

# This Week's Citation Classic®

Frenk S, Antonowicz I, Craig J M & Metcoff J. Experimental nephrotic syndrome induced in rats by aminonucleoside. Renal lesions and body electrolyte composition. *Proc. Soc. Exp. Biol. Med.* 89:424-7, 1955. [Depts. Pediat. Pathol., Harvard Med. Sch.; Child. Cancer Res. Fdn.; and Child. Med. Ctr., Boston, MA]

A new procedure for the production of experimental nephrosis in rats is described. Originally developed for the study of body fluid distribution during massive edema, it has become a valuable tool for the experimental study of renal physiology and pathology, and for related research. [The SCF® indicates that this paper has been cited in more than 230 publications.]

## Aminonucleoside-Induced Nephropathy

Silvestre Frenk  
Institute Nacional de Pediatria  
04530 Coyoacan, DF  
Mexico

The search for a pathobiological basis of a clinical problem led to the discovery of a nephrosis-inducing compound. While Federico Gomez and his group at the Hospital Infantil de Mexico studied the clinical and biochemical features of advanced protein-energy malnutrition, they had been puzzled by the seemingly incongruous coexistence of massive hypoalbuminemic edema and severe diarrheal "dehydration." Thus, in 1953, having been admitted by Harvard as a trainee and research fellow in pediatrics with Jack Metcoff's group at Children's Medical Center, I was assigned the investigation of the patterns of body composition in edematous weanling rats. Achieving severe hypoalbuminemia by feeding a protein-deficient diet turned out to be impossible, and a different approach was sought.

The recent availability of the aminonucleoside of puromycin (6-dimethylamino purine, 3-amino-D-ribose) provided a golden opportunity, as our first experiments showed. Indeed, "daily subcutaneous injection of [this compound] into immature male rats for 10 to 12 days results in generalized edema, ascites, marked proteinuria, hypoproteinemia, hyperlipemia, and azotemia." Salt loading greatly magnified the amount of ascites and edema. The renal lesions in the fully developed syndrome consisted of thickening of glomerular basement membranes and loss of

mitochondria in the renal tubular cells, closely resembling the so-called minimal-change disease, i.e., the predominant lesion in the nephrotic syndrome as seen in children. Besides ascites, the major tissue reservoir for edema fluid accumulation was shown to be the skin and subcutaneous tissues. Total body and muscle potassium content decreased slightly in the nephrotic rats.

These interesting observations on fluid distribution and electrolyte changes enjoyed relatively little scientific resonance. The procedure itself did, as predicted in the original paper, and became, "a convenient tool for exploring many features of renal disease." The initial findings on renal pathology were confirmed almost immediately. Metcoff's group continued working on the correlation of kidney ultrastructure and enzyme activities in these animals, and observed that the biochemical preceded the morphological changes.<sup>2-4</sup> It quickly became evident that the severity, persistence, and histopathologic features of the aminonucleoside nephropathy are related to factors as variable as the strain and the age of the animals,<sup>5</sup> the route of administration of the compound, and the size and frequency of the doses, as well as the diet and the pharmacological action of other intervening drugs. In some experimental modalities the "clinical" picture and the renal lesions are totally reversible, but the severe forms may be characterized by histological features and an evolution resembling focal and segmental progressive glomerulosclerosis in humans.<sup>6</sup>

This procedure has fostered considerable advances in kidney physiology and continuing progress in the understanding of human renal disease, as well as of the pathodynamics of related ailments, such as atherosclerosis and arterial hypertension.<sup>7</sup> The recent addition of adriamycin might provide a valuable alternative.

■ At the present pace of technological progress, the survival of a procedure for such a long period is indeed an increasingly uncommon experience. Scientific discovery, no matter how fortuitous, is still the basis of legitimate human ascent.

1. Fiegelson E B, Drake J W & Recant L. Experimental aminonucleoside nephrosis in rats. *J. Lab. Clin. Med.* 50:437-46, 1957.
2. Yoshida T & Metcoff J. Metabolic basis of aminonucleoside nephrosis in rats. I. Inhibition of alpha-oxoglutarate oxidation by aminonucleoside. *J. Lab. Clin. Med.* 72:565-75, 1968.
3. -----, Metabolic basis of aminonucleoside nephrosis in rats. II. Inhibition of renal gluconeogenesis by aminonucleoside. *J. Lab. Clin. Med.* 72:576-81, 1968.
4. Metcoff J, Kaiser F & Spargo B. Correlation of ultrastructure and enzyme activities in kidneys of rats with aminonucleoside nephrosis. *Proc. Internat. Congr. Nephrol.* 8:511-3, 1973.
5. Grond J, Muller E W, Van Goor H, Weening J J & Elemma J D. Differences in puromycin aminonucleoside nephrosis in two rat strains. *Kidney Internat.* 33:524-9, 1988.
6. Diamond J R & Kamovsky M J. Focal and segmental glomerulosclerosis following a single intravenous dose of puromycin aminonucleoside. *Amer. J. Pathol.* 122:481-7, 1986.
7. Amato D, Tapia E, Bobadilla N A, Franco M, Calleja C, Garcia-Torres R, Lopez P, Alvarado J A & Herrera-Acosta J. Mechanisms involved in the progression to glomerular sclerosis induced by systemic hypertension during mild puromycin aminonucleoside nephrosis. *Amer. J. Hypertens.* 5:629-36, 1992. Received November 2, 1993