A STUDY OF THE ACIDOSIS, BLOOD UREA, AND PLASMA CHLORIDES IN URANIUM NEPHRITIS IN THE DOG, AND OF THE PROTECTIVE ACTION OF SODIUM BICARBONATE.

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PLATES 57 AND 58.

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HISTORICAL.

Numerous investigations have been made concerning the relation between nephritis and the alkalinity of the blood. The earliest studies were made by titration of the blood serum or of a dialysate of the serum with a weak acid, usually phosphoric or tartaric acid with litmus paper as an indicator. By such a method von Jaksch (1) noted a decrease in the alkalinity of the blood in uremia and concluded that the diminished alkalinity of the blood is a factor in inducing some of the phenomena of uremic intoxication. Brandenburg (2, 3), using a similar method, confirmed von Jaksch's finding. The methods employed by these investigators are, however, admittedly inadequate. In 1912 Straub and Schlayer (4), using Haldane's method, found a diminution in the carbon dioxide content of the alveolar air in uremia and thus established on a secure basis the association of acidosis with uremia. Von Noorden (5), however, considered that although a slight grade of acidosis may be present in uremia, it represents merely an associated phenomenon (perhaps the result of inanition) and not the underlying cause of the intoxication. Sellards (6) observed that a larger quantity of sodium bicarbonate must be ingested by certain nephritics, in order to render their urine alkaline, than is the case with normal individuals. This phenomenon he called "increased tolerance to sodium bicarbonate" and concluded that it indicates a condition of acidosis. In 1913 Palmer and Henderson (7), applying the principle of Sellards, but with a more highly developed method for determining the acidity of the urine, found evidence of some degree of acidosis in many pathological conditions. Among these were certain acute infections, severe anemias, the cachexias of malignant neoplasms, and certain types of nephritis.

There are also numerous investigations concerning the effect of alkali and acid upon the alkalinity of the blood and of the urine. Miquel (8) noted a diminution of the alkalinity of the blood of normal animals following the administration of acids. Gaethgens (9), on the other hand, observed a rapid excretion of the acid introduced without detecting any depletion of the bases of the blood. Lassar (10) using the tartaric acid titration method with litmus paper as an indicator reported a slight, but unquestionable decrease in the alkalinity of the blood of a dog to which acid had been administered. A more reliable method was that employed by Walter (11) in 1877, who made use of the fact that the carbon dioxide content of the blood is proportional to the content of available base in the blood. He demonstrated that when an animal is treated by injecting an acid into the blood stream, the blood undergoes a diminution in its content of base as shown by its diminished carbon dioxide content. He also showed that under such conditions there is an increased ammonia excretion in the urine and eventually a respiratory death, which may be delayed by the administration of soda. Von Hösslin (12) found an intimate relation between the acidity of the urine as determined by the method of Moritz and the amount of albumin and casts in the urine. He observed that following a lowered acidity of the urine after administration of soda, the albumin in the urine as well as casts diminishes, and, furthermore, that such lowered acidity is accompanied by an improvement in the renal functional capacity as indicated by a better excretion of sodium chloride. Von Hösslin (13), therefore, advocated the administration of sodium bicarbonate in order to reduce the acidity of the urine in nephritis. He pointed out that the initial acidity of the urine is no gauge of the amount of soda that must be given to render the urine alkaline. Henderson and Palmer (14) have investigated the effect of acid ingestion upon the hydrogen ion concentration in urine and found a constant increase of acidity in the urine after the ingestion of considerable amounts of acid, but they were not able to produce a urine of an acidity as great as that common in many pathological conditions. Scheltema (15) also obtained favorable effects from the administration of alkali to nephritic individuals. Henderson and Palmer (16), in a study of the factors of acid excretion in nephritis, found "first, that the urinary concentration of ionized hydrogen is, in a statistical sense, increased in the various forms of nephritis; and secondly that such pathological states are frequently marked by a condition of acidosis." They found (17) a renal retention of alkali in those cases of nephritis in which excretion of ammonia is diminished in the urine.

EXPERIMENTAL.

The present investigation was undertaken to study the development of acidosis in nephritis produced by uranium nitrate and the relation of this acidosis to the changes in urea and chlorides of the blood, and also to study the effect of administration of sodium bicarbonate upon all these factors. In these experiments the following determinations were made: (1) the carbon dioxide content of the plasma and the hydrogen ion concentration of the serum, (2) the urea nitrogen of the blood, (3) the chlorides of the plasma, and (4) the reaction of the urine and its content of albumin and casts. For the carbon dioxide content of the plasma, the Van Slyke-Stillman-Cullen (18) method was used; for the hydrogen ion concentration of the serum, Marriott's modification of the Levy-Rowntree-Marriott method (19, 20); for urea determinations, the Van Slyke-Cullen method (21, 22); and for the plasma chlorides, the method of McLean and Van Slyke (23). In every instance duplicate determinations were done.

The blood for these determinations, except for the hydrogen ion concentration of the serum, was obtained by drawing the blood from the external jugular vein through a tube passing to the bottom of a centrifuge tube containing either sodium oxalate or potassium oxalate crystals and a layer of paraffin oil which, floating on the surface of the blood, excluded contact with the air. The amount of oxalate employed was about 1 per cent by weight of the amount of blood. A portion of the whole blood was removed for urea determination and the remainder was centrifuged. Of the plasma so obtained, 1 cc. was transferred directly from beneath the paraffin oil to the Van Slyke burette for determination of its carbon dioxide content. The results of these determinations are given in the tables in the columns headed "direct." The remainder of the plasma was removed from the cells and used for chloride determination and for the carbon dioxide content after saturation in an atmosphere of 5.5 per cent carbon dioxide at room temperature. This saturation was performed by introducing about 3 cc. of the plasma into a 250 cc. separatory funnel and filling this with normal alveolar air by exhaling deeply five times through the funnel. The funnel was then closed and the plasma shaken in this atmosphere for 1 minute. 1 cc. portions were then transferred to the burette for analysis. The results of these determinations are given in the columns headed "funnel." These readings were always completed within an hour of the drawing of the blood. For the hydrogen ion concentration of the serum, blood was drawn directly from the vein into a small test-tube and the serum separated by centrifuging. In addition, plasma was examined by Marriott's method. The columns headed "direct" represent the reading obtained at the close of dialysis; the columns headed "A. B." are the readings after the removal of carbon dioxide from the dialysate by aeration.

Plasma Carbon Dioxide Content, Blood Urea, and Plasma Chlorides in Dogs with Uranium Nephritis.

Since it has been noted by MacNider (24) that the age of a dog has an important bearing on the degree of nephritis caused by uranium nitrate, dogs of the same age have been used as far as possible. The importance of diet in determining the toxicity of uranium nitrate has been shown by Opie (25). Animals have been shown to be more susceptible to this poison when kept upon a diet rich in meat than when upon a diet rich in carbohydrates. For this reason, the animals employed have received a constant diet of milk and dog biscuit with no meat. The animals were fed daily at 5 p.m. In regard to the method of injection, the crystalline uranium nitrate has been dissolved in distilled water and given to the dogs, at the first injection in the proportion of 0.015 gm. per 10 kilos of body weight. After an interval of 20 days another injection of the same dose was given, followed by two subsequent injections at 10 day intervals. The amount of uranium given was increased in the third and fourth injections; in the third injection 0.0185 gm. and in the fourth injection 0.045 gm. per 10 kilos of body weight. The object of the increased doses was to produce severe nephritis, in which the carbon dioxide content, urea, and chlorides of the blood might undergo a more marked alteration. Finally, at the end of the experiment, the animals were killed and the kidneys examined. Four dogs were used in the experiments. They were bled at 9 a.m. on the days when the blood was studied. Three preliminary examinations were made on each dog before administering either uranium or soda. The results of these examinations are shown in Table I. The results following the administration of uranium to Dogs 1 and 2 are shown in Tables II and III and Text-figs. 1, 2, and 3.

In Dog 1, after the first injection of uranium, the carbon dioxide content of the plasma underwent a considerable diminution in the course of a week, and, at the same time, the urea and chlorides of

TABLE I.

Normal Dogs.

	Van Slyke method.		Marriott method.				Urea nitrogen in 100 cc. of blood.	Chlorides in 1 cc. of plasma.	Urine.		
			Serum.		Plasma.						
	Direct.	Funnel.	Direct.	A. B.	Direct.	A. B.			Reaction.	Albumin	Casts.
	per cent	*per cent*	*log.*	*log.*	*log.*	*log.*	*mg.*	*mg.*			
Dog 1	55	58	7.5	8.0	7.4	7.9	11	5.6	Acid.	–	–
	63	66	7.9	8.1	7.5	7.8	13	5.9	"	–	–
	62	65	7.8	8.0	7.4	7.9	12	6.0	"	–	–
Average........	60	63	7.7	8.0	7.4	7.9	12	5.8			
Dog 2	56	61	7.4	7.9	7.3	7.7	14	5.4	Acid.	–	–
	60	65	7.8	8.0	7.4	7.7	13	5.9	"	–	–
	61	65	7.6	8.0	7.4	7.8	12	5.6	"	–	–
Average........	59	64	7.6	8.0	7.4	7.7	13	5.6			
Dog 3	55	62	7.8	7.9	7.6	7.9	13	5.8	Acid.	–	–
	56	62	7.9	8.0	7.6	8.0	13	5.9	"	–	–
	57	64	7.9	8.0	7.4	8.0	13	5.8	"	–	–
Average........	56	63	7.9	8.0	7.6	8.0	13	5.8			
Dog 4	55	60	7.8	7.9	7.3	7.9	13	5.5	Acid.	–	–
	58	65	7.8	7.9	7.4	7.7	15	6.0	"	–	–
	60	66	7.9	8.0	7.4	7.8	14	5.8	"	–	–
Average.......	58	64	7.8	7.9	7.4	7.8	14	5.8			

Extent of Variability.

Van Slyke method.		Marriott method.				Urea nitrogen.	Chlorides.
		Serum.		Plasma.			
Direct.	Funnel.	Direct.	A. B.	Direct.	A. B.		
per cent	*per cent*	*log.*	*log.*	*log.*	*log.*	*mg.*	*mg.*
55–63	58–66	7.4–7.9	7.9–8.1	7.3–7.6	7.7–8.0	11–15	5.4–6.0

TABLE II.

Dog 1. Weight 8 kilos.
First injection, 2 p.m., July 3, 1916.

Day.	Date.	Van Slyke method. Direct.	Van Slyke method. Funnel.	Marriott method. Serum. Direct.	Marriott method. Serum. A. B.	Marriott method. Plasma. Direct.	Marriott method. Plasma. A. B.	Urea nitrogen in 100 cc. of blood.	Chlorides in 1 cc. of plasma.	Urine. Reaction.	Urine. Albumin.	Urine. Casts.
		per cent	*per cent*	*log.*	*log.*	*log.*	*log.*	*mg.*	*mg.*			
Average		60	63	7.7	8.0	7.4	7.9	12	5.8	Acid.	–	–
	1916											
1	July 3	12 mg. of uranium nitrate at 2 p.m.										
2	July 4											
3	" 5	57	63	7.8	7.9	7.1	7.6	21	6.3	Acid.	Tr.	–
4	" 6									"	"	–
5	" 7	53	56	7.7	7.8	7.3	7.7	28	6.7	"	"	+
6	" 8	48	55	7.1	7.8	7.0	7.8	32	6.7	"	++	+
7	" 9									"	+	+
8	" 10	45	50	7.1	7.7	6.9	7.9	36	6.8	"	+	+
9	" 11	40	46	7.0	7.8	6.9	7.8	23	7.0	"	+	+
10	" 12									"	+	+
11	" 13	55	60	7.2	7.9	7.1	7.8	21	6.0	"	+	–
12	" 14									"	+	–
13	" 15	60	65	7.5	7.7	7.3	7.6	19	6.3	"	+	–
14	" 16									"	+	–
15	" 17									"	Tr.	–
16	" 18	58	60	7.7	8.0	7.3	7.8	21	5.8	"	"	–
17	" 19									"	"	–
18	" 20	60	65	7.8	7.9	7.4	7.7	16	5.8	"	"	–
19	" 21									"	"	–
20	" 22	63	65	7.9	8.0	7.4	7.9	16	6.2	"	"	–
21	" 23											
22	July 24	12 mg. of uranium nitrate at 9 a.m.								Acid.	Tr.	–
23	July 25									Acid.	Tr.	–
24	" 26			7.7	7.8	7.3	7.4	23	6.6	"	+	–
25	" 27									"	+	+
26	" 28			7.6	7.8	7.3	7.8	26	6.6	"	++	+
27	" 29									"	++	+
28	" 30									"	++	+
29	" 31			7.5	7.8	7.3	7.8	20	6.3	"	++	+
30	Aug. 1									"	+	+
31	" 2			7.6	7.8	7.4	7.7	21	6.2	"	+	–
32	" 3									"	Tr.	–
33	" 4	60	65	7.7	7.8	7.4	7.6	21	6.1	"	"	–

TABLE II—*Concluded.*

Day.	Date.	Van Slyke method. Direct.	Van Slyke method. Funnel.	Marriott method. Serum. Direct.	Marriott method. Serum. A. B.	Marriott method. Plasma. Direct.	Marriott method. Plasma. A. B.	Urea nitrogen in 100 cc. of blood.	Chlorides in 1 cc. of plasma.	Urine. Reaction.	Urine. Albumin.	Urine. Casts.
33	Aug. 4	15 mg. of uranium nitrate at 9 a.m., after bleeding.								Acid.	Tr.	–
		per cent	*per cent*	*log.*	*log.*	*log.*	*log.*	*mg.*	*mg.*			
34	Aug. 5									Acid.	Tr.	–
35	" 6									"	"	–
36	" 7									"	+	–
37	" 8	48	52	7.8	7.8	7.4	7.8	21	6.5	"	+	–
38	" 9									"	+	–
39	" 10	46	50	7.6	7.8	7.2	7.6	22	6.9	"	+	–
40	" 11									"	+	+
41	" 12	49	55	7.9	8.0	7.4	7.8	22	6.7	"	++	+
42	" 13									"	+	–
43	" 14									"	+	–
44	Aug. 15	36 mg. of uranium nitrate at 9 a.m.								Acid.	+	–
45	Aug. 16	49	53	7.6	7.9	7.4	7.8	29	7.0	Acid.	+	+
46	" 17	45	47	7.4	7.8	7.2	7.7	29	7.1	"	++	+
47	" 18	42	46	7.2	7.8	7.1	7.7	26	7.3	"	++	+
48	" 19	40	47	7.2	7.8	7.1	7.6	25	7.3	"	++	+
49	" 20	45	49	7.3	7.8	7.1	7.6	26	7.4	"	++	+
50	" 21									"	+	+
51	" 22	52	56	7.7	7.8	7.2	7.6	25	7.1	"	+	+

the blood exhibited an increase associated with the appearance of albumin and casts in the urine. It will be noted that the minimum of the plasma carbon dioxide content coincides approximately with the maximum of the blood urea and plasma chlorides in time of occurrence. At about this period casts also appeared in the urine. During the 3rd week after the first injection, the plasma carbon dioxide content returned to its normal level, and on the 20th day, the values for plasma chlorides and blood urea nitrogen were 6.2 and 16 respectively. The chlorides, however, had three times been within normal limits between the 11th and 20th days. Urine at

TABLE III.

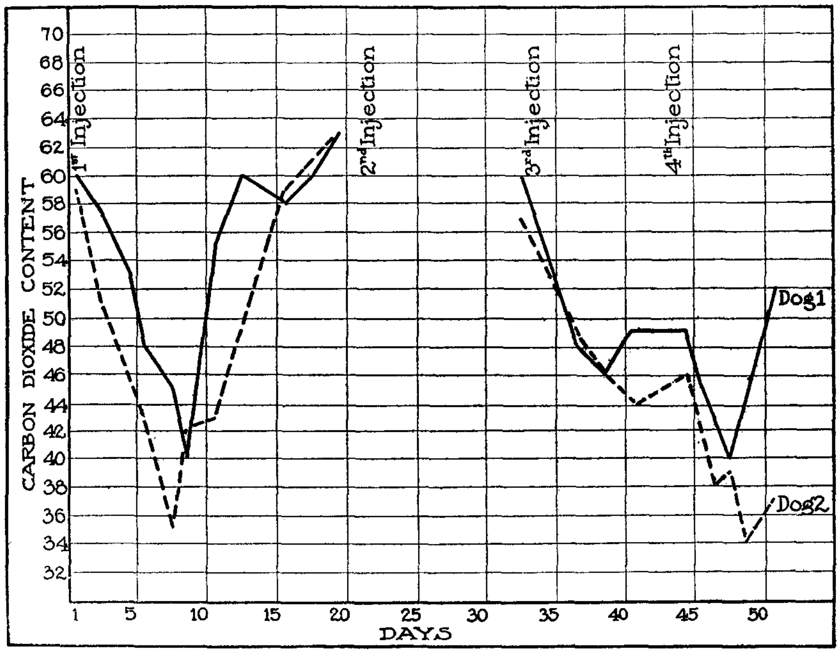
Dog 2. Weight 27 kilos.
First injection, 2 p.m., July 3, 1916.

Day.	Date.	Van Slyke method.		Marriott method.				Urea nitrogen in 100 cc. of blood.	Chlorides in 1 cc. of plasma.	Urine.		
				Serum.		Plasma.						
		Direct.	Funnel.	Direct.	A. B.	Direct.	A. B.			Reaction.	Albumin.	Casts.
		per cent	*per cent*	*log.*	*log.*	*log.*	*log.*	*mg.*	*mg.*			
Average........		59	64	7.6	8.0	7.4	7.7	13	5.6	Acid.	–	–
	1916											
1	July 3	40 mg. of uranium nitrate at 2 p.m.										
2	July 4									Acid.		
3	" 5	51	58	7.8	8.0	7.3	7.8	21	6.4	"	Tr.	–
4	" 6									"	"	–
5	" 7	46	48	7.6	7.8	7.4	7.6	23	6.6	"	+	+
6	" 8	43	47	6.9	7.7	6.8	7.6	25	7.2	"	++	+
7	" 9									"	++	+
8	" 10	35	39	6.9	7.4	6.8	7.3	42	7.3	"	++	+
9	" 11	42	45	7.1	7.8	7.0	7.5	41	6.9	"	++	+
10	" 12									"	++	+
11	" 13	43	46	7.1	7.8	7.0	7.5	42	6.9	"	+	+
12	" 14									"	+	+
13	" 15	49	52	7.5	7.7	7.3	7.5	41	6.6	"	+	+
14	" 16									"	+	–
15	" 17									"	Tr.	–
16	" 18	59	62	7.7	7.9	7.4	7.9	36	6.1	"	"	–
17	" 19									"	"	–
18	" 20	61	63	7.9	8.1	7.3	7.6	26	6.0	"	"	–
19	" 21									"	"	–
20	" 22	63	65	7.8	8.0	7.4	7.8	16	5.9	"	"	–
21	" 23											
22	July 24	40 mg. of uranium nitrate at 9 a.m.								Acid.	Tr.	–
23	July 25									Acid.	Tr.	–
24	" 26			7.8	7.9	7.4	7.8	22	5.9	"	+	–
25	" 27									"	+	+
26	" 28			7.6	7.8	7.3	7.7	26	6.3	"	++	+
27	" 29									"	++	+
28	" 30									"	++	+
29	" 31			7.4	7.7	7.3	7.7	26	6.5	"	++	+
30	Aug. 1									"	+	+
31	" 2			7.5	7.7	7.3	7.6	20	6.1	"	+	?
32	" 3									"	+	?
33	" 4	57	60	7.6	7.7	7.3	7.5	20	6.1	"	+	+

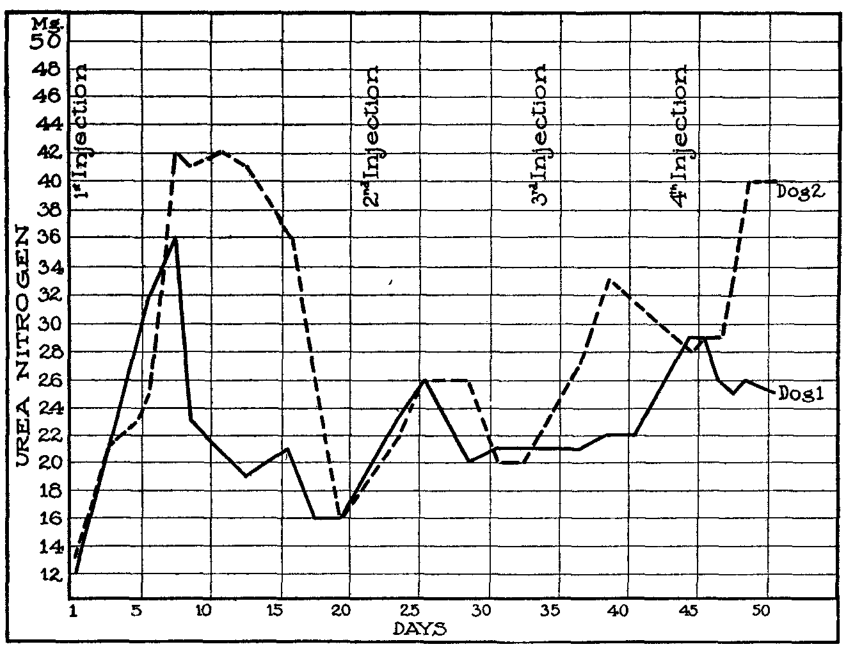
TABLE III—*Concluded.*

Day.	Date.	Van Slyke method.		Marriott method.				Urea nitrogen in 100 cc. of blood.	Chlorides in 1 cc. of plasma.	Urine.		
				Serum.		Plasma.						
		Direct.	Funnel.	Direct.	A. B.	Direct.	A. B.			Reaction.	Albumin.	Casts.
33	Aug. 4	50 gm. of uranium nitrate at 9 a.m., after bleeding.										
		per cent	*per cent*	*log.*	*log.*	*log.*	*log.*	*mg.*	*mg.*			
34	Aug. 5									Acid.	+	+
35	" 6									"	+	+
36	" 7									"	+	+
37	" 8	49	53	7.7	7.7	7.4	7.7	27	6.7	"	++	+
38	" 9									"	++	+
39	" 10	46	48	7.6	7.8	7.3	7.7	33	7.0	"	++	+
40	" 11									"	++	?
41	" 12	44	46	7.7	7.8	7.3	7.8	31	6.9	"	+	+
42	" 13									"	+	+
43	" 14									"	+	+
44	Aug. 15	120 mg. of uranium nitrate at 9 a.m.								Acid.	+	+
45	Aug. 16	46	49	7.6	7.7	7.3	7.6	28	7.0	Acid.	+	+
46	" 17	42	45	7.3	7.7	7.2	7.6	29	7.3	"	+	+
47	" 18	38	40	7.1	7.7	7.0	7.5	29	7.2	"	++	+
48	" 19	39	45	7.1	7.6	7.0	7.5	34	7.3	"	++	+
49	" 20	34	40	7.1	7.7	7.0	7.6	40	7.3	"	++	+
50	" 21									"	++	+
51	" 22	37	43	7.1	7.6	7.1	7.5	40	7.1	"	++	+

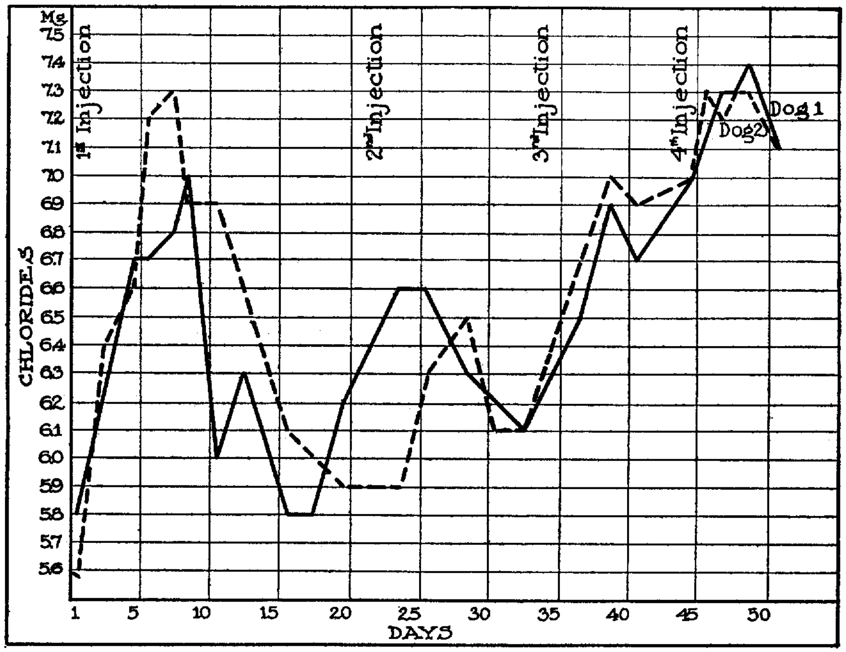
this time still showed the presence of a trace of albumin, although casts were absent. After the second injection of uranium similar changes occurred in the blood urea and plasma chlorides, but less pronounced in degree; the carbon dioxide content could not be studied at this time as the only burette at hand was broken. After the third and larger injection, a marked reduction of the carbon dioxide content occurred and a synchronous marked rise of plasma chlorides; no significant change was noted in the blood urea. It may be noted that casts in the urine appeared rather late. After the fourth injection, which was given before the blood had returned to a normal



TEXT-FIG. 1. Curves showing the carbon dioxide content of the plasma of Dogs 1 and 2 after injections of uranium nitrate. No soda administered.



TEXT-FIG. 2. Curves showing the urea nitrogen in 100 cc. of blood in Dogs 1 and 2 after injections of uranium nitrate. No soda administered.



TEXT-FIG. 3. Curves showing the chlorides in 1 cc. of the plasma in Dogs 1 and 2 after injections of uranium nitrate. No soda administered.

condition, the minimum of plasma carbon dioxide content and the maximum of plasma chloride coincided approximately in their occurrence about the 4th day after injection. During this last period the chlorides in the blood were much higher and the albumin in the urine was much greater in quantity than after the previous injections. The increase in the quantity of blood urea, however, was less than after the first injection.

In the second dog nearly identical relations in the carbon dioxide content, urea, and chlorides of the blood and albumin and casts in the urine were observed as in the first dog. We may, however, note the following slight differences. After their reappearance 3 days after the second injection, the urinary casts persisted throughout the experiment. After each injection the carbon dioxide content, the chloride content, and the blood urea showed greater disturbances than in the first dog. This is probably to be attributed to the much larger absolute dose of uranium, although the same dose was used per kilo. We may conclude from these experiments (Dogs 1 and 2) that the plasma carbon dioxide content undergoes a considerable diminution in uranium nephritis, while the plasma chlorides and blood urea increase, and, furthermore, that the occurrence of the minimum content of carbon dioxide coincides approximately with the occurrence of the maximum content of chlorides and of urea in the blood. Both the carbon dioxide content and plasma chlorides returned nearly to their normal condition 2 to 3 weeks after the first injection. Urea, on the other hand, did not return quite to its normal level at any period, although 3 weeks after the first injection, the change from the normal value was slight. Albumin after appearing did not disappear entirely from the urine, although casts occasionally did.

Influence of Sodium Bicarbonate on the Plasma Carbon Dioxide Content, Blood Urea, and Plasma Chlorides in Dogs with Uranium Nephritis.

For this experiment Dogs 3 and 4 were used. Each dog received through a stomach tube 1 gm. of sodium bicarbonate dissolved in 10 cc. of water per kilo of body weight at 9 a.m. throughout the entire period of the experiment. On the 3rd day uranium nitrate was injected. The amounts of the uranium per kilo and the intervals between succeeding injections were exactly the same as in the experiment on Dogs 1 and 2. The blood was taken at 9 a.m., before administering the soda. The results are shown in Tables IV and V and Text-figs. 4, 5, and 6. While the dogs were receiving sodium bicarbonate alone, that is, before the giving of uranium, a considerable increase of the plasma carbon dioxide content was observed. Following the first uranium injection this carbon dioxide content showed a decrease and at the same time there occurred an increase in the plasma chlorides and blood urea, as in Dogs 1 and 2.

The relative decrease in the carbon dioxide content following uranium in the dogs receiving soda is comparable with that in the dogs receiving no soda, but the absolute level reached was not so low, because of the higher level already existing when the uranium

TABLE IV.

Dog 3. Weight 13.5 kilos.
First injection, 9 a.m., July 5, 1916.
July 3. 12 a.m. 13.5 gm. of sodium bicarbonate + 135 cc. of water.
From July 4 sodium bicarbonate + water was given every day, after bleeding.

Day.	Date.	Van Slyke method.		Marriott method.				Urea nitrogen in 100 cc. of blood.	Chlorides in 1 cc. of plasma.	Urine.		
		Direct.	Funnel.	Serum.		Plasma.				Reaction.	Albumin.	Casts.
				Direct.	A. B.	Direct.	A. B.					
		per cent	*per cent*	*log.*	*log.*	*log.*	*log.*	*mg.*	*mg.*			
Average.......		56	63	7.9	8.0	7.6	8.0	13	5.8	Acid.	—	—
	1916											
1	July 3, 2 p.m.	69	71	7.8	8.0	7.5	7.9	13	5.6			
2	" 4									Alkaline.	—	—
3	July 5	20 mg. of uranium nitrate at 9 a.m.								Alkaline.	—	—
4	July 6	66	68	7.8	8.0	7.4	7.9	14	6.1	Alkaline.	Tr.	—
5	" 7	56	60	7.7	8.0	7.3	7.9	15	6.2	"	"	—
6	" 8	55	60	7.4	7.9	6.9	7.8	19	6.2	"	"	—
7	" 9									"	"	—
8	" 10	47	52	7.3	7.7	6.9	7.8	26	6.8	"	"	+
9	" 11									"	"	+
10	" 12	48	50	7.2	7.8	6.9	7.6	29	6.7	"	+	+
11	" 13									"	+	+
12	" 14	55	58	7.4	7.8	7.0	7.6	30	6.0	"	+	+
13	" 15									"	+	—
14	" 16									"	+	—
15	" 17	61	64	7.7	7.9	7.4	7.9	29	6.4	"	Tr.	—
16	" 18									"	"	—
17	" 19	65	68	7.9	8.1	7.4	7.9	32	6.0	"	"	—
18	" 20									"	"	—
19	" 21	70	75	8.0	8.1	7.5	7.9	16	6.0	"	"	—
20	" 22									"	"	—
21	" 23									"	"	—
22	" 24	70	73	7.9	8.1	7.5	7.9	22	5.6	"	"	—
23	" 25											
24	" 26											
25	" 27			8.0	8.1	7.4	7.8	25	5.9	Alkaline.	Tr.	—

TABLE IV—*Concluded.*

Day.	Date.	Van Slyke method.		Marriott method.				Urea nitrogen in 100 cc. of blood.	Chlorides in 1 cc. of plasma.	Urine.		
				Serum.		Plasma.						
		Direct.	Funnel.	Direct.	A. B.	Direct.	A. B.			Reaction.	Albumin.	Casts.
25	July 27	20 mg. of uranium nitrate at 9 a.m., after bleeding.										
		per cent	*per cent*	*log.*	*log.*	*log.*	*log.*	*mg.*	*mg.*			
26	July 28									Alkaline.	+	–
27	" 29			7.8	8.0	7.4	7.9	26	6.5	"	+	–
28	" 30									"	+	–
29	" 31									"	+	–
30	Aug. 1			7.5	7.8	7.3	7.5	17	6.0	"	+	–
31	" 2									"	+	–
32	" 3			7.6	7.8	7.2	7.5	15	5.8	"	+	–
33	" 4									"	+	–
34	" 5	62	55	7.6	7.8	7.3	7.6	15	6.0	"	Tr.	–
35	" 6									"	"	–
36	Aug. 7	25 mg. of uranium nitrate at 9 a.m.								Alkaline.	Tr.	–
37	Aug. 8									Alkaline.	Tr.	–
38	" 9									"	+	–
39	" 10	52	55	7.5	7.8	7.3	7.6	28	6.3	"	+	–
40	" 11									"	+	–
41	" 12	49	52	7.3	7.8	7.2	7.6	23	6.2	"	+	–
42	" 13									"	+	–
43	" 14	50	55	7.5	7.9	7.3	7.5	26	6.4	"	+	–
44	" 15									"	+	–
45	" 16									"	+	–
46	Aug. 17	60 mg. of uranium nitrate at 9 a.m.										
47	Aug. 18	62	67	7.7	7.8	7.4	7.8	28	6.4	Alkaline.	+	–
48	" 19	56	59	7.6	7.8	7.4	7.8	20	6.3	"	+	+
49	" 20									"	+	+
50	" 21	54	61	7.5	7.8	7.3	7.7	19	6.6	"	+	+
51	" 22									"	+	+
52	" 23	58	62	7.5	7.8	7.3	7.6	18	6.3	"	+	+
53	" 24	62	65	7.7	7.9	7.4	7.8	15	6.6	"	+	+

TABLE V.

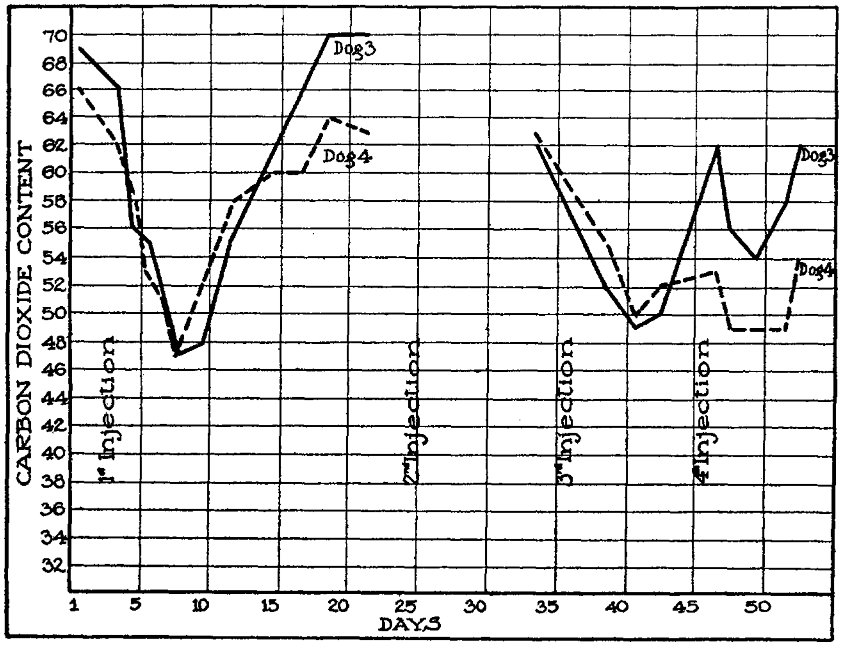
Dog 4. Weight 19 kilos.
First injection, 9 a.m., July 5, 1916.
July 3. 12 a.m. 19 gm. of sodium bicarbonate + 190 cc. of water.
From July 4 sodium bicarbonate + water was given every day, after bleeding.

Day.	Date.	Van Slyke method. Direct.	Van Slyke method. Funnel.	Marriott method. Serum. Direct.	Marriott method. Serum. A. B.	Marriott method. Plasma. Direct.	Marriott method. Plasma. A. B.	Urea nitrogen in 100 cc. of blood.	Chlorides in 1 cc. of plasma.	Urine. Reaction.	Urine. Albumin.	Urine. Casts.
		per cent	*per cent*	*log.*	*log.*	*log.*	*log.*	*mg.*	*mg.*			
Average........		58	64	7.8	7.9	7.4	7.8	14	5.8	Acid.	–	–
	1916											
1	July 3, 2 p.m.	66	70	7.8	8.0	7.5	8.0	13	6.0			
2	" 4									Alkaline.	–	–
3	July 5	29 mg. of uranium nitrate at 9 a.m.								Alkaline.	–	–
4	July 6	62	66	7.9	8.0	7.4	7.8	16	5.6	Alkaline.	Tr.	–
5	" 7	58	60	7.7	7.9	7.3	7.7	18	6.0	"	"	–
6	" 8	53	56	7.4	7.8	7.2	7.7	29	6.3	"	"	–
7	" 9									"	"	–
8	" 10	47	52	7.2	7.6	7.0	7.4	32	6.8	"	+	–
9	" 11									"	+	+
10	" 12	52	55	7.3	7.8	7.2	7.7	32	6.7	"	+	+
11	" 13									"	+	+
12	" 14	58	61	7.4	7.8	7.2	7.6	38	6.3	"	+	+
13	" 15									"	+	–
14	" 16									"	Tr.	–
15	" 17	60	65	7.8	8.0	7.5	7.9	28	6.3	"	"	–
16	" 18									"	"	–
17	" 19	60	66	7.8	7.9	7.4	7.9	36	6.1	"	"	–
18	" 20									"	"	–
19	" 21	64	68	7.9	8.0	7.4	7.8	26	5.8	"	"	–
20	" 22									"	"	–
21	" 23									"	"	–
22	" 24	63	66	7.8	8.0	7.4	7.8	25	5.8	"	"	–
23	" 25									"	"	–
24	" 26									"	"	–
25	" 27			8.0	8.1	7.4	7.7	20	6.0	"	"	–
25	July 27	29 mg. of uranium nitrate at 9 a.m., after bleeding.										
26	July 28									Alkaline.	+	–
27	" 29			7.9	8.0	7.5	7.9	28	6.1	"	+	–
28	" 30									"	+	–
29	" 31									"	+	+

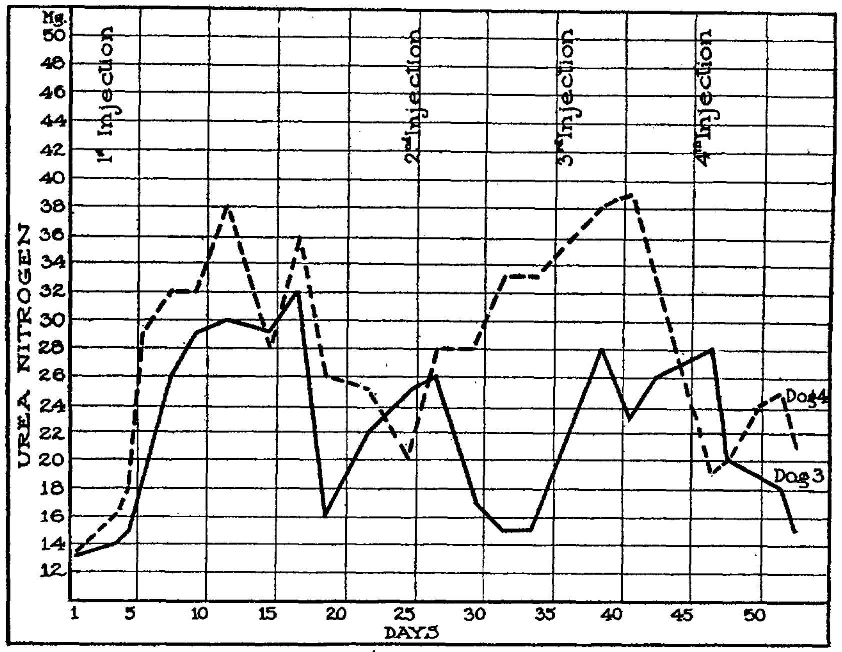
TABLE V—*Concluded.*

Day.	Date.	Van Slyke method.		Marriott method.				Urea nitrogen in 100 cc. of blood.	Chlorides in 1 cc. of plasma.	Urine.		
				Serum.		Plasma.						
		Direct.	Funnel.	Direct.	A. B.	Direct.	A. B.			Reaction.	Albumin.	Casts.
		per cent	*per cent*	*log.*	*log.*	*log.*	*log.*	*mg.*	*mg.*			
30	Aug. 1			7.7	7.9	7.3	7.7	28	5.8	Alkaline.	+	+
31	" 2									"	+	–
32	" 3			7.8	7.9	7.4	7.8	33	6.3	"	+	–
33	" 4									"	+	–
34	" 5	63	65	7.7	7.8	7.4	7.7	33	6.1	"	Tr.	–
35	" 6									"	"	–
36	Aug. 7	36 mg. of uranium nitrate at 9 a.m.								Alkaline.	Tr.	–
37	Aug. 8									Alkaline.	Tr.	–
38	" 9									"	+	–
39	" 10	55	58	7.5	7.6	7.2	7.5	38	5.8	"	+	–
40	" 11									"	+	–
41	" 12	50	52	7.5	7.6	7.3	7.6	39	6.0	"	+	–
42	" 13									"	+	–
43	" 14	52	54	7.6	7.7	7.3	7.5	33	6.4	"	+	–
44	" 15									"	+	–
45	" 16									"	+	–
46	Aug. 17	87 mg. of uranium nitrate at 9 a.m.								Alkaline.	+	–
47	Aug. 18	53	55	7.7	7.8	7.4	7.8	19	6.6	Alkaline.	+	–
48	" 19	49	52	7.6	7.9	7.3	7.7	20	7.0	"	+	+
49	" 20									"	+	+
50	" 21	49	53	7.6	7.7	7.3	7.7	24	6.9	"	+	+
51	" 22									"	+	+
52	" 23	49	52	7.6	7.7	7.3	7.7	25	7.0	"	+	+
53	" 24	54	58	7.7	7.8	7.4	7.7	21	7.0	"	+	+

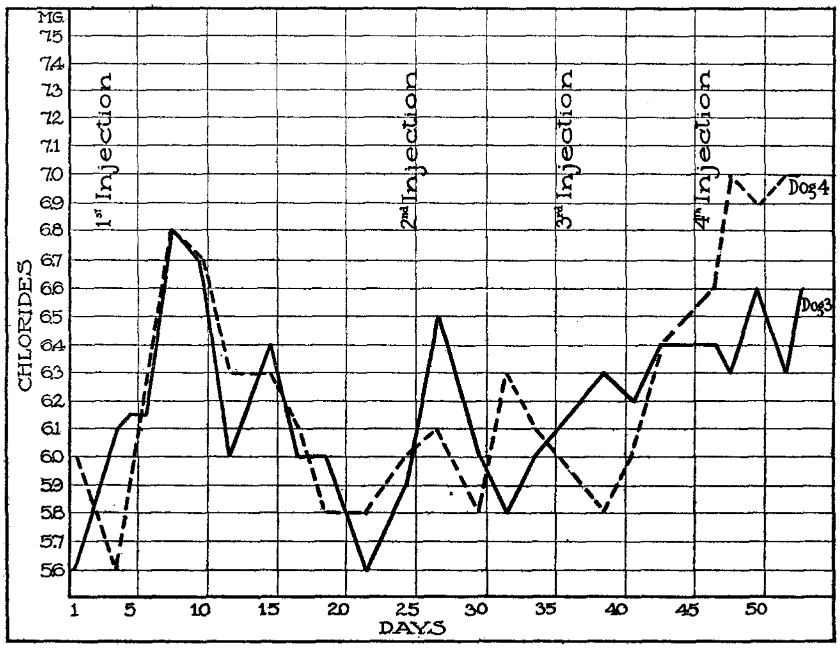
administration was commenced. The increase in the blood urea in the dogs receiving soda is comparable with that in the dogs receiving no soda except following the large fourth injection, when the dogs receiving soda showed a less pronounced rise. The increase in the plasma chlorides was consistently lower throughout the experiments in the dogs receiving the soda. This was especially marked following the fourth injection of uranium. The soda administered was sufficient to keep the urine in these dogs persistently



TEXT-FIG. 4. Curves showing the carbon dioxide content of the plasma of Dogs 3 and 4 after injections of uranium nitrate. Soda administered.



TEXT-FIG. 5. Curves showing the urea nitrogen in 1 cc. of blood in Dogs 3 and 4 after injections of uranium nitrate. Soda administered.



TEXT-FIG. 6. Curves showing the chlorides in 1 cc. of the plasma in Dogs 3 and 4 after injections of uranium nitrate. Soda administered.

alkaline. The albuminuria was persistent from the time of the first appearance, but was definitely less marked than in the animals receiving no soda. Casts were likewise less abundant in these animals and disappeared entirely for longer intervals of time. In general, following the fourth injection, the carbonate dogs showed a considerable difference from the control dogs as to the diminution of carbon dioxide content and as to increase of chlorides and urea in the blood.

The protocols of the histological examination of the kidneys follow.

Dog 1. Weight 8 Kilos. No Soda.

Day of experiment.	Uranium nitrate. Absolute dose.	Uranium nitrate. Relative dose per kilo.
	gm.	*mg.*
1	0.012	1.5
22	0.012	1.5
33	0.015	1.85
44	0.036	4.5
52	Killed.	

Interval before fixation of tissues: a few minutes.

Under the low power the glomeruli appear normal. The epithelium of the proximal convoluted tubules appears swollen, especially in the tubules in the region of the corticomedullary junction. The epithelium of the ascending loops of Henle appear swollen. The medulla appears normal. The medullary rays stand out conspicuously.

Under high power some of the glomeruli exhibit moderate congestion, others appear normal. The epithelium of the proximal convoluted tubules is greatly swollen, but the nuclei are well preserved and only rarely is there any evidence of necrosis. The distal convoluted tubules are almost all normal, except for the presence of serum in the lumina of some. The medulla appears normal.

Diagnosis.—Marked cloudy swelling of the proximal convoluted tubules, especially those near the corticomedullary junction (Fig. 1).

Dog 2. Weight 27 Kilos. No Soda.

Day of experiment.	Uranium nitrate. Absolute dose.	Relative dose per kilo.
	gm.	*mg.*
1	0.040	1.5
22	0.040	1.5
33	0.050	1.85
44	0.120	4.5
52	Killed.	

Interval before fixation of tissues: a few minutes.

Under low power this kidney appears highly abnormal with moderate to marked congestion of the glomerular tufts and with patches of marked epithelial swelling in the proximal convoluted tubules, of interstitial edema, and of serum in the lumina in the cortex, especially in the corticomedullary region. The medulla exhibits marked congestion and edema with some swelling of epithelium and with serum or casts in the lumina.

Under high power congestion of the glomeruli is confirmed. The proximal convoluted tubules show intense epithelial swelling and in many places the nuclei are pale or necrotic. In many places the epithelium has entirely desquamated from these tubules, leaving simply the basement membrane. The distal convoluted tubules and ascending limbs of Henle are in many places encroached upon and compressed by interstitial edema and exhibit degeneration of epithelium and serum or casts in many of the lumina. In some of the epithelial cells of the distal convoluted tubules there is a yellowish pigment resembling hemosiderin.

Diagnosis.—Intense cloudy swelling and necrosis of the epithelium of the proximal convoluted tubules. Moderate cloudy swelling of the epithelium of the ascending limbs of Henle and the distal convoluted tubules. Interstitial edema of the cortex and medulla. Serum and casts in tubule lumina. Congestion of glomerular tufts (Fig. 2).

Dog 3. Weight 13.5 Kilos. Soda.

Day of experiment.	Uranium nitrate. Absolute dose.	Relative dose per kilo.
	gm.	*mg.*
1	0.020	1.5
23	0.020	1.5
34	0.025	1.85
44	0.060	4.5
52	Killed.	

Interval before fixation of tissues: a few minutes.

Under low power the picture is practically normal.

Under high power the glomeruli appear normal. The epithelium of all the tubules is in fair condition with little swelling, although this can be observed in occasional cells in the proximal convoluted tubules. The medullary cells are normal. The lumina are almost entirely free from serum.

Diagnosis.—Approximately normal.

Dog 4. Weight 19 Kilos. Soda.

Day of experiment.	Uranium nitrate. Absolute dose.	Relative dose per kilo.
	gm.	*mg.*
1	0.029	1.5
23	0.029	1.5
34	0.036	1.9
44	0.087	4.6
52	Killed.	

Interval before fixation of tissues: a few minutes.

Under low power the picture is normal except for serum or casts in the lumina of the medullary tubes.

Under high power the glomeruli seem normal. The proximal convoluted tubules show little cloudy swelling. The medulla is normal except for serum or casts in the lumina in a considerable number of the tubules.

Diagnosis.—Slight cloudy swelling. Serum or casts in the medullary tubules (Fig. 3).

It is a well established fact that uranium nitrate produces primarily and most conspicuously degeneration and necrosis of the epithelium of the renal tubules, and especially of the proximal convoluted tubules. The physiological studies of Schlayer and Hedinger (26), Pearce, Hill, and Eisenbrey (27), and others have shown that the reaction of the vascular apparatus of the kidney may be impaired or not by uranium nitrate, depending upon the dosage employed. Christian and O'Hare (28) have found that uranium nitrate causes also a lesion of the glomeruli characterized by the presence of hyaline droplets in the capillary loops and by other changes.

MacNider (29) reported a difference in the degree of pathological change in the kidney following uranium in dogs given sodium carbonate intravenously as compared with control dogs receiving no soda. The most marked difference was seen in the degree of involvement of the epithelium of the convoluted tubules.

It is evident from a study of the histology of the kidneys that the kidneys from both dogs receiving no soda exhibited more pronounced nephritis than those of either of the dogs receiving soda. The most severe nephritis occurred in Dog 2, which received the largest absolute dose of uranium; Dog 1, which received the smallest absolute dose of uranium, but no soda, showed also definitely more marked lesions than did Dogs 3 and 4, which received soda.

From the facts given both in the functional studies and in the pathological examination, it is clear that the nephritis in the dogs receiving sodium bicarbonate is less severe than that in the control dogs.

The toxic effect of uranium for the kidney is usually ascribed to the action of the metal as such. According to the experimental results of MacNider the toxicity of uranium runs parallel with its ability to lead to the formation of various acid bodies, and if the appearance of these substances in the urine is delayed and their amount in the body diminished by the administration of alkali, there is less evidence of the toxic action of the metal. In order to exclude the possibility of the toxic salt of uranium having been itself rendered inert by the direct action of sodium carbonate, he injected two animals with uranium nitrate in which the solvent for the uranium was a 3 per cent solution of sodium carbonate in 0.9 per cent sodium chloride. The toxic effect of uranium was in no way diminished when employed in a 3 per cent solution of the carbonate. He ascribes the protective action of sodium carbonate in uranium nephritis to the neutralization of acid bodies produced by the uranium in the animal economy.

In the study of the hydrogen ion concentration of the blood, the most consistent results were obtained by Marriott's modification of the technique, the figure obtained after aeration of the dialysate from the serum and given in the tables in the column "serum A. B." Determination upon the plasma by the same method gave, on the whole, parallel but probably less consistent results. A comparison of the methods of Marriott and of Van Slyke shows a greater delicacy in the Van Slyke method, so that while the evidences as to the acid base equilibrium of the blood afforded by the two methods agree, Marriott's method is hardly delicate enough to permit of as satisfactory conclusions in such experiments as the present ones.

Action of Alkali and of Acid upon the Carbon Dioxide Content in Plasma.

Acid was administered by stomach tube to two dogs and alkali to two other dogs. For the acid, hydrochloric acid was chosen, and for the alkali, sodium bicarbonate. 1 cc. of 0.5 per cent hydrochloric acid per kilo of body weight was introduced into the stomach through the stomach tube. When acid was thus administered a diminution of the plasma carbon dioxide content developed, but since in this experiment a severe nephritis resulted, it might be questioned whether the decrease of the carbon dioxide content was produced wholly by the acid administered or in part also by the acidosis of the nephritis.

The microscopic examination gave clear evidence of nephritis in these kidneys.

When alkali (10 per cent sodium bicarbonate) was administered, the plasma carbon dioxide content of the blood showed a constant increase (Tables VI to XI.)

TABLE VI.

Dog 5. Weight 20.5 kilos.
Bled every day at 9 a.m.

Date.	Van Slyke method.		Urine.			Remarks.
	Direct.	Funnel.	Reaction.	Albumin.	Casts.	
1916	*per cent*	*per cent*				
Aug. 5	57	59	Acid.	–	–	
" 6	56	59	"	–	–	Acid at 10 a.m., after bleeding.
" 7	49	52	"	++	++	Died at 11 a.m.

TABLE VII.

Dog 6. Weight 18 kilos.
Bled every day at 9 a.m.

Date.	Van Slyke method.		Urine.			Remarks.
	Direct.	Funnel.	Reaction.	Albumin.	Casts.	
1916	*per cent*	*per cent*				
Aug. 5	58	60	Acid.	–	–	
" 6	55	58	"	–	–	Acid at 10 a.m., after bleeding.
" 7	48	53	"	++	++	

TABLE VIII.

Dog 7. Weight 10.5 kilos.
Bled every day at 9 a.m.

Date.	Van Slyke method.		Urine.			Remarks.
	Direct.	Funnel.	Reaction.	Albumin.	Casts.	
1916	*per cent*	*per cent*				
Aug. 5	56	58	Acid.	–	–	
" 6	55	58	"	–	–	After bleeding, 200 cc. of 10 per cent sodium bicarbonate were given.
" 7	60	63	Alkaline.	–	–	

TABLE IX.

Dog 8. Weight 14 kilos.
Bled every day at 9 a.m.

Date.	Van Slyke method.		Urine.			Remarks.
	Direct.	Funnel.	Reaction.	Albumin.	Casts.	
1916	*per cent*	*per cent*				
Aug. 5	56	58	Acid.	–	–	
" 6	55	58	"	–	–	After bleeding, 280 cc. of 10 per cent sodium bicarbonate were given.
" 7	60	63	Alkaline.	–	–	

TABLE X.

Dog 3. Weight 13.5 kilos.

	Van Slyke method.		Urine.			Remarks.
	Direct.	Funnel.	Reaction.	Albumin.	Casts.	
	per cent	*per cent*				
Average.....	56	63	Acid.	—	—	
	69	71	Alkaline.	—	—	2 hrs. after 135 cc. of 10 per cent sodium bicarbonate were given.

TABLE XI.

Dog 4. Weight 19 kilos.

	Van Slyke method.		Urine.			Remarks.
	Direct.	Funnel.	Reaction.	Albumin.	Casts.	
	per cent	*per cent*				
Average.....	58	64	Acid.	—	—	
	66	70	Alkaline.	—	—	2 hrs. after 190 cc. of 10 per cent sodium bicarbonate were given.

DISCUSSION.

These investigations show that the nephritis produced by means of uranium nitrate presents a diminution of the plasma carbon dioxide content, associated with an increase of blood urea and plasma chlorides and the appearance of albumin and casts in the urine. These changes indicate the presence of an acidosis in the nephritis produced by uranium nitrate.

Moreover, both the nephritis thus produced and the acidosis which accompanies it can be diminished by means of sodium bicarbonate. In dogs receiving sodium bicarbonate and given uranium nephritis, there is maintained a higher plasma carbon dioxide content, a less pronounced increase of chlorides in the blood, as well as a diminution of albumin and casts in the urine as compared with animals given uranium nephritis and receiving no soda. In severe nephritis the amount of urea is also diminished in the carbonate dogs as compared with the controls. The nephritis of the carbonate dogs is less severe as regards the histological picture than that of the controls.

CONCLUSIONS.

1. The presence of an acidosis in dogs with experimental uranium nephritis is demonstrable by the Van Slyke-Stillman-Cullen method and that of Marriott. It is detected more readily by the former method.
2. This acidosis is associated with increase in the blood urea and plasma chlorides and with the appearance of albumin and casts in the urine.
3. The oral administration of sodium bicarbonate diminishes the acidosis, the increase in plasma chlorides, the amount of albumin and casts in the urine, and, to a lesser degree, the increase in the blood urea following the administration of uranium. It also diminishes the severity of the changes produced by uranium in the kidneys.
4. The oral administration of sodium bicarbonate to normal dogs raises the carbon dioxide content of the plasma as determined by the Van Slyke-Stillman-Cullen method.

I wish to thank Dr. J. Harold Austin for his constant suggestions and interest throughout the course of this investigation, and Dr. Herbert Fox, Director of the William Pepper Clinical Laboratory, for extending to me the privileges of the laboratory.

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EXPLANATION OF PLATES.

PLATE 57.

FIG. 1. Dog 1. Section of the kidney of a dog with uranium nephritis, to which no soda was given.

FIG. 2. Dog 2. Section of the kidney of a dog with uranium nephritis, to which no soda was given.

PLATE 58.

FIG. 3. Dog 4. Section of the kidney of a dog with uranium nephritis, to which soda was given.

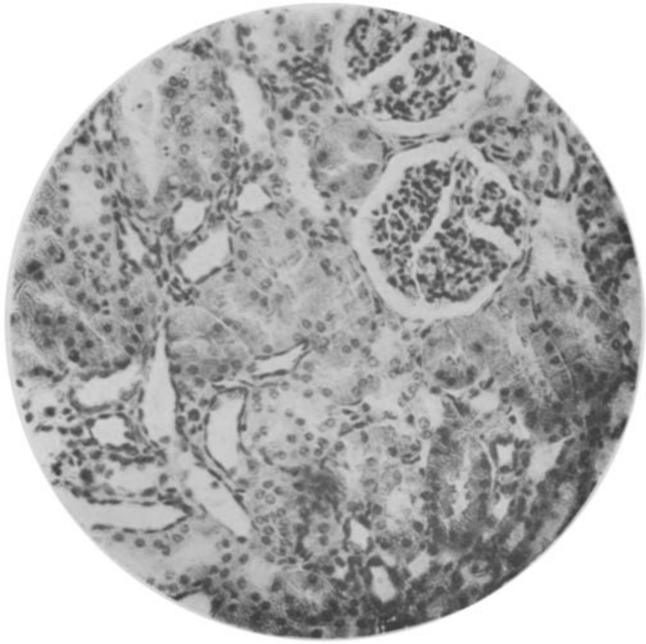

FIG. 1.

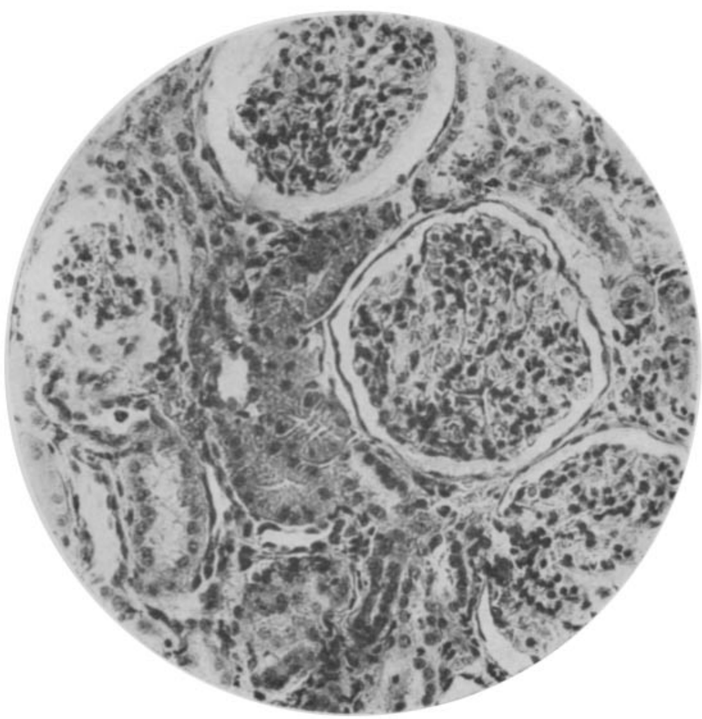

FIG. 2.

(Goto: Uranium Nephritis in the Dog.)

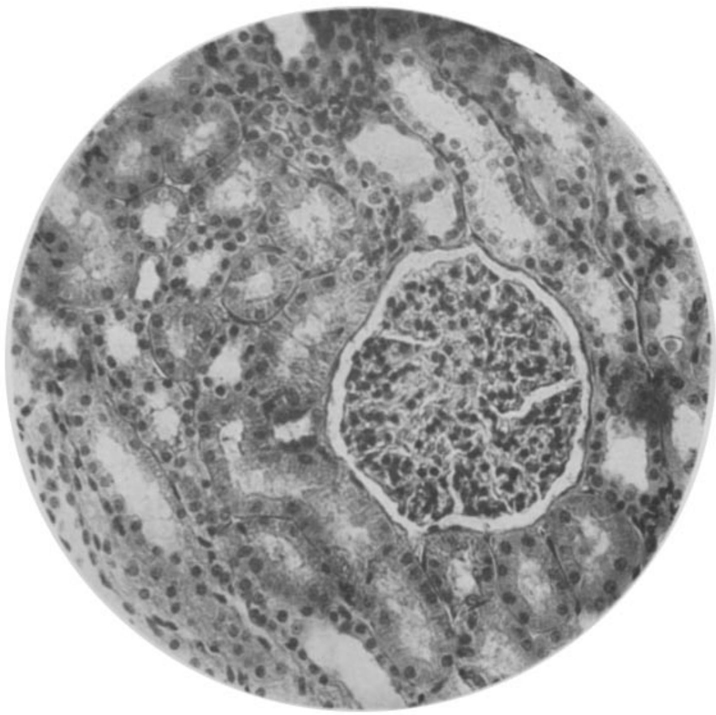

FIG. 3.

(Goto: Uranium Nephritis in the Dog.)