The Relation of the Kidneys to Metabolism.—Preliminary Communication.

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The effects following on the removal of large portions of the kidneys of dogs were studied by Rose Bradford in 1892. In the first place, he found that animals deprived of three-quarters or more of their total kidney weight rapidly wasted, and died in two or three weeks, or even less; and, although they often refused food, they passed daily an amount of urea almost or quite equal to that passed by the same animals on full diet before operation. Secondly, he observed that after the removal of a portion of one kidney, the urine became more abundant and more dilute, and the dogs were apparently unable to excrete a concentrated urine; this effect was intensified by the subsequent removal of the opposite kidney. Bradford concluded that the kidneys in some manner normally control the nitrogenous metabolism, and that in the absence of sufficient kidney substance this metabolism becomes excessive.

In view of their extreme importance, a repetition of these experiments appeared advisable; it was hoped, too, that more complete analysis of the urine might throw some light on the course of nitrogenous metabolism as a whole. This paper contains a preliminary account of our observations.

Methods.

Cats were used for these experiments. They were anæsthetised with chloroform and ether, the anæsthesia being maintained by ether throughout the operation.

The abdomen was opened in the middle line, and the kidney drawn up into the wound; the capsule was opened, and stripped off the kidney. The renal vessels were digitally compressed, a wedge cut out of the kidney, and the cut surfaces brought into apposition and kept together by two or three sutures passing deeply through the kidney substance. The kidney was then replaced in its capsule and the latter was closed by a continuous suture; the kidney was returned to its place and the abdominal wound closed. No vessels were ligatured, since forceps are so apt to damage the kidney substance: a little blood collects between the kidney and capsule, where it clots and checks further loss of blood.

Two or three weeks later the opposite kidney was removed under ether anæsthesia through an abdominal incision.

The animals were kept in cages whose floor consisted of a wire netting; the cages stood upon a zinc plate, sloping towards the centre, which was perforated by a small hole. The urine ran down the zinc sheet through the hole into a basin containing a little chloroform. The urine and fæces were collected every 24 hours, and very great care was taken to keep the urine free from food or fæces.

The cats were kept at a fairly even, moderate temperature, and were allowed some exercise daily in the laboratory.

The food was measured daily, and any food left over was also measured. Their diet consisted of minced meat, milk and water; the amount of the latter, of course, was not restricted.

The total nitrogen in the meat and milk was estimated by Kjeldahl's method. A considerable amount of meat was minced, and mixed into a uniform mass; a sample of this was analysed, and the rest kept in an ice chest; the cats received a definite quantity each day.

The urine was analysed daily; the fæces were collected for several days, and the total nitrogen present estimated. The total nitrogen of the urine and fæces was estimated by Kjeldahl's method, the urea by a modification of Folin's method, the ammonia by Schaffer's method, and the creatinin by the colorimetric method of Folin. All the analyses were made in duplicate.

Results.

The effects of removing portions of the kidneys may be grouped as follows:—Firstly, the general conditions of the animals including changes in body weight; secondly, the nitrogenous metabolism; thirdly, alterations in the amount and concentration of the urine.

I. *The Condition of the Animals.*—After the first operation, the cats usually drank a little milk on the same day, but for several days their appetite was poor, and they lost weight. Eventually they ate very well, and appeared to be more hungry than normal cats. For a day or two the urine contained blood, and for another two or three days albumen was present.

Three cats survived the second operation for some time; they rapidly recovered from the anæsthesia, and showed very little shock.

Two of the three cats ate very little after the second operation, and refused food altogether during the last few days of life; the third cat ate well for 10 days, when its appetite also failed.

Vomiting and diarrhœa were observed in all the cats, and they seemed

very susceptible to cold. They acquired a very foul breath, and soreness of the lips and gums; their fur came off very rapidly.

Cat I lived six days, Cat II lived seven days, and Cat III lived 17 days after the second operation. The rectal temperature was maintained at 100° or more until the last few days of life.

The Body Weight.—It will be seen from the following table that normal cats lose weight when kept in confinement, notwithstanding some exercise daily. The loss of weight, however, is less than that observed in Rose Bradford's dogs, most of which lost 10 per cent. or more of their initial weight before the first operation. In our experiments, the cats were not put into the collecting cage before the first operation, so that this initial loss of weight was avoided.

Table I.

	Initial weight.	Final weight.	Loss.	Time in cage.
	grammes.	grammes.	Per cent.	days.
Normal cat.....	3650	3580	1·9	19
Normal cat.....	2300	2140	6·9	8

The effect of the two operations upon the weight of the cats is shown in the following table:—

Table II.

	Initial weight, first operation.	Weight at time of second operation.	Loss.	Final weight.	Loss.	Life after second operation.
	grammes.	grammes.	Per cent.	grammes.	Per cent.	days.
Cat I	2420	2120	12·3	1600	33·8	6
Cat II	2880	2550	11·4	1840	36·1	7
Cat III	2500	2220	11·2	1640	34·4	17

The final percentage loss of weight is much the same, and was reached in Cat III in 17 days, and in a much shorter time in the other cats, because Cat I ate well for 10 days, whereas the others ate very little after the second operation. These figures correspond closely with those of Rose Bradford; he also found that the animals lived much longer after the second operation when they took food.

II. *The Nitrogenous Metabolism.*—The total nitrogenous metabolism was determined in three cats before and after the second operation; the urinary nitrogen was also estimated in one of these cats before the first operation. The results are summarised in the following protocols:—

Cat I.—October 12. Weight 2420 grammes. Removed part of left kidney, weight, 6·3 grammes.

Date.	Weight.	Total N in urine.	N as urea.	N as ammonia.	N as creatinin.	N in food.
	grammes.	grammes.	Per cent.	Per cent.	Per cent.	grammes.
October 26.....	2130	1·69	—	3·9	1·6	3·0
,, 27.....	2160	3·44	90	4·3	1·7	3·0
,, 28.....	2090	1·09	—	2·2	1·5	2·6
,, 29.....	Removed right kidney: weight 10·5 grammes.					
,, 30.....	2050	0·94	74	2·6	2·3	
,, 31.....	1950	0·86	90	1·6	2·4	
November 1 ...	1820	0·84	—	3·6	2·7	0·83
,, 2 ...	1770	1·73	—	2·0	2·0	
,, 3 ...	1660	1·02	70	6·0	1·6	
,, 4 ...	1600	Found dead.				

	N intake.		N output.		Fæces.
	Total.	Average.	Total.	Average.	
After first operation—	grammes.	grammes.	grammes.	grammes.	gramme.
3 days' period.....	8·5	2·84	6·22	2·07	0·59
After second operation—					
6 days	1·2	0·2	5·71	0·95	0·52

Post mortem.—No evidence of sepsis. Some subcutaneous fat still present. Remainder of kidney weighed 3·8 grammes.

Total kidney weight ..... = 20·6 grammes.

Amount after second operation (3·8 grammes) = less than $\frac{1}{5}$ total kidney weight.

= 1·5 grammes per kilo.

Cat II.—October 19. Weight, 2880 grammes. Removed part of left kidney, 8·8 grammes.

Date.	Weight.	Total N in urine.	N as urea.	N as ammonia.	N as creatinin.
	grammes.	grammes.	Per cent.	Per cent.	Per cent.
October 26	2600	2·65	73·9	3·8	1·4
November 1	2510	3·08	92·8	3·3	1·7
,, 3	2550	3·43	79·9	—	1·2
,, 4	2550	3·59	—	3·8	1·4
,, 5	Removed right kidney, weighing 14·1 grammes.				
,, 6	2450	1·10	88·2	3·4	2·2
,, 7	2380	1·69	84·0	1·6	2·1
,, 11	2000	1·79	89·9	2·0	1·2
,, 12	Cat moribund. T. 95° ·0. Killed by chloroform. Weight 1840 grs.				

	N intake.		N in urine.		Total fæces.
	Total.	Daily average.	Total.	Daily average.	
After first operation—	grammes.	grammes.	grammes.	grammes.	grammes N.
Period of 10 days	39·7	3·9	29·01	2·9	2·26
After second operation—					
6 days	4·46	0·74	8·78	1·46	1·0 (approx.)

Post mortem.—Remainder of kidney adherent to spleen, normal in appearance, very little omental fat; none visible elsewhere. Muscles not obviously wasted. No evidence of sepsis.

Total kidney weight..... = 29·6 grammes.
Weight found *post mortem* = 6·7 „
= $\frac{2}{9}$ total kidney weight.
= 2·3 grammes per kilo.

Cat III.—September 4. Weight, 2500 grammes. Removed part of left kidney—4 grammes.

Date.	Weight.	Total N in urine.	N as urea.	N as NH_3.	N as creatinin.	N intake.
	grammes.	grammes.	per cent.	per cent.	per cent.	grammes.
September 11.....	2140	3·52	—	3·1	1·3	10·4
„ 12.....	2120	4·51	88·8	4·5	—	7·6
„ 16.....	2220	5·12	90·1	3·6	1·3	7·3
„ 19.....	Removed right kidney, wt. 10·25 grammes; wt. of cat, 2220 grammes.					
„ 23.....	2020	3·26	75·0	9·9	2·0	9·0
October 2	1880	1·13	83·1	10·0	1·7	nil
„ 5	1670	0·89	—	2·0	1·1	nil

After the second operation, the cat ate well for 12 days; after that it ate very little and wasted rapidly. It was moribund on October 6, and was killed by chloroform. Weight at death 1640 grammes.

Post mortem.—There was no sepsis; very little fat was visible in the subcutaneous tissues.

Total kidney weight..... = 20·65 grammes.
Amount left *post mortem* = 6·4 „
= less than $\frac{1}{3}$ total kidney weight.
= 2·5 grammes per kilo.

	Total N intake.	Daily average.	Total N in urine.	Daily average.
After first operation—	grammes.	grammes.	grammes.	grammes.
3 days' period.....	25·2	8·4	11·3	3·77
After second operation—				
First 6 days	23·4	3·9	12·86	2·14
Second 6 days	24·2	4·03	16·0	2·6
Last 4 days.....	0	0	3·72	0·93

The nitrogen intake for Cat III is not absolutely exact, since the meat and milk were not analysed every day.

The clinical condition of these cats was apparently identical with that of Rose Bradford's dogs; in both cases, the second operation was usually followed by rapid wasting. In two of the three cats considerably more than three-quarters of the total kidney weight was removed; in the third cat rather less than three-quarters was removed, but since the animal died, one may conclude that cats need rather more kidney than dogs in order to maintain life. In this connection it may be noted that in cats the average kidney weight is 9·1 grammes per kilo., as compared with 6·7 grammes per kilo. in dogs.

There is no doubt, then, that the experimental conditions of Bradford's dogs were strictly reproduced. Yet one of the cats showed no increased output of nitrogen after the second operation; in one cat the increase of nitrogen first occurred five days after the operation, when the cat had lost 28 per cent. of its weight, and was almost moribund; and in the other cat the increase occurred four days after the operation, when the loss of weight was 22·5 per cent.

In none of the cats did the nitrogen output after the second operation ever reach that observed after the first operation, and it never greatly exceeded that found in normal fasting cats. The greatest daily output of urinary nitrogen after the second operation, when the cats refused food, was 1·79 in Cat II on the last day of life. For normal cats kept without food for 24 hours the output of urinary nitrogen is about 1 gramme and the loss of weight about 100 grammes.

The protocols, moreover, show that the second operation has no appreciable effect upon the percentage of urea, ammonia and creatinin relatively to the total nitrogen. There is no increase in the output of creatinin (on a milk diet) such as might be expected if muscular metabolism were excessive.

We find, therefore, that the removal of three-quarters of the kidney weight of cats has no influence upon their nitrogenous metabolism until the last

two or three days of life. This terminal increase of nitrogen only occurs when the cats have lost 22 per cent. or more of their body weight, and are obviously in a state of inanition. The two cats which showed this terminal increase of urinary nitrogen ate very little after the second operation, and wasted rapidly.

The effect of starvation upon the body weight and urinary nitrogen of normal animals has been investigated by Voit, Schöndorff, Kaufmann, and others. It is clear, from a comparison of their results with the condition of our cats, that the condition of starving animals is identical with that of cats which refuse food after the second operation on the kidneys.

There is in both cases a progressive loss of weight, a fall of temperature during the last few days of life, and usually a terminal rise in the output of nitrogen in the urine. E. Voit and others have shown that, in starvation, the nitrogen output may increase several days before death, and that the time of its onset is directly related to the amount of fat originally possessed by the animal. A very fat animal may never exhibit the increase of nitrogen, whereas, if the original store of fat is small, a very few days of starvation suffice to evoke an increased output of nitrogen. For example, a starving dog, observed by Schöndorff, showed an increased output of nitrogen when it had lost 20 per cent. of its weight; in our cats the nitrogen rose coincidently with a loss of 22 per cent. or more of the body weight.

We consider, therefore, that the wasting, fall of temperature and final increase of urinary nitrogen occur simply because the cats refuse food after the second operation; they die from inanition, and the rise of urinary nitrogen, when it occurs, merely means that the animal's store of fat is much diminished, and that more energy must be supplied by proteid breakdown.

We consider, further, that the same explanation fully accounts for the results obtained by Rose Bradford, and that there is no evidence from his experiments that the kidneys directly influence nitrogenous metabolism.

It may be added that Dr. Pembrey has investigated the gaseous exchange of these cats; he finds that his results are such as would be given by animals in a state of inanition.

III. *The Amount and Concentration of the Urine.*—The amount and specific gravity of the urine of cats varies widely according to their diet. On a meat diet the urine is concentrated; on a milk diet it is abundant and dilute. Making allowance for variations of diet, we find no evidence that the amount and specific gravity of the urine are necessarily modified by either the first or second operation. Only one cat almost invariably passed abundant quantities of dilute urine after the first operation; the others often passed a concentrated urine. In this respect our results are at variance with those

of Rose Bradford; and it may be pointed out that the effect, even in dogs, is not a constant one, since in half of Bradford's experiments the urine was no more abundant after the second than after the first operation.

It may be concluded, therefore, that the increase in quantity and decrease in concentration of dog's urine, after operations on the kidneys, is an incidental rather than an essential result.

Table III.

	Nature of food.	Urine.		
		Amount.	Sp. gr.	Total N.
		c.c.		grammes.
Normal cat	Meat	112	1046	5·4
	Bread and milk	310	1007	1·6
After first operation—				
Cat I	Meat	128	1040	5·1
	Bread and milk	435	1005	1·55
Cat II	Meat	164	1038	3·44
	Milk	124	1020	2·1
Cat III	Meat and milk	68	1042	2·65
Cat IV	Meat	110	1040	?
Cat V	Meat	43	1054	
	Milk	150	1015	
After second operation—				
Cat I	Milk	90	1020	1·49
	Meat	182	1018	3·02
Cat II	Milk	78	1030	0·94
		81	1018	1·07
Cat III	Meat and milk	100	1019	1·10
		208	1018	2·44

Conclusions.

1. We confirm Bradford's observations that removal of three-quarters or more of the total kidney weight in cats is followed by loss of appetite, wasting, and death within a few days or weeks.

2. We find that in such cats an increased output of nitrogen is not of constant occurrence; 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.

3. We conclude, therefore, that the kidneys have no direct influence upon nitrogenous metabolism, and that the increased output of nitrogen is simply the result of inanition, and is of the same nature as that observed in starving animals.

4. We find that, after removal of a portion of one kidney, and also after subsequent removal of the opposite kidney, cats are still able to pass a concentrated urine, and that the amount of the urine is not necessarily increased beyond the normal.

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REFERENCES.

Bradford, 'Journ. Physiol.,' vol. 23, p. 415, 1898.
Folin, 'Journ. Phys. Amer.,' vol. 13, 1905.
Kaufmann, 'Zeitschrift f. Biol.,' vol. 41, 1901.
Schöndorff, 'Pflüger's Archiv,' vol. 82, p. 60, 1900.
Voit, E., 'Zeitschrift f. Biol.,' vol. 41, p. 550, 1901.

Address of the President, Lord Rayleigh, O.M., D.C.L., at the Anniversary Meeting on November 30, 1906.

Since the last Anniversary the Society has sustained the loss of twelve Fellows and two Foreign Members.

The deceased Fellows are :—

Professor Lionel Smith Beale, died March 28, 1906.
Sir Walter Lawry Buller, K.C.M.G., died July 19, 1906.
Charles Baron Clarke, died August 25, 1906.
Right Hon. Sir M. E. Grant Duff, G.C.S.I., died January 11, 1906.
Professor Charles Jasper Joly, died January 4, 1906.
Colonel Sir Alexander Moncrieff, K.C.B., died August 3, 1906.
George James Snelus, died June 18, 1906.
Professor Hermann Johann Philipp Sprengel, died January 14, 1906.
General Sir Henry E. L. Thuillier, C.S.I.
Rev. Canon H. B. Tristram, died March 8, 1906.
Professor Harry Marshall Ward, died August 26, 1906.
Professor Walter Frank Raphael Weldon, died April 13, 1906.

The Foreign Members are :—

Professor Ludwig Boltzmann.
Professor Samuel Pierpont Langley.

On this list are to be found the names of veterans distinguished in many branches of science and in public affairs. One name is a household word in