A STUDY OF THE NITROGEN METABOLISM AND OF ACIDOSIS AFTER THE TRANSPLANTATION OF A URETER INTO THE DUODENUM IN DOGS.

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Numerous reports, both clinical and experimental, have discussed the feasibility of implanting a ureter into some part of the intestinal canal, and have described methods of operative procedure. The literature was reviewed in 1909 by Steinke (1), who concluded that the results show that under certain conditions the ureter may be transplanted successfully. The failures, however, are numerous, the ultimate results uncertain, and a fatal termination is so apt to occur that no definite claim for the operation can as yet be made. Most experimental studies, as those recently made by Steinke (1909), Stewart (2) (1910), and Sweet and Stewart (3) (1914), have been especially concerned with the ascending infection of the kidney and the mechanical dilatation of the ureter following operation.

In order to avoid some of these difficulties—peritonitis, ascending infection of the kidneys, and stenosis of the ureteral orifice where it enters the intestine, with resulting hydroureter and hydronephrosis—Sweet and Stewart devised the following method of operation.

The right ureter of the dog is isolated and severed close to the bladder, and the free upper end passed through the lumen of the greater pancreatic duct into the intestine. This operation is made possible in the dog by the fact that this animal possesses at least two pancreatic ducts, both of which are separate from the bile duct. In Sweet and Stewart's series (3) eight dogs were used, and in some, nephrectomy of the left kidney was done at a later date. In none of the animals was there evidence of infection of the kidney, but in some, distinct evidence of obstruction was found, and in all, death resulted after varying intervals of time with symptoms suggestive of an intoxication.

In experiments such as those cited above an intoxication in the absence of infection suggests two possibilities: intoxication from (*a*) disturbance of kidney function or (*b*) absorption of urinary constituents draining into the intestine. It was with the hope of throwing some light upon this intoxication that the present study was undertaken at the suggestion of Dr. Sweet.

EXPERIMENTAL.

Six dogs were used; in two a ureter-intestinal transplantation[1] was performed and four were used for various controls. The dogs were kept in metabolism cages and all were kept on the same dietary régime. The diet contained 0.4 gm. of nitrogen per kilo and 70 calories per kilo of body weight. It consisted of beef heart, lard, bread crumbs, sugar, a little salt (2 gm.), and sufficient bone ash to ensure well formed feces. The food was mixed with about 300 cc. of water. During each period of collection of blood and urine food was withheld. The animals were catheterized at the end of every 24 hours. After each catheterization the bladder was washed out and the wash water added to the catheterized urine and that which was voided naturally, and the whole made up to a definite volume.

The study of the urine included the determination of the total nitrogen, urea nitrogen, and ammonia nitrogen. For the determination of total nitrogen and urea nitrogen in the urine the new Nesslerization method of Folin and Denis (4) was used, and for ammonia the aeration method of Folin and Macallum (5). Blood was obtained by aseptic puncture of the vena jugularis and utilized for the study of the non-protein nitrogen, the urea nitrogen, and carbon dioxide content. In the examination of the blood the method of Folin and Denis (4) was used for the determination of non-protein nitrogen and urea nitrogen, and Van Slyke's method (6, 7) for the carbon dioxide content. Tests for ketones with Rothera's method (8) were made from time to time. All analyses were made in duplicate and sometimes in triplicate.

The operative procedure, as carried out by Dr. Sweet, consisted first, in transplantation of the right ureter into the duodenum and then, after several days, the removal of the left kidney. In all the experiments Period A refers to control observations before the first operation, Period B to observations after transplantation of ureter but before removal of the opposite kidney, and Period C to observa-

[1] All operations were done under ether anesthesia by Dr. J. E. Sweet.

tions after removal of the opposite kidney. During Period A animals were studied before any operative procedure for periods of 4 days. After the first operation several days were allowed for recovery from the acute effects of the operation, and another period of chemical study was undertaken (Period B). Under Period B1 are given the results obtained with animals after transplantation of the ureter, and under Period B2, as control, the results with animals in which the ureter was ligated and sectioned without removal of the kidney. After the opposite kidney was removed the chemical studies of the blood were continued until the dog died (Period C).

TABLE I.

Dog No.	Period.	No. of experiments.	Urine.			Blood.			Remarks.
			Total nitrogen per day.	Urea nitrogen per day.	Ammonia nitrogen per day.	Non-protein nitrogen per 100 cc. of blood.	Urea nitrogen per 100 cc. of blood.	Carbon dioxide content of plasma.	
			gm.	*gm.*	*gm.*	*mg.*	*mg.*	*vol. per cent*	
1, 2, 3, 4	A	4	4.12	3.15	0.15	29.5	10.1	56	Control observations in normal animals.
1, 5	B1	2	4.59	3.47	0.22	38.3	14.3	56	Right ureter in duodenum.
6	B2	1	6.18	4.44	0.18	30.3	11.1	52	" " ligated.
1, 5	C	2				201.8	102.2	41	Left kidney removed after Period B1.

It is obvious that in Period C the chemical examinations were necessarily limited to the blood.

In two other dogs as a control the right ureter was cut and ligated, but as one developed distemper following the operation the results on only one are given (Table I, Period B2).

The general results are shown in Table I which gives the average results for all animals during each of the three periods. In Tables II and III the results in Periods B and C are given in detail in contrast to the averages of Period A.

A comparison of Periods A and B1 shows that in the latter there is a moderate increase in the total nitrogen, urea nitrogen, and am-

TABLE II.

Dog 5.

Period.	Date.	No. of observations.	Weight.	Urine. Total nitrogen per day.	Urine. Urea nitrogen per day.	Urine. Ammonia nitrogen per day.	Blood. Date.	Blood. No. of observations.	Blood. Non-protein nitrogen per 100 cc. of blood.	Blood. Urea nitrogen per 100 cc. of blood.	Blood. Carbon dioxide content of plasma.	Remarks.
	1916		*kg.*	*gm.*	*gm.*	*gm.*	*1916*		*mg.*	*mg.*	*vol. per cent*	
A												
Average.......	Oct. 9–15	6	16.1	4.86	3.09	0.20	Oct. 13–19	5	33.4	11.2	57	Normal.
B	Oct. 24	7		6.93	4.47	0.35	Oct. 24	4	39.2	10.4	52	Oct. 19. Right ureter in duodenum.
	" 25		15.5	6.21	4.61	0.25						
	" 26		14.6	5.14	4.41	0.16	Oct. 26		42.8	18.2	48	
	" 27		14.5	6.43	4.29	0.29						
	" 28		14.3	5.48	4.61	0.41	Oct. 28		45.2	16.9	48	
	" 29		14.0	6.42	4.39	0.37						
	" 30		13.4	4.74	3.85	0.30	Oct. 30		50.0	23.4	59	
Average.......			14.4	5.91	4.38	0.31			44.3	17.2	51	Oct. 31. Left kidney removed.
C			13.8				Nov. 2	5	108.5	51.2	42	
			13.6				" 4		207.5	88.6	29	
			13.3				" 6		231.5	92.1	37	
			13.1				" 8		245.0	106.2	40	
			12.8				" 10		306.0	187.5	35	10 a.m. Died.

At autopsy slight hydronephrosis, cortex not greatly diminished; ureter not dilated but fluid could be forced into intestine only on pressure. Microscopically the kidney does not show evidence of infection.

monia of the urine and in the non-protein nitrogen and urea nitrogen of the blood. Whether this is due to retention of nitrogenous substances held back by injury to the kidney in consequence of the anastomosis, or to absorption of urine from the intestine, is a question which we shall discuss later. The change is relatively slight as compared with that of Period C in which a true nitrogen retention undoubtedly exists. In Dog 1 the probability of absorption of urinary constituents from the intestine cannot be entertained, for the amount of functioning kidney remaining was very slight and urine could be forced through the ureter only with great difficulty. Here, atrophy of the kidney and obstruction to the ureter, the opposite kidney having been removed, led to renal insufficiency and nitrogen retention. In Dog 5 the atrophy of the kidney was not so great, and ureteral obstruction doubtful; though this experiment is not so conclusive, it supports the view that the intoxication is due to retention and not to absorption from the intestine. The phenomena of Period C may be dismissed, therefore, as those of renal insufficiency and analogous to the changes observed by Karsner, Bunker, and Grabfield (9) after removal of both kidneys at consecutive operations. The changes in Period C in the carbon dioxide content of the plasma are noteworthy. A comparison with the findings in Period A, the control period, on an identical régime as regards food intake, indicates that the acidosis is due to change in kidney function. The search for ketones in these animals was negative. That all the changes we have found in the blood may arise after removing one kidney and ligating the opposite ureter is shown in Table IV.

The observations in Period B1 are difficult to explain. An increased output of urea and ammonia nitrogen in the urine and at the same time a retention in the blood cannot be connected with either disturbed elimination or absorption of urine from the intestine. Control observations on this point were unsatisfactory. In the animal in which, as control, one ureter was ligated without removal of the corresponding kidney (Period B2), the urinary output of nitrogenous bodies increased greatly but without appreciable change in those of the blood (Table I). Also, when in Period B2, of the experiment described here, urea is given by mouth, the nitrogen of both urine and blood is increased. These experiments, since they throw no

TABLE III.

Dog 1.

Period.	Date.	No. of observations.	Weight.	Urine. Total nitrogen per day.	Urine. Urea nitrogen per day.	Urine. Ammonia nitrogen per day.	Blood. Date.	Blood. No. of observations.	Blood. Non-protein nitrogen per 100 cc. of blood.	Blood. Urea nitrogen per 100 cc. of blood.	Blood. Carbon dioxide content of plasma.	Remarks.
	1916		*kg.*	*gm.*	*gm.*	*gm.*	*1916*		*mg.*	*mg.*	*vol. per cent*	
A Average.......	Nov. 13–16	4	15.2	3.63	2.99	0.15	Nov. 13–16	4	29.9	10.9	60	Normal.
B	Nov. 22	4	14.2	3.94	3.33	0.19	Nov. 22	4	32.6	18.8	59	Nov. 20. Right ureter in duodenum.
	" 23		13.9	5.36	3.94	0.19	" 23		32.5	15.2	62	
	" 24		13.9	5.27	3.78	0.18	" 24		33.4	15.2	61	
	" 25		13.7	4.84	3.36	0.16	" 25		34.2	14.7	64	
Average.......			13.9	4.85	3.60	0.18			33.2	16.0	61	
B (repeated).	Dec. 1	4	14.2	3.31	2.98	0.23	Dec. 1	4	29.6	9.9	58	
	" 2		13.9	3.29	2.27	0.22	" 2		30.2	10.4	56	
	" 3		13.7	2.78	1.26	0.17	" 3		34.1	8.0	58	
	" 4		13.5	2.73	2.15	0.15	" 4		35.2	10.3	56	
Average.......			13.8	3.03	2.16	0.19			32.3	9.9	57	

C			13.2				Dec. 9	3	81.2	60.8	50	Dec. 7. Left kidney removed.
			12.8				" 11		215.0	96.3	46	
			12.4				" 13		257.0	144.0	44	Died over night.

At autopsy marked hydronephrosis and hydroureter, only a thin rim of kidney cortex remaining. Fluid could be forced through the ureter into the intestine only on considerable pressure. Microscopically the kidney does not show evidence of infection.

light on the problem, are not reproduced in detail. Probably both after transplantation of the ureter (Period B1) and after its ligation and section without removal of the kidney (Period B2) there arises from some unknown cause an increased tissue catabolism accounting for the increased blood urea and non-protein blood nitrogen in Period B1 and for the increased nitrogenous excretion in the urine in Period B2. It is evident, however, that the explanation of the observations in Period B1 must await more detailed and more carefully controlled studies in which, among other things, the duodenal contents must be studied as to their content of nitrogen or other urinary constituents, both in normal dogs and those with anastomosis, in order to determine whether urine enters the intestine in any amount. These observations have been made in the present study, but are not satisfactory on account of the great difficulties of control.

TABLE IV.

Dog 6.

Date.	Blood.		
	Non-protein nitrogen per 100 cc. of blood.	Urea nitrogen per 100 cc. of blood.	Carbon dioxide content of plasma.
1916	*mg.*	*mg.*	*vol. per cent*
Nov. 18	34.8	10.4	52
" 19	29.3	9.4	53
" 20	28.2	10.2	55
" 21	26.6	8.3	52
Nov. 24	Left kidney removed; right ureter severed between ligatures; right kidney not removed.		
Nov. 25	53.4	17.1	45
" 26	79.6	32.8	43
" 27	122.0	44.6	44
" 28	154.0	105.0	44
" 29	198.0	113.0	43

The marked accumulation of non-protein and urea nitrogen in the blood in Period C shows that the transplantation of the right ureter into the duodenum had so interfered with the function of the right kidney as to render it inadequate for maintaining renal function after removal of the left.

SUMMARY.

1. The present work was undertaken to study the metabolism in the dog after a ureter-intestinal transplantation. Four dogs, Nos. 1, 2, 5, and 7, were originally operated upon. Two, Nos. 2 and 7, showed kidney infection; the other two were not infected, and in these the metabolism was studied; one of the latter (No. 1) showed a marked hydronephrosis and hydroureter.

2. Both after the transplantation of the right ureter into the intestine and the ligation of the right ureter, there is generally a moderately increased output of nitrogen in the urine and, in the former instance especially, a retention of nitrogen in the blood, but no change in carbon dioxide content in the blood. The significance of this is probably an increased tissue catabolism, the cause of which is doubtful without further work.

3. After removal of the left kidney subsequent to transplantation of the right ureter into the duodenum, renal insufficiency and resulting retention developed. The non-protein and urea nitrogen in the blood steadily increased and the carbon dioxide content of the blood diminished to the level characteristic of a moderate acidosis. No ketones were found in the blood The dogs died 5 to 10 days after the nephrectomy under conditions characteristic of suspended renal activity—deep respiration, unconsciousness, and sopor.

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