# A NOTE ON THE IMMEDIATE EFFECTS OF REDUCTION OF KIDNEY SUBSTANCE.[1]

By H. T. KARSNER, M.D., H. A. BUNKER, Jr., A.B., and G. P. GRABFIELD, M.D.

*(From the Department of Pathology (Phillips Fund) of the Harvard Medical School, Boston.)*

(Received for publication, June 11, 1915.)

Several investigators have studied the nitrogenous metabolism of animals following reduction of kidney substance; notably, Tuffier,[2] Bradford,[3] Bainbridge and Beddard,[4] Pearce,[5] and Pilcher.[6] Studies of nitrogen balance and partition have been made and somewhat contradictory results obtained. de Paoli[7] observed that large quantities of kidney substance could be removed without endangering life and that the minimum necessary for life is one-half of one kidney, or one-quarter of the total kidney substance. Tuffier, on the other hand, stated that life is possible with only 1.5 gm. of kidney substance per kilo of body weight (the total is about 7 gm. per kilo in the dog). Bradford found the danger limit reached at 2 gm. per kilo; this was confirmed by Pearce and by Pilcher.

As regards function Tuffier, as quoted by Bradford, states: "It is possible to remove quantities of kidney substance equal in weight and in volume to those of the sum of the two kidneys in such a way as yet to leave behind a considerable amount of kidney substance, as shown by postmortem examination; that this diminution in the amount of kidney substance is *not* accompanied by any functional disturbance of the urine, and that the urine and urea, after oscillations due to the operation, return to their normal amount."

Bradford found that excision of less than two-thirds of the kidney volume

[1] Aided by a grant from The Rockefeller Institute for Medical Research.

[2] Tuffier, T., Études expérimentales sur la chirurgie du rein, Paris, 1889; cited by Bradford, J. R., The Results Following Partial Nephrectomy and the Influence of the Kidney on Metabolism, *Jour. Physiol.*, 1898–99, xxiii, 415.

[3] Bradford, J. R., *loc. cit.*

[4] Bainbridge, F. A., and Beddard, A. P., The Relation of the Kidneys to Metabolism, *Proc. Roy. Soc., London, Series B,* 1907, lxxix, 75.

[5] Pearce, R. M., The Influence of the Reduction of Kidney Substance upon Nitrogenous Metabolism, *Jour. Exper. Med.*, 1908, x, 632.

[6] Pilcher, J. D., On the Excretion of Nitrogen Subsequent to Ligation of Successive Branches of the Renal Arteries, *Jour. Biol. Chem.*, 1913, xiv, 389.

[7] de Paoli, E., *Centralbl. f. Chir.*, 1892, xix, 78; cited by Bradford, *loc. cit.*

resulted in temporary increase of the watery part of the urine, which became lasting when two-thirds were removed; removal of "approximately three-quarters of the total kidney weight is followed by a very great increase in the amount of urinary water, and also by an increase in the amount of urea excreted." He found also a considerable increase in the nitrogenous extractives of the blood and tissues, particularly muscles, most marked after excision of three-quarters, but quite apparent after excision of two-thirds of the kidney substance. This excess was distributed just as after double nephrectomy and after the intravenous injection of urea; he states that the quantity in the muscles is too great to be accounted for by the mere products of normal metabolism.

Bainbridge and Beddard working on cats found that removal of approximately three-fourths of the total kidney substance is not constantly followed by an increased output of nitrogen, and that it takes place only in cats which have lost 22 per cent or more of their initial body weight at the time of its onset. They concluded further that the kidneys have no direct influence upon nitrogenous metabolism and that the increased output of nitrogen is simply the result of inanition. They found the cats still able to pass a concentrated urine and that the amount of urine is not necessarily increased beyond the normal.

Pearce, using dogs, confirmed the general results of Bainbridge and Beddard and concluded further that the metabolism condition of starvation is apparently the result of the gastro-intestinal disturbance constantly associated with extensive kidney reduction and not of a disturbance of general nitrogenous metabolism. He found that the gastro-intestinal disturbance was not due to diminished absorption and found no evidence to support a theory of internal secretion on the part of the kidney.

Pilcher, using both cats and dogs, reduced the kidney substance by ligation of branches of the renal arteries. He states that with but one-fourth of the kidney substance functioning the quantity of urine was practically normal; there is marked temporary prostration, anorexia, loss of weight, and increased nitrogen output with finally a return to normal, with a slight tendency to nitrogen retention.

## REPORTS OF EXPERIMENTS.

Our experiments have been conducted because of the availability of the Folin methods[8] for the determination of the non-protein nitrogen of the blood.

Dogs were kept on a constant diet and determinations were made of the total non-protein nitrogen of the blood, obtained by aseptic heart puncture. The urine was collected in the ordinary metabolism cages and the total non-protein nitrogen and urea nitrogen were determined. All analyses were made in duplicate or triplicate.

[8] Folin, O., and Denis, W., Protein Metabolism from the Standpoint of Blood and Tissue Analysis, *Jour. Biol. Chem.*, 1912, xi, 161; New Methods for the Determination of Total Non-Protein Nitrogen, Urea and Ammonia in Blood, *ibid.*, p. 527.

All the blood results are reported in mg. per 100 cc. of blood. All the urine results are reported in mg. per twenty-four hours.

Five dogs were used, but the results can be summarized in the protocols of three (Tables I, II, and III).

TABLE I.

*Dog 1.*

*Female, Weight 6,500 Gm. Urine Negative for Albumin. Diet 200 Gm. of Dog Biscuit.*

| Date. | Blood. Total non-protein nitrogen | Urine. Total non-protein nitrogen. | Urine. Urea nitrogen. | Urine. Amount. |
|---|---|---|---|---|
| | | | | *cc.* |
| Apr. 29 | 36 | 1,840 | — | 100 |
| " 30 | 44 | 2,520 | 1,861 | 63 |
| May 1 | 45 | 2,010 | 1,903 | 201 |
| " 2 | Left kidney (weight 17 gm.) removed under ether anesthesia | | | |
| " 3 | 44 | 1,192 | 859 | 159 |
| | Slight diarrhea | | | |
| " 4 | 43 | 1,451 | 1,357 | 41 |
| | Diarrhea very severe | | | |
| " 7 | 51 | — | — | — |
| " 9 | 44 | — | — | — |
| | Diarrhea finally cleared up. | Experiment resumed | | |
| " 24 | 38 | — | — | — |

At 12.30 p. m. the right kidney (weight 22 gm.) was removed and the animal bled at more frequent intervals, as follows:

| | | Total non-protein nitrogen in blood. |
|---|---|---|
| May 24 | 12.30 p. m. | Operation |
| | 7.30 p. m. | 44 |
| " 25 | 1.00 a. m. | 56 |
| | 1.00 p. m. | 85 |
| | 7.00 p. m. | 111 |
| | 11.30 p. m. | 133 |
| " 26 | 2.00 p. m. | 196 |
| | 11.00 p. m. | 227 |
| " 27 | 10.00 a. m. | 285 |
| | 2.00 p. m. | Animal found dead. |

Autopsy shows slight superficial infection of the abdominal wound; the abdominal cavity is clean; a few cc. of gray, slightly turbid fluid are found in the left pleural cavity.

TABLE II.

*Dog 2.*

*Female, Weight 6,000 Gm. Urine Negative for Albumin. Diet 2 1/2 Dog Biscuits.*

| Date. | Blood. Total non-protein nitrogen. | Urine. Total non-protein nitrogen. | Urine. Urea nitrogen. | Urine. Amount. |
|---|---|---|---|---|
| | | | | *cc.* |
| Aug. 7 | 24 | — | — | — |
| " 8 | 18 | 4,005 | 3,337 | 89 |
| " 10 | — | 2,278 | 1,960 | 245 |
| " 11 | Left kidney (weight 35 gm.) was removed under ether anesthesia | | | |
| " 12 | 43 | — | — | 0 |
| " 13 | 27 | 2,156 | 1,705 | 55 |
| " 14 | 26 | 3,149 | 2,350 | 94 |
| " 15 | 21 | 3,393 | 3,237 | 390 |
| " 16 | — | 2,470 | 2,041 | 130 |
| " 18 | Right kidney was removed under ether anesthesia | | | |

| | | Total non-protein nitrogen in blood. |
|---|---|---|
| Aug. 18 | 11.45 a. m. | Operation |
| | 11.45 a. m. | 31 |
| | 11.45 p. m. | 72 |
| Aug. 19 | 11.45 a. m. | 95 |
| | 11.45 p. m. | 114 |
| " 20 | 11.45 a. m. | 143 |
| | 6.00 p. m. | 154 |
| | 12.00 midnight | 165 |
| " 21 | 12.00 noon | 208 |
| | 10.00 p. m. | 225 |
| " 22 | 9.00 a. m. | 282 |
| | 5.00 p. m. | Found dead. |

Autopsy showed no sepsis or other abnormalities.

TABLE III.

*Dog 3.*

*Female, Weight 4,000 Gm. Urine Negative for Albumin. Diet 120 Gm. Chopped Beef and 2 Dog Biscuits.*

| Date. | Blood. Total non-protein nitrogen. | Urine. Total non-protein nitrogen. | Urine. Urea nitrogen. | Urine. Amount. |
|---|---|---|---|---|
| | | | | *cc.* |
| Aug. 24..... | 23 | 1,823 | 1,568 | 49 |
| " 25..... | — | 3,725 | 3,053 | 192 |
| " 28..... | Upper pole of right kidney (weight 6 gm.) was removed under ether anesthesia through lumbar incision by Dr. W. C. Quinby | | | |
| " 29..... | 26 | 4,480 | 3,360 | 224 |
| " 30..... | 20 | 4,480 | 4,032 | 224 |
| " 31..... | 22 | 3,800 | 2,800 | 200 |
| Sept. 1..... | Entire left kidney (weight 22 gm.) was removed under ether anesthesia | | | |
| " 2..... | 28 | — | — | 150 |
| " 3..... | 41 | 4,620 | 3,135 | 330 |
| " 4..... | 35 | 3,995 | 2,820 | 235 |
| " 8..... | 41 | | | |
| " 11..... | 33 Diarrhea | | | |
| " 12..... | 26 Diarrhea | | | |
| " 14..... | 33 Diarrhea | | | |
| " 18..... | Remainder of right kidney (weight 17 gm.) was removed under ether anesthesia | | | |

| | | Total non-protein nitrogen in blood. |
|---|---|---|
| Sept. 18..... | 3.00 p. m.....Operation | |
| | 3.00 p. m..... | 35 |
| " 19..... | 12.00 noon..... | 68 |
| " 20..... | 11.30 a. m..... | 152 |
| | 5.00 p. m..... | 172 |
| " 21..... | 9.30 a. m..... | 227 |

2.00 p. m. Death occurred as the blood was being withdrawn. The last operation wound was infected; otherwise the autopsy showed nothing abnormal.

## DISCUSSION OF RESULTS.

From these data it may be said that removal of approximately one-sixth of the kidney substance (Dog III) results in no marked alteration of the non-protein nitrogen of the blood or of the urine, although there is, as Pilcher expresses it, a slight tendency to accumulation[9] in the blood and increased output in the urine for a

[9] The term accumulation is used instead of retention to avoid confusion with the use of the latter term as expressing the holding of nitrogen in the body for metabolic and constructive purposes.

period of twenty-four (blood) or forty-eight hours (urine), probably to be explained by the operation. Excision of one-half the total kidney substance in the case of Dog II was followed by a distinct accumulation in the blood during the first twenty-four hours, associated, however, with anuria; such accumulation, however, did not appear in the corresponding period in Dog I, which was not anuric. As seen in both dogs, however, the output for the first forty-eight hours appears to be diminished, thus again showing a slight tendency toward accumulation for at the most forty-eight hours. The removal of approximately two-thirds of the kidney substance (Dog III) was followed by a very slight increase in output, and after twenty-four hours a slight but distinct increase in the non-protein nitrogen of the blood which lasted for three days.

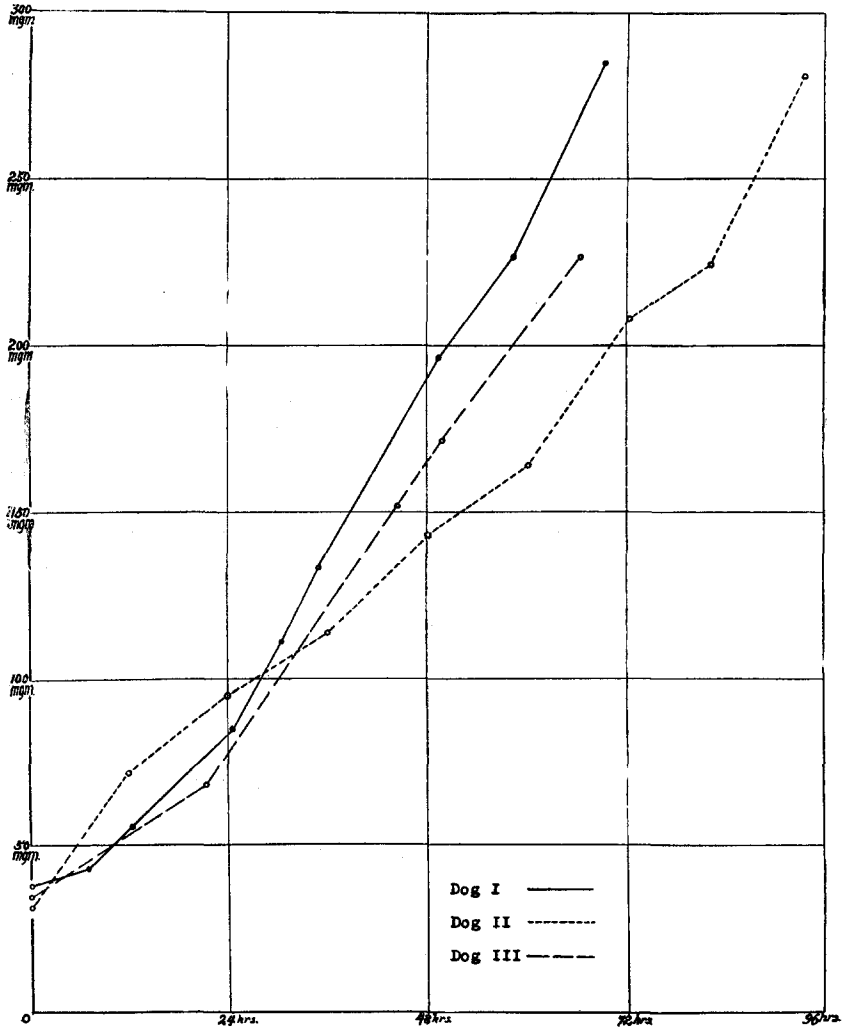
An examination of the amount of urine and its concentration shows that reduction of the kidney substance down to approximately one-third does not prevent that fragment from excreting urine in normal amounts and concentrations.

Diarrhea was found to occur frequently and followed the excision of only one-half the kidney substance. None of the dogs lost markedly in weight, and this reduction in no case reached the critical 22 per cent of Bainbridge and Beddard.

The results following the complete removal of kidney substance are shown graphically in Text-fig. 1. In Dogs I and III the rate of increase was considerably less in the first twenty-four hours than in the succeeding periods. On the second and third days the rate of increase was practically the same and from rough calculations based on the output for twenty-four hours was about what it should be per 100 cc. of blood for a twenty-four hour period. It is easily possible that operative shock might account for the relatively slight increase in the first twenty-four hours.

In Dog II the results are more constant, although in the last twenty-four hours there was a slight exacerbation of rate. In other words, for this animal the rate of increase per 100 cc. of blood should be roughly 57 mg. per day per 100 cc., so that the amounts would be for each succeeding day 88, 145, 203, and 260, whereas they actually were 95, 143, 208, and 282 (allowing twenty-one and one-half hours for the last day). It is regretted that the

actual intake of nitrogen following the total nephrectomy was not estimated and the results here presented are regarded as suggestive




TEXT-FIG. 1. Chart showing total non-protein nitrogen in blood following complete nephrectomy.

rather than conclusive. Further studies are being carried out in an attempt to elaborate on and elucidate this increase in total non-protein nitrogen in relation to intake, distribution in the body, and other factors which are known to influence protein metabolism.