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Development of an Acquired Resistance to Bichloride of Mercury by Renal Epithelium in Proximal Convoluted Tubule.*

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In previous publications[1-4] the fact has been established that when the epithelium of the convoluted tubules is sufficiently injured by uranium nitrate, a process of repair to this epithelial tissue may be inaugurated which results in the replacement of the damaged cuboidal cells by an atypical type of cell for this segment of the tubule. These cells are of a flattened order, imperfectly differentiated and with prominent, deeply staining nuclei. Such epithelial replacements not infrequently exist in the form of syncytial structures. An epithelial repair process of this type has been shown to impart to this segment of the tubule a resistance to subsequent injury by uranium nitrate. A fixed cell tissue resistance has been acquired in this segment of the tubule.

Some years ago the observation[5] was made during the study of the acute renal injury from bichloride of mercury that the predominant location in the kidney of the epithelial injury was the proximal convoluted tubule.

For several months 11 dogs have been available for study that have in past years effected a repair process to the proximal convoluted tubules as a result of a severe acute uranium injury which is characterized cytologically by the formation in this segment of the tubule of the atypical type of epithelial cell which has been previously described. All of these animals at different periods of their recovery have shown an acquired resistance on the part of this type of cell to secondary intoxications by uranium nitrate even when such intoxications were induced by an amount of this nephrotoxic agent 2 to 4 mg. per kilo in excess of the amount which induced an acute process of degeneration in the normal cuboidal cell of the proximal convoluted tubule. The object of the present experiments has been to ascertain whether or not the atypical regenerated epithelium which

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1 MacNider, Wm. deB., *J. Exp. Med.*, 1929, **49**, 387.

2 MacNider, Wm. deB., *J. Exp. Med.*, 1929, **49**, 411.

3 MacNider, Wm. deB., *Harvey Society Lectures*, 1928-29, Baltimore.

4 MacNider, Wm. deB., *Science*, 1931, **73**, 103.

5 MacNider, Wm. deB., *J. Exp. Med.*, 1918, **27**, 519.

has repaired the convoluted tubule segment and which has shown resistance to uranium is also resistant to a poison acting rather specifically on the same segment of the nephron: bichloride of mercury.

The 11 dogs used in these experiments were given subcutaneously at the time of their use 0.25 cc. of a 4% solution of morphine sulfate per kilo in order to induce emesis and later a certain degree of narcosis which state would favor the retention of a solution of bichloride of mercury. This poison was then given by stomach tube in solution in the amount of 15 mg. per kilo. The appearance of mercury in the urine was determined by employing a delicate test devised by Elliott.[6] The test is of some quantitative value. Two of the 11 dogs died in a state of shock due to an intense gastro-enteritis within 48 hours following the commencement of the intoxication. Mercury was present in the urine of both animals. The atypical epithelium in the convoluted tubule segment showed no histological evidence of injury. The 9 remaining animals developed a gastro-enteritis which varied in intensity and duration. They recovered from it. The urine of these dogs indicated the presence of mercury over periods varying from 2 to 8 days for the different experiments. The urine which contained both albumin and casts failed to undergo any marked reduction in the 24-hour total output. Biopsy material from the kidneys of these animals obtained during the periods of intoxication which was stained for histological study by Herxheimer's Scharlach R method for lipoid material and eosin and methylene blue for general study, has shown glomeruli without evidence of acute degenerative changes and in the proximal convoluted segment of the tubule, lined by atypical cells an epithelium in which both nuclei and cytoplasm stained normally and which failed to show the presence of stainable lipoid material. Such cells have failed to participate in the severe edema and vacuolation followed by necrosis which is characteristic of the epithelial injury from bichloride of mercury. The inference appears permissible, that an atypical type of epithelial cell which developed in the convoluted tubule segment of the nephron as a result of a repair process from an acute uranium intoxication and which later showed an acquired resistance to this poison has also acquired a resistance to bichloride of mercury which exerts its predominant toxic action on the epithelium of this segment of the nephron.

[6] Elliott, J. A., *J. Am. Med. Assn.*, 1917, **68**, 1693.