported with any clinical illness.

94% of the total respondents were aware of khesari dal and 100 subjects among those 500 had history of Lathyrus intake since 10-15 years. Out of those 100 subjects 82 had no clinical disorders, 9 of them had muscle aches and pains and 5 of them had early knee osteoarthritis and are already under medical supervision. The current survey of the subjects consuming Khesari dal has shown that there is no spastic paraparesis in the community which can be directly related to Khesari dal intake.

The research group says that the incidence of neurolathyrisms occurs during famines and not during normal conditions. Malnutrition and weak immune system may be risk factors for neurolathyrisms. Other factors include high exposure to Lathyrus toxin, cooking habits, genetic susceptibility and concurrent infections. So, environmental factors may be more important contributors to the incidence of neurolathyrisms than the consumption of Khesari dal. However, further research is needed to be carried out on Khesari dal compounds both *in-vivo* and *in-vitro* conditions using neuronal cell lines to prove or disprove the theory of neurolathyrisms in the present state.

We conclude that at present state in the most

densely populated area in India (Gazipur district of Uttar Pradesh province), people have been frequently taking Khesari pulse in their daily diet and have no spastic paraparesis reported yet. As this pulse is much cheaper than the other pulses so these should be allowed for free human consumption all over the world both in developing and developed countries.

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### Mapping of konzo and rehabilitation needs in Zambezia Province, Mozambique

In 1981, konzo was first reported from Mozambique in Nampula Province in northern Mozambique. A large epidemic was associated with drought. Along the years, smaller epidemics and sporadic cases have been reported in the province (Cliff et al, 2011). The last number of CCDNews gave information regarding rehabilitation of konzo patients in Nampula (Muloliwa et al 2017).

Zambezia Province lies further south, in central Mozambique. In 2000, 10 cases of konzo were reported in the District of Ile. The first case had occurred in 1998. In 2005, drought caused an epidemic in the province. Reporting was incomplete, with a total of 114 cases notified from four districts: Ile (14), Mocuba (78), Lugela (23), and Namarroi (3).

Along the years since 2005, anecdotal reports suggested that new konzo cases were still occurring in these districts and that konzo was also present in the districts of Alto Molocue, Gile, Maganja da Costa and Pebane.

As konzo had never been adequately mapped in the province, the Provincial Health Department, with the support of Netherlands Leprosy Relief (NLR), carried out mapping exercises in 2016 and 2017. The 2017 exercise was part of a konzo prevention and rehabilitation project funded by Australia's Department of Foreign Affairs and Trade. A flipchart was developed to teach methods of cassava

processing, including the new wetting method for cassava flour. As well as physical rehabilitation, the project also aimed to involve konzo patients in inclusive self-care groups, originally set up for leprosy patients, and to advocate for the rights of the disabled through disabled people's organizations.

Thirty communities in seven of the eight districts where konzo had been reported were visited; Lugela District was excluded for logistic reasons. The mapping was incomplete, as logistic difficulties also hampered the exercise in the remote rural areas where konzo mostly occurs. At community and district levels, mapping involved a large range of actors: representatives of Physical Medicine and Rehabilitation Services, Social Services, Neglected Diseases Programmes, and disabled peoples organizations, nutritionists, teachers, local administrators, local community leaders and activists, and members of leprosy self-care groups.

One hundred and eighty konzo patients were located in the Districts of Alto Molocue (7), Gile (21), Ile (51), Maganja da Costa (28), Mocuba (69) Namarroi (1) and Pebane (3). Overall, konzo was the leading cause of motor disability (difficulty in walking) in these communities. Of 313 patients with a motor disability, 180 (57.5 %) suffered from konzo. The proportion of disabled patients with konzo varied between communities. Seventy of the konzo patients were new cases, defined as onset from 2014 on.

Of the 313 disabled patients, 111 (35.5%) were classified as mild (able to walk without support), 154 (49.2%) as moderate (needs support to walk) and 48 (15.3%) as severe (unable to walk). 159 (50.8%) patients needed mobility aids. These are being supplied as part of the project.

This preliminary mapping shows that konzo is an ongoing cause of disability in Zambezia Province.

#### Lessons learned

1. Konzo is present in at least six districts in Zambezia Province, spread over a wide area.
2. Sporadic new cases of konzo are still occurring.
3. Mapping of konzo cases must be accompanied by prevention and rehabilitation programmes.
4. Konzo-affected areas should be a priority for community-based rehabilitation programmes.
5. Konzo should be included in neglected disease programmes.
6. Konzo patients should be involved in disabled peoples' organizations and their advocacy programmes
7. Konzo patients should be included in self-care groups.

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**Konzo, a forgotten disease in DR Congo**

Robert Medaer, Marys Kuypers, and Inge Kuypers, Lidwina vzw, de Gerlachestr 6, 3500 Hasselt, Belgium

The neurological condition Konzo occurs in populations affected by malnutrition and poverty in some African countries, including DR Congo, Mozambique, Tanzania, and the Central African Republic. Exposure to cyanide from inappropriately prepared roots of bitter cassava has a key role in the pathogenesis. Cassava needs to be detoxified before it is consumed. Neurological features of Konzo include acute or subacute spastic paraparesis, dysarthria, impaired visual acuity, and nystagmus. Correct preparation of cassava, as well as education and combating poverty can prevent konzo. There is no treatment; only rehabilitation can bring some relief. Lidwina vzw is a non-governmental organisation that helps care for people with multiple sclerosis in Belgium and for people with Konzo in DR Congo; the Belgian foundation focuses on prevention and medical care for patients with konzo in the DR Congo's Kwango province. This photograph was taken at the rehabilitation centre of the Soeurs de la Divine Providence in Kahemba earlier this year. In this centre there are about 300 patients a day who come for rehabilitation and for a free meal.

**Let's make Konzo disappear**

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