Sequence of Development of Hypercholesterolemia and Hypoproteinemia in Aminonucleoside Nephrosis. (26187)

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The nephrotic syndrome is characterized by proteinuria, hypoproteinemia and hypercholesterolemia. The mechanism involved in development of hypercholesterolemia is still unknown. Evidence relating the cholesterol changes to hypoalbuminemia has been presented by Rosenman, *et al.*(1) while others have challenged these concepts. Heyman and coworkers(2) showed that in experimental anti-kidney serum (AKS) nephrosis in rats, the cholesterol changes in the blood antedate the protein changes.

Since development of nephrosis following AKS is very rapid, (a matter of hours), it becomes difficult clearly to separate the time sequence of development of hypoproteinemia and hypercholesterolemia. It seemed worthwhole therefore to reevaluate this problem, using aminonucleoside nephrosis(3,4) as the experimental tool, since a latent period of at least 5 days exists prior to development of the disease, following which the lesion slowly evolves. It seemed likely that this prolonged time span might permit a sharper definition of the sequence of proteinuria, hypoproteinemia and hypercholesterolemia.

Experimental. Twenty-three male Sprague-Dawley rats with a starting weight of 100-120 g were studied. Animals were caged individually in metabolic units and provided food and water *ad lib.*

The nephrotic syndrome was produced in 15 animals with 11 daily injections of aminonucleoside(3,4) while 8 rats served as controls. Urinary protein excretion was measured daily from day 1-11 by the Esbach method(5). Blood samples were obtained daily, when possible, from tail veins of control and experimental animals. Total serum proteins were determined by the microtechnic of Lowry *et al.*(6) and cholesterol determinations were made by the micromethod of Saifer and Kammerer(7).

Results and discussion. Fig. 1 plots days of aminonucleoside injection and mean values of the 3 parameters measured for the entire group of nephrotic and control animals. It may be seen that proteinuria began by the fifth day, serum proteins began to decline by the sixth day and cholesterol levels rose definitively by the seventh day.

Sequential changes observed in individual injected animals were as follows: 1) The first change consisted in a simultaneous increase of urinary protein and decrease in serum protein in 9 rats; 2) proteinuria occurred first in 3 rats; 3) serum protein declined the day before proteinuria developed in 3 animals; and 4) 15 rats showed increased serum cholesterol levels as the third manifestation of the developing nephrosis.

These observations clearly show the almost simultaneous loss of urinary proteins and de-

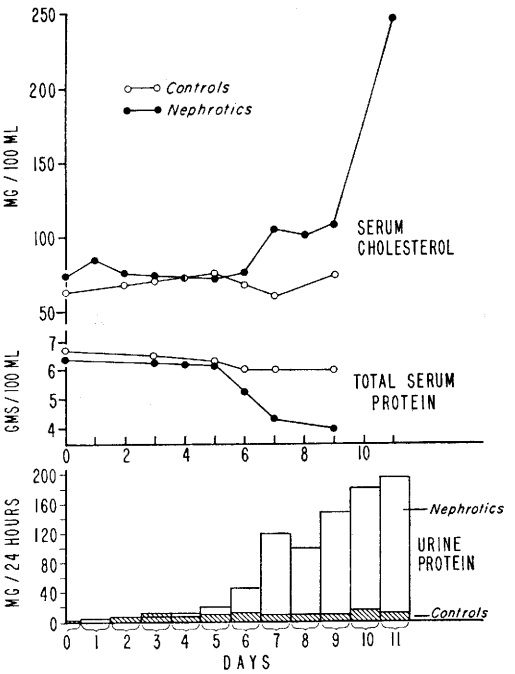

FIG. 1. Sequential changes in control and nephrotic rats during development of nephrosis.

crease in total serum protein as initial alterations in nephrosis. In all instances, a definite interval of from one to 4 days following proteinuria occurred prior to development of hypercholesterolemia. The sequence of hypoproteinemia and then hypercholesterolemia, though established here, does not necessarily indicate a causal relationship between the two.

Summary. The sequence of development of hypoproteinemia and hypercholesterolemia was studied in 15 aminonucleoside nephrotic animals. Hypercholesterolemia succeeds rather than precedes hypoproteinemia.

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The Juxtaglomerular Apparatus as an Extra-Adrenal Site of ACTH Action.*† (26188)

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We have shown that a variety of hypotensive drugs are able to produce morphological changes suggestive of hyperfunction in the renal juxtaglomerular apparatus(1). These responses occur within minutes to a few hours, in contrast to the weeks or months required for appearance of changes reported by others(2,3,4) and summarized by Tobian(5, 6). In attempting to explain the rapid responses to drugs which we have seen, we studied the relationship between the adenohypophysis and the juxtaglomerular apparatus (JGA). This report will indicate that JGA responds quickly to ACTH in absence of the adrenals and that it might be considered as an extra-adrenal target of this hormone.

Materials and methods. All experiments were performed on young male albino rats of the Harlan strain, weight approximately 150 g. Hypophysectomized rats were supplied by the Hormone Assay Laboratories. Adrenalectomized animals were maintained on 1% saline drinking water in addition to their regular rations. Some groups of rats were adrenalectomized 3 days after hypophysectomy, and were maintained on 1% saline drinking water plus their regular rations. In acute experiments, animals were used on the fourth post-operative day.

Drugs were administered intraperitoneally in doses indicated in the tables. The commercial ACTH used was Parke-Davis' brand of corticotropin. A specially purified ACTH which was virtually free of other endocrine activity was also used.‡ Other drugs used were from regular commercial sources. For hydralazine the solvent was 10% propylene glycol. Other drugs were dissolved in saline.

Radial wedges of kidney were removed at time of sacrifice, fixed in formol-sublimate-acetic acid fixative, and embedded in paraffin. Sections were cut at 6 μ and were stained by a combined Alcian blue-PAS technic. The method consisted in staining first

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‡ Purified ACTH virtually free of other endocrine activity was supplied by research division of Parke-Davis Co.