Dissecting Aneurysm Produced by Diet

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Spontaneous dissecting aneurysm of the aorta in man is most commonly a sequel of hypertension but sometimes occurs in association with degenerative liquefaction of the media of the aorta. New light has been thrown upon dissecting aneurysm by its production in growing rats by a diet high in sweet peas. The offending agent has been isolated and a number of simpler related compounds have been synthesized and found effective. The relationship of this syndrome to a spontaneous dissecting aneurysm of the aorta in man is reviewed and some suggestions are made for investigation which may lead to newer methods of therapy.

Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the unusual law of nature by careful investigation of cases of rarer form of disease.—William Harvey.

Dissecting Aneurysm of the aorta is an uncommon disease of unknown cause. Arachnodactyly or Marfan’s syndrome, an inherited mesodermal disorder, carries a high risk of dissecting aneurysm. Persons with coarctation and women during pregnancy have a high incidence of dissecting aneurysm. One variety is seen sometimes as a late complication of hypertension.

The experimental production of dissecting aneurysm of the aorta has been achieved previously by a variety of procedures which injure the vasa vasorum and the nutrition of the media. Many investigators have produced necrosis or degenerative changes in the aorta and larger arteries of rabbits by (1) crushing the vessel wall, (2) sheathing the vessel in wax, (3) dissecting off the adventitia and applying acids to the vessel wall.¹ Medial necrosis has been produced in dogs by repeated injections of histamine. In rabbits injections of epinephrine have been used to produce medial necrosis and dissecting aneurysms. Occasionally, in a rabbit fed very large amounts of cholesterol, dissecting aneurysms have appeared in conjunction with severely disorganizing atherosclerosis.

More recently, Schlichter has produced dissecting aneurysm by direct thermocauterization of the adventitia producing coagulation necrosis with destruction of the vasa vasorum and with consequent degeneration of the media with liquefaction, cyst formation and collagen fiber replacement.¹,² All these experimental methods produced a nutritional disorganization by the mechanical interference with blood supply. At best they clarified the pathogenesis of only one form of dissecting aneurysm in man.

Studies in Animals

New light has been thrown on this problem from an unexpected source by Ponseti and his co-workers.³,⁴,⁵ Working on the problem of scoliosis and disease of cartilage matrix they induced experimental lathyrism in growing rats, with results which have promise of clarifying many seemingly unrelated clinical puzzles. Lathyrism has been known as a devastating disorder of men and domestic animals under certain conditions of famine or dietary fad when the food consists largely of legumes. The resulting disease is associated with weakness and spasticity, especially of the lower extremities. In severe cases urinary and fecal incontinence develop. The main features of the disorder Stockman reviewed in 1929.⁶

Geiger, Steenbock and Parsons⁷ in 1933 noted scoliosis and hernias in white rats fed a diet made up of 50 per cent sweet pea seed. They found that a water extract of the seeds produced the same effect, whereas the extracted residue was not harmful when fed at the 50 per cent level. They did not mention any changes in the cardiovascular system. In
1934 Stockman reported that a water extract of lathyrus peas produced a toxic effect on the brain and spinal cord of experimental animals. Again in 1948 Lewis and coworkers observed spinal curvatures in rats fed various kinds of legumes. Vivanco and Jiménez Diaz in Spain observed patients with legume intoxication who had lameness of the legs, similar to the lesions observed in rats fed a diet with large amounts of pea meal. Denny-Brown has reviewed the problem of lathyrism in connection with nutritional neuropathies. In none of these studies, clinical or experimental, was there any mention of arterial lesions or of dissecting aneurysm. It may have been passed by as a nuisance which caused the death of many experimental animals which, otherwise, would have developed the expected lesions of the skeleton, nerves and connective tissue.

The present series of investigation was ushered in by Ponseti and Baird who verified and considerably extended the previous observations. In particular they called attention to the high incidence of aortic dissecting aneurysm which took a severe toll in the growing rats on the experimental diet.

Their first studies were as follows. They divided four weeks-old male rats of the Sprague-Dawley strain into three groups. To one group they gave a diet consisting of 50 per cent sweet pea meal, 28 per cent corn starch, 6 per cent sucrose, 4 per cent salt mixture, 10 per cent dried yeast, 2 per cent corn oil to which was added 0.2 cc. of halibut liver oil for each 100 Gm. of ration. Another group got the same diet to which 10 per cent casein was added and the third group had the further addition of 0.75 per cent methionine. Each week the rats were weighed and x-ray films were taken with the rats anesthetized with ether. At the end of three weeks of this program the skeleton first showed signs of demineralization, and then, or a little later, periosteal new bone was formed, especially at the level of the femoral metaphysis. Progressive bowing and deformity of the long bones followed. The animals soon appeared thin and listless with rumpled unkempt fur. Between the fourth and sixth weeks the intervertebral spaces narrowed irregularly with a tendency for the cephalad vertebra to slip forward over the caudal vertebra at the level of the changes in the intervertebral discs. About a week later collapse of two or three vertebral bodies resulted in kyphosis, and this in turn was followed by lateral slipping and vertebral rotation. Similar changes occurred in the mid-thoracic region two or three weeks later, resulting in typical kyphoscoliosis. The ribs became deformed because of the rotation of the thoracic vertebrae. All rats on the various experimental programs developed progressive scoliosis. Its severity was related to the duration of the experimental diet. If, after the scoliosis was well developed, the diet was changed to a stock diet, the long bones straightened, periosteal new bone disappeared, and the kyphoscoliosis became arrested. (fig. 1.)

Rats with additional casein and additional casein and methionine, grew much more rapidly, but the roentgenographic changes appeared earlier.

Thirty-eight to 75 per cent of the rats in different experiments died spontaneously of dissecting aneurysm of the aorta during the fifth to the ninth week. They had irregular, scattered medial necrosis throughout the thoracic aorta with extensive dissection where the fibers of the media were split by the passage of blood. Dissection continued out into the adventitia with the formation of large hematoma and rupture into the thorax. One animal had a large sacular aneurysm communicating with the lumen of the aorta by a wide opening. The media ended abruptly at this point and the intima was not distinguishable from the lining of the aneurysm. The wall of the aneurysm was formed by a thick layer of laminated clot and compressed adventitia.

In later experiments animals dying or sacrificed at various intervals had the following changes in the vertebrae and long bones. The epiphyseal plates appeared widened and distorted (fig. 2). The cartilaginous matrix lost its cohesion and there was loosening of the tendinous and ligamentous insertions. Epiphyseal slipping occurred. The endochondral ossification did not appear abnormal at first. Extensive subperiosteal new bone formation occurred in the metaphyseal region of the long bones. The intervertebral discs appeared
normal in the young animals. In some rats there were severe slippings of the vertebral epiphysis with compression and even severance of the spinal cord. In animals with compression of the spinal cord there was great distortion of the posterior funiculi and gray matter. In later stages the intervertebral discs were greatly distorted and narrowed. Degenerative arthritis was observed in many experimental animals.

In other experiments when the pea meal diet was fed to fully grown rats the cortical bone grew very thick (fig. 3). Histologic sections revealed dense bone with mosaic patterns.

Fig. 1. A and B, roentgenograms of a 10-week-old rat fed the 50 per cent sweet pea diet since 4 weeks of age. The shoulders are dislocated, there is kyphoscoliosis, and abundant new bone is being formed around both femurs. C and D, roentgenograms of the same rat taken at 16 weeks of age. At 10 weeks of age the diet was changed to the regular stock diet. The skeleton is better ossified than in A and B and the extraneous bone around the femurs has disappeared. The kyphoscoliosis has not changed but the sternum, which was deformed in A and B, is straighter.

Fig. 2. Photomicrograph of the upper tibial epiphyseal plate of a 6-week-old rat which had been fed the 50 per cent sweet pea diet for three weeks. The clumped cartilage cells are separated by septa of metachromatic, fibrillated, cartilage matrix (Toluidine blue stain).

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and thick trabeculae resembling the bone seen in Paget's disease in man.

In all animals the bone changes antedated the muscle spasticity and the unsteady jerking gait which commonly occurred, presumably because of the periostal detachments, slipped epiphyses and degenerative arthritis, and spinal cord lesions produced by the deformed spine. Muscles looked normal microscopically but they had a significantly higher oxygen utilization than the muscle of normal control animals.4

Scrotal and ventral hernias occurred in many of the affected animals, a disorder not seen in normal control animals of this strain. Electron microscope studies of the fibers of the tail tendon revealed nothing abnormal in the structure of the collagen fibers. Hernias appeared to be a result of a defect of ground substance rather than of collagen fibers.

The occurrence of dissecting aneurysm of the aorta was related to the age of the rat when the diet was started. In several groups of 22 and 23 day old rats, dissecting aneurysms occurred in anywhere from 38 to 75 per cent of the animals. Deaths from the aortic lesions occurred as early as 12 days after starting the diet. No aneurysms were produced when feeding the pea meal diet was started later than the age of 51 days.

Dissecting aneurysms occurred in the ascending portion and the arch of the thoracic aorta. None was observed in the abdominal aorta. The lesions started in the media. The elastic and the muscle fibers did not appear abnormal at first. There was a loss of cohesion of fibers seemingly due to a defect of the binding power of the ground substance. Then patchy necrosis occurred in the smooth muscle cells. The elastic fibers remained unaltered. The intima ruptured at the site of the weakening of the media. Blood penetrated and dissected along the degenerated areas. The adventitia usually ruptured and the blood produced hemotherax or hemopericardium (figs. 4 and 5). In some of the young rats sacrificed two or three weeks after beginning the diet, dissecting aneurysms were smaller and had not ruptured. There was an attempt at repair with very cellular connective tissue patching the defect in the arterial
No lesions were observed in the smaller arteries, veins or the capillaries.

No abnormalities were observed in the lungs, liver, spleen or kidney. Two rats kept on the diet for 216 days developed testicular abnormalities with arrest of spermatogenesis, sloughing of cells and giant cell formation. There were no special changes in the other endocrine glands.

Testosterone and vitamin B₁₂ singly or together did not protect. The substitution of cotton seed oil or cod liver oil made no difference. It was impossible to prevent the development of the lesions by large doses of vitamin E.

Presumably all these lesions occurring under the experimental conditions result from a similar process. They all occurred in areas where the ground substance contains chondroitin sulfate as the chief or sometimes only mucopolysaccharide. All the lesions encountered in the experimental animals could be a result of defective formation or excessive destruction of chondroitin sulfate in the ground substance.

So-called idiopathic scoliosis in man usually begins before puberty. The deformity ceases to progress as soon as the skeletal growth of the spine is completed and the epiphyseal plates become obliterated. Radiograms indicate that patients with rapidly progressing scoliosis have defects in the vertebrae particularly in the areas adjacent to the cartilaginous plates. The deformity is worse when the mid-thoracic vertebrae are involved. Childhood diseases, such as rickets, which produce weakening of the epiphyseal plate do not lead to scoliosis presumably because there is no weakening of the ligamentous insertions.

STUDIES IN MAN

On the basis of these striking demonstrations by Ponseti and associates we reviewed our clinical experience with patients with dissecting aneurysm who had come to autopsy. Of 27 records available in the files of the Department
of Pathology there were 20 with x-ray films, or a description of the skeleton detailed enough to establish whether there had been any significant deformity. Seven, or 35 per cent, had gross abnormalities. Five had deforming kyphoscoliosis and two had severe pigeon breast deformity. In so small a group chance may have had some effects; and there are too few cases for statistical treatment. In an effort to get some group for comparison, we selected autopsied patients who had had hypertension during the same period, selected to match the age and sex of those with dissecting aneurysm, and a random selection of similar patients admitted to the Medical Service during the past six years. In 100 adequate autopsy records and in 500 medical admissions the incidence of a significant kyphoscoliosis was not over 2 per cent. Such comparisons are suggestive only and we need a clinical study to search for correlations along these lines.

These observations must not lead us to underrate the commonest clinical basis for dissecting aneurysm which still remains hypertension with sclerosing lesions of the small nutrient arteries of the media. There is a group of persons, however, without hypertension or much arteriosclerosis, in whom a metabolic flaw in production or maintenance of ground substance produces widespread disorders of the body's supporting matrix of binding material. They have a high incidence of deforming weakness of the bony skeleton and more than the chance frequency of dissecting aneurysm. Casual comments on kyphosis and other bone deformities with dissecting aneurysms are found in Sheman's monograph\textsuperscript{12} and elsewhere.\textsuperscript{13}

Other Conditions in Which Dissecting Aneurysm is Common

Marfan's syndrome is a mesodermal defect with a variety of deformities occurring separately or in combination.\textsuperscript{14} During the past decade it has become apparent that cardiovascular anomalies in Marfan's syndrome are very frequently the cause of death. In reviewing a series of 37 published autopsied cases, including all of those currently available, in 41 per cent there has been dissecting aneurysm of the aorta.\textsuperscript{15} If one adds to this figure the number with cystic necrosis of the media or with fusiform or saccular nondissecting aneurysm of the aorta, more than 50 per cent were affected. The microscopic appearance of the lesion is quite regular. The elastic muscle fibers are deficient and replaced by loose collagenous fibrous tissue. The lesion is indistinguishable from the medial necrosis first described by Erdheim as a cause of dissecting aneurysm. Lesions of the heart valves commonly mistaken for those of rheumatic fever have been found in a number of instances but microscopic examination generally does not confirm the diagnosis of rheumatic heart disease. An explanation for the fundamental abnormality in Marfan's syndrome is obscure. Many of the suggestions of some endocrine abnormality are far from convincing. Sloper and Storey\textsuperscript{16} have suggested that the disturbance in ground substance seen in the aorta might be responsible for such diverse lesions as the loose joints, the dislocation of the optic lens and perhaps even a disturbance of ossification of bone. Histologic studies of the ligaments and of the bones are not available from any autopsy report of Marfan's syndrome.

There are a number of other and miscellaneous suggestions that hormonal and endocrine disorders affecting the ground substance may be responsible for the occurrence of dissecting aneurysm. For instance in 1940 Kuntz and Hemplemann\textsuperscript{17} reported three patients who had hypertension and who developed dissecting aneurysm following total thyroidectomy as a palliative measure for the treatment of hypertension. They suspected that the observed mucoid degeneration of the media was related specifically to the metabolic disturbance following the removal of thyroid activity.

A curious clinical feature of dissecting aneurysm is its frequency in pregnant women, particularly towards term. Indeed this has been reported in at least one woman who had arachnodactyly. It has been suggested that the general relaxation of pelvic joints, the depolymerization of ground substance of the symphysis and other similar changes in pregnancy may all be related to the same sort of
disorder of ground substance which has given rise to spontaneous dissecting aneurysm.

A final situation in which dissecting aneurysm may occur with undue prevalence is coarctation of the aorta. In this condition, however, a combination of the changes associated with hypertension, reducing the blood flow through the vasa vasorum and the mechanical disorganization of the coats of the aorta associated with the lesion of coarctation itself are adequate to explain the high incidence of dissecting aneurysm. No defect of ground substance has been found in this condition.

**DISCUSSION**

We have presented the outlines of the story of how new understanding has come to the problem of clinical dissecting aneurysm in man from the improbable vantage point of research on bone lesions. The facts are simple. A diet high in legumes produces a variety of lesions in growing rats. All the lesions have as their basis a fault in the ground substance, the glue which holds the frame together. A number of workers have pushed the problem ahead and it is now established that B-aminopropionitrile, a simple chemical compound, is the toxic substance in peas which produces the lesions.

Such a compound presumably acts as an antimetabolite. Efforts are being made to find some related compound which by neutralizing or blocking its action might be called an antiantimetabolite. The structural resemblance of B-aminopropionitrile and pantothenic acid suggests a possible analogy with the disorder produced in human subjects by a pantothenic-acid-free diet and omega-methylpantothenic acid.18

Dissecting aneurysm in man has been recognized as a usually fatal complication in a few instances of hypertension and arteriosclerosis, in many persons with Marfan's syndrome, occasionally in pregnancy and coarctation of the aorta, and rarely in myxedema with hypertension. Another variety, mysterious in etiology, is caused by a dissolution of the aortic media with cystic degeneration. This last kind we have found in association with a very high frequency of deforming skeletal disease, notably "idiopathic" kyphoscoliosis. We suggest, but have not demonstrated, that this represents a widespread disorder of ground substance, probably an inborn error of metabolism, perhaps from a dietary lack, possibly from a toxic factor in food though this is the merest guess. A clue to one possible cause has been found in the series of brilliant studies which culminated in isolating a simple chemical compound which in low concentration can produce a disorder of ground substance in growing rats.

Marfan's syndrome, an inherited mesodermal defect with general characteristics of an entirely different order, may represent a genetically conditioned flaw in the integrity of ground substance as well as in mesodermal tissues. It is possible that part of the mechanism giving rise to its multiple deformities is related to the mechanism which destroys the patterned growth of rats. For the present the differences are more striking than the similarities.

We have no clear idea of how the general tissue softenings of pregnancy, or the myxomatous changes of hypothyroidism are related to the experimental lesion in rats. We do not know that they have any relation.

**SUMMARY**

Taking the hint from clinical lathyrism, studies directed towards the elucidation of kyphoscoliosis have disclosed the fact that multiple lesions can be produced in growing rats by feeding small amounts of such simple chemical compounds as B-aminopropionitrile and aminoacetonitrile. The basic trouble is a ground substance disorder causing bone matrix failure, hernias and dissecting aneurysm. Searching for clinical correlates, we found a high frequency of skeletal deformities in persons who died of dissecting aneurysm.

As speculation we suggest that many, but by no means all, dissecting aneurysms arise from a failure of the ground substance to fulfill its natural function of holding things together. It may represent a genetic, metabolic or dietary fault. We suggest that some form of Marfan's syndrome may consist of a related but not identical dysfunction, an inborn error, genetically transmitted.

An experimental attack on fundamental
mechanisms now lies before us. Cardiologists may be grateful for light cast on any dark area and congratulate their orthopedic colleagues on an unexpected assist.

**SUMMARY IN INTERLINGUA**

Inspirate per methodos previamente usate in le investigation de lathyrismo clinico, nos ha succedite a avantiar nostre effortos a elucidar le essentia de cyphoscoliosis usque al constatazione que multiple lesiones pote esser producute in rattos crescente per un alimentation a parve quantitates de simple compositos chimic de typo de B-aminopropionitrilo o aminoacetoni-trilo. Le disordine fundamental involve le substantia basal e causa secundarimente dys-functionamento in le matrice ossee, hernias, e aneurysma dissecante. In nostre cerca de correlatos clinico nos trova un alte frequenta de deformitates skeletal in personas qui habeva morite de aneurysma dissecante.

Speculatamente nos postula le theoria que multe aneurysmas dissecante—sed certo non omnes—resulta del facto que le substantia basal non exercite su function natural de mantener un coherentia general. Le vitio in le situation pote esser de natura genetic, metaboliche, o dietari. Nos opina que certe formas del syndrome de Marfan consiste possibilemente de un dysfunctionamento affin, ben que non identic, i.e. un falla innate que es geneticalmente transmittite.

Nos nunc nos trova confrontate con le problema de organisar un attacco experimental super le area del mechanismos fundamental.

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