2824

Chronic nephropathy induced by prolonged administration of an alcoholic beverage. Recovery experiments.*

WM. de B. Mac NIDER.

[*From the Laboratory of Pharmacology, the University of North Carolina, Chapel Hill, North Carolina.*

In a recent publication[1] observations were recorded concerning the toxic effect (on kidneys of normal and of naturally nephropathic dogs) of an alcoholic beverage produced by fermenting with yeast a mixture of either corn meal and sugar or meal and molasses. The distillate from such a fermented mixture had an ethyl alcoholic content which varied 28 to 42 per cent. When normal dogs were given 10 cc. per kilogram of such a distillate, they developed a loss of muscular co-ordination and a staggering gait which was followed by a period of complete muscular relaxation and sleep. The distillate was given to the animals by stomach tube once a day over periods which varied from six weeks to three months. In such animals the functional evidence of renal injury consisted in an increase in the twenty-four hour output of urine, later followed by a reduction in urine formation below the amount established as normal for the animal before the use of the distillate. The urine from all of the animals showed albumin which varied from a trace to 4.8 gm. per liter. Casts of the hyaline or finely granular variety were only occasionally observed. During such intoxication the elimination of phenolsulphonephthalein was but slightly reduced. There was no retention of blood urea or nonprotein nitrogen. The reserve alkali of the blood remained unaffected.

The twelve dogs used in this study were killed at periods of six weeks or three months from the commencement of the use of the alcoholic distillate. The histological study of the kidneys of the animals showed an acute injury which was very largely confined to the glomeruli. The capillary loops were engorged with blood, and the endothelial cells of the loops showed a marked deposition of stainable lipoid material. Such material was also found in

* Aided by a grant from the Ella Sachs Plotz Foundation.

[1] Mac Nider, Wm. de B., *J. Pharmacol. and Exp. Therap.*, 1925, xxvi, 97.

the cells of the loops of Henle. In this latter location this material is normal for the dog kidney. In the convoluted tubule cells fine, dust-like particles of lipoid material could rarely be demonstrated.

The animals in this initial series of experiments have shown a lack of functional disturbance of the kidney, except a marked albuminuria with occasional hyaline and finely granular casts, and a variation in the output of the watery element of the urine. In the previous publication the suggestion was made, on the basis of functional and histological findings, that the altered output and composition of the urine might be explained on the assumption of an increase in the permeability of the glomerular vessels.

RECOVERY EXPERIMENTS.

Fourteen normal dogs were given 10 cc. per kilogram of an alcoholic distillate obtained from the fermentation by yeast of a mixture of corn meal and sugar. In addition to this fluid, the animals were given by stomach tube 250 cc. of water twice a day. The distillate was administered for ninety consecutive days. Its use was then stopped, and the animals were further studied at intervals of four days for eight months in order to obtain observations associated with the changes in renal repair during this period of recovery. At the end of the eight month period the animals were killed, and the kidneys studied histologically.

During the period of ninety days when the animals were receiving the alcoholic distillate, the changes in the urine were in general similar to those outlined in the preceding group of experiments. The detailed account of the two experiments which follow are characteristic for the animals of this series during the period when the distillate was being used as well as for the period of recovery when the use of the distillate had been discontinued. The animal of Experiment 2 had a normal daily output of 427 cc. of urine which was free from albumin, glucose and ketone bodies. The two hour elimination of phenolsulphonephthalein was 79 per cent. Blood urea was 12 mg. and nonprotein nitrogen 27 mg. per 100 cc. of blood. The alkali reserve of the blood was 8.1. On the fifth day of the use of the distillate, the urine had increased to 789 cc. It contained 3.8 gm. of albumin per liter and an occasional hyaline cast. The elimination of phenolsulphonephthalein was reduced to 65 per

cent. There was no retention of blood urea or nonprotein nitrogen. The reserve alkali of the blood was unaffected. On the sixtieth day of the use of the distillate, the urine contained 6.2 gm. of albumin per liter. There was apparently no increase in the number of casts. The elimination of the dye was 67 per cent. The blood urea, nonprotein nitrogen and reserve alkali of the blood remained unchanged. The output of urine on three consecutive days was 741 cc., 589 cc., and 702 cc.

Two months after the use of the alcoholic distillate was discontinued a study of this animal gave the following findings: The animal had a twenty-four hour output of urine of 784 cc. The urine contained 1.9 gm. of albumin per liter. The elimination of phenolsulphonephthalein was 65 per cent. There was no change in the blood findings other than a slight reduction in the blood urea of from 12 to 10 mg. per 100 cc. of blood.

At the termination of the experiment after a period of eight months had been allowed for the recovery, the output of urine on four successive days varied from a minimum output of 431 cc. to a maximum output of 914 cc. The urine contained only a trace of albumin, and very rarely a hyaline cast. The phthalein elimination was 68 per cent, as opposed to the normal elimination for this animal of 79 per cent. The blood urea and nonprotein nitrogen determinations during the course of the experiment showed but slight variations from the normal. There was no change in the reserve alkali of the blood.

The animal of Experiment 10 has shown in general the same type of response as the animal of Experiment 2. Prior to the use of the distillate, the animal had an average daily output of urine of 508 cc. which was free from albumin, casts, glucose and ketone bodies. The elimination of phenolsulphonephthalein in a two-hour period was 80 per cent. The blood urea was 18 mg. and nonprotein nitrogen 30 mg. per 100 cc. of blood. The reserve alkali of the blood was 8.0. On the ninetieth and final day of the use of the distillate the animal had an output of urine of 530 cc. The urine contained 2.4 gm. of albumin per liter, and showed occasional hyaline and finely granular casts. The elimination of phenolsulphonephthalein was 70 per cent, the blood urea determination was 14 mg. and the nonprotein nitrogen 32 mg. The reserve alkali reading was 8.05. At the termination of the experiment, eight months after the discontin-

uance of the distillate, the average daily output of urine was 714 cc. The urine contained 0.8 gm. of albumin per liter. The elimination of phenolsulphonepthalein was 73 per cent, as contrasted with the normal elimination of 80 per cent. The blood contained 14 mg. of blood urea, and 36 mg. of nonprotein nitrogen. The reserve alkali of the blood was 8.0.

The histological study of the kidneys of these twelve animals which were given a period of eight months in which to recover from the effect of the alcoholic distillate, shows a chronic type of injury confined to the glomeruli. The injury is uniform in its distribution, and in this respect differs markedly from such injuries developing as a result of bacterial invasion of the glomeruli. The lobulation of the capillary tufts has disappeared. The capillary loops appear matted together. Many of the loops have become obliterated by the proliferation of large spindle shaped cells. Mitotic figures have been found in six glomeruli in which this type of cell proliferation was taking place. These cells appear different from the ordinary fibroblast. They are larger, and the cytoplasm of the cell is clearer. In capillary loops in which the cell proliferation is sufficiently marked there is an absence of blood cells. In other capillary loops of the glomeruli, where the process of cell hyperplasia has not been so marked, the loops are distended with blood. There has been no demonstrable thickening of the capillary wall. In a few glomeruli the most advanced evidence of injury is shown by areas of hyaline degeneration. The capsular epithelium has failed to show evidence of hyperplasia. The capsule of the glomeruli and the pericapsular area has not shown connective tissue formation. The chronic injury at this stage of its formation is certainly a pure intracapillary reaction. The tubular epithelium has shown no evidence of injury.

CONCLUSIONS.

1. The chronic renal injury in dogs following the use of the alcoholic distillate when sufficient time is allowed for the development of processes of repair, consists in a type of glomerulonephropathy, characterized by the obliteration of the capillary loops by a large type of connective tissue forming cell. The capsule of the glomerulus does not participate in the reaction. The epithelial cells in the various portions of the tubule appear normal.

2. Following the glomerular injury which may have advanced to the stage of hyaline degeneration of the capillary loops, there occurs only slight evidence of an impairment of renal function. Urine from such kidneys constantly contains albumin and occasional hyaline and finely granular casts. The twenty-four hour output of urine when studied on successive days is variable. There is no constant decrease in the output. In four of the animals the output of urine has been markedly in excess of the intake of fluid. Such animals have shown a reduction in body weight. With the development of this type of glomerular injury there has been no other marked evidence of an impairment of renal function. The elimination of phenolsulphonephthalein has not been below 60 per cent in any of the animals. There has been no retention of blood urea or nonprotein nitrogen. The reserve alkali of the blood has been unaffected.

3. The kidney may be the seat of a diffuse and advanced type of chronic glomerular injury with only two indications of a functional disturbance: a marked variation in the twenty-four hour output of urine, and a urine which contains albumin and an occasional cast.