pacted, with more or less complete urinary obstruction. A chemical analysis of these concretions indicated 6.4% sulfapyridine and 64.1% acetylsulfapyridine. These findings were absent in untreated rats, and in rats treated with sulfanilamide; all of which had been on the same diet. The dosage employed was the same for both drugs: one-half to one gram per kilo per day for 8 to 14 days.

Higgins[8] has produced urinary calculi in rats with vitamin A deficient diet. The calculi described by Higgins were spherical and light brown, consisted chiefly of calcium phosphate, and were associated with alkaline urine. The diet of our rats consisted of fresh carrots, dog biscuits (said to contain vitamins A and D), oats, and white bread. The urine of normal rats fed on this diet has a pH 5.5 to 6.5. The urine of the rats with calculi had a similar range.

The possibility must not be overlooked that similar concretions with necessarily delayed symptomatology may develop in man as a result of sulfapyridine administration.

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Experimental Vascular Disease in Rats Produced by Multiple Depletions of Vitamin A.*

LINCOLN OPPER. (Introduced by Barnett Sure.)

From the Laboratory of Agricultural Chemistry, University of Arkansas, Fayetteville.

The pathology of chronic vitamin deficiency is usually studied in laboratory animals which have been subjected to a partial deficiency over a long period of time. This dietary method has been considered to represent the closest analogy to the course of the human disease.[1] The present experiment was designed to effect pathologic changes in the rat by successive and complete depletions of vitamin A rather than by sustained and partial withdrawal of the vitamin. To obtain this end, multiple avitaminotic episodes of varied severity were interspersed with periods of relative recovery.

Procedure. Twenty-four pairs of rats, litter-mates of the same

8 Higgins, C. C., *J. A. M. A.*, 1935, **104**, 1296.

* Research paper No. 619, Journal Series, University of Arkansas. Aided in part by a grant from the Committee on Scientific Research of the American Medical Association.

1 Editorial, *J. A. M. A.*, 1938, **111**, 2019.

sex and ranging in weight from 50 to 100 g, were given a basal ration† deficient in vitamin A and supplemented only in the control rat of each pair with 3 drops of carotene in oil.‡

Successive depletions in each pathologic rat were usually terminated by the oral administration of carotene. This vitamin was provided only until the fall in weight was definitely checked. Diarrhea sometimes made necessary the subcutaneous injection of 0.5 cc of cod liver oil for a brief period. Response to the resumption of vitamin therapy varied in each animal with each depletion, due apparently to variations in degree of the underlying pathology, chiefly of the renal or of the respiratory tract. Two or 3 depletions were obtainable in each rat during an experimental period ranging from 127 to 238 days. For histologic study of the arterial system, the tissues following autopsy were fixed in Bouin's solution, embedded in paraffin and stained with hematoxylin-eosin or v. Kossa's method for calcium.

Vascular Pathology. All but 3 of the 24 multiply depleted rats showed some degree of vascular injury. No trace of morphologic change was observed in the vessels of any of the 24 control rats. The majority of the involved aortas were characterized grossly by loss of elasticity, dilatation and the presence of firm, intramural plaques. The major branches of the aorta revealed marked tortuosity. Histologically the changes were in the nature of a degenerative medial process which affected practically the entire arterial system down to the larger arterioles. Arteries within the stroma of the liver, kidney and spleen, however, were invariably spared. Necrosis of the smooth muscle cells of the media was accompanied by a deposition of calcific granules in pericellular and perilamellar distribution. This was followed by the formation of large calcium plaques and the growth of granulation tissue in the media, and by a proliferation of fibrous connective tissue in the subintima. The latter sometimes led to the complete closure of small visceral arteries. When this took place in the heart, myocardial fibrosis was the result.

The pathogenesis of the arterial injury is uncertain. If the lesions are due directly to the avitaminosis, this represents the first instance of primary pathology in tissues other than those of epithelial origin. Before this interpretation may be accepted, however, further studies of the secondary effects of chronic vitamin A deficiency are necessary.

† Casein, 20; McCollum's salts No. 185, 4; Northwestern yeast (dehydrated), 10; Dextrin, 51; Crisco, 15. The ration was irradiated for 30 minutes to provide vitamin D.

‡ Generously supplied by S. M. A. Corporation, Cleveland, Ohio.