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Etiology of Renal Failure Following Crush Injuries.*

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The work of Bywaters[1] has indicated that renal failure following crush injuries may be caused by the excretion of myoglobin. In a recent observation by the same author the injection of myoglobin into the acidified rabbit was seen to produce death from renal failure.[2] The present study was undertaken to examine the effect of dog's metmyoglobin on the renal function of the acidified dog and to compare its action with that of dog's hemoglobin and methemoglobin in the acidified and normal animal.

Methods. All experiments were performed on unanesthetized trained female dogs. Creatinine and mannitol clearances were used to measure glomerular filtration rate, and *p*-aminohippuric acid clearances for the determination of the effective renal plasma flow.[3] Alternatively, 60 to 80 cc of dog's blood which had been hemolyzed by freezing and thawing, from 4.1 to 7.8 g of crystalline dog's hemoglobin, or 5 g of metmyoglobin or myoglobin were infused into the leg vein of dogs acidified with 100 g of ammonium chloride *per os*. Crystalline dog hemoglobin and methemoglobin were prepared by the usual procedure using ammonium sulfate to salt out the proteins, a slight excess of potassium ferricyanide being used to oxydise hemoglobin to methemoglobin. Metmyoglobin and myoglobin were prepared from dog muscle using a slight modification of the method of Morgan.[4] In a series of control experiments acidosis alone was produced by feeding 100 g of ammonium chloride or by infusion of lactic acid varying in strength from 4 to 6%.

Results and Discussion. The infusion of hemolysed blood or crystalline hemoglobin into a series of 4 animals acidified with ammonium chloride produced no effect on the renal plasma flow and filtration rate during the period of infusion or in the following 3 days. In 3 experiments in which hemolysed blood or crystalline hemoglobin were infused into dogs with normal alkali reserve, similar negative results were obtained.

The effect of metmyoglobin on acidotic dogs was studied in 5 experiments. The infusion of this pigment produced no change in the renal clearances of creatinine or mannitol and *p*-aminohippuric acid during the 10 days of observation. No increase in blood urea occurred at any time. No pathological changes were present in these kidneys. These results differ from those obtained by Bywaters on the acidotic rabbit.[2] It is possible that this discrepancy represents differences in the reaction of the test animals.

The effect of methemoglobin infusion into animals acidified with ammonium chloride was observed in 12 experiments. In 2 of these the infusion failed to cause renal failure. In 10 instances, however, the onset of infusion was followed by a rapid decline in the glomerular filtration rate and the renal plasma flow. During the 3 days following the infusion the renal clearances fell to 5% of their normal control values. The blood pH remained below 7.2, and the blood urea rose to levels ranging from 140 and 200 mg %. The kidneys of these animals, which died or were sacrificed on the third day after the infusion, showed hydropic degeneration of the proximal convoluted tubules, cellular necrosis in the distal tubules, and some cast formation. Similar lesions have been observed by Bywaters and Dible in patients with crush syndrome.[5]

In 5 experiments dealing with the effect of acidosis produced by ammonium chloride alone, no fall in the clearances of creatinine or

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1 Beall, D., Bywaters, E. G. L., Belsey, R. H. R., and Miles, J. A. R., *Brit. Med. J.*, 1941, **1**, 432.

2 Bywaters, E. G. L., *Brit. Med. J.*, 1942, **2**, 643.

3 Finkelstein, N., Aliminosa, L. M., and Smith, H. W., *Am. J. Phys.*, 1941, **133**, 276.

4 Morgan, V. E., *J. Biol. Chem.*, 1937, **112**, 557.

5 Bywaters, E. G. L., and Dible, J. H., *J. Path. Bact.*, 1942, **54**, 111.

p-aminohippuric acid were observed. However, when the acidosis was produced, by infusion of lactic acid (5 cases), a marked fall in all clearances was observed, coinciding with the appearance of methemoglobin in the urine. This observation makes it apparent that the renal failure was caused by the combined effect of acidosis and methemoglobin.

Summary. The infusion of crystalline methemoglobin into dogs acidified with ammonium chloride is followed by a fall in the effective renal plasma flow and the glomerular filtration rate of the dog. The dog may die in uremia on the third day following the infusion. Infusions of metmyoglobin and hemoglobin into acidified animals, and of methemoglobin and hemoglobin into normal animals, fail to depress renal function. The renal lesions of acidified dogs infused with methemoglobin resemble those observed in cases of crush syndrome and blackwater fever.

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Excretion of Penicillin in Man.*

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Florey[1] has demonstrated that penicillin appears in the urine when administered to the experimental animal or to man. More recently Rammelkamp and Keefer[2] showed that 58% of penicillin administered by the intravenous route is excreted by the kidneys largely during the first hour after the injection. This rapid loss of penicillin in the urine is undesirable since frequent injections are required to maintain adequate concentrations in the blood during the treatment of infections. The fact that substances, such as diodrast, which are excreted by the renal tubules exhibit a similar rapidity of elimination suggested the possibility that penicillin is also excreted by the tubules in addition to being filtered through the glomeruli, and further that this portal of exit could be blocked and the elimination of penicillin decreased. The present study was undertaken, therefore, to determine the mechanism of excretion of penicillin.

Methods. Penicillin† was used in the form of the sodium salt dissolved in 0.85% sodium chloride in a concentration of 1000 Florey units per cubic centimeter. All injections were made with this standard solution.

In one subject a constant intravenous infusion of penicillin was administered for a period of 5½ hours. The flow was adjusted so that 9600 Florey units per hour were delivered. The urine collected 30 minutes after institution of the constant drip of penicillin was discarded, thereafter hourly collections of urine were made. From the second to the fourth hours diodrast was given at the rate of 0.3 cc per minute after a priming dose of 10 cc.

The elimination of penicillin was studied in 5 subjects after a single injection of 5000 Florey units and again 24 hours later after the simultaneous injection of 5000 Florey

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1 Florey, H. W., Abraham, E. P., Chain, E., Fletcher, C. M., Gardner, A. D., Heatley, N. G., and Jennings, M. A., *Lancet*, 1941, **2**, 177.

2 Rammelkamp, C. H., and Keefer, C. S., *J. Clin. Invest.*, 1943, **22**, 425.

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