THE EFFECT OF URANIUM NEPHRITIS ON THE EXCRETION OF CREATININ, URIC ACID AND CHLORIDS, AND THE EFFECT OF CREATININ INJECTIONS DURING URANIUM NEPHRITIS *

WALTER M. KRAUS, M.D.
NEW YORK

I. INTRODUCTION

The experiments described in this paper were begun with the intention of determining the effect of uranium nitrate on the excretion of creatinin by the kidney, and the effect of creatinin injections on the nephritis produced by uranium nitrate. Chlorids were estimated in the last three experiments to check up the results with creatinin. Uric acid estimations were added, as it was found that no work had been done on the subject. The work was begun in the winter of 1911, during the writer's second year at the Johns Hopkins Medical School, but was not successful at that time. The experiments described below were conducted in this laboratory during the two succeeding summers of 1911 and 1912.

II. EXPERIMENTAL

A. Methods.—Dogs which had not previously been used for any experimentation were taken. They were kept in cages of the type described by Dr. Gies.¹ The urine was collected daily at 8:30 a. m. Powdered thymol was used as a urinary preservative. The cages were carefully cleaned each morning.

The dogs were fed on uniform quantities of hashed lean beef, cracker-meal, lard and distilled water in a homogeneous mixture. Bone ash was added to the food to insure the elimination of formed feces, which were found except when stated to the contrary in the protocols. The dogs were fed regularly at 9 a. m.

A word must be said here concerning the meat included in the diet. The amount was always small—15 grams. Closson,² Klercker³ and Lefmann⁴ have shown that muscle as food does not increase urinary crea-

* Submitted for publication April 9, 1913.

* From the Biochemical Laboratory of Columbia University, at the College of Physicians and Surgeons, New York City.

1. Gies, W. J.: *Am. Jour. Physiol.*, 1905, xiv, 403.

2. Closson: *Am. Jour. Physiol.*, 1906, xvi, 252.

3. Klercker: *Beitr. z. chem. Physiol. u. Pathol.*, 1906, v, No. 8, p. 59.

4. Lefmann: *Ztschr. f. physiol. Chem.*, 1908, lvii, 476.

tinin; and furthermore, it has been noted by Underhill and Kleiner⁵ that there is no decrease in dogs in urinary creatinin during a fast of ten days. These observations warrant the belief that the absence of so small an amount as 15 grams of meat, during refusal of food by the animals, could not have made any difference in the output of urinary creatinin.

Intravenous injections were made from a buret through a small cannula into a saphenous vein. A very small quantity of 2 per cent. cocain solution was used as a local anesthetic.

The subcutaneous injections were made in the skin of the back or hind leg.

The creatinin was estimated by Folin's⁶ method, the uric acid by the Folin-Shaffer⁷ method; the chlorids by Harvey's⁸ method; albumin with Tsuchaya's⁹ reagent using Esbach tubes. The urines were analyzed as soon as collected.

B. Lesions Caused by Uranium Nitrate.—The acute renal lesions caused by uranium nitrate have been shown to be the same by all investigators except two. These lesions consist in general of a severe tubular injury combined with a vascular change, the latter of which has been demonstrated by physiological, but not by anatomical observations.

As to the tubular lesions, Pearce¹⁰ states that "the anatomical changes due to uranium and to the chromates are in the early stages confined essentially to the tubules, especially the convoluted tubules, and consist of granular or fatty degeneration and definite necrosis often affecting large groups of tubules." This is in essence what has been found by Schlager and Takayasu,¹¹ Schlager, Hedinger and Takayasu,¹² Pearce, Hill and Eisenbrey,¹³ MacNider,¹⁴ Pohl,¹⁵ Christian,¹⁶ and Heineke and Meyerstein.¹⁷ As to the vascular changes, Chittenden and Lambert¹⁸ showed as early as 1889 that uranium in its early action on the kidney caused an increased urinary volume which, when the toxic action became more decided, changed to a partial or complete stoppage of urinary secretion. Schlager states that the serious disturbances of the integrity of the renal vessels shown by functional investigation in uranium nephritis are not recog-

5. Underhill and Kleiner: Jour. Biol. Chem., 1908, iv, 165.

6. Folin, O.: Ztschr. f. physiol. Chem., 1904, xli, 223.

7. Folin and Shaffer: Ztschr. f. physiol. Chem., 1901, xxxii, 556.

8. Harvey, E. C.: THE ARCHIVES INT. MED., 1910, vi, 12.

9. Tsuchaya: Centralbl. f. inn. Med., 1908, xxix, 105.

10. Pearce, R. M.: Harvey Lectures, 1909 and 1910.

11. Schlager and Takayasu: Deutsch. Arch. f. klin. Med., 1910, xeviii, 17.

12. Schlager, Hedinger and Takayasu: Deutsch. Arch. f. klin. Med., 1907, xci, 59.

13. Pearce, Hill and Eisenbrey: Jour. Exper. Med., 1910, xii, 196.

14. MacNider: Jour. Pharmacol. and Exper. Therap., 1912, iii, 423.

15. Pohl: Arch. f. Exper. Path. u. Pharmacol., 1912, lxxvii, 233.

16. Christian, Smith and Chandler: THE ARCHIVES INT. MED., 1911, viii, 468.

17. Heineke and Meyerstein: Deutsch. Arch. f. klin. Med., 1907, xc, 101.

18. Chittenden and Lambert: Ztschr. f. Biol., 1889, xxv, 513.

nizable from the anatomical picture. These disturbances Schlayer, Hedinger and Takayasu¹² showed to be an initial increase in the dilatability and contractibility of the blood-vessels of the kidney and an increased permeability followed, in a day or two, by a reversed condition (Fig. 1). Pearce, Hill and Eisenbrey¹³ confirmed this. Pohl,¹⁵ working on rabbits with very small doses of uranium nitrate (0.035 mg.), produced a sub-acute nephritis, which exhibited, physiologically, a polyuria reaching its height in a week or ten days; and showed, anatomically, at the end of two weeks, that the glomeruli were intact, but that the tubular epithelium was flattened or entirely destroyed. MacNider,¹⁴ and Heineke and Meyerstein¹⁷ found engorgement of the intertubular vessels and of the glomerular capillaries.

As further proof of the tubular lesion Eisenbrey,¹⁹ found that phenol-sulphonephthalein is often excreted in increased amounts in the first twenty-four hours of uranium nephritis and always is excreted in

Fig. 1.—Effect of uranium on the kidney. 1. Faint spot-like clouding. 2. More diffuse clouding and spot-like necrosis. 3. Wider areas disturbed. 4. More widely-spread disturbance. 5. Practically no normal tubules remain.

decreased amounts thereafter. In view of the statement of Rowntree and Geraghty,²⁰ “that experimental evidences indicate that phenolsulphonephthalein is excreted mostly by the tubules,” the work of Eisenbrey becomes confirmatory evidence of what has been said above concerning the lesions of uranium nephritis; that is, that uranium nitrate produces a vascular reaction of one or two days’ duration followed by a tubular disturbance of wide extent. Christian pointed out that in addition to the tubular lesion “there occurs in the glomeruli a degenerative condition consisting usually of the appearance of hyaline droplets of varying size in the wall of the capillary.” MacNider states that similar structures have been observed in several of his experiments. He also notes that

19. Eisenbrey: Jour. Exper. Med., 1911, xiv, 462.

20. Rowntree and Geraghty: THE ARCHIVES INT. MED., 1912, ix, 284.

TABLE 1.—CREATININ INJECTIONS AND ACUTE NEPHRITIS

Date	Weight Kilos	Temp. F.	Urine				Feces	Remarks
			Vol., c.c.	Sp. gr. 10 xx	React. Litmus	Creatinin, Mg.		
July 21-22	8.40	101.2	250	19	Acid	...	...	
July 22-23	8.33	101.6	240	13	Acid	235	..	
July 23-24	8.27	101.6	275	11	Acid	203	..	
July 24-25	8.33	101.6	245	10	Acid	172	..	
July 25-26	8.25	102.0	330	10	Acid	237	..	
July 26-27	8.24	102.0	345	08	Acid	186	..	
July 27-28	8.31	102.0	305	08	Acid	265	..	
July 28-29	8.28	101.8	250	10	Acid	146	..	
July 29-30	8.36	101.8	190	14	Acid	226	..	
July 30-31	8.31	101.8	...	..	Acid	...	+	
July 31-Aug. 1	8.31	101.8	285	11	Acid	190	+	
Aug. 1-2	8.34	102.4	200	..	Acid	360	+	Feces admixed.
Aug. 2-3	8.34	101.8	280	08	Alk.	090	+	
Aug. 3-4	8.34	101.8	315	14	Acid	340	+	0.1056 gm. creatinin injected intravenously 10:40 a. m. 20 c.c. saline.
Aug. 4-5	8.24	102.4	...	..	Acid	...	+	Foamy vomitus.
Aug. 5-6	8.26	101.8	345	10	Acid	321	+	
Aug. 6-7	8.30	102.0	280	10	Acid	224	+	
Aug. 7-8	7.80	101.4	375	17	Acid	202	+	0.1087 gm. creatinin injected intravenously 10:40 a. m. 20 c.c. saline. Vomited after operation.
Aug. 8-9	8.15	100.8	190	25	Acid	421	—	
Aug. 9-10	8.27	102.2	205	07	Acid	114	+	
Aug. 10-11	8.27	102.2	300	08	Acid	216	+	
Aug. 11-12	8.22	102.3	205	11	Acid	222	+	
Aug. 12-13	8.20	102.2	340	10	Acid	205	+	
Aug. 13-14	8.20	102.6	285	10	Acid	210	+	
Aug. 14-15	8.17	102.4	275	15	Acid	317	+	0.1012 gm. creatinin injected intravenously. 10:10 a. m. 18.8 c.c. saline. Vomited after operation. Vomitus taken at 3:45 p. m.

Aug. 15-16	8.12	102.5	290	11	Alk.	234	+	Vomitus foamy only.
Aug. 16-17	8.20	102.5	160	10	Alk.	120	+	
Aug. 17-18	8.24	102.3	215	10	Alk.	192	-	
Aug. 18-19	8.17	102.8	312	10	Alk.	243	+	Injected 0.1000 gm. creatinin intravenously 4:30
Aug. 19-20	8.16	102.7	460	10	Alk.	369	+	p. m. 20 c.c. saline.
Aug. 20-21	8.16	102.5	255	07	Alk.	107	+	
Aug. 21-22	8.23	102.4	275	11	Alk.	327	+	
Aug. 22-23	8.27	102.3	235	12	Alk.	105	-	Slight diarrhea, 10 mg. uranium subcuta. 5:13 p. m.
Aug. 23-24	8.12	103.8	331	..	Alk.	281	+	Some food not taken.
Aug. 24-25	7.73	102.3	681	..	Alk.	228	-	All food refused.
Aug. 25-26	7.60	102.2	420	..	Acid	114	+	All food refused. Injected 0.1067 gm. creatinin intra-
Aug. 26-27	7.48	100.6	*	..	Acid	21	+	venously 4:30 p. m. 20 c.c. saline.
Aug. 27-28	7.13	100.6	*	..	Acid	0	+	All food refused. Apathetic, weak, does not respond
Aug. 28-29	7.02		*	..	Acid	0	+	to calls.
Aug. 29-30	6.94		130	..	Acid	0	+	All food refused. Same. Right eye has purulent
Aug. 30-31	6.82	98.8	72	..	Acid	0	+	discharge, feces bloody.
								All food refused. Same. Left eye involved also,
								feces bloody.
								All food refused except 400 c.c. aq. Same. Irregular
								contractions of masseters and intercostal muscles.
								Occasional spasm of fore paws. Cannot stand
								steadily. Subcutaneous edema. Feces bloody.
								All food refused except 400 c.c. aq. a. m., weaker.
								Complete spasm of fore legs. Partial of rear. Can-
								not stand. Feces bloody. p. m., dyspnea marked.
								Other conditions worse. Rear legs spastic now.
								Died in convulsions at 3:30 p. m.
Aug. 31-Sept. 1	6.77	95.0	275	..	Acid	0†	+	

* Total three days 289 c.c. Average each day 96 c.c.

† No creatinin present.

different animals vary greatly in their response to the same quantity of poison per kilo. This has been found to be the case in my own experiments also.

The accompanying chart taken from the article of Schlayer and Takayasu (p. 615) shows graphically what has been stated above.

The lesions produced in my experiments, so far as concerns acute nephritic conditions aggravated by injections of creatinin, were essentially the same as those in the cases mentioned above. In the gross, the kidney was enlarged, the capsule tense; microscopically, the tubular epithelium (mainly of the convoluted tubules) was swollen, sometimes occluding the lumina, and showed granular degeneration and necrosis. The nuclei, especially in the convoluted tubules, could not be made out in most of the cells. The glomeruli were intact. Bowman's capsule was distended in many instances and the intracapsular space was partially filled with a granular material. There was no proliferation of the epithelium of the capsule. The blood-vessels were much engorged.

The kidney in Experiment 3, which was examined two weeks after uranium had been injected four times during twenty-two days, showed a somewhat different picture. Macroscopically, the kidney was swollen. The capsule was tense and not adherent. The surface was smooth. Microscopically, the lesions were mainly tubular. There were not as many injured tubules visible as in the other cases, but those which were injured seemed more severely affected. In many instances the cells had entirely separated from the basement membrane and lay as an ill-defined granular mass in the lumina. In other instances, practically normal tubular epithelium could be seen. The glomeruli showed thickening of Bowman's capsule in several instances and in a few places there was round-cell infiltration about the capsules.

C. Polyuria.—There is almost unanimity of opinion that polyuria occurs in the early stages of uranium nephritis. Chittenden and Lambert¹⁸ noted it in 1889. Since then, Schlayer and Takayasu,¹¹ Pearce, Hill and Eisenbrey,¹³ Schlayer, Hedinger and Takayasu,¹² and MacNider¹⁴ have observed this same reaction. As stated above, this reaction has not been definitely associated with pathological lesions. The recent work of MacNider¹⁴ and of Pohl¹⁵ shows that with small doses of uranium nitrate, this vascular reaction may persist for more than the one or two days stated by the investigators named above.

It is interesting to note that MacNider¹⁴ differentiates between anuric and polyuric animals and states that, though the vascular lesions are identical in these two groups, the tubular involvement differs markedly. In the anuric group this consists in swollen epithelium which occludes the tubular lumina, while in the polyuric group no epithelial involvement is present.

TABLE 2.—ACUTE NEPHRITIS AND CREATININ INJECTIONS
Experiment 2.—Diet: water, 500 c.c.; meat, 15 gm.; cracker-meal, 75 gm.; lard, 35 gm.; bone ash, 8 gm.

Date	Weight, Kilos	Urine						Feces	Remarks
		Vol. c.c.	Sp. Gr. 10 xx	Reac- tion, Litmus	Creat- inin, Mg.	Uric Acid, Mg.	Chlo- rids Gm.	Albu- min, Gm.	
July 23-24	8.82	460	05	Ac.	210	15	0.276	T	5 gm. NaCl per os from this date on.
July 24-25		415	05	Ac.	170	20	0.249	T	
July 25-26	8.90	445	12	Amph.	195	23	3.160	T	
July 26-27		380	13	Amph.	185	29	4.710	T	8.5 mg. uranium nitrate, subcut. 1 p. m. Vomit us frothy only.
July 27-28	9.00	435	14	Amph.	187	25	3.603	1.75	
July 28-29		650	16	*	187	33	8.190	2.5	
July 29-30	7.60	850	17	*	065	123	11.390	*	Dog refused food henceforth; 500 c.c. water offered. Vomited most at once. Amount retained (calculated) 100 c.c. Retained amount 125 c.c. 110 gm. creat- inin injected intravenously. 5 p. m.
July 30-31		525	12	*	123	42	7.870	*	
July 31-Aug. 1	7.23	200	06	*	086	19	11.100	*	
Aug. 1-2		160	13	Ac.	088	08	2.930	2.0	30 c.c. saline. Retained 20 c.c. Fine tremor. Retained 20 c.c. Fine tremor, apathetic and weak.
Aug. 2-3	6.90	67	13	Amph.	054	08	0.970	2.0	
Aug. 3-4		37	17	Ac.	039	09	1.160	4.1	
Aug. 4-5	6.66	67	20	Ac.	073	22	0.201	1.5	Retained 150 c.c. Fine tremor. Weaker, easily pushed over. Retained 15 c.c. Fine tremor. Weaker, easily pushed over.
Aug. 5-6		50	18	Ac.	053	09		0.4	
Aug. 6-7	Dog dead.								

* Vomit us admixed.

TABLE 3.—ACUTE AND SUBACUTE NEPHRITIS. CREATININ INJECTIONS
Experiment 3.—Diet: water, 700 c.c.; meat, 15 gm.; cracker-meal, 125 gm.; lard, 50 gm.; bone ash, 13 gm.

Date	Weight, Kilos	Vol. c.c.	Sp. Gr. 10 xx	Reac- tion to Litmus	Urine			Chlo- rids, Gm.	Albu- min, Gm.	Feces	Remarks
					Creat- inin, Mg.	Uric Acid Mg.					
July 16-17	9.30	310	06	Ac.	166	11		0.155	T	+	
July 17-18		260	06	Ac.	152	10		0.156	T	+	
July 18-19	9.35	465	07	Ac.	279	20		0.372	T	+	
July 19-20		330	06	Ac.	198	11		0.198	T	+	
July 20-21	9.30	380	09	Ac.	151	14		0.228	..	—	
July 21-22		370	07	Ac.	232	15		0.222	T	+	
July 22-23	9.35	410	07	Ac.	258	17		0.164	T	+	
July 23-24		285	11	Ac.	169	18		0.215	1.0	+	8 mg. uranium nitrate subcuta. 12 noon.
July 24-25	9.25	515	12	Ac.	174	27		0.309	1.5	+	7 mg. uranium nitrate subcuta. 10 a. m.
July 25-26		190	13	Ac.	74	10		0.414	1.5	+	
July 26-27	8.85	325	06	Ac.	92	28		0.065	T	+	
July 27-28		150	..	Ac.	...	23		0.300	..	+	Urine lost in part.
July 28-29	9.30	445	09	Ac.	220	23		0.356	T	+	
July 29-30		450	10	Ac.	226	28		0.630	T	+	
July 30-31	9.15	390	10	Ac.	252	44		1.014	T	+	7.5 mg. uranium nitrate injected sub- cutaneously 5:50 p. m.
July 31-Aug. 1		410	10	Ac.	200	23		0.902	T	+	
Aug. 1-2	9.00	340	10	Ac.	158	19		0.816	T	+	
Aug. 2-3		420	10	Ac.	211	26		0.840	T	+	
Aug. 3-4		415	10	Ac.	212	27		0.747	0.5	+	20 mg. uranium nitrate injected subcu- taneously 5 p. m.

Aug. 4-5	9.00	150	17	Alk.	99	18	0.075	1.75	+	Fecal mixture, no diarrhea.
Aug. 5-6		480	11	Ac.	193	58	0.192	0.5	+	
Aug. 6-7	8.90	355	15	Ac.	187	30	0.177	1.0	+	
Aug. 7-8		330	13	Ac.	197	45	0.231	1.0	+	25 mg. uranium nitrate subcutaneously
Aug. 8-9	8.95	335	14	Ac.	231	36	0.435	1.0	+	4:30 p. m.
Aug. 9-10		400	13	Ac.	148	56	0.640	1.0	+	
Aug. 10-11		260	20	Ac.	152	49	0.416	1.0	+	Fecal mixture, no diarrhea.
Aug. 11-12	9.00	230	20	Alk.	130	26	0.345	1.0	+	
Aug. 12-13		305	13	Ac.	140	29	0.884	0.5	+	91 mg. creatinin injected intravenously
Aug. 13-14		435	11	Ac.	241	26	1.174	0.5	+	5 p. m. 30 c.c. saline.
Aug. 14-15	8.95	325	12	Ac.	187	29	0.910	0.5	+	
Aug. 15-16		280	14	Ac.	153	25	0.840	1.0	+	
Aug. 16-17		260	12	Ac.	128	15	0.806	1.0	+	
Aug. 17-18	9.00	300	13	Ac.	156	23	0.750	1.0	+	
Aug. 18-19		225	14	Ac.	136	29	0.562	0.5	+	
Aug. 19-20		255	13	Alk.	96	22	0.612	0.75	+	Fecal mixture, no diarrhea.
Aug. 20-21		340	10	Ac.	122	27	0.544	0.5	+	
Aug. 21-22	8.95	415	11	Ac.	182	31	0.830	0.5	+	70 mg. creatinin injected intravenously
Aug. 22-23		180	08	Ac.	100	19	0.396	0.5	+	4:31 p. m. 30 c.c. saline.
Aug. 23-24	8.95	330	10	Ac.	142	23	1.528	0.5	+	
Aug. 24-25		290	12	Ac.	77	26	0.464	0.5	+	
Aug. 25-26		230	10	Ac.	99	20	0.506	0.5	+	

TABLE 4.—ACUTE NEPHRITIS AND CREATININ INJECTION

Experiment 4.—Diet: water, 700 c.c.; meat, 15 gm.; cracker-meal, 125 gm.; lard 50 gm.; bone ash, 15 gm.												
Date	Weight, Kilos	Urine							Feces	Remarks		
		Vol. c.c.	Reac- tion to Litmus	Sp. Gr. 10 xx	Creat- inin, Mg.	Chlo- rids, Gm.	Uric Acid, Mg.	Albu- min, Gm.				
.....		...	...		...	...	...	...	...	30 mg. uranium nitrate injected subcu- taneously 11:30 a. m.		
.....		...	...		...	...	...	...	...			
.....		...	...		...	...	...	...	...			
Aug. 8-9	14.0	480	Amph.	12	284	1.594	28	T	+			
Aug. 9-10		470	Amph.	07	272	1.598	32	T	+			
Aug. 10-11		450	Amph.	08	185	1.495	27	T	+			
Aug. 11-12	14.0	525	Amph.	08	291	1.365	31	T	+			
Aug. 12-13		130	Ac.	20	172	1.300	43	0.5	+			
Aug. 13-14		600	Ac.	16	302	2.040	34	2.5	+			
Aug. 14-15	13.10	650	Alk.	20	280	0.390	56	4.5	+			
Aug. 15-16		380	Alk.	21	170	0.532	34	5.0	+			
Aug. 16-17		285	Ac.	18	90	0.342	17	2.0	+			
Aug. 17-18	13.30	400	Ac.	10	83	0.960	36	1.0	+			
Aug. 18-19		160	Ac.	10	50	0.736	09	1.0	+			
Aug. 19-20		70	Ac.	07	11	0.196	17	0	+			
Aug. 20-21	14.10	212	Ac.	10	36	0.805	14	0	+			
Aug. 21-22		315	Ac.	07	94	0.882	19	0	+			
Aug. 22-23		545	Ac.	06	117	1.417	34	0	+			
Aug. 23-24	13.20	850	Ac.	08	161	1.700	37	0	+			
Aug. 24-25		840	Ac.	08	184	2.688	44	0	+			
Aug. 25-26		270	Ac.	09	202		..	0	+			

The figures in the accompanying table (Table 5) indicate that polyuria was obtained in all cases. As to anuria, this was not clearly observed in any case, due to the necessity of proceeding promptly with further injections.

TABLE 5.—POLYURIA

Experiment	Vol in c.c.—			
	1	2	3	4
Average normal	266	425	360	431
Maximum normal	345	460	465	525
Uranium nitrate nephritis.....	331	435	285	130
	681	650	515	600
	420	850	190	650*
	...	525	325	...

* Vomitus admixed.

D. Chlorids.—The excretion of chlorids has been carefully investigated by Schlayer and his associates as well as by Austin and Eisenbrey.²¹ These authors found a decrease in the excretion of chlorids. Mosenthal²² has found that the excretion of chlorids may be increased, normal in amount or diminished at times, according to the conduction of the experimental nephritis. It has also been stated by Pohl,¹⁵ and Austin and Eisenbrey that there is an initial increase coincident with the polyuria, after which the excretion of chlorids decreases. This was found to be the case in Experiment 4. The results of the other experiments are inconclusive.

E. Uric Acid.—The question of uric acid excretion in uranium nephritis, acute or subacute, does not seem to have attracted the attention of investigators up to now, for no references have been found in the literature. Table 6 presents some results in this connection.

From the data in this table (Table 6) we may conclude that uranium nitrate nephritis causes an increase in the amount of endogenous uric acid in the urine; that in the subacute form the excretion remains high.

F. Creatinin.—It appears that the elimination of creatinin in acute uranium nephritis has not been studied. It is, however, interesting to note that in potassium chromate nephritis—a tubular form—Levene and Kristeller,²³ and Lefmann⁴ found a decrease in the excretion of creatinin. J. L. Green²⁴ notes that “creatinin was slightly reduced,” but his results are by no means conclusive. Table 7 shows the results for acute uranium nephritis.

In subacute nephritis the amount of creatinin excreted is reduced. The protocol of Experiment 3 shows that after four doses of uranium had been given over a period of twenty-one days, the succeeding seven

21. Austin and Eisenbrey: Jour. Exper. Med., 1911, xiv, 366.

22. Mosenthal: Personal communication.

23. Levene and Kristeller: Am. Jour. Physiol., 1909, xxiv, 45.

24. Green, J. L.: Jour. Pathol. and Bacteriol., 1909, xiii, 296.

days showed an average excretion of 129 mg., and the days thereafter 108 mg. The normal, as may be seen in Table 7, was 205 mg.

TABLE 6.—URIC ACID EXCRETION

Experiment 2.	Mg.		
Normal average	21		
Nephritis	25	Uranium nitrate,	
	33	8.5 mg. subcutaneously.	
	123		
	42		
Experiment 3.	Mg.		Mg.
Normal average	14		56
Nephritis	18	Uranium nitrate, 8 mg.	49
	27	Uranium nitrate, 7 mg.	26
	10	subcutaneously.	29
	28		26
	23		29
	23		25
	28		15
Nephritis	44	Uranium nitrate, 7.5 gm.	23
	23	subcutaneously.	29
	19		22
	26		27
Nephritis	27	Uranium nitrate, 20 mg.	31
	18	subcutaneously.	19
	58		23
	30		26
	45		20
Nephritis	36	Uranium nitrate, 25 mg. subcutaneously.	
Experiment 4.	Mg.		
Normal average	29		
Nephritis	43		
	34	Uranium nitrate, 30 mg.	
	56	subcutaneously.	
	34		
	17		

Intravenous Creatinin Injections.—No record of excretion after intravenous injections of creatinin has been found. There are, however, several observations on its excretion when fed or subcutaneously injected. Folin²⁵ found that if creatinin were ingested by a normal patient, 75 per cent. was excreted. Wolf and Shaffer²⁶ found that 80 per cent. of ingested creatinin was excreted. Voegtlin and Towles²⁷ found that when creatinin was ingested, 36.3 per cent. and 62.5 per cent. (two experiments) were excreted in twenty-four hours, while if injected subcutaneously, 54.5 per cent. and 72.7 per cent. (two experiments) were excreted.²⁸ Mellanby,²⁹ Lefmann,⁴ and Klercker³ state that ingested

25. Folin, O.: Am. Jour. Physiol., 1905, xiii, 66.

26. Wolf and Shaffer: Jour. Biol. Chem., 1908, iv, 439.

27. Voegtlin and Towles: Jour. Biol. Chem., 1912, x, 479.

28. Calculated from protocols.

29. Mellanby, E.: Jour. Physiol., 1907-08, xxxv, 447.

30. v. Hoogenhuyze and Verploegh: Ztschr. f. physiol. Chem., 1905, xlvi, 415.

creatinin is excreted in great part. Van Hoogenhuyze and Verploegh³⁰ state that 100 per cent. of injected creatinin is excreted. The data in Table 8 lead us to the conclusion that when intravenously injected, creatinin is excreted "in toto." From the protocols it will be seen that this did not take more than forty hours.

TABLE 7.—CREATININ EXCRETION IN ACUTE URANIUM NEPHRITIS

Experiment	1	2	3	4
	Mg.	Mg.	Mg.	Mg.
Normal average	210	190	205	258
Uranium nitrate nephritis.....	281*	187*	169*	172*
	228	187	174	302
	114	65	74	280
		123	92	170
				90

* Uranium nitrate subcutaneously. Exp. 1, 10 mg.; Exp. 2, 8.5 mg.; Exp. 3, 15 mg.; Exp. 4, 30 mg.

G. Creatinin Injections During Uranium Nephritis.—No record of creatinin injections in dogs or other animals having uranium or other experimental nephritides has been found. In view of the results, this phase of the subject deserves careful consideration.

TABLE 8.—EXCRETION OF CREATININ

Experiment	1	1	1	1	3	3
	Mg.	Mg.	Mg.	Mg.	Mg.	Mg.
Normal (average)	210	210	210	210	165*	127*
Average 3-day period following injection	330	245	223	267	193	141
Average 3-day period with injected amount subtracted	280	209	190	234	163	114

* Excreted during chronic nephritis.

When a dog with uranium nephritis was injected with an amount of creatinin equivalent approximately to one-half the normal excretion, the animal either died (two cases) or showed a remarkable decrease in renal activity (one case). The data show (Tables 9 and 10) that not only was the injected creatinin not excreted, but the excretion lay far below either the normal or the amount excreted in the previous nephritic period.

TABLE 9.—CREATININ EXCRETION AFTER INJECTION OF APPROXIMATELY ONE-HALF THE USUAL EXCRETION DURING NEPHRITIS

	Experiment 2		
	Volume, c.c.	Creatinin, Mg.	Uric Acid, Mg.
Average normal	425	190	21
Average after nephritis.....	615	140	55
Average after creatinin injection.....	96	65	13

The excretion of the other substances subjected to study shows a noteworthy state of affairs, namely, a great decrease in the excretion of water, chlorids and uric acid; in other words, there was an apparent

arrest of renal function, followed in two instances by death and in one by recovery. This last case (Table 11) deserves further attention, since an examination of the figures shows that after a certain period (three days) the kidney began to excrete more readily, and that the substances increased daily in amount until the creatinin had reached the normal amount, and until uric acid, chlorids and water had far exceeded it; in other words, what appeared to be a physiological compensation took place.

TABLE 10.—CREATININ EXCRETION AFTER INJECTION OF APPROXIMATELY ONE-HALF THE USUAL EXCRETION DURING NEPHRITIS

	Experiment 1—	
	Creatinin, Volume,	
	Mg.	c.c.
Average normal	210	266
Average nephritis	207	477
Average creatinin injection	3	127

The following is a description of the animals' condition after creatinin was injected. Dogs 1 and 3 will be described together, as they showed practically the same symptoms and in the same order. These dogs one day after the creatinin injection became apathetic. They did not jump about their cages when approached as had previously been the case. Two days later a fine muscular tremor was noted. The dogs lay quietly in their cages. If placed on their feet they were easily bowled over by a

TABLE 11.—APPARENT PHYSIOLOGICAL COMPENSATION IN CREATININ EXCRETION AFTER INJECTION OF EXCESS DURING NEPHRITIS

	Experiment 4.			
	Volume, Cc.	Creatinin, Mg.	Uric Acid, Mg.	Chlorids, Gm.
Average (normal)	431	258	29	1.513
Average (nephritis)	403	231	41	1.065
Creatinin injection	400	83	36	0.960
	160	50	9	0.736
	70	11	17	0.196
	212	36	14	0.805
	315	94	19	0.882
	545	117	34	1.417
	850	161	37	1.700
	840	184	44	2.688
	270	202	..	

gentle push and did not jump up again. The following day a coarse tremor was noted which was spasmodic only. The respiration was labored, perhaps due in part to a nasal infection of a purulent nature.³¹ The eyes also now showed a purulent discharge. Neither of these inflam-

31. The fact that this infection occurred but one day before death, and after the renal reaction to the creatinin injection had commenced, warrants the belief that it was in no way responsible for the animal's death, and was only a manifestation of lowered resistance due to the toxic influence on the animal as shown by his changed actions and urinary excretions.

matory changes had been present before. In Dog 3, percussion near the scapular spine gave a very active reflex contraction of the fore leg, which on two occasions developed into a clonus. The dogs became more and more apathetic, lying quietly in their cages, not reacting to calls and unable to stand when placed on their feet. This lasted until they died. If at any time after the creatinin injection water was placed in the cages the dogs drank, but vomited at once. Dog 4 showed no symptoms whatsoever and throughout the experiment appeared normal.

But before offering any explanation of these phenomena, the results of creatinin injections in a subacute uranium nephritis must be noted. Here, as the figures in Table 12 show, the secretion of neither creatinin, uric acid, chlorids nor water was affected. It is on this finding that a possible explanation of the phenomenon in the acute nephritis may be

TABLE 12.—RESULTS OF INJECTION OF CREATININ DURING SUBACUTE URANIUM NEPHRITIS

Experiment 3.	Vol., c.c.	Creat- inin, Mg.	Uric Acid, Mg.	Chlo- rids, Gm.	Remarks
Average normal	360	205	14	0.213	
After four uranium injections during 21 days	435	241	26	1.174*	Injected 91 mg. creatinin.
	325	187	29	0.910	
	280	153	25	0.840	
	260	128	15	0.806	
	300	156	23	0.750	
	225	136	29	0.562	Injected 70 mg. creatinin.
	255	96	22	0.612	
	340	122	27	0.544	
	415	182	31	0.830*	
	180	100	19	0.396	
	330	142	23	0.528	
	290	77	26	0.464	
	230	99	20	0.506	

* Raised chlorid excretion due to saline injection fluid.

based. In the acute nephritis, the tubules are all more or less severely injured. If to the normal burden (which, as the figures show, is poorly borne so far as creatinin goes), we add the additional burden of excreting more creatinin, we can readily imagine that the injured cells, now taxed far beyond their powers, would fail to act as well as before, and a more or less complete arrest of renal function would result. In subacute nephritis, cellular regeneration or atrophy takes place, so that the kidney probably contains sufficient normal tubular epithelium to take care of a certain amount of creatinin beyond that presented to the kidney by body metabolism, and thus no ill effects occur. What this amount is, and whether it approaches the normal, has not been demonstrated up to now.

The whole matter seems, moreover, to have another interesting side when we consider that creatinin is increased in fever in general

(Leathes³²), and specifically in acute fevers, e. g., pneumonia (Wolf and Lambert³³) and typhoid fever (Shaffer,³⁴ and Ewing and Wolf³⁵); and when we consider that the diphtheria, cholera and colon bacilli, as well as the pneumococcus, cause a tubular nephritis (Aschoff³⁶).

The manner of production of a kidney condition which would give rise to uremia in certain febrile diseases might be explained as follows: Taking creatinin as an example of a normal urinary substance excreted by the tubules of the kidney, and reviewing briefly what occurred in Experiments 1, 2, 3, and 4, we may conclude that animals with a tubular nephritis and given a hypercreatininemia, showed an arrest of renal function followed in two instances by death. When the hypercreatininemia was omitted, there was no death from nephritis of similar intensity.³⁷ In other words, hypercreatininemia taxed the kidney beyond its power of function and the margin of safety or limit of function was overstepped.

Let us now suppose the existence of a febrile condition, in which the excretion of creatinin is raised; the tubules would then be taxed beyond the usual. Add to this a tubular nephritis and we have the reverse of what took place in the experiment; that is, instead of tubular nephritis followed by hypercreatininemia we have hypercreatininemia followed by tubular nephritis, both of which would naturally entail similar results, so far as effects on the tubule are concerned.

As stated above, creatinin is taken only as an example of a urinary substance normally excreted by the kidney tubule. There seems no reason to believe that other normal substances which are increased in fever and excreted by the tubules would not act in a similar way; that is, to overtax an already overfunctioning kidney whose condition had been aggravated by a tubular nephritis.

In brief, it would seem probable that the factors which reduced the total functioning powers of the kidney in the above experiments have been a tubular nephritis followed by a further taxing of the tubules by the presentation of excessive amounts of a substance normally excreted by them; and that the same factors, even though reversed in order of occurrence, might act in the same way in human febrile diseases complicated by tubular nephritides.

What may cause the uremia, normal or abnormal substances, is not known. We have only been concerned here with the mechanism of the retention of these substances.

32. Leathes, J. B.: *Jour. Physiol.*, 1909, xxxv, 205.

33. Wolf and Lambert: *THE ARCHIVES INT. MED.*, 1910, v, 406.

34. Shaffer: *Am. Jour. Physiol.*, 1908, xxiii, 1.

35. Ewing and Wolf: *THE ARCHIVES INT. MED.*, 1909, iv, 330.

36. Aschoff: *Pathologische Anatomie*, 1911, ii, 450.

37. This has been shown by many of those quoted above who have worked with uranium.

CONCLUSIONS

1. In acute uranium nitrate nephritis, (1) creatinin is excreted in decreased amounts, and (2) uric acid is excreted in increased amounts (Experiments 2, 3, 4).

2. In subacute uranium nitrate nephritis, (1) creatinin is excreted in decreased amounts (two weeks), but (2) uric acid and (3) chlorids are excreted in increased amounts (two weeks) (Experiment 3).

3. Creatinin injected in normal dogs is excreted "in toto" (Experiment 1).

4. Creatinin injected in acute uranium nephritis causes (1) endogenous and (2) injected creatinin (Experiments 1, 2, 4), (3) uric acid, (4) chlorids and (5) water, to be excreted in decreased amounts (Experiments 2, 4); (6) death may ensue.

5. Creatinin injected in subacute uranium nephritis (Experiment 3) is excreted "in toto," and apparently does not affect the excretion of endogenous creatinin, uric acid, chlorids or water since these are unchanged.

I wish to express my thanks to Dr. Wm. J. Gies for the valuable assistance I have received while carrying out this work.

437 West Fifty-Ninth Street.