Effect of Water and Electrolyte Restriction on Pathologic Changes in Kidney of Jaundiced Rats. (19756)

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The occurrence of reduced renal function (and renal injury) in the presence of hepatic insufficiency or jaundice has long been recognized. This present study was made in order 1) to investigate the early pathologic changes in the kidney of the rat following the production of jaundice by occlusion of the bile duct and 2) to determine the influence of restricted intake of water and electrolytes on such changes. The lesions observed in the kidney of the rats studied were comparable to those associated with jaundice in man and in other experimental animals as described by other investigators(1-4). In general, restriction of water and electrolytes appeared to exaggerate the severity of the lesions.

Methods and results. The bile duct was occluded in albino rats weighing 100 to 250 g. General anesthesia was employed for all surgical procedures. After the desired number of days, during which jaundice developed, the rats were killed, and the kidneys were removed and placed immediately in a 10% solution of formalin for fixation. Sections were stained with hematoxylin and eosin for microscopic study.

Fourteen rats were killed and the kidneys were removed 2 to 11 days after complete obstruction of the bile duct. In 4 of these rats tubular damage was observed. The kidneys of 10 other rats were removed 4 to 11 days after complete obstruction of the common bile duct and, in addition, after the concomitant restriction of water for 4 to 7 days. In 8 of these 10 animals tubular damage was present. However, the animals in this second group lost considerable weight and were severely dehydrated.

Grossly, the kidneys of both of these groups of rats were diffusely bile stained. The surfaces of some of the kidneys were mottled. The predominant microscopic change was vacuolation in the cytoplasm of the tubular cells, especially the proximal convoluted tubules (Fig. 1 and 2). In 2 rats of the series in which intake of water was restricted the tubular changes were severe and considerable necrosis was present. A few scattered casts were seen

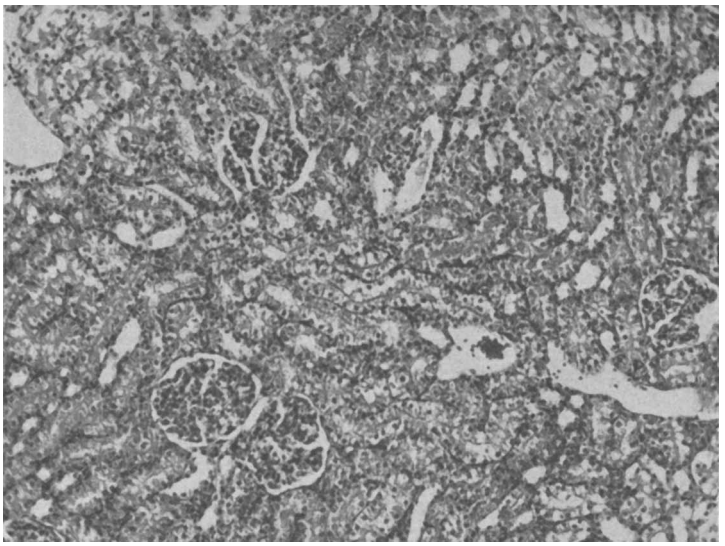

FIG. 1. Vacuolar degeneration and necrosis of tubular cells of the kidney of the rat associated with jaundice and severe restriction of water (hematoxylin and eosin; × 115).

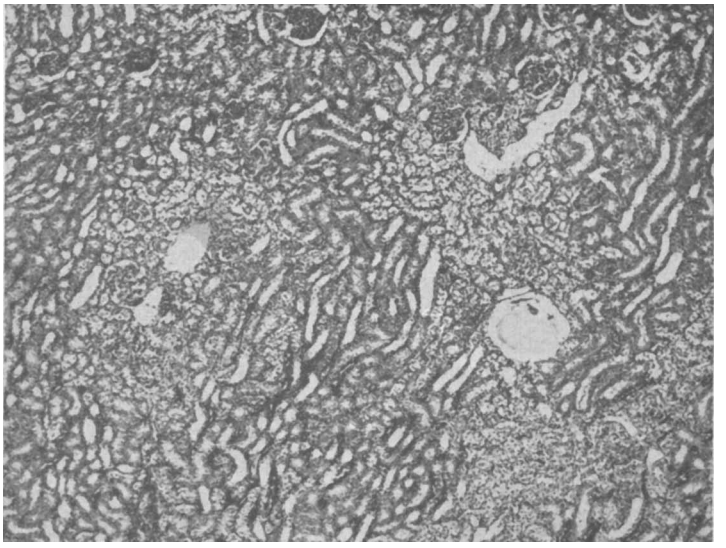

FIG. 2. Focal areas of vacuolar degeneration of tubular cells of the kidney of the rat associated with jaundice and severe restriction of water (hematoxylin and eosin; × 60).

in the tubules. A few casts resembled pigmented casts and were stained orange-red. Scattered hyaline and granular bile-stained casts were present. Usually casts were a relatively inconspicuous histologic feature but a number of casts may have been lost during the preparation of the sections. A few scattered dilated tubules were also present. The renal changes did not appear sufficiently severe to disturb renal function seriously. The tubular changes usually appeared most marked in the cortex and were usually restricted to discrete areas of varying size. The changes were not predominant in any one segment of the nephron. The glomeruli appeared normal. In 6 of 8 rats in which the effects on the kidney of severely restricted intake of water alone were studied, small focal areas of vacuolar degeneration of tubular cells were present.

In a series of 8 additional rats which had been receiving distilled water and a diet free of inorganic salts for 4 to 5 weeks, the bile duct was occluded. These rats either failed to gain weight or lost weight while on the diet but drank adequate amounts of water *ad lib.* The kidneys of all of these rats contained varying degrees of gross and microscopic changes similar to those just described. However, in the kidneys of 2 of these animals bile-stained casts were prominent and the microscopic changes resembled those of hemoglobinuric nephrosis (Fig. 3). The casts were located for the most part in the distal tubules and especially in collecting tubules and were most numerous in the corticomedullary region. Granular bile-stained casts were most numerous, but hyaline casts which stained bright red and casts of degenerating tubular cells were present also. Tubular dilatation, lymphocytic infiltration, tubular degeneration and necrosis, mitotic figures, multinucleated giant cells in tubular lumina were all present. Grossly, the cut surface of the kidneys of one of these rats showed a deep yellow band at the corticomedullary region.

In other experiments on the effect of prolonged intake of food and water free of inorganic salts on the kidney of the rat we have frequently observed tubular degeneration of varying severity and extent in the absence of jaundice. Therefore, in the experiments in which jaundice was produced after prolonged restriction of salt, the renal changes that followed the occlusion of the bile duct were probably superimposed on and possibly dependent on those associated with the restriction of salt.

Comment. This study indicates that degenerative changes in the renal tubules may be associated with jaundice produced by occlu-

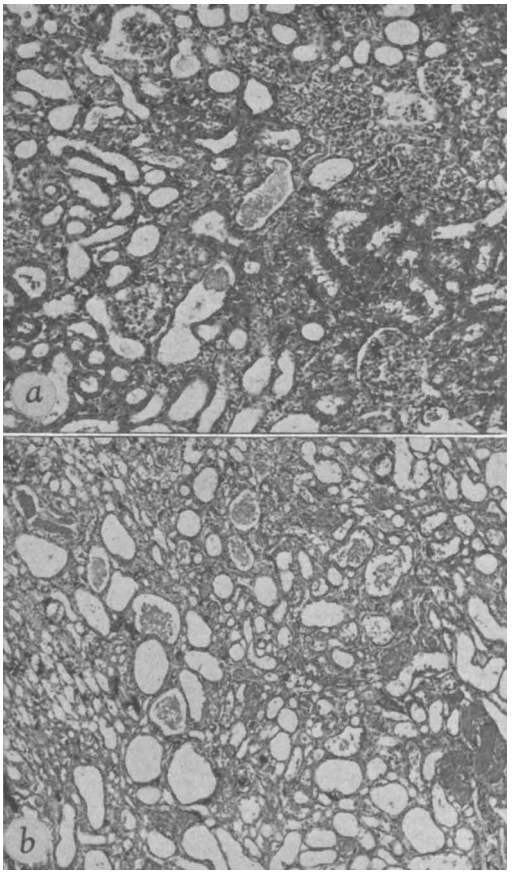

FIG. 3. Bile-stained and hyaline casts, tubular degeneration and necrosis plus tubular dilatation in the kidney of the rat following production of jaundice and restriction of intake of inorganic salts (hematoxylin and eosin: a, × 75; b, × 50).

sion of the bile duct. However, the lesions do not appear severe or extensive. Furthermore, other factors such as dehydration from depletion of electrolytes or water or both appear to intensify the severity of the lesions. Depletion of water had to be severe, however, to influence the microscopic findings during the period of observation. Wartman and associates(3) reported that obstruction of one renal artery increased the incidence and severity of renal changes after occlusion of the bile duct in the rabbit. A number of investigators have reported vacuolation and necrosis of the cytoplasm of renal tubular cells in water and electrolyte deficiency in experimental animals(5-10). These changes are different from those of osmotic nephrosis. We too observed that areas of tubular degeneration and necrosis occur in kidneys of rats after exclusion of inorganic salts from the diet over a long period. The renal lesions appear more severe and extensive when jaundice and electrolyte and water depletion are combined than when each condition is present separately.

Whether ischemia plays a role in the production of renal lesions as seen in this study is unknown. The microscopic features of the lesions could not be differentiated from the vacuolar degeneration and tubular necrosis we have observed in renal tubules resulting from ischemia produced by temporary occlusion of the renal artery or severe acute hemorrhage (11). In 5 jaundiced rats of the present study India ink was injected intravenously prior to removal of the kidneys. The ink was uniformly distributed throughout the kidneys, including the areas in which microscopic changes were observed.

In general, 2 types of renal lesions were seen associated with jaundice in rats in this study. The first and most common consisted essentially of tubular vacuolar degeneration, varying greatly in extent and severity, and associated with a few casts and dilated tubules. In more severe lesions, necrosis of tubules occurred. The second but relatively infrequent lesion resembled that of hemoglobinuric nephrosis with the exception that the casts appeared to be bile casts. This latter type of renal lesion may be the result of the superimposition of the effects of jaundice on kidneys containing recent degenerative tubular changes due to other causes. Of course, a mixture of the 2 patterns of lesions listed may occur. Ayer(2) found that in infants dying with jaundice from congenital atresia of bile ducts the renal lesions were similar to hemoglobinuric nephrosis. Thompson and associates(1) emphasized that the renal damage present in cholemic nephrosis was intensified when a preexisting lesion was present. Lalich(12) found that injections of homologous hemoglobin into rabbits previously dehydrated by water restriction resulted in hemoglobinuric nephrosis, if the dehydration was sufficiently prolonged. Thus, the pathogenesis of the renal lesions in the 2 entities, bile nephrosis and hemoglobinuric nephrosis, may be similar.

Summary and conclusions. Severe deple-

tion of water or electrolytes or both appears to increase the incidence and severity of renal lesions associated with jaundice produced by occlusion of the bile duct in rats. The renal lesions under these conditions may vary greatly in extent and severity but usually do not appear sufficient to produce either significant or fatal renal insufficiency. They usually consist of vacuolation of the tubules, especially proximal convoluted tubules, with a few casts and dilated tubules. Necrosis of tubules occasionally occurs. The renal lesions in this study infrequently closely resembled those of hemoglobinuric nephrosis. The casts, however, appeared to be mostly bile-stained casts. Rarely the lesion was extensive enough to cause severe renal damage.

The renal lesions seen in bile nephrosis then may be due in part to or may be superimposed on those due to severe electrolyte and water depletion or other causes of renal tubular degeneration.

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Concentrations of Nineteen Amino Acids in Plasma and Urine of Fasting Normal Males.* (19757)

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The data on the concentrations of individual amino acids in the plasma and urine of normal humans are somewhat limited. Furthermore, the findings which are available are scattered, and, until recently, have been confined to reports concerned with one or two of those amino acids which could be determined chemically. Specific quantitative chemical methods have been applied only to the determination of glutamine(1-3), glutamic acid (4,5), glycine(6), alanine(7), arginine(8), and tyrosine(9), and normal levels of these substances have been reported for human plasma and urine. However, since the introduction of microbiological and chromatographic technics, it has become possible to assay biological fluids for almost all of the amino acids of physiological importance. Therefore, it is now feasible to study variations in plasma and urine concentrations of at least 19 individual amino acids both in health and in disease. Some studies of this nature have been reported. Ackermann *et al.* (10,11) have studied plasma levels of 9 amino acids in human subjects of various age groups. Kirsner *et al.*(12,13) and Steele *et al.*(14) have applied microbiological methods to studies of the effect of variations in protein intake on levels of amino acids in human plasma and urine. Hier and Bergeim(15) reported plasma levels of 10 amino acids determined microbiologically in normal human beings. Harper *et al.* have reported on the normal levels of

* The opinions expressed in this paper are those of the authors and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

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