LATHYRISM: A REVIEW OF RECENT DEVELOPMENTS*

WILLIAM J. GERMAN, M.D.

Department of Surgery, Yale University School of Medicine, New Haven, Connecticut

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Lathyism has been defined by Selye,36† in his excellent article on the subject, as “a disease induced by the ingestion of certain Lathyrus pulses or treatment with the toxic principles of such pulses and related compounds most of which are aminonitriles.” The name is derived from the Greek lathros, vetchlings. Its Greek root is thought to be thouros, exciting, impetuous. The name lathyism was applied to the clinical disease by Cantani in 1873, though the disease had not escaped the attention of Hippocrates.

The classical form of the disease is one affecting the nervous system, termed neurolathyism by Selye. The clinical syndrome11 usually consists of an acute onset of weakness of the lower extremities, sometimes with prodromal sensory manifestations of pain or paresthesia, progressing to spastic paraplegia. Symptoms indicative of involvement of the sensory tracts of the spinal cord are not unusual. Loss of sphincter control and impotence are often present. Finally, there may be muscular atrophy. The upper extremities are less frequently affected than the lower. Symptomatic regression is uncommon and no effective therapy is known. The disease is said to be more common in young males. In addition to man, cattle, horses, swine, ducks, peacocks and elephants are subject to neurolathyism. The human disease tends to occur during periods of famine and has been associated with the ingestion of considerable quantities of one of the following pulses: L. sativus (dog-tooth pea), L. cica (chick pea), Veelia sativa (tare or acta), Ervum erv.:va (bitter vetch). The common pea, Pisum sativum, is benign. Numerous epidemics of the disease have occurred in India and there have been occasional outbreaks in Spain, France, Italy, Algeria, Syria and Russia. None has been reported in North America, though domestic animals have been affected by the foliage of L. sylvestris.

The pathology of the disease in man is lacking in many details. It is summarized as follows: “Partial degeneration of the motor tracts of the spinal cord,” “Microgliosis of the anterior horns and the lateral cords,” “Anterolateral sclerosis in the dorsolumbar spinal cord.” Buzzard and Greenfield described a single lesion thus: “The lesions were very similar to those seen in ergotism, i.e., a pseudo-systematised degeneration of the long ascending and descending tracts of the cord. This was particularly marked in

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† The original sources of articles published prior to 1957 may be found in Selye’s paper.

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the pyramidal tracts, both lateral and ventral, in the direct cerebellar tracts, and in the dorsal columns. In the lumbar and thoracic regions the margins of the cord showed the same loose, honeycombed structure as is seen in the more rapid cases of 'subacute combined degeneration,' with oedema at the point of entrance of the dorsal roots. The nerve roots showed a definite increase of connective tissue, and in the peripheral nerves a similar increase was seen, chiefly in the epi- and peri-neurium. These changes are all of the same character as those found in ergotism, and it is probable that the two diseases are closely connected."

The foregoing is a brief summarization of the accumulation of knowledge of lathyrism over about 2,500 years. However, in the early 1930’s, Beatrice Geiger,\textsuperscript{14} at the University of Wisconsin, undertook for her Ph.D. thesis the study of the effect of sweet peas in the diet of young rats. The results, published in 1933, included retardation of growth, lameness, spinal curvature, sternal curvature, enlargement of the costochondral junctions, malformation of the long bones, and hernia formation. Thus emerged experimental osteolathyrism. These findings were soon corroborated. Ponseti and co-workers\textsuperscript{31,32} have made extensive studies of the mesodermal deformities produced by \textit{L. odoratus} seeds. The basic pathology appears to be loss of cohesion of the cartilage matrix of the epiphyseal plates in young rats, with loosening and detachments of osseous insertions of tendons and ligaments. There resulted the following abnormalities: Slipped epiphyses, metaphyseal fibrous defects, kyphoscoliosis, thoracic deformities, detachments of the tibial tuberosity, subluxations and dislocations of the shoulder, diastasis of the sacro-iliac joints, degeneration of the intervertebral discs, disc herniations, Legg-Perthes-like disease of the femoral head, periosteal detachments with new bone formation, and degenerative arthritis. As a final damnation of the otherwise \textit{sweet} pea, they found a very high incidence of dissecting aneurysms of the thoracic aorta. It appears obvious that \textit{L. odoratus} is meant to be smelled, not eaten. In full justice, it must be admitted that it does not produce primary lesions of the nervous system. However, fatal fetal edema and absorption are among its effects.

The year 1954 ushered in the chemical phase of lathyrism. From numerous reports there emerged three aminonitriles capable of producing osteolathyrism. The basic chemical structure seems to be an amino group separated from the terminal cyanide group by one or two methyl linkages. The three osteolathryogens are: Aminoacetonitrile, \(\beta\) aminopropionitrile, and methyleneacminoacetonitrile. Many closely related compounds have been found to be non-lathyrogenic. However, one of special interest is \(\beta,\beta'\)-iminodipropionitrile which produces a form of "neurolathyrism"\textsuperscript{26} to be described later. A considerable number of chemicals, including a series of antioxidants, have been tested for possible neutralizing effects upon the osteolathryogens without success.

We arrive now at the pathophysiological phase of lathyrism, where Selye\textsuperscript{36} has made major contributions. Several "conditioning factors" have
been found to influence both the degree and type of pathology induced by lathyrogens. The somatotrophic (growth) hormone facilitated the development of osteolathyrisrn. Conversely, when the lathyrogen was discontinued, the hormone accelerated healing of the bone lesions. It is of special interest that the “growth hormone” failed to exhibit growth-stimulating effects while the lathyrogen was present. By combined administration of the somatotrophic hormone and a very small amount of lathyrogen over a period of two to three months, pathological changes suggestive of senility were produced. Among these were: Premature closure of the epiphyseal plates, osteoporosis with dilatation of the blood-vessel channels in solid bone, joint lesions reminiscent of osteoarthritis, transformation of myeloid into fatty bone marrow, excessive growth and enamel defects in the incisor teeth, loss of body weight, shagginess and dullness of fur with a tendency to alopecia. Other osteolathyrific aggravating factors were luteotropic hormone (prolactin), thyroparathyroidectomy, partial hepatectomy, alizarin, kernechtrot, phenylbutazone, and exposure to systemic stress. Conversely, lathyrogen effects were partially inhibited by ACTH, cortisone, thyroxin and denervation.

The intimate pathology of osteolathyrisrn is still an unfinished story. However, the following facts have emerged: Maturation of epiphyseal cartilage cells is defective and several histochemical abnormalities have been identified in the involved areas. The formation of exostoses is dependent upon muscle pull against insecurely attached periosteum. The dissecting aneurysms are associated with lysis of the elastic fibers of the media of arteries, the loss of elastic interlaminar fibers being especially notable.

The subject of experimental neurolathyrisrn has received scant attention. \(\beta,\beta'-\text{iminodipropionitrile}\) produces a syndrome characterized by excitement with choreiform and circling movements. A single intravenous injection of this nitrile produces no apparent effect for several days, after which interval the nervous symptoms appear and persist indefinitely. Large doses of this chemical produce an unusual form of optic pathology, characterized by swelling, conjunctivitis, corneal erosions, retinal detachment with hemorrhage and inflammation, progressing to panophthalmia. Other aminonitriles do not produce neurolathyrisrn, except in turkey poult's, in which the evidence is incomplete. However, osteolathyrogens may augment the effect of the neurolathyrogen. Experimental neurolathyrisrn is apparently unaffected by the various agents that were found to modify osteolathyrisrn. Hartmann et al.17 have recently demonstrated marked degeneration of spinal anterior horn cells in rats after administration of \(\beta,\beta'-\text{iminodipropionitrile}\), which is also called bis-cyanooctylamine.

Lathyrisrn, in its various forms, has obvious points of special interest to neurosurgeons. Among these are ruptured intervertebral discs, spinal deformities and compression of the cord, neuronal degeneration, vascular lesions including aneurysms and delayed wound healing. Less obvious
is the fact that experimental lathyrysm is a model of chemically induced disease, a tool for the study of some of the basic processes of disease. The excellent article by Menzies and Mills\textsuperscript{28} on the pathology of osteolathyrysm indicated that the fundamental pathological process in the bones and aorta was an excessive accumulation of intercellular ground-substance, which appeared to be chondroitin sulfate. A subsequent feature was the retarded development of elastic fibers. They suggested that the lathyrous factor “may act as an enzyme poison, interfering in some way with the maintenance or elaboration of connective-tissue materials.” Chondroitin sulfate is a complex polysaccharide which is normally linked to protein. The proteins of elastin and collagen have amino acid contents\textsuperscript{4,30} characterized by large amounts of glycine, alanine, proline and hydroxyproline. Glycine and alanine account for almost half the dry-weight of elastin.

Relation of these facts to the mechanisms by which lathyrogens may exert their effects requires brief consideration of the nature of these chemicals. The compound first extracted from \textit{L. odoratus} in 1954 was identified as β-(glutamyl)-aminopropionitrile but it was soon demonstrated that the active component was β-aminopropionitrile. The closely related aminocacetonitrile is also a powerful lathyrogen. The third active compound, methyleneaminoaconitnitrile, is capable of hydrolysis to aminocacetonitrile. Note the structural resemblance of these aminonitriles to the amino acids glycine and alanine:

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\begin{align*}
\text{NH}_2\text{CH}_2\text{CN} & \quad \text{NH}_2\text{CH}_2\text{CH}_2\text{CN} \\
\text{Aminoacetonitrile} & \quad \beta\text{-aminopropionitrile} \\
\text{NH}_2\text{CH}_2\text{COOH} & \quad \text{CH}_3\text{CHCOOH} \\
\text{Glycine} & \quad \text{NH}_2 \\
& \quad \text{Alanine}
\end{align*}
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The basic organic chemistry of the nitriles is still in the developmental stage.\textsuperscript{2,3,12,18,19,29} They are said to be amine reactors under physiological conditions\textsuperscript{35} and as such might be expected to enter into peptide linkages in the fabrication of proteins. Present information concerning the metabolism of lathyrogens is incomplete but the toxic principle has been found to pass the placenta and to appear in the milk of mice.\textsuperscript{27} Studies of urinary amino acid excretion, using two-dimensional chromatograms, showed considerable variations from normal, including β-aminopropionitrile, in animals on a sweet-pea diet.\textsuperscript{43} In fact, 80 to 90 per cent of C\textsuperscript{14} cyanide-labeled β-aminopropionitrile has been found in the urine of rats within 20 hours.\textsuperscript{24} Of this, 40 per cent was unchanged β-aminopropionitrile and 25 to 30 per cent cyanoacetic acid. Similar isotope studies with aminoacetonitrile resulted in the identification of radioactive glycine and serine in the liver,\textsuperscript{32} indicating an appreciable conversion of the cyanide radical into the carboxyl group of the closely related amino acids. Radioactivity was also detected in the sulfated polysaccharides of the enlarged epiphyseal plates.\textsuperscript{32} Autoradio-
graphic studies of $S$\textsuperscript{50} in osteolathyritic cartilage indicated no apparent defect in sulfur metabolism.\textsuperscript{1} Both the hydroxyproline and collagen contents of the involved epiphyseal cartilages were normal,\textsuperscript{6,13} but hexosamine was significantly decreased.\textsuperscript{6,7} Homogenized fractions of such cartilages were virtually devoid of collagen fibers when examined by electron microscopy.\textsuperscript{13} There was no deficit of total polysaccharides of bone or skin\textsuperscript{21} but lathyrinic muscle was found to lack a chromatographic spot identified with glycine and glutamic acid.\textsuperscript{42} Dramatic regression of osteolathyrinous lesions has been observed after the lathyrogen was discontinued.\textsuperscript{15,33}

Correlation of the above data with biochemical aspects of fibrogenesis may now be attempted. For a review on fibrogenesis, reference is made to the excellent article by Jackson.\textsuperscript{20} The crucial feature, in relation to lathyrism, is that C\textsuperscript{14}-labeled glycine is rapidly incorporated into a soluble precursor of fibrous collagen. Further, the polysaccharide moiety of collagen is linked to certain C-terminal amino acids, one of which has been identified as glycine.\textsuperscript{22} It is highly probable, in the opinion of the writer, that the osteolathyrogens act as antimetabolites,\textsuperscript{39,40} competing with glycine and possibly alanine for incorporation into developing connective tissue. The protective effect of cortisone noted by Selye\textsuperscript{36} may be related to the direct growth-retarding action of cortisone on developing cartilage and bone.\textsuperscript{37}

Recently three other substances have been found to produce skeletal lesions similar to those of the aminonitriles; these are semicarbazide, $\beta$-mercaptoethylamine and cystamine.\textsuperscript{8,10} A new method for testing lathyrogenic agents has just been reported by Levy,\textsuperscript{28} who noted that salamander and toad embryos reared in water containing lathyrogens, exhibited gross tumors of the notochord within three days. Additional lathyrogens by this method were phenylhydrazine and its methyl and butyl congeners, two congeners of semicarbazide, and urea. It was suggested that lathyrogens may be water-soluble aldehyde blocking agents and that the defect might be concerned with carbohydrate metabolism of the connective-tissue ground substance. So far there has been no information concerning the mechanism of the lone, known neurolathyrogen: $\beta,\beta'$-iminodipropionitrile. However, its structural similarity to glutamic acid, shown below, suggests

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\begin{align*}
\text{HOOC CH}_2\text{CH}_2\text{COOH} & \quad \text{NC CH}_2\text{CH}_2\text{NH CH}_2\text{CH}_2\text{CN} \\
\text{Glutamic acid} & \quad \beta,\beta'$-iminodipropionitrile
\end{align*}
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an antimetabolite relationship. Glutamic acid, together with its amide, glutamine, account for about 80 per cent of the free $\alpha$-amino acids in the central nervous system. The irreversible effects of neurolathyrm indicate irreversible cell damage and correlate with the absence of neuronal regeneration.

REFERENCES


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