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THE EXCRETION OF HEXAVALENT URANIUM FOLLOWING INTRAVENOUS ADMINISTRATION

II. STUDIES ON HUMAN SUBJECTS

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Abstract

Tracer studies employing uranium enriched in the isotopes U^{234}, U^{235} have been carried out in six human subjects; four males and two females. The uranium was given intravenously in the hexavalent state as uranyl nitrate in amounts ranging from 6 micrograms to 70 micrograms per kilogram of body weight.

Each individual of the series received a single injection of the metal except for Subject 6 who was given two widely spaced doses. The first of these was when his condition was normal and the second after an acidosis had been produced by ingestion of ammonium chloride. Renal function tests including urinary catalase, protein, amino N to Creatinine N ratio, and clearances of mannitol and p - aminohippurate were done before and after administration of uranium. Only at the 70 microgram per kilogram level in Subject 6 was there a slight rise in urinary catalase and protein suggesting that tolerance had been reached. All other tests were negative.

The excretion of uranium was mainly in the urine, where from 70 to 85 per cent of the administered dose appeared in the first twenty-four hours. Urine of the second twenty-four hours contained about 4 per cent, and the third twenty-four hour urine, 1.5 per cent of the administered dose. Detectable amounts were excreted for at least two weeks. It is surmised that this late excretion represented uranium originally stored in the bones. Negligible amounts of uranium were found in the feces.

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The production of an acidosis with ammonium chloride (Subject 6) decreased the rate of excretion. Attempts at mobilization of the fraction retained by injection of citrate and by the use of a low calcium diet plus dihydrotochysterol were ineffective.

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THE EXCRETION OF HEXAVALENT URANIUM FOLLOWING INTRAVENOUS ADMINISTRATION

II. STUDIES ON HUMAN SUBJECTS

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I. Introduction

The toxicological work on uranium has conceived of the metal mainly as a chemical hazard, and it is along these lines that the present experiments have been directed. While uranium compounds are highly poisonous when they gain access to the circulation, there is little reason to fear that serious toxic exposures will occur during the ordinary course of industrial activities. Uranium salts are absorbed poorly when ingested and unless there is gross carelessness, the inhalation of contaminated dust can be controlled readily.

It is possible, however, that long continued exposure to the dust of concentrates of U^{234}, U^{235} may, because of more intensive alpha emission, constitute a radiological hazard particularly for lung and bone.

Hexavalent uranium forms complexes with bicarbonate, citrate, phosphate, and protein, and when given in small amounts, is filtered rapidly through the glomeruli combined with bicarbonate. A fraction of the total dose, from 10 to 20 per cent, becomes fixed to the phosphate groups of bone (1) (2), from which it is released gradually. Because of the manner of it elimination, the chief toxicity of uranium is for the kidney, where it produces a severe tubular nephritis (3).

It has been found recently that rabbits and dogs often show responses in increased urinary catalase and protein to injections of uranyl acetate given intravenously at a level of 0.01 mg. per Kg. of body weight (0.006 mg. of uranium metal) (4). This dose is well below the level that will produce

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gross symptoms of toxicity. The daily urinary excretion of uranium for some workers in uranium plants has been reported to be about 0.3 mg. in twenty-four hours (5). Obviously it is of interest to determine whether man will react with catalasuria and proteinuria to such small quantities of uranium. From animal studies we find different degrees of tolerance; the most susceptible animal that has been investigated is the rabbit, while the toxic effects of uranium are produced less readily in the cat, dog, and rat in approximately the order mentioned. The experiments which we have been able to carry through suggest to us that the chemical toxicity for adult humans as measured by catalase and proteinuria, is more nearly the order of that for the rat and suggests that genus homo occupies a position in the more resistant group of mammals.

II. Purpose of Experiment and Methods

The investigation was undertaken with these objectives in mind.

A. To find that dose of soluble uranium salt which, when introduced intravenously as a single dose, would produce just detectable renal injury. The tests employed to ascertain renal damage were urinary catalase (Dounce) (4), urinary protein (6), ratio of amino nitrogen to creatinine nitrogen in the urine (7), glomerular filtration (mannitol) (8), renal plasma flow, maximum tubular excretory capacity (para aminohippuric acid) (9), and urea clearance (10). Not all of the more complicated tests of renal function were done in every patient; however, urinary catalase and protein which are very sensitive indicators of renal injury were followed carefully in each case.

B. To measure the rate at which soluble uranium compounds are

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eliminated from the human body once they have entered the circulation. Both urine and fecal specimens were obtained from the experimental subjects. Urine was collected in individual voidings on the day of the injection and thereafter in pools of twenty-four hours. The excretion was determined by the method of electroplating and alpha counting as given in Part I of this report. It was soon found that the amount of uranium appearing in human feces after intravenous administration of salts of U_6 was negligible and the fecal analyses were discontinued.

C. To observe the effect of measures aimed at increasing or decreasing the rate of excretion of uranium.

Three experiments of this nature were performed. Mobilization of the small fraction of the dose which was apparently retained was not affected by the intravenous administration of citrate, nor by placing one of the subjects on a low calcium diet together with large doses of A.T. 10.* Production of an acidosis with ammonium chloride, on the other hand, clearly delayed the excretion of uranium in the urine. The details of these experiments appear in Section V.

III. Selection of Subjects and Size of Dose

The experimental subjects were chosen from a large group of hospital patients. Criteria of importance in making the selection were reasonably good kidney function with urine free from protein and with a normal sediment on clinical examination. The probability that the patient would benefit from continued hospitalization and medical care was also a factor in the choice. When higher levels of dosage were contemplated, individuals from the older age groups were preferred in view of the remote possibility that late

[redacted]

radiation effects might occur, and the enriched isotopic mixture was diluted with ordinary uranium.

The initial dose was set at approximately 6 micrograms of the metal per kilo of body weight and was chosen because this is the amount which will occasionally produce just detectable temporary renal damage in the rabbit, a susceptible animal (4). The plan called for a slowly increasing dosage provided that no signs of injury to the kidney were detected. Until it was established that the rate of, and total excretion were of the same order as that for experimental animals, no subject received more than a single dose. When the amount given approached 50 micrograms per kilo, the enriched mixture of isotopes of U^{234}, U^{235} was diluted 1-4 using uranyl acetate of the ordinary isotopic composition. It was estimated that this would decrease the radioactivity to a point where any late radiation effects would be highly improbable.

Subject 6 received the largest amount of uranium, about 71 micrograms per kilo and was given a second injection after acidification with ammonium chloride. No renal toxic action was noted.

IV. Nature of Material and Technique of Administration

Portions of the sample of uranium oxide (U_3O_8) enriched in U^{234} and U^{235} and described in Part I of this report were weighed out and used in the preparation of solutions of uranyl nitrate for intravenous injection. When the subject had been selected and the size of the dose agreed upon, enough of the uranyl nitrate solution to contain several times the quantity of metal required was diluted with a 1.15 per cent solution of sodium acetate, the pH of which had been adjusted to 4.5 by addition of a little

[redacted]

acetic acid. The dilution was arranged so that the quantity of uranium to be injected would be present in 5 to 8 ml. After autoclaving to insure sterility about 20 ml. of the buffered uranium salt was transferred aseptically to a sterile rubber capped vial. Trial analysis were run on the remaining solution by the method of plating and alpha counting to serve as a check on the accuracy of the initial weighing and dilution. If the amount of uranium present as calculated from these two procedures was found to be in agreement, the sterile solution was considered ready for use.

Technique of Administration

The necessary amount of sterile, buffered uranyl solution was drawn from the vial into a 10 ml. all-glass syringe and the needle removed. The syringe was handed to an assistant and held so that none of the contents would escape. A number 20 needle attached to another syringe partly filled with physiological saline was used to cannulate the median basilic vein of the patient and enough saline injected to insure that none of the liquid was leaking into the adjacent tissues. The needle was left in place and the syringe containing the solution of uranium was attached. A few drops of blood were drawn into the barrel to indicate the continued patency of the needle and the injection was made promptly. The syringe was rinsed once by withdrawing the plunger slowly until blood reached the mark of the previous filling, and the blood was reinjected into the vein.

Preparation of Dummy Solutions

The same syringe used for the injection was rapidly cleaned and dried. The solution of uranium was again drawn from the vial to the proper mark and the needle removed. A second 20 guage needle filled with water was attached and the solution ejected through it into a 200 ml. volumetric flask. Water

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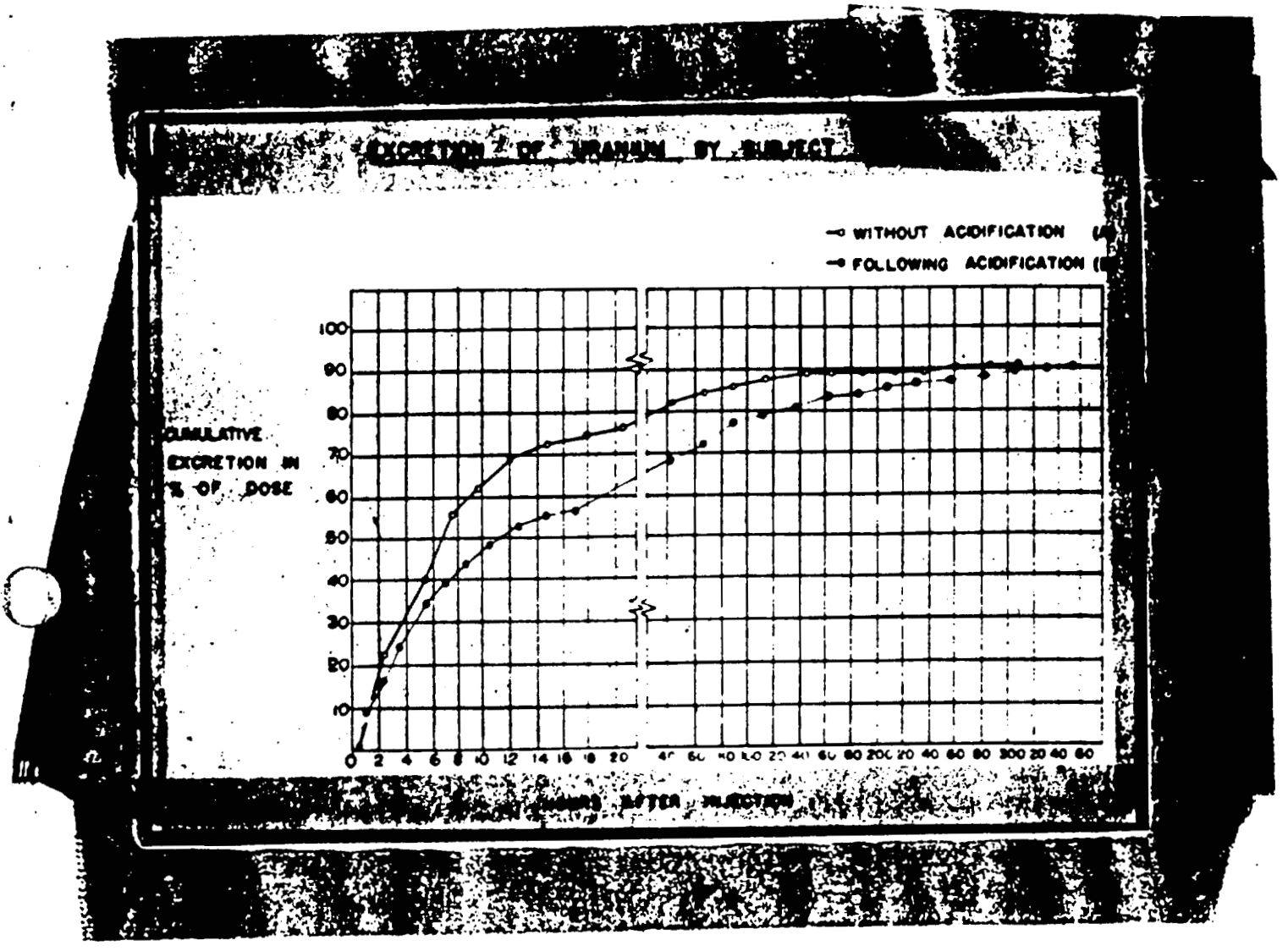
FIGURE 1



A. - Condition Normal

B. - Condition Acidotic from Ingestion of Ammonium Chloride

[redacted]

point, animal experiments suggest that it becomes fixed in the kidney and particularly in the bone and that it is slowly released from the latter site (1). The details of the human experiments are as follows:

Subject No. 1 - White male, aged 32 years, Ht. 171.5 cm., Wt. 60.5 Kg. B. P. 110/75

In hospital because of rheumatoid arthritis and uretheral strictures. At the time of study his disease was quiescent. The urine contained neither protein nor casts and the catalase activity was low. Control analyses of urine and feces did not disclose the presence of uranium. On 8/9/46 he was given 385 micrograms of uranium metal intravenously as the nitrate diluted to 5 ml. with sodium acetate buffer. Collections of urine and feces were started immediately. Blood was drawn four hours later and found to be without detectable alpha activity. The pertinent clinical laboratory data are to be found in table 2. Tables 3 and 4 present the values found on analyses of urine and feces respectively for uranium.

Daily tests of a fresh specimen of urine did not reveal increased catalase activity in the post injection period; there was no proteinuria; the ratio of amino N/Creatinine N did not show a significant variation from the control values and as may be seen from table 2, urea clearance, blood counts and blood chemistry was not affected by the injection.

In summary the intravenous injection of hexavalent uranium prepared from a mixture of isotopes enriched in U^{234}, U^{235} at a level of 6.3 micrograms (of metal) per kilogram did not produce demonstrable renal damage.

Subject No. 2 - White female, aged 40 years, Ht. 165.5 cm., Wt. 72.6 Kg. B.P. 136/90

Hospitalization was required because of acute alcoholism.

[redacted]

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SUBJECT NO. 1

TABLE 2

Clinical Tests

	Before Injection		After Injection
Urea Clearances	8/5/46		8/13/46
	Standard 102%		Standard 100%
	Maximum 115%		Standard 91%
Blood Counts	8/2/46		8/12/46
	R.B.C. 5.5	million	5.3
	Hb. 13.8	gm/100/ml	13.8
	W.B.C. 6,800	cu mm	8,850
Differential Count			
	Neut. 66	percent	64
	S. L. 6		15
	L. L. 13		5
	M. 9		11
	E. 1		2
	Deg. 5		3

Blood Chemistry	8/5/46		8/12/46
Icterus Index	5	Units	5
Sugar	66	mg %	62
N.P.N.	31	mg %	31
Total Protein	7.2	gm %	7.2
Alb/Glob.	4.3/2.9	gm %	4.4/2.8
Inorganic P.	4.3	mg %	4.5
Alk. Phosphatase	2.3	Bodansky Units	2.5
Carbon Dioxide	70	vols. %	63
Chloride	----	meq/liter	94

These tests likewise indicate a negative effect at the present level of dosage.

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TABLE 3

Excretion of Uranium in Urine of Human Subject #1

Date	Time after injection in hours	µgm. Uranium in specimen	% of Dose excreted in specimens	% of dose excreted per ml. of Urine
8/9/46 1:45 pm	3	204.70	53.27	.154
2:45 pm	4	37.22	9.66	.047
8:00 pm	9¼	59.67	15.50	.062
10:00 pm	11¼	8.03	2.08	.017
8/10/46 8:00 am	21¼	7.00	1.82	.004
8/11/46 8:00 am	45½	8.76	2.27	.0015
8/12/46 8:00 am	69¼	3.76	.97	.00043
8/13/46 8:00 am	93¼	less than .77	less than .20	less than .00014
8/14/46 8:00 am	117¼	less than .79	less than .20	less than .00009
8/15/46 8:00 am	141¼	less than .27	less than .07	less than .000045
Total Excretion:		330.57	86.07	
Excretion during first day: (21¼ h.)		316.22	82.33	.0599
Excretion during five following days.		14.35	3.74	.0004

SUBJECT NO. 1

TABLE 4

Excretion of Uranium in feces of Human Subject #1

All analyses on feces yielded less than one count per minute over background (equivalent to approximately .05 μgm.) which we consider the lower limit of analysis of our plating and counting method, utilizing only the emission of alpha particles to determine the amount of uranium present.

The following table gives the maximum values of uranium which might have been present in the feces. The values are not constant because fecal excretions varied and the size of the aliquot was not always the same.

Date	Time after injection	Maximum total uranium in μgm.	Maximum total uranium in % of dose	Maximum uranium in % of dose per gm. feces, wet wt.
8/10/46	21¼ h.	less than .40	less than .10	less than .00056
8/11/46	45¼ h.	less than .60	less than .15	less than .0013
8/12/46	69¼ h.	less than .40	less than .10	less than .0007
8/13/46	93¼ h.	less than 1.21	less than .32	less than .0016
8/14/46	117¼ h.	less than .40	less than .10	less than .0010
8/15/46	141¼ h.	less than .40	less than .40	less than .0002

[redacted]

hallucinatory state, cirrhosis of the liver with congestive splenomegaly and a neuropathy probably due to deficiency of the vitamin B complex. At the time of this study the more acute symptoms had subsided and while still a bed patient, she was able to give adequate cooperation in the collection of specimens. On 9/18/46 she was given an intravenous injection of the enriched isotopic mixture of U^{234}, U^{235} similar in composition to that received by Subject 1. In this instance the dose was equivalent to 476.7 micrograms of the metal and was contained in 5 ml. of the buffer. The amount given per kilogram was thus 6.5 micrograms. Collections of urine were begun immediately but the feces were not saved. Clinical laboratory data and the results of analyses of the urine for uranium may be found in tables 5 and 6. Table 7 gives the ratios observed for amino nitrogen to creatinine nitrogen in the urine before and after the uranium injection. It is evident that these did not change.

As in the first patient, the excretion of U_6 in urine was very rapid during the first twenty-four hours and accounted for 64 per cent of the amount given. The total excretion by this route was 87 per cent at the end of six days. Again there was no increase in urinary catalase or protein or other indication of renal injury.

Subject No. 3 - White female, aged 24 years, Ht. 155.5 cm., Wt. 37 Kg. B. P. 100/60

This young woman was in fairly good physical condition except for mild chronic undernutrition which was thought to be secondary to an emotional maladjustment.

Five ml. of acetate buffer containing uranium nitrate equivalent to 584 micrograms of the metal in the form of the enriched mixture of

[redacted]

SUBJECT NO. 2

TABLE 5

Blood Counts

	9/28	and	10/7
R.B.C.	4.89 4.59	million	4.32
Hb.	13.3	gm/100 ml	14.5
W.B.C.	10,050		11,000

Differential

Bas.	3	per cent	1
Eos.	3		
Segs.	62		68
Lymphs.	19		29
Monos.	9		2
Abnormal	4		2

Blood Chemistry, Etc.

Date	8/31	9/5	9/10	9/20	10/5
Icterus Index	40	20			8
Bilirubin					
Direct	--	--	1.14 mg	0.59	
Total	--	--	2.89	1.07	
Cephalin Flocculation	3+				1
Thymol Turbidity	--				24

[redacted]

SUBJECT NO. 2

TABLE 5
(con't)

Total Protein	6.85	7.2
Albumin	3.0	4.4
Globulin	3.85	2.8
NPN	21 mg %	21

Owing to difficulty in performing venupuncture, only one determination of CO_2 in serum was made. This was 46 Vols. % on 9/26. Alkaline phosphatase was 4.6 Bodansky units on 10/5.

Renal function tests performed under the direction of Dr. Waterhouse were as follows:

	9/11	9/26	Normals
Renal Blood Flow	462.8 ml/min	402	594 ± 102
Glomerular Filtration	114.7 ml/min	118	117 ± 16
Maximum Tubular Excretory Capacity	69.6 mg/min	79	77.5 ± 13

[redacted]

SUBJECT NO. 2

TABLE 6

Excretion of Uranium by Patient 2

Date	Hour	Time After Injection hr.	min.	gm. Uranium in Specimen	Amount of Uranium in Specimen in % of Dose	% of Dose Excreted per ml. of urine
9/18/46	10:30 am		30	125.00	26.20	.153
	12:05 pm	2	05	100.80	21.15	.076
	3:20 pm	5	20	95.48	20.00	.068
	5:45 pm	7	45	23.48	4.92	.020
	7:30 pm	9	30	18.36	3.85	.025
9/19/46	2:50 am	16	50	31.40	6.59	.0125
	8:00 am	22		9.72	2.04	.0105
9/20/46	8:00 am	46		8:35	1.75	.00075
9/21/46	8:00 am	70		1.60	.34	.00023
9/22/46	8:00 am	94		.68	.14	.00010
9/23/46	8:00 am	118	less than	.30	less than .06	less than .00005
9/24/46	8:00 am	142	"	.30	" .06	" .00004
Total Excretion:				415.47	87.10	
Excretion During First 22 hr:				404.24	84.73	.0431
Excretion During 5 Following Days				11.23	2.37	.00023

SUBJECT NO. 2 [redacted]

TABLE 7

Ratio of Urinary Amino Acid Nitrogen to Urinary Creatinine

(Analyzed by H. Berke and M. Crossmon)

Date	Amino Acid N / Creatinine: All day specimen except for 8 am	Date	Amino Acid N / Creatinine: 8 am Specimen
9/10-11	.64	9/11	.46
9/11-12	.64	9/12	.57
9/12-13	.63	9/13	---
9/13-14	.96	9/14	.49
9/14-15	---	9/15	.42
9/15-16	.51	9/16	.37
9/16-17	.65	9/17	.51
9/17-18	.52	9/18	.62
	Point of Uranium Administration		
9/18-19	.54	9/19	.54
9/19-20	.56	9/20	.52
9/20-21	.61	9/21	.48
9/21-22	.46	9/22	.45
9/22-23	.58	9/23	.48
9/23-24	.56	9/24	.44
9/24-25	.48	9/25	.47
9/25-26	.56		
9/26-27	.44		
9/27-28	.61		
9/28-29	.42		
9/29-30	.67		

[redacted]

[redacted]

isotopes of U^{234} and U^{235} was injected into an arm vein on October 1, 1946. This dose represented 15.5 micrograms of +6 uranium per kilogram.

Urine and feces were analyzed for uranium by the electroplating and alpha counting method. The quantity of uranium excreted in the feces was too small to measure accurately and no tabulation of the results is shown. Table 8 gives the urine values obtained by the alpha counting method. The excretion appeared to be somewhat less complete at the end of five days than in the first two instances but the curve of elimination followed the usual pattern. The clinical tests are recorded in table 9, and the urinary amino N/Creatinine N ratios in table 10.

Although the dose of uranium on a kilogram basis had been more than doubled, there was no increase in urinary catalase or protein; the renal clearances remained unchanged and the urinary amino nitrogen/creatinine nitrogen ratio was not altered.

Subject No. 4 - White male, aged 42 years, Ht. (not obtained), Wt. 64 Kg.
B. P. 100/72

Entered hospital because of chronic alcoholism and bleeding from the gastrointestinal tract. His acute symptoms subsided after ten days and he was transferred to the Metabolism Unit. Stools continued to show positive tests for occult blood for a week but were normal thereafter. X-ray studies with barium sulphate of the esophagus, stomach and intestinal tract were negative except for coarse gastric and upper small bowel mucosal patterns. The urine was normal. However, during tests of urea clearances, the patient experienced difficulty in voiding at the times requested. There was no evidence of urethral stricture or enlargement of the prostrate as a contributing factor.

[redacted]

SUB NO. 3

TABLE 8

Excretion of Uranium by Patient 3

Date	Hour	Time after Injection Hr.	Min.	µgm uranium in specimen	Amount of uranium in specimen in % of Dose	% of Dose excreted per ml. of urine
10/1/46	1:20 pm	1	30	203.04	34.78	.1298
	6:00 pm	6	20	151.44	25.95	.0649
	9:25 pm	9	45	24.60	4.21	.0229
10/2/46	6:30 am	18	50	22.00	3.76	.0098
	10:30 am	22	50	2.80	.48	.00254
10/3/46	8:00 am	46	50	6.66	1.14	.00077
10/4/46	8:00 am	70	50	3.18	.545	.00031
10/5/46	8:00 am	94	50	1.75	.30	.00019
10/6/46	8:00 am	118	50	1.51	.26	.00019
10/7/46	8:00 am	142	50	.725	.125	.00008
10/8/46	8:00 am	166	50	.66	.115	.00008
10/9/46	8:00 am	190	50	less than .5	less than .1	less than .00005
10/10/46	8:00 am	214	50	less than .5	less than .1	less than .00007
Total Excretion:				419.365	71.865	
Excretion during first 23 hours:				403.88	69.18	.0485
Excretion during 5 following days:				13.825	2.370	.00030

TABLE

Blood Counts

9/27/46	Date		10/10/46
Red Blood Cells	4.99 million cu. mm.		5.13
Hemoglobin	12.0 grams/100 ml.		Not Done
White Blood Cells	8,750 cu. mm.		5,500
Differential Count:			
Neutrophiles	70%		68%
Lymphocytes	20%		18%
Monocytes	3%		10%
Eosinophiles	3%		2%
Basophiles	2%		1%
Degenerate forms	2%	Stab cells	1%
	100%		100%

[redacted]

[redacted]

SUBJECT NO. 3

TABLE 9 (con't)

Blood Chemistry

	9/28/46	10/11/46
Serum Chloride	99 m. eq/liter	101
Serum CO_2	54 vols. percent	51
Blood Sugar	62 mg/percent	72
Non-Protein Nitrogen	26 mg/percent	32
Inorganic Phosphorus	3.7 mg/percent	3.7
Alkaline Phosphotase	1.3 Bodansky units/100 ml	1.3
Total Serum Protein	5.8 gm percent	5.5
Albumin	4.1 gm percent	3.6
Globulin	1.7 gm percent	1.9
Total Bilirubin	0.56 mg/percent	0.37

Renal Function

(Dr. Waterhouse)

	9/23/46	10/21/46
Glomecular filtration rate --	118 ml/min.	117 ml/min.
Renal Plasma Flow --	593 ml/min.	638 ml/min.
Maximum tabular Excretory Capacity -- (para amino hippuric acid)	81 mg/min.	Not done

[redacted]

[redacted]

SUBJECT NO. 3

TABLE 10

Ratio of urinary amino acid nitrogen to urinary creatinine

(Analyzed by H. Berke and M. Crossmon)

All Day Specimens

	Amino Acid N / Creatinine	
9/20-9/21/46	.26	
9/21-9/22	.26	
9/22-9/23	.27	
9/23-9/24	.31	
9/24-9/25	.27	
9/25-9/26	.21	
9/26-9/27	.30	
9/27-9/28	.34	
9/28-9/29	.27	
9/29-9/30	.17	
9/30-10/1	.21	
		Point of uranium administration
10/1-10/2	.24	
10/2-10/3	.24	
10/3-10/4	.21	
10/4-10/5	.22	
10/5-10/6	.22	
10/6-10/7	.26	
10/7-10/8	.28	
10/8-10/9	.22	
10/9-10/10	.24	

[redacted]

[redacted]

Urea Clearances

Date	Type of Clearance	Per cent of Normal
10/14/46	Maximum	61
10/16/46	Standard	43
10/18/46	Maximum	71
10/30/46	Technician #1	
	Maximum	60
	Standard	53
10/30/46	Technician #2	
	Maximum	56
	Standard	50

The reduction of urea clearance was not felt to be a contraindication to continuance of the experiment, for the urine was normal to clinical examination and had a low catalase activity. The injection of +6 uranium was given on October 23, 1946. In this case equal parts of the enriched isotopic mixture and of the natural mixture of isotopes were given. The total dose of uranium metal was 1918 micrograms or 29.9 micrograms per kilogram.

No significant amount of uranium could be detected in the feces. Table 11 gives the excretion of uranium in the urine. It is to be noted that the rate and percentage excretion was much the same as in Subject 3. Urinary catalase and protein did not increase in the post injection period.

At the end of twelve days the excretion in the urine per twenty-four hour period was of the order of 1 microgram and there was an apparent retention of 535 micrograms presumably in the bones. In view of the fact that hexavalent uranium complexes readily with citrate (13), it was decided

[redacted]

to determine the effect of i.v. citrate on mobilization of the residual metal.

On November 4, 1946 the patient was given 2000 ml of a solution containing 4.6 gm. sodium citrate and 1.1 gm. citric acid per liter Unfortunately this solution was so hypotonic that although given slowly by intravenous drip over a three hour period, the next two voidings of urine contained hemoglobin and his temperature rose to 39.5° C. As may be noted from inspection of table 11, this maneuver did not affect the excretion of uranium.

One sample of blood was drawn eight minutes after completing the injection and was found to contain 0.043 micrograms of uranium per ml. If the blood volume of this man be estimated at 5000 ml, then 11 per cent of the dose was still within the vascular system.

The citrate excretion in the urine was measured on two control days during the administration of sodium citrate, citric acid solution and in a follow-up period. There was comparatively little increase in the urinary excretion of citrate (table 12) which suggests that much of the citrate administered must have been metabolized rather than excreted.

Blood counts and blood chemistry may be found in table 13.

The range of dosage had now been reached where mild toxic effects on the kidney were to be anticipated (14). There was no evidence of such damage in this subject. The level of urinary catalase and protein remained unaltered as did the amino N/Creatinine N ratio. Subsequent follow-up examinations in the clinic revealed steady improvement in his general condition.

[redacted]

TABLE 11

EXCRETION OF URANIUM BY PATIENT NO. 4

Date	Hour	Time after injection hr.	min.	Uranium in Specimen ug	Uranium in Specimen % of Dose	% of Dose Excreted per ml of Urine	Time in days (approx.)
10/23/46	2:35 pm	3	15	449.5	23.43	.0889	
	4:25 pm	5	05	238.0	12.41	.03075	
	10:15 pm	9	55	336.1	17.52	.0475	
10/24/46	12:30 am	13	10	114.1	5.95	.00965	
	3:30 am	16	10	87.2	4.55	.0131	
	8:00 am	20	40	52.8	2.75	.0172	1
10/25/46	8:00 am	44	40	60.1	3.14	0.0017	2
10/26/46	8:00 am	68	40	21.65	1.13	0.0053	3
10/27/46	8:00 am	92	40	7.15	0.37	0.00016	4
10/28/46	8:00 am	116	40	3.95	0.21	0.00011	5
10/29/46	8:00 am	140	40	3.4	0.19	0.00010	6
10/30/46	8:00 am	164	40	2.4	0.12	0.00008	7
10/31/46	8:00 am	188	40	2.3	0.12	0.00007	8
11/1/46	8:00 am	212	40	less than 0.70	less than 0.04	less than 0.00003	9
11/2/46	8:00 am	236	40	1.85	0.10	0.00007	10
11/3/46	8:00 am	260	40	0.95	0.05	0.00005	11
11/4/46	8:00 am	284	40	less than 1.15	less than 0.06	less than 0.00003	12

T 11
(Part)

Date	Hour	Time after injection hr.	min.	Uranium in Specimen µg.		Uranium in Specimen % of Dose		% of Dose Excreted per ml of Urine	Time in Days (Approx.)
		Na citrate administered 11/4/46 - 2 pm - 5 pm							
11/4/46	5:00 pm	293	40	less than	0.20	less than	0.01	0.00003	12
11/5/46	8:00 am	308	40	less than	0.50	less than	0.03	0.00007	13
11/6/46	8:00 am	332	40		0.85		0.04	0.00003	14
11/7/46	8:00 am	356	40		1.95		0.10	0.00005	15
11/8/46	8:00 am	380	40		0.5		0.03	0.000016	16
11/9/46	8:00 am	404	40	less than	0.5	less than	0.03	0.000015	17

Total Excretion:	1384.	72.2	
Excretion during first 20 hours, 40 min.	1277.	66.6	.0029
Excretion during five following days	96.	5.0	.00058
Total subsequent excretion	10.8	.56	
U in blood sample withdrawn	1.2		

SUBJECT NO. 4

TABLE 12

EFFECT OF INTRAVENOUS CITRATE ADMINISTRATION ON MOBILIZATION OF URANIUM DEPOSITED IN THE BODY TWELVE DAYS AFTER INTRAVENOUS ADMINISTRATION OF URANIUM*

Time Interval		Concentration of Citrate mg/ml	Urinary Volume ml	Total Excretion of Citrate per Day mg		Excretion of Uranium per Day % of Dose
10 am 11/2/46 to 8 am 11/3/46		0.115	1005	115.5		0.05
10 am 11/3 to 8 am 11/4		0.081	1934	156.8	less than	0.06
2 pm - 5 pm 11/4/46		0.147	310	45.5	less than	0.01
6:35 pm 11/4 to 8 am 11/5	less than	0.069	3625	less than 250.	less than	0.03
10 am 11/5 to 8 am 11/6		0.110	1537	169.		0.04
10 am 11/6 to 8 am 11/7		0.138	1972	272.		0.10
10 am 11/7 to 8 am 11/8		0.163	1654	270.		0.03
10 am 11/8 to 8 am 11/9		0.083	1722	143	less than	0.03

*Citrate analyses performed by Dr. Walter Mann and Janet Gruschow using the pentabromacetone colorimetric method.

[redacted]

TABLE 13

BLOOD COUNTS, etc.

10/7/46 (Student)

Red Blood Cells	2.2×10^6 per cu mm.
Hgb.	11 gm/100 ml whole blood
Hematocrit	27% R.B.C.'s.
Mean Corpuscular Vol.	123 c.μ
Mean Corpuscular Hgb.	50 μμ
Mean Corpuscular Hgb. Conc.	41% probably too high
Reticulocytes	7%

10/16/46 (Dr. Lawrence's Technician)

Red Blood Cells 2,670,000
2,640,000 per cu. mm.

WBC's 10,350

Differential Count

Neutrophiles (segmented)	55%
Stab Cells	4%
Lymphocytes	15%
Abnormal Lymphs	5%
Mononuclears	10%
Eosiophiles	8%
Basophiles	3%
	100%

11/5/46

Hb. 10 gm/100 ml whole blood

Hematocrit 29% R.B.C.

[redacted]

Table 13
(con't)

[redacted]

BLOOD CHEMISTRY

Determination	10/1	10/12	11/1
Sugar	81 mg/%	71	86
Non-Protein Nitrogen	42 mg/%	38	42
Serum Albumin	2.8 gm/%	3.9	3.4
Globulin	1.6 gm/%	1.6	1.7
Total Protein	4.4 gm/%	5.5	5.1
Choleoteral	1120 mg/%		
Serum CO_2	45 vols./%		53
Serum Chloride	540 mg/%		614
Fibrinogen	266 mg/%	426	284
Alkaline Phosphatase	21.5 units	4.8	2.7
Calcium	8.3		
Phosphorus	2.9	4.3	3.4
Icterus Index	30	10	6
Total Bilirubin		0.94 mg/%	
Thymol Turbidity	208 units	14	15
Cephalin Floc.	neg (?)	1+	

[redacted]

[redacted]

Subject No. 5 - Male negro, aged 51 years, Ht. 160 cm., Wt. 56.2 Kg., B. P. 120/80, T. 36.8°C

Chronic cough had been present for about one and a half years and there was a history of rather high consumption of beer and ale. Three weeks prior to his hospitalization on October 30, 1946, his cough became worse. The sputum was streaked with blood, he had fever at night, he became anorexic, dyspneic and complained of marked weakness. Physical examination revealed signs of consolidation of the right upper lobe of the lung. Type 14 pneumococcus was recovered from the sputum by direct typing and by injection into a mouse. The temperature was 40.4°C, leukocyte count 20,750, icterus index 24, cephalin flocculation 2+, CO_2 content of serum 39 volumes per cent, chlorides of serum 98 meq./liter, total serum protein 4.8 gm. per cent, non protein nitrogen 44 mg. per cent. His illness ran a stormy course, but gradually reponded to combined therapy with penicillin and sulfadiazine. These medications were discontinued on November 19, 1946 after he had received a total of 8,765,000 units of intramuscular penicillin and 87 gms. of sulfadiazine orally. He remained afebrile from this point on but his convalescence was slow and signs of consolidation of the right upper lobe, both by physical examination, and by X-ray, persisted. Bronchoscopy was performed on November 11, 1946 but no obstruction to the right upper lobe bronchus was discovered.

During the period of observation on the metabolism ward his appetite was excellent and he gained 1.5 Kg. in weight.

Since the tolerance for uranyl nitrate appeared good in Subject 4 at a level of about 30 micrograms per kilogram (as uranium metal), a further moderate increase in the dose was given Subject 5. The mixture of isotopes

[redacted]

[redacted]

enriched in U^{234}, U^{235} was diluted 1-4 with ordinary uranium and injected in the amount of 2746 micrograms or 48.8 micrograms per kilogram on December 17, 1946.

The analyses of the urine appear in table 14. Again no significant amount of uranium could be detected in the feces by the method of analysis employed. Although there was no increase in urinary catalase (table 15), a trace of protein appeared in the urine on the fourth post injection day. While it is suspected that this was a chance observation and without significance as far as the uranium was concerned, it is unfortunate that the patient could not have been followed longer. He was feeling much improved at the time and insisted on being discharged from the hospital. There was no follow-up.

Other clinical data and the amino N/Creatinine N ratios in the urine may be found in tables 16 and 17.

Subject No. 6 - White male, aged 61 years, Ht. 163 cm., Wt. 55.2 Kg. B. P. 150/84, T. 36.5°C

The fifth admission of this patient was on October 14, 1946. He remained in the hospital continuously from this date until completion of the metabolic studies on April 1, 1947. His transfer to the metabolism unit of the purpose of the studies recorded here was effected on January 3, 1947.

Some of the previous diagnoses were: arteriosclerosis general, hypertension secondary, heart disease arteriosclerotic and hypertensive Class IIa; alcoholism chronic; spontaneous pneumothorax; pneumonia right upper lobe, pneumococcus Type II; tuberculosis pulmonary. The last diagnosis was probably based upon insufficient evidence for after

[redacted]

[redacted]

SUBJECT NO. 5

TABLE 14

Excretion of Uranium by Patient No. 5 –

Date	Hour	Time after injection hr.	Time after injection min.	Uranium in specimen. µg.	Uranium in specimen. % of dose	% of dose excreted per ml. of urine
12/17/46	3:50 pm	6	10	1442.0	52.50	.160
	5:30 pm	7	50	257.0	9.34	.0486
	9:25 pm	11	45	119.0	4.34	.0157
	11:40 pm	14	00	78.0	2.84	.0101
12/18/46	1:30 am	15	50	44.4	1.62	.0034
	5:00 am	19	20	43.8	1.59	.00365
	8:00 am	22	20	29.0	1.06	.0056
12/19/46	8:00 am	46	20	48.1	1.75	.0012
12/20/46	8:00 am	70	20	3.8	.14	.00015
12/21/46	8:00 am	94	20	1.1	.04	.000041

Total excretion:	2240.0	75.22	
Excretion during first 22 hours and 20 minutes	2187.0	73.29	.0334
Excretion during three following days:	53.0	1.93	.00057

[redacted]

[redacted]

SUBJECT NO. 5

TABLE 15

Urinary Catalase and Protein

Date	Hour	Catalase (cm. of H_2O)	mg. Albumin/5 ml. urine
12/12/46	10:30 am	8	0
12/13/46	10:30 am	2	0
12/14/46	10:30 am	3	0
12/15/46	10:30 am		
12/16/46	10:30 am	3	0
12/17/46	9:00 am	2	0
		Uranium Administered 9:40 am 12/17/46	
12/18/46	10:30 am	2	0
12/19/46	10:30 am	4	0
12/20/46	10:30 am	4.5	0
12/20 - 12/21,24 hr. sample			0
12/21/46	10:30 am	4	20

[redacted]

[redacted]

SUBJECT NO. 5

TABLE 16

Laboratory Data:

Urea Clearance 12/11/46

1. Standard Clearance 79% of normal.
2. Standard Clearance 75% of normal.

Urine Examination: Specific Gravity — 1.015, no albumin casts or sugar.

Blood Count (11/27/46)

Red blood cells 3.7×10^6 per cu. mm.

W.B.C.'s 12,500 per cu. mm.

Hemoglobin 13 gms./100 ml. whole blood

Differential Leucocyte count

Neutrophiles 80, lymphocytes 18, monocytes 1

Basophiles 1

Blood Chemistry

	12/12/46	12/21/46
Non-protein nitrogen	33 mg.%	35
Sugar	78 mg.%	—
Chloride	590 mg.%	563
CO_2	55% Vols.%	63
Total Serum Protein	6.4 gm.%	6.7
Albumin	3.9 gm.%	4.3
Globulin	2.5 gm.%	2.4
Fibrinogen	327 mg.%	—
Icterus	8	3
Total Plasma Bilirubin	0.3 mg.%	—
Cephalin Flocculation	1+	negative
Thymol Turbidity	19 units	—

[redacted]

SUBJECT NO. 5

TABLE 17

Ratio of Urinary Amino Acid Nitrogen to Urinary Creatinine

(Analyzed by H. Berke and M. Crosmon)

Date	Amino Acid N / Creatinine (all day specimen)	Urinary pH.	
12/7/46 - 12/8/46	.25	5.92	
12/8/46 - 12/9/46	.16	5.70	
12/9/46 - 12/10/46	.16	5.87	
12/10/46 - 12/11/46	.15	5.45	
12/11/46 - 12/12/46	.15	5.54	
12/12/46 - 12/13/46	.16	5.56	
12/13/46 - 12/14/46	.09	5.77	
12/14/46 - 12/15/46	.12	5.41	
12/15/46 - 12/16/46	.16	5.45	
12/16/46 - 12/17/46	.13	5.32	
12/17/46 - 12/18/46	.15	5.67	Uranium administered 9:40 am 12/17/46
12/18/46 - 12/19/46	.11	5.68	
12/19/46 - 12/20/46	.16	5.38	
12/20/46 - 12/21/46	.06	5.39	

[redacted]

[redacted]

three months observation in a tuberculosis sanatarium, he was discharged with a diagnosis of chronic pulmonary fibrosis secondary to his previous Type II pneumonia. The present admission was for symptoms suggesting a gastric lesion. This was confirmed by X-ray and gastroscopy and was thought to be a benign ulcer. He improved promptly on medical treatment and the ulcer appeared to heal. Further pulmonary studies including concentration of the sputa, bronchoscopy and X-ray failed to reveal evidence of active pulmonary tuberculosis. As he had no home, he agreed willingly to enter the metabolic unit for special studies.

Two experiments were set up. In the first of these the patient served as his own control for the second experiment.

Experiment 1 - Condition Normal

Laboratory Data:

Blood: Hb. 13.8 gm./100 ml

RBC 4.62 million/cu. mm.

WBC 8,300

Differential Count:

Neutrophiles 75, Lymphocytes 22, Monocytes 3

Urine:

Specific Gravity 1.024, Albumin 0, Sugar 0.

Acetone 0. Microscopic 2-3, WBC per high power field

Stool:

Negative guaiac reaction for blood on admission to metabolism

X-ray of Lungs:

Resolving pneumonic process in right upper lobe with residual fibrosis.

[redacted]

X-ray of Stomach:

Decrease in size of the ulcer on the lesser curvature.

Renal Function: 1/9/47 (Condition normal)

Renal plasma flow	482 ml./min.	(Normal 697 ± 130)
Glomerular Filtration Rate	99 ml./min.	(Normal 131 ± 22)
Maximum Tubular Excretory Capacity	95 mg./min.	(Normal 77.5 ± 12.9)
Filtration Fraction	0.205	(Normal 0.19 ± 0.02)

Blood Chemistry: 1/6/47

NPN	30 mg. per cent	Globulin	2.3 gm. per cent
Total Serum Protein	6.5 gm. per cent	Chloride	98 meq./l
Albumin	4.2 gm. per cent	CO_2	64 vols. per cent

Uranium (as +6 metal) in the amount of 3910 micrograms was injected intravenously at 10:25 A. M. on January 10, 1947. As in the case of Subjects 4 and 5, the enriched mixture of the isotopes U^{234}, U^{235} was diluted by addition of uranyl acetate of natural isotopic composition. The total activity of the dose was computed as 0.03 microcuries, and the metal injected per kilogram of body weight was 70.9 micrograms. The uranium analyses for the urine are given in table 18 by the method of electroplating and alpha counting.

The catalase and protein tests for tubular damage enumerated in table 19 for the first time are slightly higher on the fifth and sixth days after the injection. While it cannot be stated that either test is unequivocally positive, it would seem advisable that any further increase in the dose should be made in small increments. There was no change in the ratio Amino N/Creatinine N in the urine (table 20).

[redacted]

SUBJ NO. 6

TABLE 18

Excretion of Uranium by Patient No. 6
Normal

Date	Hour	Time After Injection hr.	min.	Uranium in Specimen µg.	Uranium in Specimen in % of Dose	Cumulative Excretion in % of Dose	% of Dose Excreted per ml. of Urine
1/10/47	10:25 am		25	46.75	1.19	1.19	.027
	12:30 pm	2	30	855.0	21.81	23.00	.096
	3:25 pm	5	25	672.0	17.20	40.20	.089
	5:45 pm	7	45	600.0	15.32	55.52	.0715
	7:45 pm	9	45	301.0	7.70	63.22	.050
	10:05 pm	12	05	222.0	5.68	68.90	.029
1/11/47	12:40 am	14	40	144.9	3.70	72.60	.0145
	3:55 am	17	55	101.7	2.60	75.20	.0072
	7:05 am	21	05	60.6	1.55	76.75	.0072
	8:00 am	22	00	34.3	.86	77.61	.0093
1/12/47	8:00 am	46	00	204.7	5.24	82.85	.0033
1/13/47	8:00 am	70	00	70.9	1.81	84.66	.0009
1/14/47	8:00 am	94	00	70.9	1.81	86.47	.001
1/15/47	8:00 am	118	00	38.9	1.00	87.47	.00045
1/16/47	8:00 am	142	00	29.5	.75	88.22	.00045
1/17/47	8:00 am	166	00	16.5	.42	88.64	.00025
1/18/47	8:00 am	190	00	less than 18.1	.46	89.10	.0003

SUBJECT NO. 6

TABLE 18
(con't)

Date	Hour	Time After Injection hr.	Uranium in Specimen µg.	Uranium in Specimen in % of Dose	Cumulative Excretion in % of Dose	% of Dose Excreted per ml. of Urine
1/19/47	8:00 am	214	17.1	.44	89.54	.00025
1/20/47	8:00 am	238	16.9	.44	89.98	.00025
1/21/47	8:00 am	262	17.9	.46	90.44	.00025
1/22/47	8:00 am	286	16.4	.41	90.85	.00025
1/23/47	8:00 am	310	10.6	.27	91.12	.00015
1/24/47	8:00 am	334	less than 6.5	less than .17	less than	.00008

Excretion during first 22 hours	3038.25 µg.	77.61%
Excretion during following 5 days	414.9 µg.	10.61%
Excretion during seven days following the first six days	113.5 µg.	2.90%
Total Excretion:	3566.65 µg.	91.12%

[redacted]

SUBJECT NO. 6

- TABLE 19

Urinary Catalase and protein

Date		Catalase (mm. of H_2O)	mg. Albumin/5 ml. urine
1/4/47	10:30 am	5.5	0
1/6/47	10:30 am	8	0
1/7/47	10:30 am	10.5	0
1/8/47	2:00 pm	7.5	0
1/9/47	10:30 am	16	0
1/10/47	9:40 am	9.5	0
Uranium administered 10 am 1/10/47			
1/11/47	10:30 am	8	0
1/12/47	9:30 am	8.5	0
1/13/47	10:30 am	11	0
1/14/47	10:30 am	10.5	0
1/15/47	9:45 am	12.5	trace (less than 5 mg.)
1/16/47	8:00 am	12.5	trace (less than 5 mg.)
1/17/47	10:30 am	11	0
1/18/47	10:30 am	8	0
1/19/47	10:30 am	11	0
1/22/47	10:30 am	12	0

[redacted]

[redacted]

SUBJECT NO. 6

TABLE 20

Ratio of urinary amino acid nitrogen to urinary creatinine.

(Analyzed by H. Berke and M. Crossmon)

Date	Amino Acid N. / Creatinine	Urinary pH.
1/4/47 - 1/5/47	.16	6.02
1/5/47 - 1/6/47	.15	5.75
1/6/47 - 1/7/47	.15	5.61
1/7/47 - 1/8/47	.13	5.34
1/8/47 - 1/9/47	.13	5.22
1/9/47 - 1/10/47	.13	5.52
Uranium administered 10:00 am 1/10/47		
1/10/47 - 1/11/47	.04	5.67
1/11/47 - 1/12/47	.14	5.44
1/12/47 - 1/13/47	.14	5.34
1/13/47 - 1/14/47	.15	5.31
1/14/47 - 1/15/47	.14	5.35
1/15/47 - 1/16/47	.14	5.87
1/16/47 - 1/17/47	.12	5.54
1/17/47 - 1/18/47	.15	5.36
1/18/47 - 1/19/47	.17	5.32
1/19/47 - 1/20/47	.28	5.28
1/20/47 - 1/21/47	.16	5.41
1/21/47 - 1/22/47	.12	5.44

[redacted]

[redacted]

Renal clearance tests were repeated six days after the injection at a time when, according to the animal work, injury would be apt to manifest (14). No significant difference from the control values is evident.

Date of Tests, January 16, 1947

Renal Plasma Flow	499 ml./min.
Glomerular Filtration Rate	93 ml./min.
Maximum Tubular Excretory Capacity for para aminohippuric acid	83 mg./min.
Filtration fraction	0.185

Experiment 2 - Condition Acidotic

About 90 per cent of the first dose of uranium had been excreted in the urine by January 22nd. Acidification was begun by giving 8 gm. of ammonium chloride daily for three days and the dose was increased to 12 gm. a day on the fourth and fifth days. The second dose of uranium was given intravenously on January 27, 1948. It was somewhat smaller than the first dose, 3170 micrograms of U_6 metal, or 56.6 micrograms per kilogram body weight. At the same time the dose of ammonium chloride was reduced to 4 gm. a day and discontinued after January 31st. The effect of NH_4Cl on the blood chemistry was as follows:

Blood Chemistry:

	Jan. 27	Jan. 28	Jan. 31	Feb. 4
CO_2 content of Serum Vols per cent	32	36	48	70
Chloride in Serum, meq./liter	116	112	105	104
Non protein nitrogen, mg. per cent	60	50	41	

It is evident that since the control values for CO_2 content of serum were above 60 vols. per cent, a considerable acidosis was achieved by the administration of the ammonium chloride.

[redacted]

[redacted]

Table 21 gives data on the rate and cumulative excretion of uranium during acidosis. The slower excretion is appreciated best by referring to Figure 1. The twenty-four hour urinary excretion of uranium had fallen to a very low level fifteen days after the second injection and analyses were discontinued. The amount retained in the body at this time may be estimated roughly as:

Total uranium (U_6) administered (Sum of the two doses)	7080 micrograms
Less total uranium eliminated in urine	5913 micrograms
Possible retention in body	1167 micrograms

The final tests of kidney function were done on January 31, 1947 during the period of acidosis.

Renal plasma flow	555 ml./min.
Glomerular Filtration	102 ml./min.
Maximum tubular excretory capacity for para aminohippuric acid	92 mg./min.
Filtration Fraction	0.184

The apparent retention of U_6 by this man offered the opportunity to test the effect of measures aimed at mobilization of the uranium presumable retained in the bones. To this end the dietary calcium was reduced to 0.2 gm. a day which is less than the amount required for equilibrium (15) and gradually increasing doses of dihydrotachysterol (A. T. 10) were simultaneously administered.

It was hoped that this program would have a moderate decalcifying effect and perhaps liberate some uranium from its combination with the phosphate groups of bone. We have assembled the data on serum Ca + P and urinary Ca and P for this experiment in table 22. The maximum dose

[redacted]

Table 21

Subject 6

Excretion of Uranium by Subject No. 6 Following Acidification

Date	Hour	Time After Injection hr.	min.	Uranium in Specimen µg.	Uranium in Specimen in % of Dose	Cumulative Excretion in % of Dose	% of Dose Excreted per ml of Urine	Urinary pH.
1/27/47	3:00 pm	1		315.7	9.95	9.95	.0506	5.04
	4:10 pm	2	10	229.5	7.24	17.19	.060	5.13
	5:30 pm	3	30	235.7	7.43	24.62	.056	5.19
	7:30 pm	5	30	327.0	10.32	34.94	.051	5.28
	9:00 pm	7		159.5	5.03	39.97	.032	5.22
	10:35	8	35	147.9	4.66	44.63	.034	5.32
	12:35	10	35	119.5	3.77	48.40	.024	5.33
1/28/47	2:50 am	12	50	143.8	4.54	52.94	.014	5.21
	4:50 am	14	50	75.5	2.38	55.32	.010	5.06
	7:05 am	17	05	63.7	2.01	57.33	.011	5.00
1/29/47	8:00 am	42		363.7	11.15	68.48	.0057	5.25
1/30/47	8:00 am	66		158.3	4.99	73.47	.0025	5.38
1/31/47	8:00 am	90		115.3	3.64	77.11	.0017	5.38
2/1/47	8:00 am	114		75.7	3.39	79.50	.00094	5.43
2/2/47	8:00 am	138		67.9	2.14	81.64	.0011	5.38
2/3/47	8:00 am	162		49.0	1.55	83.19	.0008	5.34
2/4/47	8:00 am	186		52.1	1.64	84.83	.0007	5.30

Table _ (Continued)

Date	Hour	Time After Injection hr.	Uranium in Specimen µg.	Uranium in Specimen in % of Dose	Cumulative Excretion in % of Dose	% of Dose Excreted per ml. of Urine	Urinary PpH.
2/5/47	8:00 am	210	40.0	1.26	86.09	.0007	5.91
2/6/47	8:00 am	234	27.8	.88	86.97	.0007	
2/7/47	8:00 am	258	27.6	.87	87.84	.00065	6.84
2/8/47	8:00 am	282	25.8	.81	88.65	.0004	6.75
2/9/47	8:00 am	306	31.1	.98	89.63	.00055	7.14
2/10/47	8:00 am	330	14.4	.45	90.08	.00035	6.83
2/11/47	8:00 am	354	16.2	.51	90.59	.0004	7.01

Excretion during first 17 hours:	1817.8 µg.	57.33%
Excretion during following 5 days	770.9 µg.	24.31%
Excretion during seven days following the first six days	253.4 µg.	7.99%
Excretion in next two days	30.6 µg.	.96%
Uranium in blood sample of January 1, 1947	2.7	.08
Total Uranium Recovered	2875.4 µg	90.67%

[redacted]

SUBJECT NO. 6

TABLE 22

Daily intake:

Calcium 235 mg.
Phosphorus 1127 mg.

Day	Blood Ca mg.%	Blood P mg.%	Urine Ca mg. 24 hrs.	Urine P mg. 24 hrs	A.T. 10 Daily cc	Uranium in urine micrograms in 24 hrs.
1			49	1008	None	
2			31	812	"	
3			33	705	"	
4			31	655	"	
5			32	765	"	
6	9.7	3.4	22	711	"	
7			30	868	"	
8			34	785	"	
9			26	730	"	12.5
10			27	753	"	14.7
11			38	704	"	8.9
12			30	699	"	6.5
13			34	688	2 ml	9.7
			40	716	2 ml	13.0
			43	730	2 ml	7.2
16			45	681	2 ml	2.9
17			39	722	2 ml	8.2
18			35	720	2 ml	5.2
19			47	748	2 ml	
20	9.5	3.5	36	702	4 ml	9.2
21			43	758	4 ml	9.1
22			37	747	4 ml	5.9
23			38	797	4 ml	8.1
24	9.3	4.0	17	529	6 ml	9.9
			29	771	6 ml	8.2
26			28	782	6 ml	2.0
27			32	750	6 ml	11.3
28	10.0	3.6	44	726	6 ml	5.2
29			47	721	6 ml	1.0
30			44	753	6 ml	1.9
31			54	858	6 ml	8.4
32	8.7	4.1	61	832	6 ml	10.6
33			67	806	6 ml	7.4
34			84	881	6 ml	0.0
35	9.9	3.5	76	844	6 ml	0.0
36			86	798	6 ml	4.3
37			91	811	6 ml	2.2
38			85	710	6 ml	5.5
[illegible]			97	764	6 ml	7.1
			97	730	6 ml	10.6
[illegible]			104	682	6 ml	0.0
42			38	728	None	3.2

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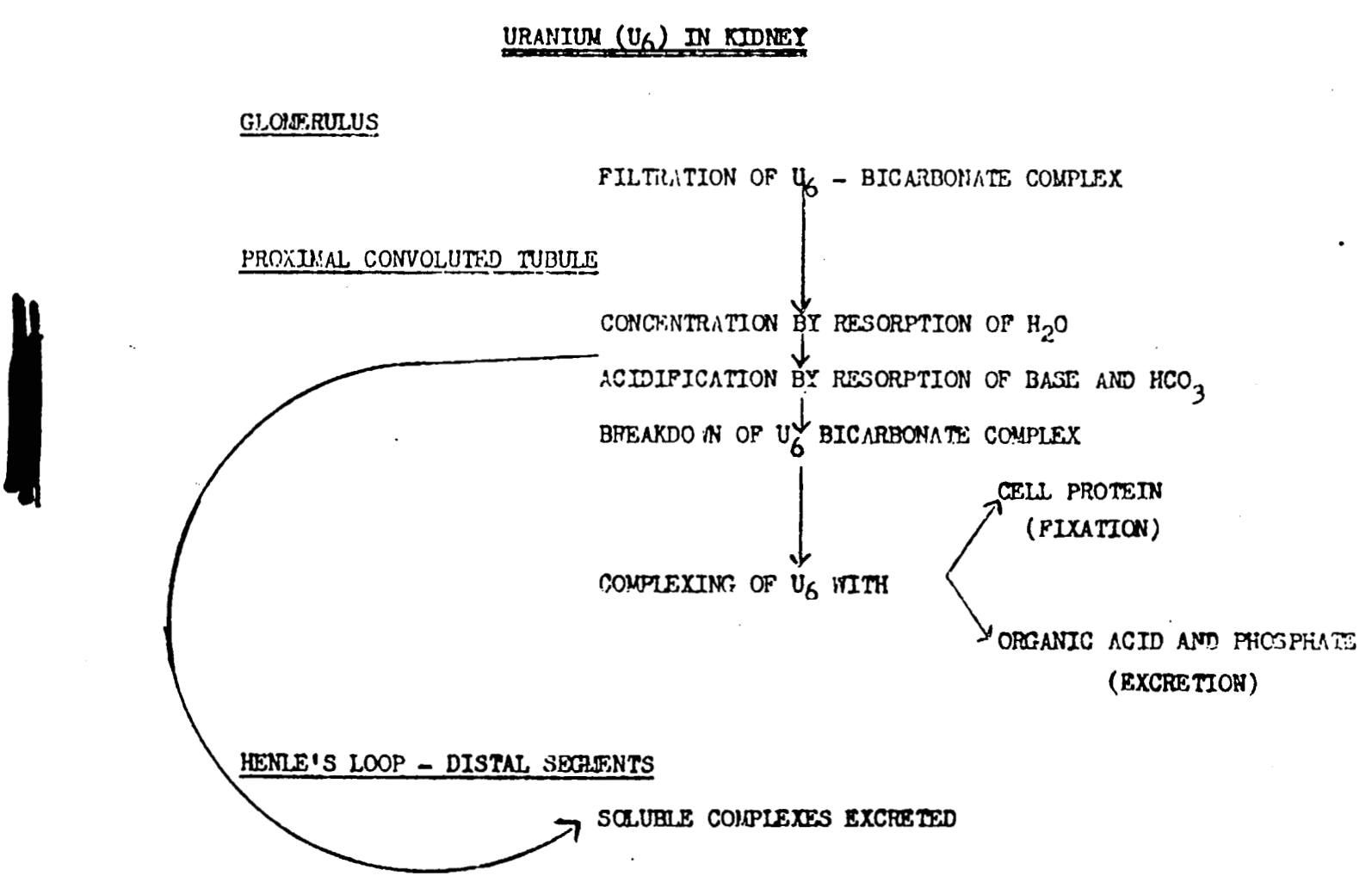
[redacted]

of A.T. 10 was 7.5 mg. a day continued for eighteen days. While this about tripled the excretion of calcium in the urine, it did not affect urinary phosphorus and there was no increase in the excretion of uranium.

VI. Mechanism of Excretion of Hexavalent Uranium

Dounce (13) has shown that uranyl ions complex readily with carbonate or bicarbonate, organic acids as citrate, malate and acetate, with protein and with phosphate. In blood where there is a large excess of bicarbonate, about 60 per cent of U_6 is thought to form a firm complex of the type $UO_2(CO_3)_2$. Evidently from the studies we have been able to carry out, man behaves as does the rabbit and other animals with regard to excretion of uranium. A schema giving the probable mechanism of excretion of U_6 by the kidney is given in Figure 2 (modified from Dounce (14)). The diffusable bicarbonate complex is filtered at the glomerulus. Measures which cause acidification of the urine decrease the concentration of bicarbonate in it and hence its ability to complex uranium. Complexing of the metal with the cell protein of the renal tubules is thus favored. This mechanism is well illustrated in the animal studies of Wills (11). In Subject 6 it seems probable that the production of a highly acid urine through the administration of ammonium chloride is responsible for slowing the excretion of U_6. The lowered content of bicarbonate in the urine permitted uranium to complex with cell protein where it was held temporarily. Its removal from the cell was accomplished slowly through the presence of traces of strongly complexing amions such as citrate, malate and bicarbonate which when present even in very small quantities successfully compete with protein for uranium (16). If sufficiently damaged, these cells may be shed

FIGURE 2



MECHANISM OF EXCRETION OF URANIUM (U_6) BY THE KIDNEY

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into the urine or at least become more permeable and leak catalase into it. The early proteinuria of uranium poisoning no doubt has a similar etiology.

The small and in our experiments inconsequential amounts of uranium (U_6) found in the feces are also in agreement with the animal work. Possibly a very minute fraction of the injected dose is excreted in the bile and traces probably appear in other intestinal secretions. The presence of dietary phosphorus and the reaction of the intestinal contents would favor fixation of any uranium entering the gut as a phosphate complex (16) or as a precipitate of uranyl phosphate.

The retention of 15 to 20 per cent of the amount administered may be later significantly reduced by continued slow excretion. From the work of Neuman and collaborators (2) uranyl ions appear to be fixed to bone "by a slightly dissociated linkage with two phosphate groups adjacent to each other in the bone surface". The U_6 held in the skeleton without doubt represents that fraction of the total dose which is not eliminated within the first few days.

VII. Summary

Tracer studies employing uranium enriched in the isotopes U^{234}, U^{235} have been carried out in six human subjects; four males and two females. The uranium was given intravenously in the hexavalent state as uranyl nitrate in amounts ranging from 6 micrograms to 70 micrograms per kilogram of body weight.

Each individual of the series received a single injection of the metal except for Subject 6 who was given two widely spaced doses. The

first of these was when his condition was normal [illegible] after an acidosis had been produced by ingestion of ammonium chloride. Renal function tests including urinary catalase, protein, amino N to Creatinine N ratio, and clearances of mannitol and p - aminohippurate were done before and after administration of uranium. Only at the 70 microgram per kilogram level in Subject 6 was there a slight rise in urinary catalase and protein suggestion that tolerance had been reached. All other tests were negative.

The excretion of uranium was mainly in the urine, where from 70 to 85 per cent of the administered dose appeared in the first twenty-four hours. Urine of the second twenty-four hours contained about 4 per cent, and the third twenty-four hours urine, 1.5 per cent of the administered dose. Detectable amounts were excreted for at least two weeks. It is surmised that this late excretion represented uranium originally stored in the bones. Negligible amounts of uranium were found in the feces.

The production of an acidosis with ammonium chloride (Subject 6) decreased the rate of excretion. Attempts at mobilization of the fraction retained by injection of citrate and by the use of a low calcium diet plus dihydrotachysterol were ineffective.

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