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

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EDITORIAL

In Memory of Prof Fernand Lambein

Prof Lambein was a leading academic and activist in the multidisciplinary network of scientists, agronomists, nutritionists, clinicians, and epidemiologists working on the paralyzing neurotoxic diseases of the poor in developing countries: konzo and neurolathyrism.

An outstanding scientist, he initially studied toxic amino acids in the grass pea (Lathyrus sativus), and applied the knowledge gained to understanding and preventing the disease, neurolathyrism. This irreversible spastic paralysis is caused by overconsumption of the grass pea under adverse agricultural conditions, particularly drought. Neurolathyrism had occurred in poor rural areas in a range of countries and persisted in Ethiopia and Asia. In1999, with Ethiopian authors, he drew attention to an epidemic in northeast Ethiopia in a letter to the Lancet. He noted the important role of the grass pea in preventing famine in drought prone areas of Asia and Africa and worked on improving its nutritional quality through biotechnology.

At the turn of the century, Prof Lambein carried out research on the paralyzing disease, konzo, in the DRC (Democratic Republic of the Congo) with Dr Delphin Diasolua Ngudi and colleagues. Clinically similar to neurolathyrism, konzo had been reported from some of the poorest rural areas of Africa during agricultural crises. Konzo was associated with a diet high in cyanogenic glucosides from insufficiently processed bitter cassava (Manihot esculenta). Both

konzo and neurolathyrism patients also suffered from essential sulphur amino acid deficiency. Like the grasspea, cassava was a lifesaving crop, helping prevent famine, but containing toxins which could cause paralysis under the most adverse conditions. Both were a mixed blessing.

I first met Prof Lambein in 2009 when he organized a workshop in Ghent on the two diseases, bringing together stakeholders and researchers from many countries. The subsequent publication in Food and Chemical Toxicology reflected the excellent standard of the presentations. In 2014, a second workshop in Kinshasa covered recent advances, innovation and engagement.

Prior to the Ghent workshop, Prof Lambein had been active in the Cassava Cyanide Diseases News (CCDN) network. The late Dr Howard Bradbury, a passionate advocate for the elimination of konzo, had founded this network and edited a six-monthly newsletter. In 2011, Prof Lambein took on the coordination of the network, with neurolathyrism now added, and continued to produce the renamed Cassava Cyanide Diseases and Neurolathyrism (CCDN) News. He sought out contributions and was the most helpful of editors, encouraging and improving our submissions. As Prof Thorkild Tylleskaar, a leading konzo researcher wrote: “he really went a long way to keep us together”.

Prof Lambein had enthusiastically taken on the cause of eliminating konzo and neurolathyrism. His dedication and skill helped bring the goal nearer. In all his research, Prof Lambein worked closely with scientists from affected countries, and coordinated research collaborations with many, including Bangladesh, the DRC, Ethiopia and India.

Thanks to Prof Lambein, a cohort of scientists has been inspired and trained to carry on the task of eliminating the two diseases, and making these lifesaving crops safer to eat and more nutritious.

We will stay together.

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On May 8, 2018, Fernand Lambein received a “Lifetime Achievement Award” for Lathyrus research from ICARDA (International Center for Agriculture Research in the Dry Areas)

Eulogy of Prof Fernand Lambein (1938-2020)

I first met Fernand at a scientific meeting in Addis Ababa, Ethiopia nearly 40 years ago. We were each talking about our own research. For me that meant animal neurophysiology; for Fernand that meant plant biochemistry. However, both our efforts concerned working on a chemical found in a food plant which, when consumed by humans, was believed to damage their nervous systems. We were actually approaching the same topic from opposite directions! On my return to London, I told my colleague, Professor Arthur Bell, Director Emeritus of the Royal Botanic Gardens at Kew, that I had met Fernand and he replied: Ah! He is an excellent plant biochemist. And so he was – but Fernand was much more than that!

The topic that Fernand was interested in was neurolathyrism. This disease occurred in rural India, Pakistan, Bangladesh and importantly then in Ethiopia, where a massive drought had caused widespread famine. It was associated with eating exclusively or predominantly a small seed, named grass pea (*Lathyrus sativus*). Those of us of more

than a certain age will remember Band-Aid, when a group of rock musicians performed in locations that were relayed across the world to raise money for the Ethiopian famine. In Ethiopia the drought resulted in a large increase in the incidence of neurolathyrism. My association with Fernand continued when he raised money for a research project on neurolathyrism from the European Union and he invited scientists in Europe, including myself, and in Ethiopia, India and Bangladesh to join him in that enterprise, which was highly successful.

Subsequently, Fernand became interested in another human neurological disease, in some ways resembling the pathophysiology of neurolathyrism, named konzo, which had a high incidence in parts of Sub- Saharan Africa, for example in the Democratic Republic of Congo and Mozambique, where cassava, a root crop, was eaten as staple food without being retting adequately. He then took on the Editorship (in 2012) of a Newsletter devoted to research on both konzo and neurolathyrism and somehow maintained its regular twice-yearly distribution until the very last, and recent, copy.

Fernand's ability to communicate with scientists around the world was remarkable. If you look at his extensive list of published scientific papers one is struck immediately by the geographical distribution of his collaborators. Japan, China, many countries in Africa, Syria, many states in America and, of course, many countries in Europe. This ability to communicate with others was shown at its best at the remarkable scientific meeting he organised in Gent in September 2009. There scientists from around the world presented their work on neurolathyrism and konzo. The effort involved to organise such a meeting must have been enormous – and that does not include raising the money to sponsor it. And Fernand was adamant that the conference proceedings would be published – the final result was a special issue of the *Journal of Food and Chemical Toxicology*.

Fernand and I talked science over many years and more than once I benefited from his assistance in the face of unhelpful reviewers or publishers, for which I was very grateful. Fernand had a great sense of humour and, as a master of the English language, his jokes in English were always excellent. He would tease me about the number of pairs of shoes that I took with me on our trips to Ethiopia. I actually own about 55 pairs (the number is imprecise!) so the choice was always difficult. I visited Fernand in Gent late in 2019 and he and Dianna took me to an excellent restaurant for lunch. Afterwards, at home, Dianna had laid out a wonderful afternoon snack for us and we toasted each other in champagne.

Fernand Lambein (left) and Peter Nunn (right) toasting to each other
Credit: *Photo Dianna, April 2019*

But, as I left for home, Fernand insisted on examining the shoes I was wearing - and Dianna took a photograph of them!

Fernand was a great family man and his wife, Dianna, and daughters (Ingrid and Kathleen) meant the world to him. Those of us who were privileged to know the family appreciated Dianna's subtle influence - always there behind the scenes - as well as being the Yu-haey Kuo of so many publications. Our thoughts are

with them all in their time of loss, but I am sure that the admiration that Fernand attracted, both as a person and as a scientist, will be a continuing comfort for them.

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Neurolathyrism in Ethiopia is downing in the discourse: the epic sight of Prof. Lambein - 'the antidote '- is prevailing

Persistent in the struggle for the Vulnerable

Listen to the voice for the voiceless victims of Neurolathyrism and konzo in the developing world. Neurolathyrism and Konzo, are human crippling diseases remaining a persistent problem in many low income countries of sub Saharan Africa and Asia. (https://www.youtube.com/watch?v=LEYzIOBwLSs) These health concerns can't be discussed without mentioning the late Prof. Dr. Ir. Fernand Lambein, 'I call the antidote", who dedicated his scientific career in developing solutions and thus try to save the life of those vulnerable and voiceless victims. The sunset of the professor seems to coincide with the last episode of the threat. Lathyrism is now more than a health issue, it is a social issue too.

I am probably one of the latest students trained by the Prof. Lambein, and would like to testimony the sparkling legacy left by him for the next generations in the lathyrism response. Prof. Lambein has marked my life, is resonating in me as a citizen of a lathyrism hit nation. I remember my first arrival in Europe in 2004 when, along with two Ethiopian colleagues Lijalem and Dejene, and after 7 hours of flight from Addis to Brussels, he warmly welcomed us at the airport and shared a lunch with us in Ghent. It was the beginning of a learning period of science and Belgian culture that punctuated with our academic graduation. Therefore, it is impossible for me to take distance from those memories.

Prof. Lambein's struggle to understand the aetiology and traceability (Kuo, et al, 2007) of the disease even went to his courage to commit himself as test subject (what he told me). The voiceless including many thousands Ethiopians and manifolds in Asia (India, Pakistan, Bangladesh, Nepal, China) who have been his main concern along his scientific life since early 1980s and until his last days. In sympathy, he tried his best to share his view what a young crippled fellows could have been doing when otherwise casted of any societal affairs including marriage and other social norms due to contracting lathyrism. He co-published neurolathyrism symptomatology, its possible cause, its socio-economic impact, and actually he firmly did not curse Lathyrus but the perceptions. He has well rationalized this in the different topics of publications he authored or co-authored. And the his salient point of message was that the crop is both health threats and lifesaving depending on the scientific understanding of its safe utilization. He described the clinical manifestation of the disease that varies depending on personal physiological response or on grasspea consumption level.

Prof. Lambein was among the pioneer academics to map-out the neuro-degenerative pathway of the disease under development curve neurolathyrism. However, the genomic era couldn't help advancing the scientific tool application of the crop yet, due mainly to priority issues, despite hundreds of millions are consuming this climate-resilient crop today.

The crop

Lathyrus sativus is among the climate smart crops of the world, equally responding to contrasting extremes of over and under moisture stresses. In climatic calamities, particularly drought, millions

could have died, however survived with the price of only few thousands (5-10%) left with persistent crippling (Lambein et al, 2007). The Ethiopian drought in the 1980s put 6% of the population at epidemic location with not more to eat than grasspea. Prof. Lambein, has been instrumental in establishing the epidemiological understandings of this vital but misunderstood crop, citing Vapinarica re-visited (Lambein et al, 2001).

In Ethiopia, according to central statistical authority (CSA1999 and 2019) grasspea cultivation is expanding (#households, area (ha), production (q) and yield (q/ha) have been changed between 1999 and 2019, respectively 562000 to 633000, 125000 to131000, 1.8mill to 2.6mill, 14.7 to 19.9), however, the new disease incidence is shapely going down for a number of reasons. The socioeconomic changes, knowledge-based consumption, market value improvement of the crop are among the key change makers, which Prof. Lambein's communications and advises were among central to perception changes. In the same manner, a study clearly revealed that β-N-Oxalyl-l-α,β-diaminopropionic Acid (β-ODAP), a free amino acid known to cause the oxidative stress is a highly ecological functions molecule (Asnake et al, 2006, Haque, 1997). Hence, a package on the safe utilization of the crop with great potential was formulated and recommended for consumers and farmers.

Scientifically, the molecule is blamed of causing an irreversible spastic paraparesis, neurolathyrism, after over-consumption, a negative aspect for an otherwise very tasty, nutritious, easily cultivated and hardy food crop in Asia and Africa. One of the key propositions of Prof. Lambein that zero ODAP grasspea may be an illusion, as the molecule is a biofunction of the plant that possibly affect the nature of the crop as it is linked to life functionality (Lambein et al, 2007), if avoided is still waiting the time to proof. However, he dedicated five decades of his life for the purposes of millions and has promoted grasspea globally, explained its challenges and his understanding of the crop to make it no more a health threat but an opportunity for the future world.

Changing the challenges to opportunities

Following its safe utilization, grasspea could be hope of livelihood improvement, cash generation and nutrient dense food security for millions in the world. Despite the ban posed on the crop in some parts of the globe, and limited research and development investment made to the crop, lathyrus is competitive in the field and expanding, replacing some of the weak legumes. In Ethiopia the grown area (>130 000ha) of the crop and productivity (>2t/ha) level are increasing just a leap. Many gravy /shiro/ houses in many cities and towns of Ethiopia have processed grasspea as their main ingredient, which is a staple food used with Injera (Getahun et al, 2002, Kelebesa and Mengistu, 1993). An estimated 20-30 million population of Ethiopian are using the product at home or on those service houses.

The Unfinished Journey

Professor Lambein in a global collaborative research has moved the status of the crop from less known to more understandable and spelt out precautionary measures. However, this crop, which has been used as a pulse for at least 8000 years (https://www.youtube.com/watch?v=LEYzIOBwLSs), has made little progress as a food crop during this time. The genomic era ought to have the robust marker tools in developing progeny lines not only free of ODAP but as well with favorable agronomic traits. The value of the crop is suppressed for failure of science to come up with intended products for utilization. It should also be clear that this crop of future global potential would have to be part of the policy and development agenda of producer nations. The journey in developing cultivars free of the toxin at times would be commercialized. Advance in science and technology could capture the technical gaps of lathyrus products based on beneficiary demands.

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ARTICLES

A non-toxic plant can help millions of people over the hunger threshold

Everything in his lab revolved around that very nutritious grasspea

(*Translated with the permission of the author from his Flemish article published in a local newspaper ' De Serrist' on March 19*)

Once during their career, every journalist writes a piece that touches him personally. I realise this even better now, because this is one of those articles. It's about an almost 82-year-old honorary professor at Ghent University. Fernand Lambein. I already wrote about him in 2015. That's when I introduced you to the grasspea. That was 'his' plant, because its characteristics and peculiarities fascinated him for decades. As a young bio-engineer, he was already driven to learn all about it. Why is this nutritious plant so poisonous? How and why... By the way, his wife is also a bioscientist, and together they formed a solid scientific tandem for decades. Until his passing on March 4th 2020, he remained very active. He was the editor of a biannual scientific newsletter, reaching out to like-minded researchers worldwide. His life-long research leaves a legacy on Lathyrus, and beyond.

Science is passed on from generation to generation. Each research result is like a seed, a small grain of a plant from which a new plant can grow. A plant scientist is like a gardener who has an eye for everything living, with a lot of passion and patience to harvest something beautiful. Blessed with peace and wisdom to cope with adversity, Fernand was one of those people. By the way, he also was a gardener at heart. He could arouse the interest of many in research. Long-term research work such as that carried out by Fernand and his colleagues all over the world provides building blocks for future research.

Prof Fernand Lambein with Lathyrus sativus plants at the green house of Ghent University in 1987
***Credit**: Jean-Pierre Dubois - Science Press vzw, Ghent.*

TELEVISION

I've known Fernand Lambein since the early 1980s and interviewed him in 1986. On July 1st 1987 he was filmed for my first television report for Belgian Radio & Television (BRT). A few months later he was in the tiny studio of the science magazine Horizon.

His wife had given him some flat bread to share with the presenter. They were mainly baked with flour from that plant, the grasspea or Lathyrus sativus, and proved that the protein-rich seeds can be tasty as well. Fernand Lambein was one of those scientists we didn't often see on television. He usually remained in the anonymity of the lab or the international scientific scene. I will forever remember that first television broadcast at the beginning of October 1987. Then, finally, there was that much talked about documentary in the series Recover the Earth by Canvas (Belgian TV). That was the documentary “Bound Legs” during the Easter holidays of 2004. A film that reappeared on television in 2007. A long time ago, but you may remember, it was an exceptionally beautiful documentary taking a closer look at that research work, in Ghent and in Congo. Research by Fernand Lambein and his then Congolese doctoral student Delphin Diasolua Ngudi. They each conducted their own research but with similarities.

The seeds studied by Fernand, those of the grasspea, are poisonous if eaten as a main staple food for a long period of time. Delphin's cassava, if it is not soaked or not soaked long enough before being eaten, is poisonous as well. Everyone could see and understand those similarities, in a cinematic attractive way. Staged? Sometimes it is, because the professor was in a library of the department, and not in his much smaller office. But, that too is television, and everyone could see that Fernand and Delphin were attuned to each other. I know Delphin from around the end of 1999. He once confided to me that Fernand was like a father to him. A real dad. Delphin knows why.

CLASSICS

Soon it will be summer again. In many gardens some of the classic ornamental plants will bloom. Once they were brought from faraway places and became established here. For example, because they have very attractive and highly scented flowers. You might not be familiar with that grasspea, Lathyrus sativus? But very likely you do know a related species. That's the fragrant Lathyrus or Lathyrus odoratus. Originally that plant grows in Sicily and southern Italy.

It belongs to the butterfly-flower family and is a climbing plant with stems of up to three meters long. Its flowers are two to three and a half centimeters wide and turn purple-blue to crimson purple. That "sweet pea" or "runner bean", to address them with just two folk names, is very fragrant. Unless it is one of the not so fragrant cultivated varieties in one of the color variations from white, creamy white, pink, lilac, light purple, purple, red, crimson… to two-tone. That sweet-scented Lathyrus is also called sweet pea or runner bean, because it also bears long, fluffy and brown-colored legumes from five to nearly eight inches. I’m sure that Lathyrus varieties grow and bloom in Fernand's garden.

From Left to right: Delphin Diasolua Ngudi, Yu-Haey Kuo and Fernand Lambein presenting their research work in 2012

***Credit**: Dianna, IPBO-VIB/ UGENT*

TOXICITY

There is more than one story to tell about Fernand's seed Lathyrus. For him it was certainly the most peculiar Lathyrus strain. In the spring of 1986 I already interviewed him for the new monthly magazine for Flemish researchers, which I compiled and published: ‘Wegwijs in wetenschappen’, a magazine with an emphasis on how scientists presented their research to journalists and the public.

I quote from the first edition of April 1986, about those feral or sometimes ornamental Lathyrus varieties: "No harmless herbs, because all plant parts are poisonous, especially the seeds. Their toxic components consist of certain amino acids. Amino acids are the building blocks of proteins. But in the Lathyrus varieties, these are special amino acids that cause two forms of poisoning (Lathyrism) in humans and animals: firstly osteolathyrism: the poisonous amino acid in the seeds mainly affects the musculoskeletal system. It blocks the normal production of the proteins collagen and elastin. This leads to softening of blood vessels, tendon and bone tissues and skeletal abnormalities. Poisoning occurs in rats, chickens and ruminants. Lathyrus seedlings can accidentally end up in animal feed and further processing. The second form is called neurolathyrism, when special amino acids that act on the nervous system. This poisoning is accompanied by, among other things, stiff, difficult gait and paralysis. The seeds are only dangerous if they are eaten in large quantities (for example in feed meal) for a long time (weeks or even months). In Belgium and in the Netherlands, the risk of poisoning is virtually excluded, because seedling Lathyrus is not grown here as a fodder plant. "

HUNGER THRESHOLD

Of course I can't tell you all about that curious plant. The crux of the story, however, is that the grasspea is poisonous yet also carries very nutritious seeds. Those seeds have a high protein value of 28 to 40 percent. In short, those seeds are very nutritious, and that has been known since ancient times. Just like their toxicity. "A nontoxic variety of the grasspea can help millions of people breach the hunger threshold," Fernand Lambein emphasized in my 1987 TV report. He often said very clearly and firmly that the poisonous plant could and can save a lot of lives. After all, it grows in dry, semi-arid areas, where it is sometimes the only food-bearing species. In the BRT report, Fernand showed a handful of dried seeds as they are sold in markets in India and Bangladesh, among others. The flour from broken seeds is processed in flat breads or in soup. When the seeds are cooked and the cooking water is poured off, they contain a lot less poison and can be safely consumed. However, water is scarce in these areas. The same holds true for cassava, the root that is staple food in Congo, among others. Unsufficiently soaked cassava is poisonous, because it contains hydrocyanic acid (cyanide). Hence the similarities between the research of Fernand Lambein (grasspea) and nutritionist Delphin Diasolua Ngudi (cassava). In dry or parched regions of the earth, the grasspea is often the only crop to survive a dry season. I never saw Fernand get angry, but he could get excited about injustice. Who not? Especially if you, as a researcher, realize that a plant like the grasspea could become a very important and safe food crop. If it were deployed with thorough research. If more money for important biotechnology research would be available. If scientists were heard.

IDENTITY

The researchers have known the identity of the poison in those very nutritious seeds since 1964. In 2015 I wrote here: “A small number of researchers, together with Fernand Lambein and his wife as driving forces, persevere and want to know the reason for that poison.” There are many valid reasons for this, not just scientific curiosity. The goal is to ultimately prevent neurolathyrism, which affects the poorest and most vulnerable people in India, Pakistan, Bangladesh and Ethiopia. The consequences of neurolathyrism are not unknown there. In 1986 I wrote in my newsletter Wegwijs in Sciences: "The treacherous, crippling disease occurs in different degrees: the one-stick stage, the two-stick stage and the crawling stage. The patient goes with one stick, needs two sticks or can only crawl. The cause is Lathyrus sativus (grasspea), a plant that is almost insensitive to drought. It is normally grown in mixed cultures or as an intermediate culture in winter. In severe droughts, sometimes only this pea survives and even yields a normal harvest. The triangular peas are nutritious and delicious. The toxic component can be partially removed by boiling and discarding the cooking water. But in a dry period, people cannot waste the scarce water for that. They eat the flour of the untreated peas in flat bread and in soup. Sometimes they refuse to accept that

something that keeps them alive can be poisonous".

MISERY

So much misery from a "misery plant"? People don't realize that their misery was caused by the uncooked seeds. "There are 10,000 sick in Bangladesh," I wrote in 1986, to emphasize that many people are involved. "The worst affected region is Madhya Pradesh," I then remarked. "In this northern, yet feudal state of India, more than 3 percent of the male population is affected. In the Rewa district alone, there are believed to be about 25,000 victims. The social system is partly responsible for its spreading. The poorest agricultural workers are sometimes tied to a large landowner for life. In the event of food scarcity, their scant in-kind wages mainly consists of Lathyrus seed. The cultivation and sale of grasspea is prohibited by law. But this does not prevent the poisonous plant in India from being grown on almost 1 million hectares. The seed is also used to dilute more than fifty percent flour from other grains. The Indian government does little or nothing. "Old news? Certainly not. The research should continue. With Fernand's drive and vision.

Fernand Lambein (°Ostend, June 3rd, 1938) passed away on Wednesday March 4th 2020 in Ghent.

Due to the corona crisis, the funeral ceremony had to be postponed. So long Professor!

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International Collaboration to Identify and Edit Cassava Genes Associated with Cyanogen Accumulation

On January 16–17, 2020, scientists gathered at the Innovative Genomics Institute (IGI, California, USA) to share findings and coordinate efforts to reduce cyanogen accumulation in cassava. The IGI (https://innovativegenomics.org/) is an academic partnership between the University of California campuses at Berkeley and San Francisco that supports a wide range of research projects including sustainable agriculture. At the IGI, Drs. Jessica Lyons and Michael Gomez lead a project to reduce toxic cyanogen accumulation in cassava plants using the genome editing tool CRISPR. They were joined by Professor Roslyn Gleadow (Monash University, Australia), and Drs. Alex Ogbonna and Guillaume Bauchet of the Lukas Mueller lab (Boyce Thompson Institute, New York, USA). The goals of this meeting were to facilitate information exchange, coordination of activities, capacity building, and technology transfer toward the goal of modulating cyanogen accumulation. Professor Brian Staskawicz, IGI Scientific Director for Sustainable Agriculture, Dr. Myeong-Je Cho, Director and PI of the IGI's Plant Genomics and Transformation Facility, Professor Daniel Rokhsar, and graduate student Nicholas Karavolias also participated in these fruitful discussions.

IGI members and UC Berkeley affiliates were invited to a mini-symposium featuring presentations by Gleadow and Ogbonna. Gleadow has advanced research on the effect of climate change on food security, with a focus on plants that make cyanide, and the impact on human and animal health. She is President of the Global Plant Council, an expert advisor to the Agricultural Biotechnology Council of Australia, and a founder of the International Safe Cassava Working Group. This organization aims to develop and share food safety strategies including farm management, classical breeding, GMO solutions, governance, and effective food processing methods. In her presentation "Cyanogenesis, Stress, and Photosynthesis are Entangled," Gleadow delivered a fascinating examination of how plants allocate resources to energy production and defensive chemical synthesis. Rather than being distinct alternatives for resource allocation, these processes are interconnected. Understanding these relationships is valuable for minimizing inadvertent effects on plant growth arising from the reduction of cyanogens in cassava.

Ogbonna worked on the cassava molecular breeding team at National Root Crops Research Institute in Nigeria, and with Bauchet and Mueller to develop database tools to assist breeders of cassava (cassavabase.org), banana, yam, sweet potato, maize, and solanaceous crops. His talk on the

"Genetic Architecture and Gene Mapping of Cyanogenic Glucoside in Cassava" exhibited the first genome-wide association study (GWAS) to characterize cyanogen accumulation. This work was a collaboration between the NextGen Cassava Breeding Project (https://www.nextgencassava.org/) and EMBRAPA in Brazil. Their genomic analysis of over 3000 cassava landraces identified two novel genes of interest. Further study of their roles and contributions to cyanogen accumulation is underway. Ogbonna, Bauchet, and Mueller's work provides a valuable resource for genetic studies of cyanogens in cassava.

At the IGI, Lyons and Gomez capitalize on technical expertise in genome editing and a well equipped cassava transformation platform. They aim to modulate the levels of cyanogen accumulation using CRISPR. In addition, they are developing and applying non-transgenic methods for cassava genome editing, which would obviate drawn-out regulatory hurdles. Targeted genome editing provides the opportunity to shut off particular genes of interest with little to no impact on other genes responsible for desirable traits. While it is impractical to apply the slow methods of conventional breeding to a diverse set of cassava cultivars, genome editing can in principle be applied directly to any existing germplasm. Leveraging this technology with the expertise and resources of these international partners amplifies the potential for quick widespread impact on food security in many tropical and subtropical regions around the world.

A CCDNN article regarding a symposium last year on cassava, cyanide, and konzo, and the founding of the International Safe Cassava Working Group may be found at: http://ipbo.vib-ugent.be/wp-content/uploads/2019/08/CCDNN-33.pdf (pages 6–7). A recent article from Gleadow on temperature, carbon dioxide, and cyanogenesis in cassava may be found at: https://www.sciencedirect.com/science/article/abs/pii/S009884722030023X. More information on Ogbonna's and Bauchet's research may be found at: https://www.biorxiv.org/content/10.1101/2020.06.19.159160v1. More information on Lyons' and Gomez's research may be found at: https://innovativegenomics.org/projects/genome-editing-staple-crop-cassava-eliminate-toxic-cyanogen-production/

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Neurolathyrism in Madhya Pradesh, India, 1833-34: from *Rambles and Recollections of an Indian Official* by W.H. Sleeman

When first I came to study neurolathyrism, I was intrigued by constant references in the literature to a book by one W.H. Sleeman, containing a description of an outbreak of neurolathyrism in Madhya Pradesh, India, early in the 19th century. I had not met anyone who had read this account and, although I had often looked for the work in libraries and bookshops, I had never found it. One day in the southern British coastal town of Brighton, my wife disappeared into an up-market dress shop – no surprises there! Nearby was an attractive antiquarian bookshop, which I entered and asked if they knew of the Sleeman book. To my surprise the answer was: "We have both volumes"! I hadn't realised that there were two and the price for the pair was breathtakingly high. However, I had been searching for over 25 years and so I took the plunge. I realised only later that, of the 937 pages contained within my two precious volumes, only a little over two pages were devoted to neurolathyrism! Further, it seemed the volumes had been rebound at some stage for, on the spines, the word 'Recollections' had been mis-spelled on both volumes. Worse was to come when I showed my prizes to a colleague who was interested in old books. "Didn't you try Abe Books on the web"? I didn't know of the existence of Abe Books then (warning: it is owned now by Amazon!), but I quickly found a number of copies of Sleeman's book on their website, some in pristine original bindings and all at one-half the price I had paid!

Earlier this year I proposed to Fernand Lambein that I would write something on neurolathyrism for the next edition of the CCDN Newsletter. It is difficult to write something new about a disease that is

apparently disappearing (Singh and Rao, 2013), probably as a result of better nutrition now that rice has become more plentiful even to the poorest people previously at risk of neurolathryism. However, it occurred to me that many of us are unaware of the scourge that neurolathyrism had been to people of the Indian sub-continent in times past. Those who worked on this subject hoped that, if one could discover the mechanisms that underpinned neurolathyrism, they might also unlock the mechanisms behind the sporadic neurological disease, motor neurone disease (MND; also named amyotrophic lateral sclerosis, ALS). Although many mechanisms have been proposed to explain the causation of neurolathyrism, none offers a full understanding nor, despite considerable advances in medical genetics, have the origins of sporadic MND/ALS been revealed. Whether the two subject areas will eventually coalesce is not foreseeable.

I have transcribed, as accurately as I can while preserving the original syntax and punctuation, the account by Sleeman (first published in 1844) of his experience in an unnamed village close to the Mahadeo Hills in southern Madhya Pradesh. As the book is so difficult to find, I hope that this transcription will make the text available to more researchers than know it at present. It appears that the book was written as a diary while the author travelled from Jabalpur, Madhya Pradesh, to Meerut, Uttar Pradesh, in 1836 (UCLA Social Sciences), a distance of 424 miles (682 km). Nowadays, Sleeman would not have had as much time for writing as he had in his time, for a train service now takes just 20 hours! Sleeman became a major-general in the Bengal army and an administrator in the city of Gwalior, in northern Madhya Pradesh. Volume 1 contains an introductory preface, an affectionate letter to his sister, but I can find no indication of the reason for his journey.

Sleeman wrote “In 1829 the wheat and other spring crops in this and surrounding villages were destroyed by a severe hail-storm; in 1830 they were deficient for the want of seasonable rains; and in 1831 they were destroyed by blight. During these three years the teoree, or what in other parts of India is called kesāree, (the lathyrus sativus of botanists,) a kind of wild vetch, which, though not sown itself, is left carelessly to grow among the wheat and other grain, and given in the green and dry state to cattle, remained uninjured, and thrived with great luxuriance. In 1831 they reaped a rich crop of it from the blighted wheat fields; and subsisted on its grain during that and the following years, giving the stalks and leaves only to their cattle. 1n 1833 the sad effects of this food began to manifest themselves. The younger part of the population of this and surrounding villages, from the age of thirty downwards, began to be deprived of the use of their limbs below the waist by paralytic strokes, in all cases sudden, but in some more severe than in others. About half the youth of this village of both sexes became affected during the years 1833 and 1834; and many of them have lost the use of their lower limbs entirely, and are unable to move.

The youth of the surrounding villages, in which the teoree from the same causes formed the chief article of food during the years 1831 and 1832, have suffered in an equal degree. Since the year 1834 no new cases occurred; but no person once attacked had been found to recover the use of the limbs affected; and my tent was surrounded by great numbers of the youth in different stages of the disease, imploring my advice and assistance under this dreadful visitation. Some of them were very fine-looking young men of good caste and respectable families; and all stated, that their pains and infirmities were confined to the parts below the waist. They described the attack as coming on suddenly, often while the person was asleep, and without any warning symptoms whatever; and stated, that a greater proportion of the young men were attacked than of young women. It is the prevailing opinion of the natives throughout the country, that both horses and bullocks, which have been much fed upon teoree, are liable to lose the control of their limbs; but it the poisonous qualities abound more in the grain than in the stalk or leaves, man, who eats nothing but the grain, must be more liable to suffer from the use of this food than beasts, which eat it merely as they eat grass or hay.

I sent the son of the head man of the village and

another, who were among the young people least affected, into Saugor with a letter to my friend Dr. Foley, with a request that he would try what he could to do for them; and if he had any fair prospect of being able to restore these people to the use of their limbs, that measures might be adopted through the civilian authorities, to provide them with accommodation and the means of subsistence, either by private subscription or by application to government. The civil authorities, however, could find neither accommodation nor funds to maintain these people while under Dr. Foley's care; and several seasons of calamity had deprived them of the means of maintaining themselves at a distance from their families."

The author continues in the most sympathetic terms to deplore the lack of medical assistance afforded to the affected population by local administrators. According to an entry in Wikipedia, Sleeman held a liberal social attitude that was uncommon at the time in his colleagues and compatriots.

I hoped that Fernand would forgive me for the lack of originality of this article, but the transparency of the writing seems to bring us, almost 200 years after it was written, so close to Sleeman's experience that it might have been our own.

References

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Konzo and cassava toxicity and the legacy of Hans Rosling in global health

(Abstracts from the 11th European Congress On tropical Medicine and International health, 16-20 September 2019-Liverpool, United Kingsdom)

OUTBREAK OF AN UNKNOWN PARALYTIC DISEASE IN NORTHERN MOZAMBIQUE – DISCOVERING THE EPIDEMIOLOGY OF KONZO

In August 1981, Hans Rosling was working as a district medical officer in northern Mozambique when he received the news of an outbreak of paralysis at a remote mission station, 100 km away. He went there immediately and found that the patients had a uniform history of sudden onset of spastic paraparesis. The number of cases was rapidly increasing, and reports began to come in from a wide area covering hundreds of kilometres, with a population of around half a million people. A classic epidemiological investigation followed, with Hans organizing community leaders to carry out active case finding. After six weeks, 1102 cases had been identified. The epidemic had begun in May, peaked in August and lasted until October. Children over two years of age and women of reproductive age predominated. The nearby coastal region and urban centres were spared. The area was suffering from a severe drought. The cause of the disease was not known, and laboratory results from patients showed no infectious agent. Suspicion fell on a toxin, but the grass pea, known to cause spastic paraparesis, was not consumed in this area. Hans turned to anthropology, staying with rural families and taking detailed histories of food consumption. He found that people were dependent on a diet of newly harvested bitter cassava, the only crop to have survived the drought. Bitter varieties of cassava contain high concentrations of cyanogenic glucosides that need to be removed by processing. People were hungry and taking short cuts in processing. The lab therefore tested for serum thiocyanate and found extremely high concentrations (mean 298 µmol/l). We hypothesized that the cause was cyanide intoxication from a monotonous diet of bitter cassava. The epidemiology fitted – the peak of the epidemic coincided with the cassava harvest, children over two and women of reproductive age were more

dependent on cassava and on the coast, people had access to fish. Although we had not found the disease in our textbooks a thorough grey literature search subsequently revealed that an identical disease, konzo, had been described by Trolli in the then Belgian Congo in 1938.

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A SECOND OUTBREAK OF KONZO IN TANZANIA – DEFINING THE CLINICAL PICTURE OF KONZO

Introduction: Outbreaks of paraplegia are known historically to occur in the tropics and have been documented from the early part of the last century. Their aetiology has been mostly attributed to nutritional causes varying from lathyrism caused by consumption of large quantities of chic pea (lathyrus sativus) to B vitamin deficiency and more recently cassava consumption.

Aim: The aim of this presentation is to report the neurological findings from an outbreak of paraplegia occurring in a drought affected cassava growing rural area of northern Tanzania in 1985.

Methods: A detailed neurological examination was carried out on 39 affected persons.

Results: The clinical findings was similar in all cases: characterised by an abrupt onset of initial difficulty in walking progressing to paraparesis over 2-3 days. Typically a previous heathy child or young adult developed heaviness in the legs or inability to stand either during or after long walk or present on waking. Less than one third complained of transient lumbar pain, numbness in legs, difficulty speaking and difficulty seeing typically clearing in the first days or week. On examination, the physical findings were characterized by a symmetrical spastic paraparesis with hyperreflexia in the legs 100%, ankle clonus 90% and extensor plantar response 85%. Power was reduced in the legs in 82% varying from severe 54% to mild 23%. Arms were involved in 56% typically with isolated hyperreflexia or mild weakness except in 2 most severely affected cases with severe weakness. Optic pallor was noted in 6 cases 15% 5 (83%) of whom had had a previous episode of paraplegia. A selection of the affected patients were re-examined at 1, 2, 10 months and 3 years after the first examination and the neurological findings remained unaltered with the same degree of spastic paraparesis and a characteristic scissors gait.

Conclusion: The clinical findings were those of a unique form of epidemic spastic paraparesis, which resulted in almost identical upper motor findings in affected patients but differing only in degree.

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A THIRD AND LARGE OUTBREAK OF KONZO IN THE DEMOCRATIC REPUBLIC OF CONGO – GETTING CLOSER TO THE CAUSATION OF KONZO

A brief notice in 1982 in the WHO Weekly Epidemiological Records about an outbreak of an unknown spastic paraparesis in Zaire, present-day Democratic Republic of Congo, had made Hans Rosling very curious, wondering if this was the same disease as the one found in Mozambique and Tanzania. This led to contacts with CEPLANUT, the National Nutrition Planning Centre at the Ministry of Health in Kinshasa. The Swedish-Congolese team conducted three large field studies (1988, 1990 and 1996) and in the first one, we noted that the disease was identical to that of Mozambique and Tanzania. The staple crop was cassava as in the two previous outbreaks. However, there had been no drought in the area as in the two previous areas. Instead a new road had been constructed which had led to intensive sales of cassava to the capital Kinshasa. This in turn had forced the population to short-cut the cassava processing and high concentrations of urinary thiocyanate in the population confirmed a similar toxic exposure as in the two previous outbreaks. Further development of biochemical methods to assess cyanide exposure was needed and in the second field study we were able to conduct the smallest case-control study ever published in the

Lancet: 3 persons with a history of 1-3 days of falling ill with konzo were proven to have elevated blood cyanide concentrations, compared to 20 controls in the same villages. In the third field study, we conducted an intervention to see if sulphur amino acids could decrease the toxic exposure with no effect. We concluded that konzo is similar to a traffic accident; the damage that happens with the accident cannot be reversed. Focus must therefore be on prevention of the exposure or the accident.

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MOLECULAR ANTHROPOLOGY – WHAT WE CAN LEARN FROM HANS ROSLING'S INTERDISCIPLINARY WAY OF CONDUCTING RESEARCH IN AFRICA

Hans Rosling had a bright research career in the 1980s and 1990s before his career as 'edutainer' and stand-up statistician from Karolinska Institute and the Gapminder foundation. It started during his time a district medical officer in Nacala in northern Mozambique in 1981 when he was confronted with this outbreak of konzo. This was the starting point for a series of field studies in several African countries. His research was characterized by an extreme interdisciplinary approach, which he called molecular anthropology. In the first outbreak in Mozambique, he noticed that the field staff he sent out in the rural villages where there was drought and famine came back with cassava for their own consumption – every day. In the then strictly socialist society, this required a lot of tact, sensitivity, patience and anthropologic methods to reveal the truth about how cassava was handled because of the stigma attached to it. No one had heard of cyanide or cyanogen compounds causing paralysis, so biochemical methods had to be developed and then brought out in the field for confirmatory use. The larger research community could not understand why people we so "stupid" to grow toxic food crops but Hans was convinced that poor people were not stupid, there was a good reason for why they did what they did. Again, this required tact, sensitivity, patience and anthropologic methods to understand the agricultural aspects of growing cassava. Hans was able to show that the mostly female cassava farmers had good food security reasons for growing bitter cassava containing high concentrations of cyanogen compounds, which requires processing before consumption. Today, some of his methodology would be called 'mixed-methods' but it rarely stretches so far as from anthropology via medicine and chemistry to agricultural research. In addition, Hans supervised a dozen PhD-candidates in clinical medicine, clinical chemistry, nutrition and agronomy.

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SUMMARY OF PRESENT-DAY KNOWLEDGE OF KONZO AND CASSAVA TOXICITY

Introduction: Cassava toxicity is still a problem in many areas of Africa. Updated prevention methods may be needed.

Aim: In this presentation, recent studies of cassava, cassava toxicity, and clinical aspects of konzo and prevention efforts will be summarised.

Methods: Literature review

Results: Studies in agronomy, food processing, clinical studies and prevention efforts show that 1) there are good reasons to grow bitter cassava, the idea of 'choosing sweet cassava instead' is not valid; 2) konzo may be affecting more than just the upper motor neurons; 3) cassava toxicity may also be associated to ataxic neuropathy in Nigeria; 4) proper processing of cassava is primordial in prevention.

Conclusion: Cassava toxicity is closely linked to extreme poverty, ecological degradation and extremely tough socio-economic conditions. In the worst-off societies, prevention must focus on cassava processing that is not too taxing on the available work force.

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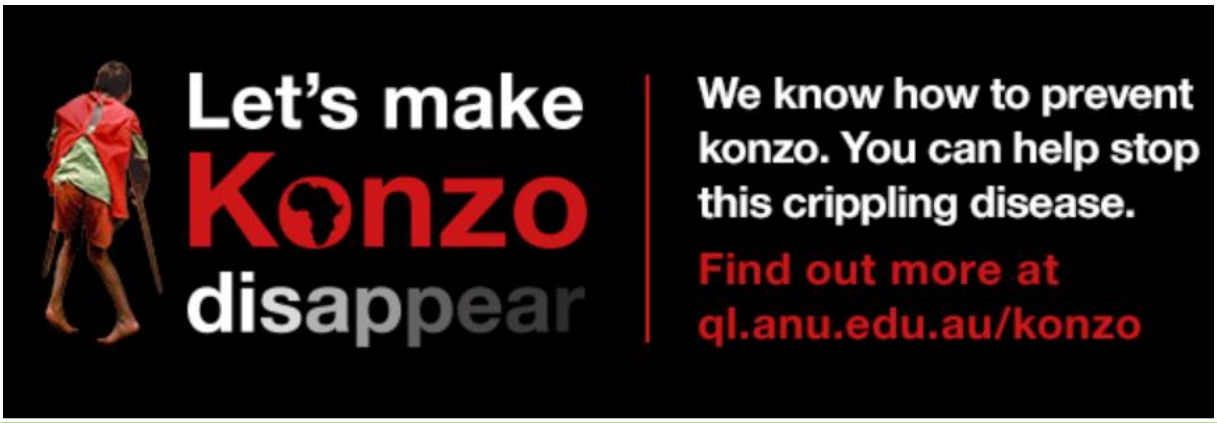

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