Lathyrism: A Review

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NEUROLATHYRISM (HUMAN LATHYRISM)

NEUROLATHYRISM in its classic form is a neurologic syndrome of man and domestic animals manifested chiefly by a spastic paraplegia of the lower extremities.[1] The harmful effects of the Lathyrus species were known to Hippocrates who wrote, "At Ainos, all men and women who ate peas continuously become impotent in the legs, and that state persisted."[2] Endemics and epidemics of neurolathyrism occurred in Europe and Asia in the eighteenth and nineteenth centuries; these outbreaks were associated with famines and the consequential use of certain Lathyrus species in the preparation of flours and cereals.[3,4,5] A clinically similar disease potentiated by vitamin deficiency occurred in concentration and prisoner-of-war camps during World War II.[4,5] At present, the disease is a public health problem only in India and in the Mediterranean area, where food is often scarce and famine commonplace.[3]

The etiologic factors responsible for the development of neurolathyrism have not been positively identified. Studies suggest that the potent neurotoxins L-alpha-gamma-diaminobutyric acid (isolated from *Lathyrus latifolius*) and beta-cyano-L-alanine (isolated from *Vicia sativa*, the common vetch, which often grows alongside the Lathyrus species) may be involved in the production of human lathyrism.[6,7] Beta-cyano-L-alanine is an intermediate in the conversion of asparagine to L-alpha-gamma-diaminobutyric acid, and by decarboxylation produces the naturally occurring osteolathyrogen, beta-aminopropionitrile.[6,7] The lack of a suitable laboratory assay animal has hindered the isolation, identification, and investigation of the neurotoxins responsible for human lathyrism.

Neurolathyrism is characterized by the relatively acute onset of weakness in the lower extremities, at times preceded by pain and paresthesias.[4,5] The end result is a permanent spastic paraplegia of the lower extremities characterized by paralysis, increased muscular tonus, increased deep tendon reflexes, positive pathologic reflexes, and the absence of muscle atrophy and nerve regeneration.[4,5] Transient symptoms, usually subsiding with exclusion of lathyrus from the diet, include paresis of the upper extremities and neck, irregularities in bowel and urination habits, and impaired circulation of the lower extremities.[5] Spondylosis and other skeletal lesions are thought to be secondary to the neurologic manifestations, and differ from the skeletal lesions of experimental lathyrism.[4]

Pathologically there is marginal sclerosis and degenerative changes in the lateral pyramidal tracts of the spinal cord, a reduced number and shrinkage of Betz's cells, and dilatation of the extracellular spaces in the gray matter of the brain.[5]

There is no effective treatment for the resultant spastic paraplegia. Prophylaxis or prevention of the disease is achieved only by the total exclusion of lathyrus from the diet.[5]

OSTEOLATHYRISM (EXPERIMENTAL LATHYRISM)

In 1933, Geiger[8] and his associates reported on the occurrence of multiple skele-

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tal lesions produced in rats by the feeding of sweet peas (*L. odoratus*). The similarity between the manifestations of osteolathyrism in rats and certain skeletal disorders in man led Ponseti and Shepard[9] to utilize experimental lathyrism as a model for Legg-Calvé-Perthes disease, Paget's disease, recurring dislocation of the shoulder, osteogenesis imperfecta, adolescent kyphosis, and idiopathic kyphoscoliosis. In addition to the skeletal abnormalities, Ponseti and Baird[10] noted that a high percentage of the animals fed *L. odoratus* died of aortic dissection. It is now well known that osteolathyrism can be induced in a variety of common laboratory animals, primarily affecting skin, dental tissues, bones, blood vessels, and tendons. Experimental lathyrism represents an excellent model of true collagen disease, in contrast to the diverse clinical syndromes in which collagen has been implicated but never proven to be primarily involved.

Schilling and Strong[11] demonstrated that the substance in *L. odoratus* responsible for its toxicity in rats was beta-aminopropionitrile, a well-established toxin known to cause widespread connective tissue alterations. In addition to beta-aminopropionitrile and its homolog aminoacetonitrile, a large number of unrelated chemicals give rise to osteolathyrism. Levene[12] subdivided lathyrogens into nitriles, ureides, hydrazides, and hydrazines, forming a series of diminishing potency in their ability to produce skeletal deformities and collagen abnormalities.

There are many conflicting studies concerning the various physical and chemical factors which modify experimental lathyrism. Growth hormone,[3] leuteotropic hormone,[3] thyroparathyroidectomy,[3] partial hepatectomy,[3] phenylbutazone,[3] systemic stress,[3] and amine oxidase inhibitors[13,14,15,16,17] have all been found to potentiate the development of osteolathyrism. Levene[12] presented evidence that lathyrogens do not act as monoamine oxidase inhibitors. Corticosteroids,[3,18] ACTH,[3] thyroxine,[3,19,20] denervation,[3] calcium,[21] vitamin E,[22] and numerous dietary supplements, especially amino acids and proteins,[23,24,25] have been reported to decrease the potency of lathyrogenic agents. Considerable protection against fetal resorption was obtained by treating pregnant rats (exposed to lathyrogenic agents) with estrone and progesterone.[26,27] The skeletal deformities are reversible upon withdrawal of the lathyrogen,[28,29] but studies concerning the regression of vascular lesions have not been reported.

Pathologically, lesions are seen in the skin, dental tissues, bones, tendons, and blood vessels; the changes are more extensive in younger animals. Pathologic descriptions are varied and in some instances contradictory; this diversity is due partially to the lack of specificity of the histochemical stains, which may react with a variety of connective tissue substances. Fibroblastic proliferation,[30,31,32,33] inhibitation of maturation of fibroblasts,[34,35,36,37,38] and absence of impairment of fibrogenesis[39,40] have been found. Degeneration and lysis of elastic fibers, disturbance of elastogenic and elastolytic processes, and disordered regeneration of elastic fibers have been described.[10,30,31,32,33,41,42,43,44,45,46,46,47] McCallum[47] has stated that the vascular lesions in lathyrism always involve elastic vessels; he postulated that a defect in the elastic lamina was the main cause of aortic rupture. Several workers have demonstrated by light microscopy an increase in mucopolysaccharides in lathyritic tissues[30,31,33,42,43,49]; others have proposed defective formation, excessive destruction, and depolymerization of the ground substances.[9,29,50,51,52,53] However, Zahor[45] found no change in mucopolysaccharide staining reactions.

Electron microscopic studies also have been discordant. Collagen structure has been variously described as normal[54,55] and as showing a failure of the tropocolla-

gen molecules to aggregate in a normal fashion.[39,56,57] Keech[58] and Ham[59] found that collagen was increased in amount in the lathyritic rat aorta, while Cliff, Levene, and Saunders[40] concluded that the formation of collagen was not inhibited by lathyrogenic agents. Electron microscopic studies of the lathyritic rat aorta have shown increased aortic wall thickness, increased cellularity, widely separated elastic laminae, and the presence of a periodic acid-Shiff (PAS)-positive material between the elastic laminae in the media.[58,59]

Radioisotope and autoradiographic studies are likewise conflicting. Sulfur-35 incorporation into connective tissues has been used to demonstrate sulfated mucopolysaccharide synthesis. Lathyrogens have been assumed to impair sulfur-35 incorporation.[60] However, it has been found that polysaccharides could be synthesized prior to sulfation,[61] and Peck[62] demonstrated that the minimal amount of beta-aminopropionitrile needed to produce lathyritic collagen was 1,000 times less than that amount necessary to inhibit sulfur-35 incorporation. Autoradiographic studies in lathyritic animals favor no essential change in sulfur-35 incorporation[63,64,65]; however, increased incorporation[66,67,68] and inhibition of sulfur-35 uptake[69,70] have been described. Likewise, most isotope studies suggest that collagen synthesis occurs normally in lathyritic animals,[71,72,73] but others have detected a retarded collagen synthesis[74,75] and increased collagen synthesis.[76] Recent studies suggest that lathyrogenic agents primarily affect newly synthesized collagen.[77] However, Tanzer has stated that isotope studies suggest that lathyrogenic agents do not affect all new collagen, since some lathyritic collagen can form stable aggregates *in vivo*.[78] Kundel,[79] using wide-angle x-ray diffraction, has demonstrated that normal and lathyritic collagen are identical in the dry state.

The physical property most extensively studied has been the tensile strength of lathyritic skin and aorta. Tanzer[78] reported that there was a close correlation between the tensile strength and the collagenous framework. Levene and Gross[80] found that the tensile strength was inversely related to the dose of the lathyrogen. A reduction in the tensile strength of lathyritic skin and aortae[39,80,81,82,83] and in the healing wounds of lathyritic animals[84,85,86] has been well documented. Peacock and Madden[87] recently demonstrated that lathyrogens arrested the strength gain of wounds and increased saline-extractable collagen 10-fold, but did not alter the amount of insoluble collagen in the wound.

Preceding the structural and functional alterations previously described are abnormalities in connective tissue chemistry. Collagen is synthesized by the fibroblasts and is polymerized extracellularly, yielding mature collagen.[88] The basic subunit (tropocollagen or alpha-collagen) can be extracted from mature collagen by cold saline solution, has a molecular weight of 300,000, and has a triple helix configuration.[88] The tropocollagen polymerizes first into the dimer (beta-collagen). Progressive end-to-end or side-to-side polymerization increases with age, and results in a mature collagen fiber of great tensile strength, low elasticity, and low turnover rate.[88] An increase in the saline solubility of collagen implies a decreased degree of polymerization.[88] The level of collagen extractable with saline from lathyritic tissues is increased,[12,71,80,82,89,90,91,92] and this increase is detectable 2 hours following beta aminopropionitrile administration.[71] Young rapidly growing rats normally have much higher levels of extractable collagen than older animals. This implies a higher rate of collagen synthesis in young rats.[92] A 3-fold increase in extractable collagen was found in young lathyritic rats as compared to their normal litter mates; this suggests that a defect in the maturation of collagen

is a more important source of the abnormal collagen than is the disaggregation of already mature collagen.[92] Tanzer and Gross[71] have shown that the increase in extractable collagen obtained from lathyritic animals originated from both defective maturation and disaggregation of preformed fibers. An increased urinary hydroxyproline excretion, corresponding to the increase in saline-extractable collagen, occurs in lathyritic animals, and presumably represents an acclerated breakdown of tropocollagen.[93,94] Martin[95,96] has found that lathyritic collagen is lacking in intramolecular cross-links, due either to their disruption or to interference with their formation; therefore, polymerization is inhibited, resulting in structurally weak collagen. Tanzer[78] has concluded that the intrinsic properties of the lathyritic tropocollagen molecule are the inability to form stable intermolecular aggregates and the absence of intramolecular cross-links.

In contrast to the qualitative defects, quantitative chemical analyses of various lathyritic tissues have usually shown no effect of the lathyrogenic agents on collagen content.[57,71,80,81,82,89,97,98,99] Amino acid composition, amino groups, ester linkages, carbohydrate content, denaturation temperatures, intrinsic viscosity, flow birefringence, sedimentation constant, and optical rotary dispersion are normal in the collagen obtained from lathyric tissues.[78,80,96,100,101] Lenzi and Pedrini-Mille[102] have summarized the conflicting data on mucopolysaccharides by stating that the mucopolysaccharides are not essential for the development of the typical collagenous lesions due to lathyrogenic agents; a decreased amount of mucopolysaccharides has been found only in those tissues which contain large amounts of chondroitin-4-SO_4 or chondroitin-6-SO_4.[103] The determination of the total hexosamine content as an index of mucopolysaccharide concentration is a non-specific measure and has consequently produced conflicting results.[35,65,69,78,94,98,99,102,103]

The mechanisms by which the lathyrogenic agents act to produce the previously described alterations have not been clearly delineated. Metabolic activity of the animal is required in the production of lathyritic collagen; *in vitro* studies have yielded negative results.[80,104,105] Many theories concerning the mechanism of action of the lathyrogenic agents have been advanced; those currently enjoying the most prominence are as follows:

Proteolytic enzyme release. It may be that connective tissue cells exposed to lathyrogenic agents release proteolytic enzymes (pepsin, trypsin, chymotrypsin) which are capable of removing intramolecular cross-links from the beta components of soluble collagen.[71]

Inhibition of cellular respiration. Clemmons[106,107] has found that lathyrogenic agents liberate cyanide, a potent inhibitor of the respiratory enzyme cytochrome oxidase. He has postulated that lathyrogens, by inhibiting cellular respiration, could produce specific biochemical lesions by interfering with proline metabolism, the citric acid cycle, the synthesis of glutamic acid semialdehyde and other cross-linking compounds, or they could act via a non-specific tissue injury that is the consequence of impaired respiration.[106]

Inhibition of biosynthesis of cross-linking compounds. Lathyrogenic agents have been shown to inhibit the biosynthesis of the newly isolated cross-linking compounds, desmosine and isodesmosine,[108,109] present in elastin. The synthesis of desmosine and isodesmosine from lysine proceeds through an aldehyde intermediate.[110] Levene[111] had previously suggested that aldehydes were involved in the cross-linking of collagen. Lathyrogenic agents very probably act by blocking carbonyl groups on the collagen molecule,[111,112] and by inhibiting the enzymatic reactions involved in the oxidation of lysine to aldehydes.[113] Collagen impairment is not the only major defect present in lathyritic tissues; similar biosynthetic pathways are utilized in the cross-linking of collagen and elastin, and both may be altered by lathyrogenic agents in a like manner.

Discussion

The occurrence of both skeletal abnormalities and aortic dissection in lathyritic

animals calls to mind the Marfan syndrome in man, where skeletal abnormalities and aortic dissection occur in addition to ocular and cardiac abnormalities.[1] The association of the skeletal abnormalities and aortic dissection in experimental lathyrism led Bean and Ponseti[114] to search for such an association in man. In a series of 20 patients with aortic dissection they found an unusual incidence (35 per cent) of kyphoscoliosis and severe pigeon-breast deformity. Penicillamine in rats produces alterations in collagen similar to those produced by the lathyrogenic agents.[115,116,117] Penicillamine therapy in Wilson's disease and cystinuria has been shown to produce an increase in saline-extractable collagen from the skin of treated individuals.[118,119] Accordingly, penicillamine recently has been instituted as a therapeutic agent in scleroderma, a disease in which there is a decreased amount of saline-extractable collagen.[118,119,120] Should lathyrogenic agents be used with increasing frequency in the treatment of human disease, we may begin to encounter vascular, skeletal, dental, and cutaneous abnormalities. Experimental lathyrism serves as an excellent model for creating connective tissue disturbances which mimic idiopathic human diseases of connective tissue origin, and offers an opportunity to search for the prevention and reversal of such changes.

Summary

Lathyrism is a complex disease state resulting from the excessive ingestion of seeds of certain legumes, primarily of the genus Lathyrus. Human lathyrism is a neurologic syndrome manifested chiefly by a spastic paraplegia of the lower extremities. Experimental lathyrism of laboratory animals serves as a research model for creating connective tissue disturbances which mimic idiopathic human diseases of connective tissue origin.

Summario in Interlingua

Lathyrismo es un complexe stato de morbiditate que resulta ab le excessive ingestion del semines de certe legumines, primarimente in le genere Lathyrus. Lathyrismo in humanos es un syndrome neurologic que se manifesta principalmente in un paraplegia spastic del extremitates inferior. Lathyrismo experimental in animales de laboratorio servi como modello de recerca pro crear disturbationes de tissu conjunctive que pote simular idiopathic morbos human de origine in le tissus conjunctive.

REFERENCES

1. Weaver, Arthur L., and Spittell, John A., Jr.: Lathyrism. Mayo Clin. Proc. 39: 485, 1964.
2. Hippocrates: Quoted by Selye, Hans.[3]
3. Selye, Hans: Lathyrism. Rev. Canad. Biol. 16:1, 1957.
4. Paissios, C. S., and Demopoulous, Theodore: Human lathyrism: A clinical and skeletal study. Clin. Orthop. 23:236, 1962.
5. Gardner, A. F., and Sakiewich, N.: A review of neurolathyrism including the russian and polish literature. Exp. Med. Surg. 21:164, 1963.
6. Ressler, Charlotte, Redstone, P. A., and Erenberg, Renee H.: Isolation and identification of a neuroactive factor from lathyrus latifolius. Science 134:188, 1961.
7. Ressler, Charlotte: Isolation and identification from the common vetch of the neurotoxin B-cyano-L-alanine, a possible factor in neurolathyrism. J. Biol. Chem. 237:733, 1962.
8. Geiger, Beatrice J., Stienbock, Harry, and Parsons, Helen T.: Lathyrism in the rat. J. Nutr. 6:427, 1933.
9. Ponseti, I. V., and Shepard, R. S.: Lesions of the skeleton and of other mesodermal tissues in rats fed sweet-pea *(Lathyrus odoratus)* seeds. J. Bone Joint Surg. 36A: 1031, 1954.
10. Ponseti, I. V., and Baird, W. A.: Scoliosis and dissecting aneurysm of the aorta in rats fed with *Lathyrus odoratus* seeds. Amer. J. Path. 28:1059, 1952.

11. *Schilling, E. D., and Strong, F. M.*: Isolation, structure, and synthesis of a lathyrus factor from *L. odoratus*. J. Amer. Chem. Soc. 76:2848, 1954.
12. Levene, C. I.: Structural requirements for lathyrogenic agents. J. Exp. Med. 114: 295, 1961.
13. McDonald, B. E., Bird, H. R., and Strong, F. M.: Production of aortic aneurysms in turkeys and effects of various compounds in potentiating induced aortic ruptures. Proc. Soc. Exp. Biol. Med. 113:728, 1963.
14. Roy, D. N., Lipton, S. H., Strong, F. M., and Bird, H. R.: Potentiation of lathyrogenic effect of beta aminopropionitrile in turkey poults. Proc. Soc. Exp. Biol. Med. 102:767, 1959.
15. Lipton, S. W., Lalich, J. J., and Strong, F. M.: Identification of cyanoacetic acid as a metabolite of B-aminopropionitrile (BAPN) and other nitriles. J. Amer. Chem. Soc. 80:2022, 1958.
16. Gross. J., Levene, C. I., and Orloff, S.: Fragility and extractable collagen in the lathyritic chick embryo. An assay for lathyrogenic agents. Proc. Soc. Exp. Biol. Med. 105:148, 1960.
17. Juva, K., Mikkonen, L., Tuominen, T., and Kulsnen, E.: Iproniazid and experimental lathyrism. Experientia 15:350, 1959.
18. Trnavsky, K., Trnavsky, Z., and Cebecauer, L.: Attempt to influence the increased solubility of collagen in lathyrism by hydrocortisone. Nature 207:993, 1965.
19. Bell, G. H., Khogali, A., and Sharma, D. N.: Quantitative studies on the suppression of skeletal lesions in rats produced by beta-aminopropionitrile. Quart. J. Exp. Physiol. 47:244, 1962.
20. Gabay, S., Vivanco, F., Ramos, F., and Jimenez-Diaz, C.: Influence of DL-thyroxine and cortisone on femurs of rats with odoratism. Arch. Biochem. 92:87, 1961.
21. Naber, E. C., and Blackwood, U. B.: Partial reversal of β-aminopropionitrile toxicity by calcium in the chick. J. Nutr. 78: 207, 1962.
22. Cameron, J. M., Pirie, T. G., and Robb, R. A.: The protective action of certain hormones and vitamins against lathyrogenic drugs. Brit. J. Exp. Path. 43:496, 1962.
23. Merkow, L. P., and Lalich, J. J.: Influence of diet on the incidence of angiorrhexis in beta-aminopropionitrile-fed rats. A.M.A. Arch. Path. 70:752, 1960.
24. Gardner, A. F.: The effect of various levels of sweet peas *(Lathyrus odoratus)* in the diet, with and without dietary supplements, on the growth of the mandibular ramus and articulation in young rats. J. Dent. Res. 38:805, 1959.
25. Dasler, W.: Experimental Lathyrism. Chicago Med. Sch. Quart. 18:1, 1957.
26. Walker, D. G., and Wirtschafter, Z. T.: Resorption of embryos in rats on *Lathyrus odoratus* diet. J. Nutr. 58:147, 1956.
27. Walker, D. G., and Wirtschafter, Z. T.: Estrogenic inhibition of fetal resorption in lathyrism. J. Nutr. 58:161, 1956.
28. Marwah, A. S., Dasler, W., and Meyer, J.: Reversibility of lathyritic damage to the periodontal structures. J. Periodont. 34: 142, 1963.
29. Ramamurti, P., and Taylor, H. E.: Histochemical studies of the evolution and regression of skeletal deformities due to B-aminopropionitrile. Lab. Invest. 7:115, 1958.
30. Walker, D. G.: Elastic fiber alterations in rats treated with *Lathyrus odoratus*. A.M.A. Arch. Path. 64:434, 1957.
31. Walker, D. G., and Wirtschafter, Z. T.: Histopathogenesis of aortic aneurysms in the lathyrus-fed rat. A.M.A. Arch. Path. 61:125, 1956.
32. Merkow, L., Lalich, J. J., and Angevine, D. M.: Fibrillogenesis during repair of aortic injury produced by B-aminopropionitrile. A.M.A. Arch. Path. 71:654, 1961.
33. Wirtschafter, Z. T.: Acid mucopolysaccharides in the histopathogenesis of aortic aneurysms in the lathyrus-fed rat. A.M.A. Arch. Path. 64:577, 1957.
34. Mielke, J. E., Lalich, J. J., and Angevine, D. M.: Influence of beta-aminoproprionitrile upon development of connective tissue in croton oil pouches. Proc. Soc. Exp. Biol. Med. 94:673, 1957.
35. Hurley, J. V., and Ham, Kathryn N.: The nature of the connective tissue defect produced by the aminonitriles. Brit. J. Exp. Path. 40:216, 1959.
36. Krikos, G. A., and Orbison, J. L.: Effect of beta-aminopropionitrile upon wound healing. A.M.A. Arch. Path. 65:312, 1958.
37. Hurley, J. V., Storey, E., and Ham, Kathryn N.: The effects of aminoacetonitrile and cortisone on the healing of turpentine-induced abscesses in the rat. Brit. J. Exp.

Path. 39:119, 1958.
38. Storey, E. and Varasdi, G.: Fracture repair in the rat during aminoacetonitrile administration and following its withdrawal. Brit. J. Exp. Path. 39:376, 1958.
39. van den Hoff, A., Levene, C. I., and Gross, J.: Morphologic evidence for collagen changes in chick embryos treated with beta-aminopropionitrile. J. Exp. Med. 110: 1017, 1959.
40. Cliff, W. J., Levene, C. I., and Saunders, A. G.: The effect of lathyritic compounds on collagen formation in the rabbit ear chamber. J. Path. Bact. 85:257, 1963.
41. Gillman, T.: Reduplication, remodeling, regeneration, repair, and degeneration of arterial elastic membranes. A.M.A. Arch. Path. 67:624, 1959.
42. Menzies, D. W. and Mills, K. W.: The aortic and skeletal lesions of lathyrism in rats on a diet of sweet pea. J. Path. Bact. 73:223, 1957.
43. Churchill, D. W., Gelfant, S., Lalich, J. J.: and Angevine, D. M.: Alterations in the polysaccharides and elastic fibers in the aorta of rats fed toxic lathyrus factor. Lab. Invest. 4:1, 1955.
44. Bachhuber, T. E., and Lalich, J. J.: Effect of sweet pea meal on the rat aorta. A.M.A. Arch. Path. 59:247, 1955.
45. Zahor, Z. and Czabanova, V.: The frequency and pathogenesis of aortic fibroelastosis in foetal lathyrism in rats. J. Path. Bact. 84:209, 1962.
46. Herd, K. and Orbison, J. L.: Lathyrism in the fetal rat. A.M.A. Arch. Path. 81:60, 1966.
47. McCallum, H. M.: Experimental lathyrism in mice. J. Path. Bact. 89:625, 1965.
48. McCallum, H. M.: Experimental lathyrism in tissue culture. J. Path. Bact. 89:637, 1965.
49. Krikos, G. A. and Orbison, J. L.: Histochemical studies of skin wounds in rats receiving beta-aminopropionitrile. A.M.A. Arch. Path. 70:188, 1960.
50. Schwartz, C. J.: Nature of ground substance changes in experimental lathyrism and their effect on atherogenesis in cholesterol-fed rabbits. Brit. J. Exp. Path. 40:44, 1959.
51. Gardner, A. F., Dasler, W., and Weinman, J. P.: Masticatory apparatus of albino rats in experimental lathyrism. J. Dent. Res. 37:492, 1958.
52. Belanger, L. F.: Observations on the manifestations of osteolathyrism in the chick. J. Bone Joint Surg. 41B:581, 1959.
53. Pyörälä, K., Punsar, S., Seppala, T., and Karlsson, K.: Mucopolysaccharides of the aorta and epiphyseal cartilage in lathyritic growing rat fetuses. Acta Path. Microbiol. Scand. 41:497, 1957.
54. Millington, P. F.: Studies by negative staining on the structure of collagen fibrils in normal and lathyritic rats. Z. Zellforsch. 70:108, 1966.
55. Bruns, R. R.: Studies on collagen in the lathyritic rat (Doctoral Thesis Abstract). Collagen Currents 7:171, 1966.
56. Lalich, J. J. and Ishida, K.: Alteration of elastin and orientation of collagen in angiolathyrism. A.M.A. Arch. Path. 82: 129, 1966.
57. Follis, R. H. and Tousmis, A. M.: Experimental lathyrism in the rat: nature of defect in epiphyseal cartilage. Proc. Soc. Exp. Biol. Med. 98:843, 1958.
58. Keech, M. K.: Electron microscope study of the lathyritic rat aorta. J. Biophys. Biochem. Cytol. 7:539, 1960.
59. Ham, Kathryn N.: The fine structure of rat aorta in experimental lathyrism. Aust. J. Exp. Biol. Med. Sci. 40:353, 1962.
60. Engfeldt, B. and Westerborn, O.: An autoradiographic study of the epiphyseal cartilage in normal rabbits after administration of radiosulfate. Acta. Pathol. Microbiol. Cytol. 49:73, 1960.
61. Strominger, J. L.: Nucleotide intermediates in the biosynthesis of heteropolymeric polysaccharides. Biophys. J. 4: Suppl. 139, 1964.
62. Peck, W., Mariz, I., and Daughaday, W. H.: Inhibition of collagen aggregation in rat cartilage induced by beta-aminopropionitrile *in vitro*. J. Lab. Clin. Med. 62:407, 1963.
63. Kennedy, J. S. and Kennedy, G. D.: Autoradiographic studies in experimental lathyrism. J. Path. Bact. 84:123, 1962.
64. Engfeldt, B., Tegner, B., and Berquist, E.: Early changes in epiphyseal growth zone in experimental osteolathyrism. Acta Path. Microbiol. Scand. 49:39, 1960.
65. Ponseti, I. V., Wawzonek, S., Shepard, R. S., Evans, T. C., and Steins, G.: Further studies on lathyrism in the rat. Proc. Soc. Exp. Biol. Med. 92:366, 1956.
66. Belanger, I. F.: Autoradiographic studies of sulfated mucopolysaccharide metabolism in cartilage of osteolathyritic rats and

chicks. Proc. Soc. Exp. Biol. Med. 99: 605, 1958.
67. Bauer, G. C. M., Carlson, A., and Lindquist, B.: Skeletal uptake of sulfate and phosphate in β-aminopropionitrile-poisoned rats. Acta. Path. Microbiol. Scand. 35:407, 1955.
68. Bickley, H. C. and Orbison, J. L.: Effect of lathyrogen on sulfate metabolism in culture of the strain "L" fibroblast. Lab. Invest. 13:172, 1964.
69. Karnovsky, M. J. and Karnovsky, M. L.: Metabolic effects of lathrogenic agents on cartilage *in vivo* and *in vitro*. J. Exp Med. 113:381, 1961.
70. Shintani, Y. K. and Taylor, H. E.: The effect *in vitro* of lathyrogens on the uptake of radiosulfate by epiphyseal cartilage. Lab. Invest. 11:697, 1962.
71. Tanzer, M. L. and Gross, J.: Collagen metabolism in the normal and lathyritic chick. J. Exp. Med. 119:275, 1964.
72. Smiley, J. D., Yeager, H., and Ziff, M.: Collagen metabolism in osteolathyrism in chick embryos: site of action of B-aminopropionitrile. J. Exp. Med. 116:45, 1962.
73. Gerber, G. B., Gerber, G., and Altman, K. I.: Studies of collagen turnover in lathyritic rats. Arch. Biochem. Biophys. 96: 601, 1962.
74. Bruemmer, N. C., Lalich, J. J., and Mueller, C. C.: Effect of B-aminopropionitrile on incorporation of glycine by croton oil pouches in rats. Proc. Soc. Exp. Biol. Med. 96:340, 1957.
75. Salmi, A. and Kulonen, E.: Inhibited incorporation of ammonium chloride labelled with nitrogen-15 in chick embryos treated with B-aminopropionitrile. Nature 196:895, 1962.
76. Smith, D. J. and Shuster, R. C.: Biochemistry of lathyrism. I. Collagen biosynthesis in normal and lathyritic chick embryos. Arch. Biochem. Biophys. 98:498, 1962.
77. Tanzer, M. L. and Hunt, R. D.: Experimental lathyrism: an autoradiographic study. J. Cell Biol. 22:623, 1964.
78. Tanzer, M. L.: Experimental lathyrism. *In* Hall, D. A., ed.: International Review of Connective Tissue Research. New York and London, Academic Press, 1965, p. 91.
79. Kundel, H. L.: Osteolathyrism in the rat: an x-ray diffraction study of collagen from normal and lathyritic rats. Radiol. 82:67, 1964.
80. Levene, C. I. and Gross, J.: Alterations in the state of molecular aggregation of collagen induced in chick embryos by beta-aminopropionitrile (lathyrus factor). J. Exp. Med. 110:771, 1959.
81. Levene, C. I.: Collagen as tensile component in developing chick aorta. Brit. J. Exp. Path. 42:89, 1961.
82. Fry, Phyllis, Harkness, Margaret L. R., Harkness, R. D., and Nightingale, Margaret: Mechanical properties of tissues of lathyritic animals. J. Physiol. (London), 164:77, 1962.
83. Lykke, A. W., Muller, H. K., and Robertson, J. S.: Effects of hexamethonium bromide and B-aminopropionitrile on the tensile strength of the aorta of mice. Nature 188:238, 1960.
84. Berberian, G. M., Geever, E. F., and Levenson, S. M.: Wound healing defect in lathyrism. Surg. Forum 15:50, 1964.
85. Gillespie, J. A. and Burns, J. E.: The strength and histology of skin wounds in lathyrism. Brit. J. Surg. 46:642, 1959.
86. Enzinger, F. M. and Warner, E. D.: Wound healing in experimental lathyrism. Lab. Invest. 6:251, 1957.
87. Peacock, E. E. and Madden, J. W.: Some studies on the effect of B-aminopropionitrile on collagen in healing wounds. Surgery 60:7, 1966.
88. Levene, C. I.: Collagen in experimental osteolathyrism. Fed. Proc. 22:1386, 1963.
89. Mikkonen, L., Touminen, T., and Kulonen, E.: Collagen fractions in lathyritic rats. Biochem. Pharmacol. 3:181, 1960.
90. Wirtschafter, Z. T. and Bentley, J. P.: The extractable collagen of lathyritic rats with relation to age. Lab. Invest. 11:365, 1962.
91. Gross, J. and Levene, C. I.: Effect of beta-aminopropionitrile on extractability of collagen from skin of mature guinea pigs. Amer. J. Path. 36:687, 1959.
92. Wirtschafter, Z. T. and Bentley, J. P.: Extractable collagen in the normal and aneurysmal aorta. A.M.A. Arch. Path. 79: 635, 1965.
93. Orbison, J. L., McCrary, C., and Callaban, Marie: Urinary excretion and serum composition of lathyritic rats. A.M.A. Arch. Path. 79:292, 1965.
94. Hartman, F.: Investigations on the pathogenesis of connective tissue damage in experimental lathyrism: urinary hydroxyproline and hexosamine determinations in lathyritic rats. Z. Rheumaforsch. 25:161, 1966.

95. Martin, G.R., Gross, J., Piez, K. A., and Lewis, M. S.: On the intramolecular cross-linking of collagen in lathyritic rats. Biochim. Biophys. Acta. 53:599, 1961.
96. Martin, G. R., Piez, K. A., and Lewis, M. S.: The incorporation of C^{14}-glycine into the subunits of collagen from normal and lathyritic animals. Biochim. Biophys. Acta. 69:472, 1963.
97. Lalich, J. J., Wirka, H. W., and Angevine, D. M.: Influence of B-aminopropionitrile feeding on collagen synthesis in rat aortas. Path. Microbiol. (Basel) 24:140, 1961.
98. Castellani, A. A. and Castellani-Bisi, C.: Decrease in hexosamine content of epiphyseal plates in experimental lathyrism. Proc. Soc. Exp. Biol. Med. 98:318, 1958.
99. Bolograni, L.: Hexosamine and hydroxyproline content of fracture callus in normal and aminoacetonitrile-treated rats. Proc. Soc. Exp. Biol. Med. 108:70, 1961.
100. Gross, J.: An intermolecular defect of collagen in experimental lathyrism. Biochim. Biophys. Acta. 71:250, 1963.
101. Nikkari, T. and Kulonen, E.: Components of skin of lathyritic rats. Read before the Fifth International Congress of Biochemistry, Moscow, 1961; abstracted, Collagen Currents, 2:33, 1961.
102. Lenzi, L. and Pedrini-Mille, A.: Acid mucopolysaccharides in the skin of lathyritic rats. Proc. Soc. Exp. Biol. Med. 118:270, 1965.
103. Pedrine-Mille, A. and Pedrine, V.: Mucopolysaccharide defect in experimental lathyrism. Proc. Soc. Exp. Biol. Med. 119: 322, 1965.
104. Hausmann, E.: The formation and dissolution of the gels from collagen solution: the effect of beta-aminopropionitrile. Arch. Biochem. Biophys. 103:227, 1963.
105. Orloff, S. D. and Gross, J.: Experimental lathyrism in the chick embryo: the distribution of B-aminopropionitrile. J. Exp. Med. 117:1009, 1963.
106. Clemmons, J. J.: Proline metabolism, collagen formation, and lathyrism. Fed. Proc. 25:1010, 1966.
107. Clemmons, J. J.: The effect of lathyrogenic compounds on oxygen consumption of developing chick embryos. Fed. Proc. Abstracts 25:663, 1966.
108. Miller, E. J., Martin, G. R., Mecca, C. E., and Piez, K. A.: The biosynthesis of elastin crosslinks. The effect of copper deficiency and a lathyrogen. J. Biol. Chem. 240:3623, 1965.
109. O'Dell, B. L., Elsden, D. F., Thomas, J., Partridge, S. M., Smith, R. H., and Palmer, R.: Inhibition of desmosine biosynthesis by a lathyrogen. Biochem. J. 96:35P, 1965.
110. Partridge, S. M., Elsden, D. F., Thomas, J., Dorfman, A., Tesler, A., and Ho, P.: Biosynthesis of the desomosine and isodesmosine cross-bridges in elastin. Biochem. J. 93:30C, 1964.
111. Levene, C. I.: Studies on the mode of action of lathyrogenic compound. J. Exp. Med. 116:119, 1963.
112. Bornstein, P., Kang, A., Piez, K. A.: The nature and location of the intramolecular crosslinks in collagen. Proc. Nat. Acad. Sci. 55:417, 1966.
113. Miller, E. J. and Fullmer, H. M.: Elastin: diminished reactivity with aldehyde reagents in copper deficiency and lathyrism. J. Exp. Med. 123:1097, 1966.
114. Bean, W. B. and Ponseti, I. V.: Dissecting aneurysms produced by diet. Circulation 12:185, 1955.
115. Nimni, M. E.: Lathyrism (From workshop on lathyrism held at Western Reserve University in Cleveland, March 18 and 19, 1966). Science 153:322, 1966.
116. Nimni, M. E.: Abnormality in collagen metabolism in penicillamine-treated rats. (Abstract) Arthritis Rheum. 9:526, 1966.
117. Nimni, M. E. and Bavetta, L. A.: Collagen defect induced by penicillamine. Science 150:905, 1965.
118. Harris, E., Jaffe, I., and Sjoerdsma, A.: Effect of panicillamine on collagen in man. (Abstract) Arthritis Rheum. 9:509, 1966.
119. Harris, E. D. and Sjoerdsma, A.: Collagen profile in various clinical conditions. Lancet II:707, 1966.
120. Harris, E. D. and Sjoerdsma, A.: Effect of penicillamine on human collagen and its possible application to treatment of scleroderma. Lancet. II:996, 1966.