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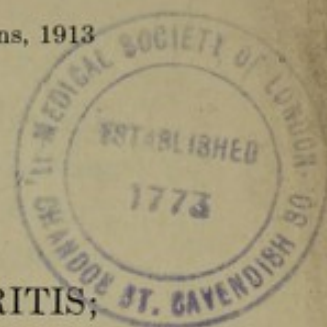
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FURTHER STUDIES OF EXPERIMENTAL NEPHRITIS; SOME EFFECTS OF DIURETICS

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At several recent meetings of the Association of American Physicians I have reported the results of studies of experimental nephritis carried on in the laboratory of the Department of Theory and Practice of Physic at Harvard by myself and colleagues. During the past year, with the assistance of Drs. O'Hare, Walker, and Dawson, the effect of diuretic drugs in animals suffering from acute severe nephritis produced with uranium nitrate has been investigated and in some of these animals, with the coöperation of Professor Polin, variations in nitrogen retention have been followed. In the latter experiments the amount of non-proteid nitrogen and urea nitrogen in the blood has been determined by Dr. W. Denis in the laboratory of Biological Chemistry of Harvard University. The general results of these studies will be given here; the details of the different experiments will be found in several papers to be published later in the *Archives of Internal Medicine*.

In the series of experiments here reported only one animal, the rabbit, was used and only one type of nephritis produced, that following injections of uranium nitrate. A variety of drugs regarded generally as having a diuretic action was employed; not all of these, however, are considered to be diuretics in any constant sense of the word, and of some of them, such as spartein sulphate, there is much doubt that they should be considered to be diuretic drugs. These drugs were used, however, because they are often employed by clinicians to produce diuresis. They were given to

the rabbits twice a day in doses, with few exceptions, equivalent per kilo of body weight to those employed therapeutically in man.

A severe, usually quickly fatal nephritis was produced and the effect of the diuretic was measured by the length of life of the animals compared with control animals that had received the same dose of uranium nitrate; all animals were kept under the same conditions in large pens, with free access to water and a food supply of carrots and hay. The amount they ate and drank depended on their appetite, and varied much with variations in their condition. One hundred and thirty rabbits were used. In addition to these number of normal rabbits received the same diuretic drugs over a longer period of time as controls to exclude any marked toxicity of the diuretic drugs.

It was found that diuretic drugs in rabbits with severe acute uranium nitrate nephritis had a detrimental effect in that they shortened the lives of the animals. With diuretin given by stomach tube (in some of these animals the doses were much larger than the usual therapeutic dose for man), rabbits with nephritis lived six days while controls lived 6.9 days. When the diuretin was given intravenously they lived four and one-fifth days while controls lived six and one-fourth days. With caffeine, soluble theocin (theocin sodium acetate), potassium acetate and sparteine sulphate given intravenously the average length of life was five and four-sevenths, four and four-sevenths, and six days respectively while controls lived eight and one-fifth days. As all the drugs were dissolved in water so that the dose per kilo of body weight was contained in 4 c.c. of sterile water, a considerable amount of water was introduced per diem intravenously in the rabbits. Hence, to determine any influence of the water in a small number of nephritic rabbits water alone was given intravenously. The rabbits lived an average of five and one-sixth days while of controls twelve survived and two lived an average of five days. In all experiments control rabbits were selected at random from stock pens at the same time the rabbits to receive diuretics were chosen.

In another series of twenty-one rabbits more accurate metabolism studies were made. These rabbits were kept in metabolism cages, their food (oats and carrots) and water intake and urine output were measured. Their non-proteid and urea nitrogen in the blood

and urinary nitrogen were determined by Dr. Denis as indicated in the introductory paragraph. The urine was collected in three-day periods to correspond with the determinations of blood nitrogen.

In normal rabbits diuretin given twice daily produced no distinct change in the three-day amounts of urine; the amounts showed no constant change and the variations were no greater than when no diuretin was given. The amount of non-proteid nitrogen and urea nitrogen in the blood did not fluctuate under the use of diuretin in normal rabbits. In rabbits with severe nephritis, diuretin sometimes increased and sometimes decreased the urine flow; the latter happened more often in the very severe types. Nitrogen retention in the blood usually steadily increased as the animals approached death; it could not be made out that diuretin influenced this rate of increase because the rate of increase varied as much in other rabbits without diuretin. While usually urine output steadily decreased, and nitrogen retention increased with the approach of death, occasionally urine output after decreasing to a small amount would increase, sometimes above normal, while nitrogen retention continued to increase. In these rabbits the rate of increase in nitrogen retention was not an indication of length of life; in one rabbit it reached a high figure (250 mgm. in 100 c.c. of blood as compared with the average normal of 35 mgm. in a rabbit) and the animal recovered. In another it reached a high figure and then began to decrease, although the animal died. In almost all of the rabbits, food and water intake fell rapidly as the rabbits sickened; urine output usually dropped faster than water intake; nitrogen retention in the blood increased; body weight fell markedly.

It is realized that the observations on metabolism in the last series are on too few animals to justify any generalization. The progressive rise in nitrogen retention, however, is of interest, and the failure of diuretin to influence it may prove of importance in a final evaluation of diuretic drugs in severe nephritis.

This particular set of experiments seems to justify the conclusion that in severe acute experimental nephritis of one type in the rabbit diuretic drugs are harmful when measured by their effect on length of life; when tested by other means, such as measuring nitrogen retention in the blood, one of them (diuretin) does not appear to exert any favorable influence.

