

Homeopathy, longevity and *Lathyrus sativus* toxicity.

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The re-launching of the Lathyrus Lathyrism Newsletter offers an occasion for renewed contacts and perhaps also for reflections on viewpoints and goals. The last international and interdisciplinary meeting where Lathyrus/lathyrism researchers could exchange ideas was in Addis Ababa in November 1995. Smaller meetings took place in Hyderabad at the occasion of the retirement of Professor SLN Rao in March 1997, in Radom, Eastern Poland in June 1997, and in Delhi we had a meeting of the *Lathyrus* germplasm working group in December 1997. Proceedings of these meetings have been published (see Recent Publications, this issue).

Perhaps this is the time to launch some provocative ideas on where we stand and where we should aim at in our endeavours to solve the problem of human lathyrism and to make *Lathyrus sativus* a crop for economic development of marginal areas. Since the publication of the structure of a neurotoxin in *Lathyrus sativus* seed in 1964, numerous studies and research programmes have been done to lower the β -ODAP content in this plant that has been used in agriculture since the Neolithic era and is still very promising for marginal lands. But when asked about the toxicity of β -ODAP-free seed, it is difficult to find a scientific basis for a correct answer.

An important problem is the absence of a well-defined toxic level of β -ODAP, under which there is no danger of developing neurolathyrism. For this we can perhaps rely on the very low levels given in homeopathy to protect against paralysis of the legs, or we can consider the levels in a daily dose of ginseng preparations sold in health food shops around the world to improve vigour and longevity for the elderly. The recommended daily dose of ginseng extract contains up to 0.4 mg of β -ODAP. Calculated on an intake of 1 kg of grass pea per day as reported by lathyrism patients, this would give a tolerated level of only 0.4 PPM, or 10,000 times less than in some present cultivars. But do we need to go this

far? In an Encyclopaedia of Plants published in 1855 (Loudun) it was already reported that bread made from a 50/50 mixture of grass pea and wheat seems to have no deleterious effect, while bread made only from grass pea causes paralysis of the legs "when used in continuance". Thus, if taken with cereals and only 0.5 kg of grass pea is consumed, the tolerance level might be closer to an intake of about 2 grammes of β -ODAP per day. Any nutritionist will explain that the amino acid score of a mixed diet containing cereals and legume seeds is much higher than for either cereals or legume seeds alone. From numerous publications, we know that lathyrism occurs mainly in periods when grass pea is consumed almost exclusively, when cereals are unavailable or too expensive for the poor. Do we then need to select more healthy grass pea varieties on the basis of amino acid score instead of only looking at β -ODAP?

"It is generally assumed that β -ODAP is the causative agent for the crippling neurodegeneration neurolathyrism" is a sentence that can be found in many variations in all careful publications mentioning the aetiology of lathyrism. As a reliable animal model still does not exist, how sure are we about the β -ODAP-toxicity in humans? Recent publications point at a more complex pharmacology of β -ODAP than only the excitation of the AMPA-receptors. Is β -ODAP really the true and only toxin present in grass pea? Or is a deficiency in an essential nutrient causing a higher susceptibility to any neuroexcitant? Perhaps in addition to the toxicity model for lathyrism we should also look for a malnutrition model as proposed by Dr D. Enneking. The survey by Dr H. Getahun of the most recent epidemic of neurolathyrism in the Wello region of Ethiopia (see Medical/Social, this issue) suggests that any addition of spices or condiments to grass pea can make it less toxic. The Ethiopian traditional *injera* pancake that is prepared by fermentation of grain also seems to be rather safe, even when containing mainly grass pea. It has been shown that fermentation of grass pea improves the amino acid score and lowers the β -ODAP content.

Since the discovery of β -ODAP in 1964, many institutes have developed low-toxin varieties. Perhaps several 10,000 lines resulting from crossings and selections have been tested for β -ODAP content, but none was completely free of the toxin. Is it then possible that the enzymes involved in the biosynthesis of β -ODAP are in fact enzymes also participating in primary metabolism, with a different specificity in grass pea than in other legumes. In that case only genetic modification may completely remove the biosynthetic potential for β -ODAP.

Selection by somaclonal variation, that was proposed by Dr A. Kaul at the Pau meeting in 1985, has been successfully done in at least four laboratories including ours. The results obtained in Delhi in 1991 and recently in ICARDA have received some publicity but were also not totally free of the neurotoxin. Strategies for elimination of β -ODAP by genetic transformation have been proposed but as far as we know, no successful regeneration of a transformed *L. sativus* plant has been achieved. The sometimes-violent opposition against genetically transformed crops has probably delayed such experiments or has made funding difficult. Considering its mostly self-pollination and the difficulty to cross with even closely related species, grass pea would be ecologically safe for such experiments and should be a good case in favour of genetic transformation. Such genetic improvement should not only aim at lowering the β -ODAP content but also at the improvement of the amino acid score, the safeguarding of its environmental tolerance and protection against insects. The infestation with *Bruchus pisorum* can destroy large portions of the stored harvest before the next crop.

If we are not 100 percent certain that β -ODAP is the sole agent responsible for lathyrism, can there be another toxin in the seeds or does β -ODAP have other pathological effects different from neuro-excitation at the AMPA-receptors? When analysing amino acids in legume seeds and seedlings, we keep finding 'unknown' compounds, to the point that such analyses not mentioning any unknowns are probably incorrect. A systematic analysis of "minor" natural products in grass pea seeds may produce an unpredictable bounty of new compounds. An important class of secondary metabolites is the flavonones. The antioxidant properties of such compounds in green tea and in red wine are thought to contribute to longevity. Two flavonones, quercetin and kaempferol are present in leaves of *L. sativus*. Such compounds might also contribute to the dietary quality and the economic value of *L. sativus*.

A "major" nonprotein amino acid in the seeds is of course L-homoarginine that is present in concentrations up to 1 % of the dry weight. To some extent this compound can replace arginine as precursor for the omnipresent but short-lived volatile nitric oxide (NO), an essential molecule for any muscle movement, neuronal signalling and many other physiological functions. It has been reported that homoarginine can neutralise the toxic action of β -ODAP in day-old chicks. Even though the acute and reversible symptoms seen in day-old chicks are different from human lathyrism, it seems that the seed contains an antidote to its own toxin; with β -ODAP increasing NO-production through its excitation of neuronal receptors and perhaps homoarginine modulating this NO-synthesis.

Recent research on neurodegenerative diseases is focussing on oxidative stress and our defence systems against aggressive oxidising molecules such as NO and its degradation products. Enzymes protecting our neurones and other cells against cell-death provoked by oxidative stress are, among others superoxide dismutase and peroxidase that happen to depend on the presence of certain micronutrients for their activity. These micronutrients include zinc, manganese, copper and selenium. Some of these micronutrients can form chelates with compounds such as β -ODAP, and perhaps then become unavailable as co-factors for those protective enzymes. A continuous daily intake of five gram of β -ODAP (when consuming 1kg of seed), may very well disturb the delicate balance of those micronutrients and by itself may cause a toxic situation. Mentioning that the toxic action of β -ODAP, or better *Lathyrus sativus* seed, is not completely known may be an understatement. There is no explanation why the symptoms of neurolathyrism, supposedly caused by neuro-excitation at the AMPA-receptors affecting primarily the upper motoneurones, are exactly the same as the symptoms of konzo, caused by over-consumption of insufficiently processed (fermented and dried) cassava (*Manihot esculenta*) containing cyanogenic glycosides as known toxins. Also in the case of konzo, malnutrition may cause a compromising of the defence against oxidative stress, and cyanides can also form chelates with some of those micronutrients mentioned before. The molecular pathology of these two neurodegenerations must have common steps in the pathway leading to the same symptoms of spastic paraparesis of the legs. Identifying these steps should bring us much closer to solving two diseases that have very different secondary plant metabolites as causative agents, but have similar clinical symptoms and similar socio-economic background: poverty, malnutrition and adverse ecological and socio-economic conditions.

It is clear that the questions posed or suggested above cannot be answered by one researcher or by one laboratory. Communication between medical people and neuroscientists on one hand, and geneticists and agronomists on the other hand needs to be improved, for which the forum of a regular Newsletter can be extremely useful. Input from nutritionists and ecologists, that may form a scientific link between these two groups has been too limited in the past.

The above ideas form an incomplete survey of unanswered problems that is limited in scope and in detail. It is intended to provoke reflections and discussions through the Newsletter or other channels.