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This Week's Citation Classic®

Ponseti I V & Shepard R S. Lesions of the skeleton and of other mesodermal tissues in rats fed sweet-pea (*Lathyrus odoratus*) seeds.
J. Bone Joint Surg. 36-A:1031-58, 1954.
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Diets containing ground *Lathyrus odoratus* seeds fed to young rats produce kyphoscoliosis, epiphyseal slippings with fibrillation and rents in the epiphyseal plate cartilage, loosening and detachments of tendon and ligament insertions, osteoarthritis, and other skeletal deformities. Some rats develop dissecting aneurysms of the aorta and hernias. [The *SCI*® indicates that this paper has been cited in over 210 publications since 1955.]

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In my search for an animal model for scoliosis, I read that B.J. Geiger, H. Steenbock, and H.T. Parsons in 1933 noted scoliosis and hernias in rats fed a diet containing sweet-pea (*Lathyrus odoratus*) seed.[1] H.B. Lewis and coauthors in 1948 noted spinal curvatures in rats fed various species of legumes.[2] The production of scoliosis by diet afforded an excellent opportunity for the study of the histopathology and pathogenesis of this deformity in animals. I was hoping that these studies might help us to understand the pathogenesis of "idiopathic" scoliosis in humans.

Early in our experiments, which were done at the University of Iowa, we noted that very young rats fed the sweet-pea meal diet frequently died from rupture of the aorta. The rupture occurs from a dissecting aneurysm of the aorta seemingly due to loss of cohesion between the elastic fibers and muscle fibers of the media. We first reported this finding in 1952.[3]

The skeletal lesions observed in very young rats occur at sites of fast growth, such as in the epiphyseal plates, where the cartilage matrix becomes fibrillated and rent. The slipping of the epiphysis occurs along the line of diminished resistance. The tendinous insertions become loose and partially detached from the underlying bone, and at many sites, the periosteum appears lifted by the muscle pull and periosteal new bone forms underneath the lifted periosteum. Kyphoscoliosis develops due to vertebral slipping at sites with a weakened vertebral growth plate and detachments of the intervertebral ligaments. Osteoarthritis is observed in rats that had been on the experimental diet for several months.

This paper stimulated the study of human disorders resembling the experimental lesions observed in rats. Thus it was found that the pathology of dissecting aneurysm of the aorta in patients with Marfan's disease, and in some of the Ehler-Danlos syndromes, is similar to the pathology seen in the experimental animals. The incidence of dissecting aneurysm of the aorta in human patients with skeletal deformities and with Marfan's disease was further explored by us in 1955.[4] The epiphyseal plate lesion seen in lathyric rats is similar to the lesion observed in children with slipping of the upper femoral epiphysis,[5] with Legg-Perthes disease,[6] and with juvenile kyphosis.[7] The pathology of "idiopathic" scoliosis in humans, however, remains to be elucidated.

The cause of the loss of strength of the newly formed connective tissue and cartilage in lathyric animals intrigued biochemists. The observations on lathyrism laid the groundwork for the study of cross-linking in collagen.[8] In the mid-1950s the active principle was isolated from the sweet pea and identified as β-aminoproprionitrile (BAPN). In 1959 C.I. Levene and J. Gross discovered that in lathyric animals the newly synthesized collagen fibrils were soluble in cold neutral physiologic salt solution. After much work by many researchers for the elucidation of the collagen cross-linking mechanism, S.R. Pinnell, G.R. Martin, and R.C. Siegel found the enzyme lysil oxidase responsible for converting the specific lysine residue to an aldehyde and discovered that the lathyrogen BAPN functions by inhibiting the enzyme. Patients with a type of Ehler-Danlos syndrome have a genetic deficiency of this enzyme.[9]

For this and related work, I received the Kappa Delta Award for Outstanding Orthopaedic Research in 1956. Robert Shepard wrote his PhD thesis on the muscle physiology of lathyric and vitamin E deficient animals and is now professor of physiology at Wayne State University.

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3. **Ponseti I V & Baird W A.** Scoliosis and dissecting aneurysm of the aorta in rats fed with Lathyrus odoratus seeds. *Amer. J. Pathol.* 28:1059-77, 1952. (Cited 200 times since 1955.)
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5. **Ponseti I V & McClintock R.** The pathology of slipping of the upper femoral epiphysis. *J. Bone Joint Surg.* 38-A:71-83, 1956.
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7. **Ippolito E & Ponseti I V.** Juvenile kyphosis. *J. Bone Joint Surg.* 63-A:175-82, 1981.
8. **Gross J.** Collagen biology: structure, degradation, and disease. *Harvey Lect.* 68:351-432, 1974. (Cited 70 times.)
9. **Krane S M, Pinnell S R & Erbe R W.** Lysyl-protocollagen hydroxylase deficiency in fibroblasts from siblings with hydroxylysine deficient collagen. *Proc. Nat. Acad. Sci. USA* 69:2899, 1972. (Cited 105 times.)