

Experimental Arteriosclerosis in Pyridoxine-Deficient Rhesus Monkeys

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FOR a number of years our laboratory has been engaged in the study of the biochemical and pathologic changes induced in monkeys by deficiencies of ascorbic acid and of various members of the B-complex. In collaboration with the late Dr. J. F. Rinehart, who was Professor of Pathology at the University of California School of Medicine, studies of pyridoxine deficiency were undertaken in 1945 with a small series of monkeys. In 1948¹ and 1949² we presented our initial observations on the occurrence of arteriosclerotic lesions in monkeys maintained on a diet deficient in vitamin B₆. In a subsequent report³ we pointed out the essential similarity of the experimental vascular lesions of the monkey with those of arteriosclerosis of man.

The studies have been continued and to date we have examined approximately 50 animals which have been subjected to acute and chronic pyridoxine-deficiency and also a considerable number of animals which have been provided with complete supplements or deprived of other vitamins. The lesions have been observed consistently in monkeys exposed to complete deficiency of pyridoxine for six months or longer and also in monkeys maintained on suboptimal intakes of the vitamin for protracted periods of time. Confirmation of the occurrence of the vascular lesions in the vitamin B₆-deficient rhesus monkey and observations on the de-

velopment of similar lesions in dogs maintained on a diet deficient in pyridoxine have been described by Mushett and Emerson.⁴

The experimental sclerotic lesions of the pyridoxine-deficient monkey are widely distributed and involve arteries of all sizes. They have been observed in the abdominal aorta, iliac and femoral arteries, in the arteries of the testicular tunic, and in the small and medium sized branches of the renal arteries. In a number of animals lesions have been observed in the coronary arteries, mesenteric arteries, and arteries of the pancreas and other viscera. For a detailed description and photographic examples of the lesions, the reader is referred to previous publications.^{2,3,5} The vascular lesions resemble those observed in human arteriosclerosis in two essential points: (1) the distribution of the lesions follows the pattern found in man; and (2) the basic pathologic process appears to be similar.

Since hypertension is a factor which may contribute to the development of arteriosclerosis, it is important to know whether monkeys deprived of vitamin B₆ develop high blood pressure. For this reason measurements of the systolic blood pressure have been carried out in a number of control and pyridoxine-deficient monkeys. In eleven control and thirteen deficient animals the mean blood pressure with mean deviation and range are, respectively, 119±10.7 (95–135 mm Hg); 120±9.4 (105–130 mm Hg). There is no significant difference between the mean blood pressures of the two groups and hence hypertension would not be expected to play any role in the development of the vascular lesions in the vitamin B₆-deficient monkey. Olson and Martindale⁶ reported an increase in systolic blood pressure of rats suffering from chronic vitamin B₆ deficiency. However, the experimental procedure used by these

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authors was not one of simple dietary restriction of the vitamin, since all their deficient rats had received the vitamin B₆ antagonist, desoxypyridoxine, at one time or another during the course of the experiment. Sinclair⁷ has stated that he has never observed hypertension in pyridoxine-deficient rats in his laboratory.

It is always of interest to attempt to find fundamental chemical mechanisms which might explain the occurrence of gross or microscopic pathology in tissues. In the case of the vitamin B₆-deficient monkey there are at least two plausible explanations for the development of the arteriosclerotic lesions. The first of these is concerned with the formation of phosphatidyl choline (lecithins). Pilgeram⁸ has published evidence in support of the thesis that in atherosclerosis there is a metabolic block in the formation of phosphatidyl choline. In order to explain the occurrence of vascular lesions in the pyridoxine-deprived macaque he has suggested that there might be a block in the decarboxylation of serine to form ethanolamine, a reaction presumably catalyzed by pyridoxal phosphate.^{9,10} Such a block could conceivably interfere with the synthesis of phosphatidyl choline by limiting the supply of ethanolamine for the formation of choline.

A second possible mechanism is related to the role of vitamin B₆ in the metabolism of essential fatty acids. Schroeder¹¹ and also Sinclair⁷ have speculated on the possibility of a deficiency of essential fatty acids being involved in the development of atherosclerosis. Sinclair has expressed the belief that a combined deficiency of vitamin B₆ and arachidonic acid may be "the reason for the occurrence of atherosclerosis in pyridoxine deficient monkeys." It is conceivable that vitamin B₆ deficiency might result in interference with the metabolism of essential fatty acids, since Witten and Holman¹² have presented evidence that vitamin B₆ is required by the rat for conversion of linoleic and linolenic acids to higher polyunsaturated fatty acids, namely, arachidonic, pentaenoic, and hexaenoic acids. At present, no pyridoxal phosphate catalyzed reaction is known which is applicable to this conversion.

Experiments designed to explore the relation-

ship of essential fatty acid deficiency to the vascular disease have been in progress for approximately 20 months. Monkeys subjected to single and combined deficiencies of essential fatty acids and vitamin B₆ are being investigated. It is still too early to make any statement concerning the effect of essential fatty acid deficiency alone or in combination with pyridoxine deprivation on the course of development of the vascular lesions. It is sufficient to say that the growth of animals on the essential fatty acid-deficient diet is perhaps only slightly inferior to that of control monkeys and there is little, if any, change in their outward appearance or behavior. On the other hand, animals on the combined deficiency may fail somewhat earlier than monkeys subjected to simple vitamin B₆ deficiency.

SUMMARY

A brief review of the occurrence of arteriosclerotic lesions in the vitamin B₆-deficient monkey is presented. Measurements of the systolic blood pressure show that hypertension is absent in these monkeys. Some of the possible mechanisms relating to the development of the arteriosclerotic lesions are discussed.

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