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

CCDN News

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IN MEMORIAM: Dr Howard Bradbury AM – 1927-2016

Dr Howard Bradbury, aged 89, passed away on Monday 28 November following surgery some weeks earlier. He is survived by his wife Ruth, daughters Meredith, Annette & Joanne and families including 20 great

grandchildren. His work on the prevention of konzo will continue through his many colleagues around the world.

“Right at the end of my career I’ve had this wonderful opportunity, by the grace of God, to be able to address a preventable disease in Africa. It’s something I’d never thought would be possible.”

Professor Bradbury followed in his father’s footsteps studying chemistry at Melbourne Technical College and Melbourne University followed by a PhD in polymer chemistry at Birmingham University. After a postdoctoral fellowship at Harvard University he worked for 6 years at CSIRO Wool Research Laboratories before accepting a senior lectureship in chemistry at the Australian National University (ANU) in 1961. From 1961-1988 he pursued his teaching and research career at ANU working on the structure of wool and NMR studies of biological macromolecules. His work pioneered the use of NMR spectroscopy and lead to the first detailed insight into the solution structure of proteins. Many of his students have gone on to eminent careers in science, government and academia. He enjoyed sabbatical appointments at Cornell University and three occasions at Oxford University and was awarded a DSc degree from Melbourne University as well as three research medals from the Royal Australian Chemical Institute and Melbourne University.

After speaking at a conference in India in 1974, he changed the focus of his research to food chemistry, analysing all the root crops of the South Pacific where he confirmed cassava, one of the most important crops, contained cyanide. In 1988 he took early retirement and joined the Botany and Zoology Department (now Research School of Biology), ANU to continue his work on cassava in a major project funded by ACIAR (Australian Centre for International Agricultural Research). He met Dr Julie Cliff, an Australian doctor working in Mozambique, at a workshop on cassava safety in Nigeria in 1994 who inspired his work in developing simple kits to determine the cyanide levels in cassava and thiocyanate levels in urine (a measure of cyanide intake). In 1996 he travelled to Mozambique to test his kits in the field which spurred later work to find a way to reduce cyanide levels in cassava flour. He developed the “wetting method” that exploited the presence of active enzymes in the flour to reduce the cyanide levels before it was cooked. The simple treatments involved wetting the flour, spreading it in a thin layer on a mat for 2 hours and allowing the cyanide that was liberated by the action of the enzymes to escape safely as gas. It was trialled in Mozambique in 2005 to much success and also rid the flour of its bitter taste. In 2007 he was awarded the inaugural $2 a day award by the Institute of Chemical Engineers and appointed a Member of the Order of Australia.

In 2008 he contacted Professor Jean-Pierre Banea, Director of the National Institute of Nutrition in Kinshasa, Democratic Republic of Congo to extend the reach of his “wetting method”. Using money raised from selling his kits to first world countries, they were able to develop an intervention protocol in villages to teach the “wetting method”. In 2009 they were able to prevent the development of new cases of konzo, a crippling neurological disease caused by increased cyanide intake, in Kay Kalenge and 13 more villages since then.

Professor Bradbury was a prodigious networker and believed in encouraging everyone who showed an interest in his work. He founded the Cassava Cyanide Diseases Network, a free worldwide network and newsletter which today has over 700 members and is coordinated by Prof Fernand Lambein. http://ipbo.vib-ugent.be/projects/ccdn

In 2016 the ANU devoted their Annual Giving Day to Professor Bradbury’s work on the prevention of konzo. A tax deductible fund has been setup to continue his work in preventing konzo in DRC. http://www.anu.edu.au/giving/support-us/konzo-eradication

At ANU Prof Bill Foley, Jan Elliott and Ursula Wiedemann will extend his legacy through continuing the supply of his kits and collaborations. Email: konzo@anu.edu.au

Some reflections

“He was a man of great intellect, enthusiasm, charm, wit, humility and good will. He was also a great humanitarian. I learnt a huge amount from him and am deeply indebted to him.” Former PhD student Prof John Carver, Director, Research School of Chemistry, the Australian National University, Australia

“We have just lost a great person. Howard combined the best qualities of a scientist – rigor and innovation – with a deep humanity. He truly used his science to help the poorest of the poor, in this case people living in communities afflicted by the paralytic disease, konzo.” Dr Julie Cliff, Eduardo Mondlane University, Mozambique

“Howard was one of the personalities who contributed much to make PRONANUT a great scientific institution, particularly in the fight against the konzo. His memory will never be forgotten and we will continue his work in DRC.” Prof Jean-Pierre Banea, Director of the National Nutrition Program (PRONANUT), the Democratic Republic of Congo

“Aging could not stop his interest and his motivating enthusiasm to use science for the prevention of this unfair disease konzo. His accomplishments are bigger than life, and will affect konzo research for a very long time to come.” Em Prof Fernand Lambein, International Plant Biotechnology Outreach (IPBO), University of

Ghent, Belgium.

"It truly is a sad day - so many of us working on cyanogenic glucosides in cassava were connected to each other by Howard. His network was extraordinary. Howard was always a rigorous scientist and made sure he published everything so the knowledge would persist." Ass Prof Ros Gleadow, Monash University, Australia

"For more than 25 years, Howard worked tirelessly to translate science into effective actions to improve the lives of some of the poorest people in the world. He did it with humility and generosity but always insisted that the science underlying the interventions be the best possible." Prof William Foley, Research School of Biology, the Australian National University, Australia

"Sometimes, as members of a University, we get caught up in the search for grants, in the need to publish or perish, and in the day-to-day ructions of a competitive environment. I think someone like Howard reminds us about the other side of our work – the joy of doing good things, the value of others, and the role we play as citizens of a broader community."

Prof Allen Rodrigo

Director, Research School of Biology, the Australian National University, Australia

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Development of grasspea (*Lathyrus sativus* L) in Ethiopia.

Grasspea (*Lathyrus sativus*) is an important highland pulse crop in Ethiopia that is poorly managed and yet improving performance. Ethiopians grow grass pea on farmlands with low fertility or on problematic plots. Research on grasspea is at a lower level compared to other crops with respect to investment, technology generation, popularization of existing packages etc. There is an enormous potential for grasspea in climate change affected agriculture. With the recent increasing importance of the crop in Ethiopia and in other parts of the world, it is crucially important to enhance the research and development of the crop for better benefit to the farmers.

Key words: *Lathyrus sativus*, safe consumption, climate change, agronomic potential

Global change scenario as a function of climate, economics, technologies and social dynamics is a gigantic evolution affecting billions of citizens. Of all challenges water and food supply have been a matter of survival or extinction in the past. Already one billion people are on forced chronic hunger or malnourishment. The planet is by no means ready to nourish the newly coming four billion in four decades time from the present agricultural resources, let alone the present malnourished billion. The development of agricultural sciences needs to cope. As the change in climate seems to accelerate, the research on food crops that are tolerant to drought and adverse environments needs more inputs. Developing the genetic basis of climate responsive or climate proof crops like grasspea *(Lathyrus sativus)* is becoming an apparent choice.

Ethiopian agriculture has long been very unstable in response to changing climatic factors particularly drought. A delay of the rainy season or the reduced length or insufficient precipitation, all contribute to drought in Ethiopia. In the face of such climatic events, or fertility deterioration of the soil, grasspea is the farmers' choice as an insurance crop or even a survival crop. This productive and efficient nitrogen fixing crop needing little or no inputs or management is a blessing for most resource poor farmers. The production of the crop is on the increase (Fig. 1) both in area coverage and production volume at the expense of other eco-competent crops.[1]

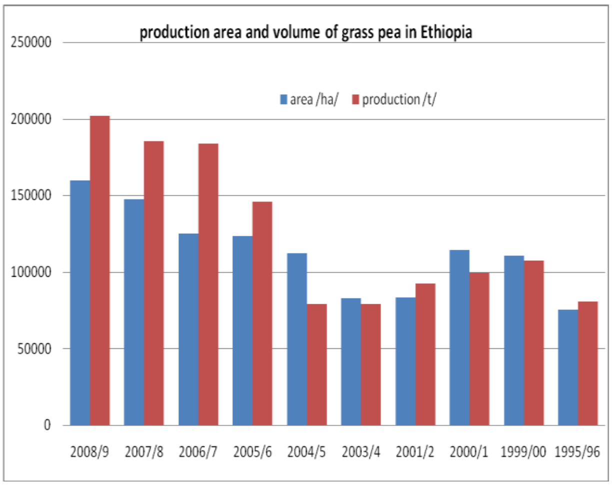

Figure 1: A recent production area (ha) and volume (t) of grass pea production in Ethiopia

Despite the low management inputs, [2] the increase in volume of the crop shows an increasing productivity which is now 1.5 t/ha, or about 1/3rd of its attainable potential. This puts it as one of the top productive pulses in the country.[3] The increasing trend in the production also suggests that the consumption and the transaction volume of this crop have considerably increased.

A number of prior reports highlighted the fact that grasspea is amongst the important pulse crops exceptionally surviving low inputs,[2,4] biotic and abiotic stress,[5,6] and adverse ecological and environmental conditions.[5,7]

Having a primary center of diversity in Ethiopia[8] the adaptation of the crop in the various sub-climates of this country has gone on since early civilization. Based on FAO grasspea production statistics (1996-2007) Ethiopia accounts for 75.3 % and 9 % in area cover and

85.4 % and 8 % in grain production of Africa and the world respectively.[9]

Ethiopian agriculture is characterized by mixed farming, both crop and animal husbandry are practiced together is small farm holdings. The soil in grasspea growing area is dominated by vertisol, of volcanic origin where both water logging and water stressed soil cracking are important for the choice of crop and for crop performances.

The significance of the expansion of this “neglected” grasspea crop (Fig. 1) in such scenario demonstrates the increasing importance of this adaptive, multi-stress tolerant and economical crop.

The number of households producing the crop has almost doubled over five years from 409233 in 2003/4 to 774051 in 2008/9. Interestingly, all the seed used for sowing are the farmers’ own cultivars. So far only one grass pea variety named ‘wasie’ (from ICARDA) is released in Ethiopia, but has reached a very insignificant number of farmers.

Although the yield per ha is far from optimal, it surpasses most of the better managed pulse crops in the country. Nonetheless, with the introduction of advanced production technologies (improved varieties and production packages) some of the other pulses are showing enormous advance in productivity. For example in the last five years the productivity of lentil and chickpea has almost doubled from 0.5 t//ha and 0.8 t/ha to 1.1 t/ha and 1.3 t/ha respectively.[1] In grasspea a considerable difference in yield between the national average (~1 t/ha) and the productivity under improved management (4 t/ha) was demonstrated for farmer cultivars in Ethiopia.[3] In spite of the many advantages this adaptable and multipurpose crop can offer, it is inadequately exploited and studied.

The production of pulses is normally in rotation with cereals. Cereals account for tenfold the size of pulses both in time and area. Double cropping is also a common practice for chickpea and grasspea after the principal cereal crop is harvested. The driving underlying principle in this cropping pattern is the total production increment per unit area for the same season.

Food and feed significance

Grasspea can be a promising agricultural crop of the future if a safe mode of consumption is established. Although grasspea is considered an insurance crop by the farmers, and must have saved many lives during periods of drought and food insufficiency, nutritional research into safe consumption received less attention than alarming reports on neurolathyrism occurring after prolonged overconsumption of the seed during famines.[10] As a consequence, grasspea is sometimes referred to as a toxic plant without mentioning any positive aspect. As a stress tolerant food crop, it is a very promising source of protein, carbohydrate and minerals for drought prone marginal lands. The seeds contain an average of 27 % protein, 0.6 % fat, 58.2 % carbohydrate (about 35 % starch).[2,11] It has also a good level of essential amino acids, except for tryptophan, methionine and cystine which commonly are deficient in legumes. The traditional food processing and consumption of grasspea in Ethiopia, unlike other pulses, is very diverse.

Besides being an important food for humans, grasspea provides animal feed. Particularly in the developing world, several studies reveal that grasspea can be an important feed input for livestock including fowl. Chowdhury *et al.*[12] studied the nutritional value of grasspea (0.4 % ß-ODAP) for growing and laying pullets and concluded that inclusion of 10, 15 and 20% of grasspea in the feed had no negative effect. Tadelle, *et al*.[13] demonstrated that grasspea can be used as a replacement for commercial protein and energy source for poultry feed with minimum processing. Grasspea grain has a high concentrations of crude protein (280 g/kg) and Fe (78 mg/kg) having lower C:N ratio (1.06) but was in general deficient in Cu and Na for feed purposes. Fikre[9] indicated that the cheap sources of grasspea grain being used for small holders fattening of chickens pays back a high net profit.

Environmental stress and crop rotation

Ethiopia has since long suffered from recurrent droughts, some of which gave rise to famines. Drought triggered famines have been the prelude to neurolathyrism epidemics in the past.[14,15] On the one hand, during drought triggered famine grasspea remains as the only affordable choice of food as all other crops fail and it must have saved millions of lives. On the other hand, prolonged overconsumption of grasspea can suddenly cause irreversible crippling of the legs or neurolathyrism. The most probable cause of this is the neuro-excitatory amino acid β-ODAP present in the seed in varying amount, depending on genotype and environment. The crop is invaluable as an insurance crop that bridged the gap between a failed crop due to drought and the upcoming season crop.

It was suggested that β-ODAP might be important for the plant by acting as a defense to various environmental stresses.[15,16] This β-ODAP might then contribute to the hardiness of the crop. Hence, the plant apparently produces less β-ODAP in the seed under optimal growing conditions than when it grows under marginal conditions. Another important point is that under favorable growing conditions, the plant produces more pods and seeds with reduced β-ODAP concentrations, possibly as a result of a dilution effect. In identical unstressed conditions, plants with only 10 pods contained 59 % more β-ODAP in the seed than plants with 100 pods.[17]. From a similar study by Cocks and co-workers[17] and Fikre et al.,[7] it was demonstrated that the effect of stress due to climatic factors (temperature, rain fall, sunshine hours) on β-ODAP accumulation was apparently stronger (doubling) when confronted by the plant during post-anthesis than during pre-anthesis. These results can contribute to the information needed for better agricultural management practices to produce a grass pea crop in more suitable agro-ecologies that may yield seed with better nutritional quality. Small-scale farmers and pastoralists in Ethiopia are likely to bear the brunt of the negative impacts of climate change. As Ethiopia is already moisture deficient, grass pea would be one of the most agro fit crops in, with important future potential

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Lathyrism after the 1936-1939 Spanish civil war

One important epidemic of neurolathyrism occurred during the famine period that followed the Spanish Civil War (1936-1939). The clinical and epidemiological studies characterizing this episode were published in Spanish language, and are thus not easily accessible to the international scientific community. This article is a very brief review of the outbreak based on part of this literature.

Lathyrus sativus and neurolathyrism were well known in Spain. In the early XIX century, Francisco de Goya illustrated this knowledge in his famous aquatint print "Gracias a la almorta" (*Thanks to the grass pea*), depicting the use of grass pea as a famine food. This picture included a crippled woman. The 1936-1939 Civil War caused numerous foci of famine not only during the war, but also in the following years, because the civil war triggered an economic collapse that lasted two decades. During the war, physicians in Spain faced many of the major nutritional deficiencies. The most important episode was that of the siege of the city of Madrid, which caused a dramatic shortage of supplies for almost two years. There, numerous cases of pellagra and other hypovitaminosis syndromes were described. In contrast, in rural and industrial areas the lathyrism epidemic appeared after the end of the war. The first cases were described in articles published in 1941 by Lopez-Ibor and Peraita,[1] and by Ley and Oliveras de la Riva,[2] from the two main epidemic foci. In comparison to the hypovitaminosis patients, the good nutritional status of these and other lathyrism cases was indicated in the reports of this epidemic.

The cases described by Lopez-Ibor and Peraita[1] were from La Mancha area, spreading over the administrative provinces of Albacete, Cuenca, Toledo and Ciudad Real. La Mancha has long been known to be a region of *Lathyrus* production and consumption, and the pulse is still grown and consumed there today, although in amounts below those associated with neurolathyrism epidemic. In this case, the authors reporting the neurolathyrism cases had previously worked with pellagra and beri-beri cases, and therefore had a good knowledge of diseases associated with deficient nutrition.

The cases described by Ley and Oliveras de la Riva[2] were from the Baix Llobregat area, a region near Barcelona, in Catalonia, with a remarkable industrial activity. Although this area grew some *Lathyrus sativus* at that time, this pulse did not have there the importance it had in La Mancha, and it has today completely disappeared from the fields and the markets. In fact, neurolathyrism in this area appeared to be associated with imported peas rather than to locally grown peas.

Soon after these two initial reports, others cases were described. Some cases were diagnosed from independent observations, but many were diagnosed at the province hospitals, after doctors received alerts asking to look for the disease among patients complaining about motor disturbances. Others were diagnosed in a number of field campaigns organized to visit the villages from which former patients had been diagnosed. A good early description of the epidemiology of the outbreak is that of Jiménez Díaz et al (1943).[3] This report includes 549 cases from 25 out of 49 provinces in Spain. While the two foci mentioned above were the first to be discovered and the main ones as for number of cases, other cases were nevertheless found in other rural areas growing *Lathyrus* (Valladolid province), as well as in industrial areas importing it (Bilbao area). The earliest cases had appeared as early as 1939, and many others appeared after the 1943 report. In fact, the same Jiménez Díaz's team still described two new cases as late as 1950 (Jiménez Díaz et al., 1950).[4] The total number of cases may have amounted to around 1000.

Many individuals were responsible for the diagnosis of cases, including neurologists working in province hospitals as well as general practitioners working in affected villages. Among these, some took a substantial share in the study of the patients, but produced no documents that are accessible to the international community. The major example is that of the team of E. Bardají, Health Chief Officer of the Barcelona Province, who carefully studied 212 cases, but whose work can be known mostly thanks to the articles published by other authors (Jiménez Díaz et al., 1943).[3] By contrast, Carlos Jiménez Díaz authored a great part of the published literature generated by the epidemics, including not only clinical and epidemiological studies, but notably also biochemical and animal model studies.[3-5]

The articles generated by the Spanish neurolathyrism epidemics include many fine descriptions of the disease (Jiménez-Díaz et al., 1942;[5] del Cura and Huertas, 2009[6]). These included detailed analyses of the main symptoms, but also of other symptoms, as those of the prodromal phase, including parestesias, cramps, coldness of the legs, and nistagmus. The most common cramps were in the legs, but pharingeal cramps were also reported. Not uncommon were individuals suffering from genito-urinary dysfunction. These prodromal symptoms were found to vary considerably among foci, in contrast to the uniformity of the main motor symptoms, which were those well described for neurolathyrism elsewhere. The reevaluation of some of the patients 25 years after the beginning of the disease revealed the stability of the motor disability (Moya et al., 1967).[7] An other study (Giménez-Roldán et al., 1994) reported a worsening of some patient's motor abilities starting more than 30 years after the onset of the disease.[8]

The Spanish epidemic illustrates many aspects of the disease. Among these, many evidences of the causal role of grass pea consumption in neurolathyrism were included. For the Baix Llobregat focus, Ley and Oliveras de la Riva (1941)[2] described how they first hypothesized an infectious cause, then a hypovitaminosis cause, and third a toxicological cause. The common factor of grass pea consumption among patients was unexpectedly discovered after a job survey allowed discarding a common toxic exposure in the workplace. Then the results of a nutritional survey, carried out to test the hypovitaminosis hypothesis, was reevaluated in search of a nutritional intoxication, only then the consumption of grass pea was exposed as a common factor. Other evidences are those provided by Jiménez-Díaz et al. (1943)[3] on the relationship between dietary habits and disease development. When these authors selected patients and their families and studied the amount of *Lathyrus* consumption, they found that as much as 36 % of the individuals with the highest consumption of grass pea developed the disease. This percentage was similar in different foci, and the authors concluded that the factor causing differences in incidence among foci was the differences in consumption, and that low incidences in *Lathyrus* consuming areas were associated to smaller amounts of consumption. They also reported several examples of patients that had very good intake of nutritionally rich foods, such as eggs and vegetables, but that did nonetheless develop the disease due to the high amounts of grass pea included in their diet. The authors concluded that, even though good nutrition may perhaps offer some protection against neurolathyrism, the amount of grass pea consumed, and thus the dose of the *Lathyrus sativus'* toxic compound, is the most important factor determining the risk of developing the disease.

The Spanish epidemic offers an evaluation of the sex ration in neurolathyrism incidence. While some variability was found among the different foci, the greater number of men among the patients was evident in the overall picture. Torres Cañamares and Vergara Olivas[9] reported 13 women for 39 men (25%), while only 44 women for 377 men (11%) were reported in the more complete estimation available (Jiménez-Díaz et al., 1943).[3]

Another point well illustrated by the literature on the Spanish neurolathyrism epidemic is the variability in the way the disease develops. As explained above, variability in the initial symptoms was recorded. Also, striking differences in the time course were noticed. While many patients developed the disease over many days and weeks, shorter time courses were found, including cases in which the patient had painful cramps at night and could not walk the following day (Jiménez-Díaz et al., 1942).[5] These resemble the abrupt onset that characterizes konzo (Tylleskär et al., 1993).[10]

Another significant result from the Spanish epidemic is one of the very few neuropathological studies of the disease published (Simarro Puig and Roca de Viñals, 1943).[11] The reported results of this study reinforced the conclusion that the spastic paraparesis in neurolathyrism results from a degeneration of the lateral column fibers, corresponding to the corticospinal tract, although the pathological lesions apparently extended to involve also the spinocerebellar tract. On a cautionary note, the patient died of aseptic meningitis, causing also inflammatory lesions whose description was excluded from the published study.

In the 1960s, Spain started a period of economical growth. The increase in wealth and social development accelerated after the end of Franco's dictatorship in 1975. This included a noticeable development of biomedical sciences, which are quite well developed in Spain nowadays. However, this increase in scientific capacity in a country struck by neurolathyrism a few decades before did not result in a further contribution to the scientific knowledge of the disease. In fact, an isolated study on neurolathyrism carried in the 1990's in Spain was promoted by foreign scientists (Giménez-Roldán et al., 1994).[8]

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