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REPORT PREPARED BY THE DIVISION OF SPECIAL PROBLEMS

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METABOLISM OF POLONIUM

VI. Tracer Studies in Three Human Subjects
Following Intravenous or Oral Administration

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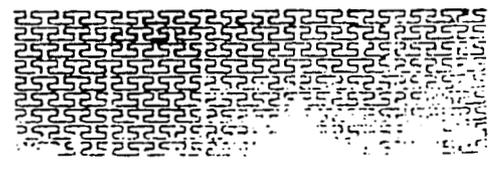
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SUMMARY

Three further studies of the blood content and rate of excretion of polonium in human subjects have been done.

The behavior of Po following single intravenous injections of 0.15 microcuries per kilogram of body weight was studied in two cases.

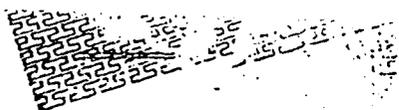
One showed a urinary excretion of 0.09 percent of the dose in the first 24 hours, and an average daily urine content during the first week of 0.12%, or 0.06% per liter. During the second week after injection the urine value averaged 0.08% of the dose per day, or 0.05% per liter. By 70 days it fell to 0.02% per day. In the second case 0.07 percent of the dose was excreted in the first day's urine; an average of 0.05% per day, or 0.03% per liter, during the first week; and 0.04% per day, or 0.03% per liter, during the second week.

The fecal excretion, analyzed only in the first case, averaged 0.56 percent of the dose per day, or 0.007% per gram, during the first week, and 0.73% per day, or 0.006% per gram, during the second week after injection. On the 70th day 0.25% of the dose was eliminated in the feces.

The rapid disappearance of injected Po from the blood stream was seen in both cases, falling to 2.3 percent of the dose estimated in the whole circulation at 15 minutes in one case, and about 5.2% circulating at 25 minutes in the other. The whole blood values were 0.001 percent of the dose per cc. at 24 hours, rose to about 0.002% at 4 or 5 days; and fell to 0.0003% per cc. at 70 days. The concentration in cells was two or three times greater than in plasma, and somewhat greater in white cells than in red.

The metabolism of ingested Po was studied in one human subject, given 18.5 microcuries (0.19 $\mu\text{c.}/\text{kilo.}$) by mouth. The first blood sample, taken one hour after administration of the dose, contained $6 \times 10^{-3}\%$ of the dose per cc., and the first urine sample, at $2\frac{1}{2}$ hours, $2 \times 10^{-4}\%$ of the dose. By 48 hours the whole blood concentration reached $5 \times 10^{-4}\%$ of the dose per cc., then after the 4th day, declined very gradually to a barely detectable value, less than $10^{-5}\%$ dose/cc. at 230 days. Daily urine excretions of 5 to $7 \times 10^{-3}\%$ of the dose were seen for 30 days post-ingestion, then gradually fell to about $2 \times 10^{-4}\%$ at 230 days. Blood and urine values were about 1/10 of those found after intravenous administration which, if the human behaves similarly to the rat, would indicate an absorption of considerably less than 10% of the dose. Fecal elimination amounted to 77% of the dose by the end of 3 days; averaged 0.26% of the dose per day, or $10^{-3}\%$ per gram, between 10 and 30 days; and finally fell to $3 \times 10^{-3}\%$ at 230 days. By this time probably less than 0.6 $\mu\text{c.}$ remained in the body, giving $10^{-4}\%$ $\mu\text{c.}$ in daily feces and $10^{-5}\%$ $\mu\text{c.}$ per day in urine.

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DETAILED REPORT OF EXPERIMENTAL RESULTS

Data on Individual Experiments:

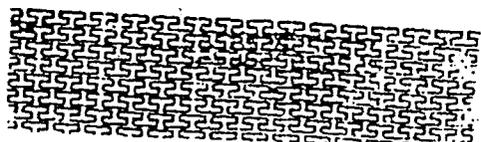
Intravenous administration: Case No. 3

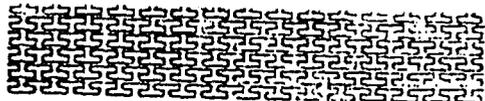
, a 39-year old male patient, with chronic myeloid leukemia, weighing 66.2 kgs., was injected intravenously with 10 cc. of sterile physiological saline, pH 7.4, containing 12.03 microcuries of polonium chloride, at 10:30 A. M., 5/22/45. This dose was equivalent to 0.182 microcurie per kilogram of body weight. The patient had a moderately elevated blood N. P. N., 53 mg. % prior to the injection, 60 mg. % on the 6th day, indicating a possible mild disturbance in renal function.

The excretion data from this case are shown in Table 1a, and Figures 1 and 2. Total daily Po in the urine was fairly constant for several days after injection. It averaged 0.097 percent of the dose per day for the first 18 days, and fell to 0.02% at 70 days. The polonium appeared in the urine as early as one hour after injection at a concentration as high as that seen two or three days later. From the end of the first to the 18th day urine concentrations varied between 0.04 and 0.09 percent of the dose per liter. The average daily fecal output during the first 17 days was 0.71 percent of the dose, nearly ten times the urine content. Though the 24-hour values show marked fluctuations, the excretion rate in terms of percent of the dose per gram of feces remained at a fairly constant level between 5 and 10 x 10⁻³ for as long as 17 days post-injection. By 70 days it dropped to about one-third the earlier values.

Blood sampling for analysis was begun 15 minutes after injection. Because of this patient's high white hematocrit we were able to follow the Po content not only in plasma and red cells but also in the white blood cells for more than two weeks after the beginning of the experiment. For this separation, the 5 cc. blood sample was poured into a conical 12 ml. centrifuge tube and let stand until the red cells settled to the bottom. Sedimentation was complete after 2½ to 3 hours in the first few samples, but later ones required 4 or 5 hours. The white cells, with most of the plasma, were then carefully pipetted into a second centrifuge tube; the two fractions centrifuged for 40 minutes; both hematocrits recorded; and the plasma removed from both tubes combined for analysis. The samples taken at 3 and 5 hours after injection were left standing overnight before drawing off the white cells and centrifuging. The analytical results are given in Table 1b and Figure 3.

The injected material disappeared rapidly from the blood stream. On the basis of an estimated total blood volume of 4.9 liters (7% of the body weight) and the observed concentrations in blood and plasma, we find that only 2.3 percent of the dose was present in the whole circulation, and 1.3% of the dose





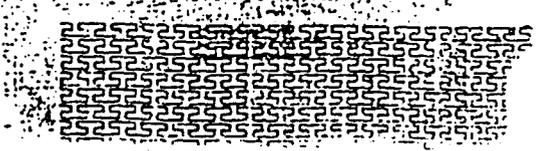
in the circulating plasma, at the end of 15 minutes. The lowest blood value was found at 3 hours but this is largely accounted for by the drop in plasma content, to less than 0.3% of the dose in total circulating plasma, while the red cells already showed a marked uptake of Po . A portion of the cell uptake seen in the early blood samples probably took place in vitro while these samples stood in the test tubes for 3 to 18 hours. The plasma content rose by the fourth day to about ten times the 3-hour level, and then gradually fell so that by 70 days it was again similar to the 3-hour value. Red cells, with a concentration always two to four times that of the plasma, contained around 2×10^{-3} percent of the dose per cc. during the second week after injection, and then began to decrease to about a tenth of that level at 70 days. White cells showed a somewhat greater uptake than reds even as soon as 15 minutes and 1 hour after injection. We have no data on the in-vitro uptake of Po by white cells, but such an uptake might well affect the results in the early white cell samples. After the 6th day, when the white cell content reached 3.6×10^{-3} percent of the dose per cc., it decreased to a value close to that of red cells on the 16th day.

Intravenous Administration: Case No. 4

The fourth subject for intravenous administration was a 44-year old female patient weighing 48 kgs., receiving palliative radio-therapy for chronic myeloid leukemia. She was given an intravenous injection of 8.65 microcuries of polonium chloride (0.18 microcuries per kilo) in 10 cc. of sterile physiological saline, pH adjusted to 7.0, on 7/5/45. No fecal collections were made in this case, but the urine and blood were followed for 13 days after injection. The data are given in Table 2 and Figs. 4 and 5.

The immediate urine output, that is in the first 100 minutes, was relatively high (3×10^{-4} of the dose per cc.) in comparison with Case no. 3, yet the total first 24-hour excretion was somewhat less than for and only a fifth of the average first day value for two previously reported cases. The daily excretion showed a very gradual decrease during the next 12 days, with an average daily value of 0.05 per cent of the dose. Concentrations remained fairly constant at a level about one tenth that found in the first sample.

The loss from the blood stream was not quite so rapid as in case. There was an estimated 5.2 percent of the dose in the total circulation at the end of 25 minutes after injection. The lowest observed blood value was at 23 hours, when the total blood content was about 3.4 and the total plasma content about 1.8 percent of the dose. Both cells and plasma rose again, cells more than plasma, so that the highest whole blood value, 2.3×10^{-3} percent of the dose per cc., was seen at 4 and 5 days. Separate red and white cell analyses were done on two occasions and showed a higher concentration in white cells. At 23 hours the percent of the dose per cc. was 1.1×10^{-3} in red cells, 1.5×10^{-3} in the white; at 4 days reds were 2.7×10^{-3} and whites 4.1×10^{-3} . In the table and graphs, calculated combined cell values are given for



these times to be consistent with the other data on total cells.

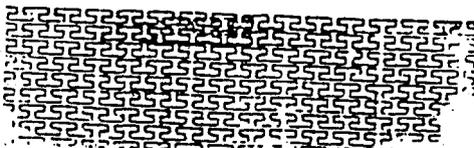
In comparing these two intravenous experiments with the two previously reported (report no. 2215), we find essentially the same urinary excretion rates, in terms of the average concentrations of Po during corresponding experimental periods, as in the more normal of the other subjects. The total urine content of who showed slight clinical indications of renal dysfunction, was somewhat higher, though not as high as in the moribund case reported before. fecal excretion of Po was about one-half as fast as Both cases of myeloid leukemia showed about a three-fold lower whole blood content of Po, at the end of 24 hours, than the other two, diagnosed as lymphosarcoma and lymphatic leukemia, though their later blood values were essentially similar. Also the differences between cell and plasma concentration were not quite as marked as in the earlier cases.

Oral Administration: Case No. 5

a 34-year old male patient, weighing 96 kgs., hospitalized for X-ray treatment of chronic myeloid leukemia, was given 18.5 microcuries of polonium chloride in 2 cc. of 0.3 N. acid, diluted in a glassful of tap water just before drinking, at 9:30 A. M., 3/29/45. This oral dose was equivalent to 0.19 microcurie per kilogram of body weight. Starting one hour after the ingestion, four blood samples, 5 cc. each, were drawn at two-hour intervals during the first day. Thereafter, the samples were taken at the end of each 24-hour period. The urine samples of the first few hours were also kept separate for analysis, but after the first day were pooled in 24-hour collections. All stool specimens represented 24-hour collections, except on two occasions when 48-hour stools were passed. After the patient's discharge from the hospital, he has continued to bring samples in whenever he comes for a check-up.

A small amount of the ingested material was found in the first urine sample, collected at 2½ hours. Although nearly 20% of the first day's urinary output was excreted during the first 7 hours, it is clear from the urine concentration figures (Table 3a) that the excretion rate lagged until sometime after 7 hours. The fourth day's urine content showed a sudden ten-fold increase to nearly 0.05 percent of the dose, an amount comparable to the early excretions following intravenous administration of similar doses. If not simply due to contamination, this might conceivably be related to the retention of feces during the same day, possibly causing a somewhat higher absorption rate in that period. Except for the fourth day, the daily urine values remained fairly constant for thirty days, fluctuating between 4.5 and 7.4 x 10⁻³ percent of the dose, and then gradually declined to 2 x 10⁻⁴% at 227 days after the beginning of the experiment.

The fecal elimination of the ingested polonium was negligible during the first 24 hours, but by the end of the third day 76.5 percent of the dose had been eliminated by this route. This elimination



rate then fell sharply to less than one percent of the dose per day by 7 days. Between 11 and 32 days, it remained about the level of 10^{-3} percent of the dose per gram of feces, thereafter decreasing gradually to a concentration of 10^{-5} , or about 3×10^{-3} per day, 227 days after ingestion. In plotting the daily fecal excretion data in Figure 6, the average of two consecutive days was used wherever possible in order to equalize the misleading irregularities in defecation. Daily total urinary excretions are also shown in Figure 6, and the concentrations in terms of percent of the dose per gram or per cc. of feces and urine are plotted in Fig. 7.

As shown in Table 3b, the Po had already appeared in the blood stream by the end of one hour after ingestion. The highest observed blood value was 5×10^{-4} percent of the dose per cc. whole blood at 48 hours. No blood sample was obtained on the third day when it is quite likely that the peak concentration occurred. After the fourth day, the whole blood content decreased quite steadily to the neighborhood of 10^{-5} percent of the dose per cc. by the 116th day. The uptake in cells was approximately 1/5 of that in the plasma during the first four days. From then on plasma and cell concentrations remained essentially the same. This is in sharp contrast with rat ingestion experiments in which, at ten days, the cell concentration was found to be in the order of 100 times that of the plasma (report nos. 1717 & 3633). Plasma and cell values are shown graphically in Figure 8. The broken lines to and from the 54-day cell value are used to indicate an obvious question concerning the accuracy of that particular determination. By the 228th day the blood activity was barely detectable, 7×10^{-6} percent of the dose per cc.

Any attempt to estimate absorption of polonium from the gastrointestinal tract, with the data available in this case, is largely conjectural. The values for both blood and urine are approximately ten-fold less than the corresponding values found following intravenous administration of similar doses. This fact indicates that possibly 10 percent of the dose, at the utmost, may have been absorbed. The absorbed material may, however, be deposited in such organs and in such a chemical form that allow it to be more readily mobilized into the blood stream and excreted through the kidneys than after injection. Something like that seems to have taken place in the rat ingestion experiments in which the urinary output and the blood concentration, in relation to the amount found in the body after sacrifice, was much higher than in injected animals. If this were the case in this human experiment, the data would indicate that considerably less than 10 percent had been absorbed.

Renal efficiency in polonium Removal?

Having a considerable collection of data available from these studies, it seemed that some expression of the effectiveness of the kidneys in removing Po from the blood stream would be useful. Evans has shown, for one human radium poisoning case, that only about one percent of the radium present in the blood stream at any one time was excreted per day in the urine; that is, less than 0.01 percent of what passed through the kidney circulation.¹

¹Footnote 1: Aub. J. C., Evans, E. D., et al.-Ann. Int. Med., 11,

Similar estimations on the basis of whole blood content in our five human subjects, as well as in several rat experiments, gave about the same value for polonium removal as for radium.

Removal of plasma constituents is, however, usually considered the better expression of kidney efficiency since that fraction is presumably more available for excretion. Total Po in the circulating plasma at the end of each 24-hour period was calculated from estimated individual blood volumes, and hematocrit and Po concentration values of each sample. The Po in each day's urine was then expressed in terms of percent of total Po in plasma at the end of the corresponding period. This value remained essentially the same in each case throughout the period of observation, in spite of day to day fluctuations. Both (the intravenous subject, reported here, with the more normal kidney function) and (the oral administration case) excreted on the average 1.5 percent of their plasma Po every 24 hours. Assuming, as Evans did, 100 passages of the blood through the kidneys per day, this means that less than 0.02 percent was continuously removed. The other intravenous case, with slight renal malfunction, showed a somewhat higher average rate of 0.05% continuously removed from the circulating plasma.

Calculating standard clearances for Po in those experiments, and from single sets of blood and urine data on 16 presumably normal individuals, we find extremely low values ranging from 0.01 to 0.08 cc. of whole blood cleared per minute. The average Po C_0 for each of the three experimental subjects fell close to the overall average of 0.04. Clearance values during the first few hours after injection were somewhat higher than the individual's average while in the early period after oral administration they were lower than the average. Judging by a very cursory glance at the literature, these values for polonium clearance by the kidneys are considerably lower than for some similar metals. Arsenic, for example, may be cleared one or two hundred times faster, and selenium at least fifty times faster than Po. Whether this is due to extremely slow glomerular filtration or to a high tendency for reabsorption of the material is impossible to say at present.

Corrections for Radioactive Decay

In this report, as in all our previous reports, except when specifically stated otherwise, the "% Dose" values given are those which would have been found if there had been no decrease in activity due to radioactive decay. In tolerance calculations the additional loss of polonium from the body due to decay should be taken into account. This additional loss is approximately 0.5% per day for short periods (half-life = 140 days).

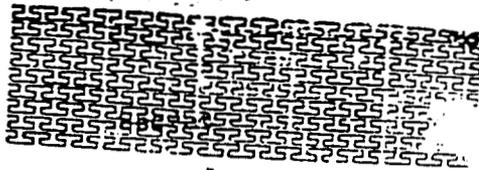


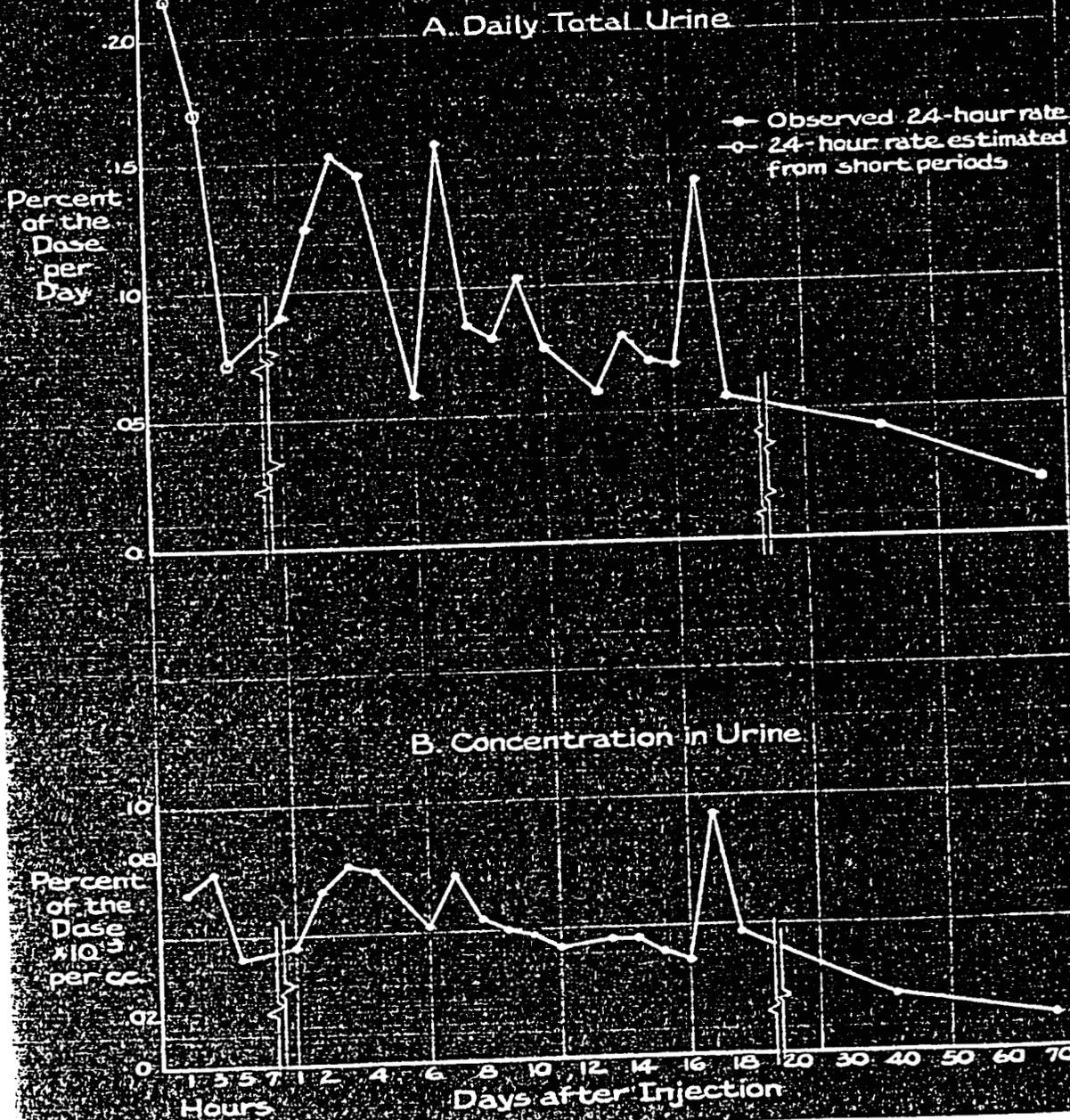
Table 1.

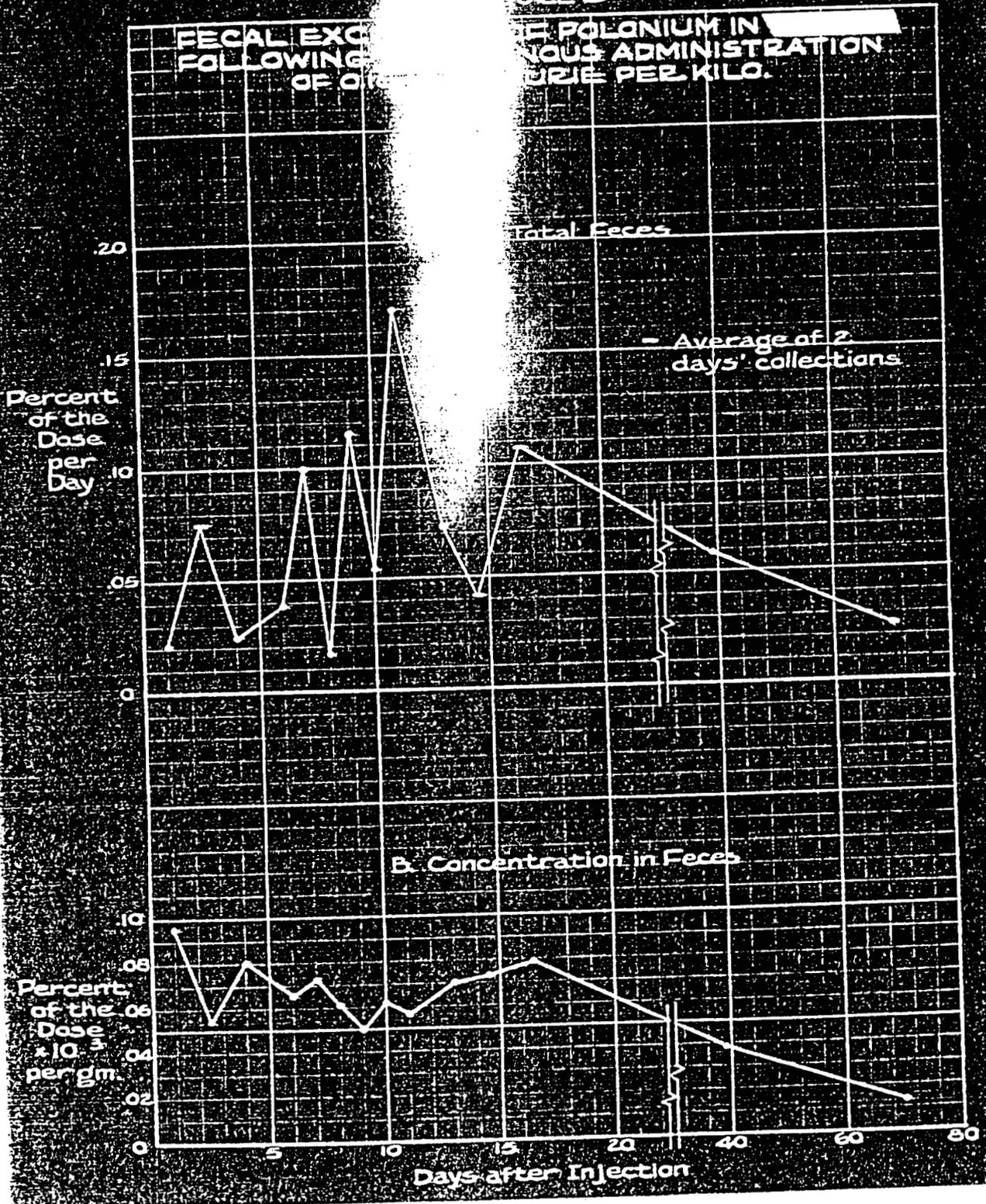
Percent of the dose in urine and feces of Mr. (chronic myeloid leukemia) after intravenous administration of 0.182 microcuries of polonium chloride per kilogram of body weight.

Time after ingestion	1 a Excretion		Concentration	
	% of dose excreted in Feces	% of dose excreted in Urine	% of dose/ μC Feces $\times 10^5$	% of dose/ μC Urine $\times 10^5$
0 - 1 hr.		.009		.067
1 - 3		.010		.075
3 - 5		.006		.042
5 - 24		.065		.045
1 day	.21 (total)	.091	9.6	----
2	----	.125	----	.067
3	1.52 (48 hr.)	.153	5.5	.077
4	.25	.145	8.0	.075
6	.39	.059	6.6	.052
7	1.00	.157	7.2	.072
8	.17	.086	6.1	.055
9	1.15	.080	5.0	.050
10	.55	.103	6.2	.048
11	1.70	.077	5.7	.043
13	.73	.059	7.0	.046
14	----	.080	----	.046
15	.82 (48 hr.)	.070	7.3	.040
16	----	.069	----	.037
17	2.13 (48 hr.)	.140	7.9	.093
18	----	.056	----	.047
39	.59	.043	3.8	.022
70	.254	.021	1.3	.013

FIGURE 1

URINARY EXCRETION OF POLONIUM
IN [REDACTED] (CHRONIC MYELOID LEUKEMIC)
FOLLOWING INTRAVENOUS ADMINISTRATION
OF 0.18 MICROCURIE PER KILO.





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Table 1 con'd.

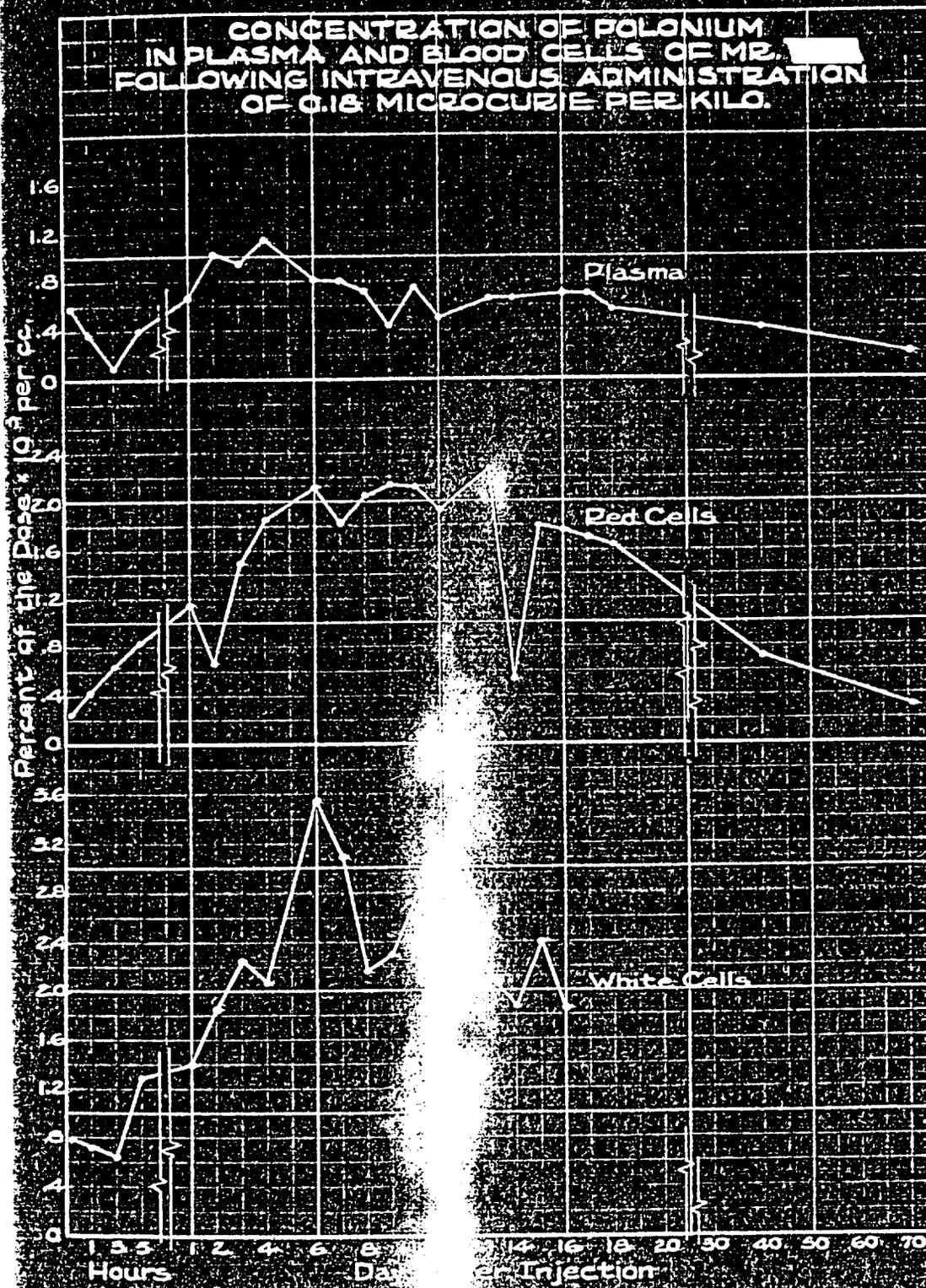
1b - Concentration in Blood

Time after ingestion	% of dose per cc. x 10 ³ in			
	Whole blood	Plasma	Red cells	White cells
15 min.	.52	.58	.25	.79
1 hour	.47	.37	.43	.72
3 hour	.35	.11	.64	.63
5 hour	.95	.40	.84	1.30
24 hour	.95	.67	1.15	1.40
2 days	1.1	1.02	.67	1.85
3	1.3	.95	1.50	2.26
4	1.5	1.14	1.85	2.08
6	1.3	.81	2.12	3.55
7	1.2	.80	1.83	3.09
8	1.2	.73	2.06	2.17
9	1.0	.44	2.14	2.30
10	1.3	.75	2.12	2.78
11	1.2	.51	1.93	2.90
13	1.2	.66	2.27	2.10
14	.7	.66	.55	1.87
15	---	---	1.30	2.40
16	1.0	.69	1.77	1.65
17	.95	.69	1.71	
18	1.0	.57	1.64	
40	.44	.41	.72	
72	.26	.20	.32	

values include
white cells.

FIGURE 3

CONCENTRATION OF POLONIUM
IN PLASMA AND BLOOD CELLS OF MR. [REDACTED]
FOLLOWING INTRAVENOUS ADMINISTRATION
OF 0.18 MICROCURIE PER KILO.



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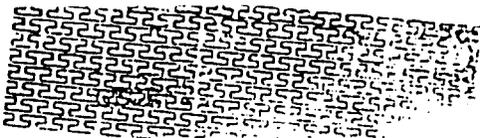


Table 2

Percent of the dose in blood and urine of (chronic myeloid leukemia) after intravenous administration of 0.180 microcuries of polonium chloride per kilogram of body weight.

Injection time	% of dose excreted in Urine	% of dose/cc. Urine x 10 ³	Concentration in Blood			
			Time	% of dose per cc. Whole	Plasma Colls	
0 - 1.7 hr.	.018	.32	25 min.	1.7	2.36	.75
			1 hour	1.5	1.95	.75
			2.5 "	2.2	2.56	1.50
			4.5 "	2.2	1.92	2.58
1.7 - 3.5 "	.009	.025	23 "	1.10	.99	1.20
3.5 - 24 "	.042	.057				
1 day	.069 (total)	----				
2	.063	.068		1.7	1.34	2.30
4	.056	.045		2.5	2.11	2.85
5	.064	.046		2.5	1.92	2.82
6	.060	.046		2.2	1.80	2.80
7	.052	.060		1.7	1.43	2.03
8	.053	.027		2.0	1.99	2.06
9	.044	.047		1.2	1.29	2.70
11	.044	.026		1.6	1.34	2.33
12	.040	.023		1.7	1.44	2.34
13	.038	.037		1.7	1.86	2.40

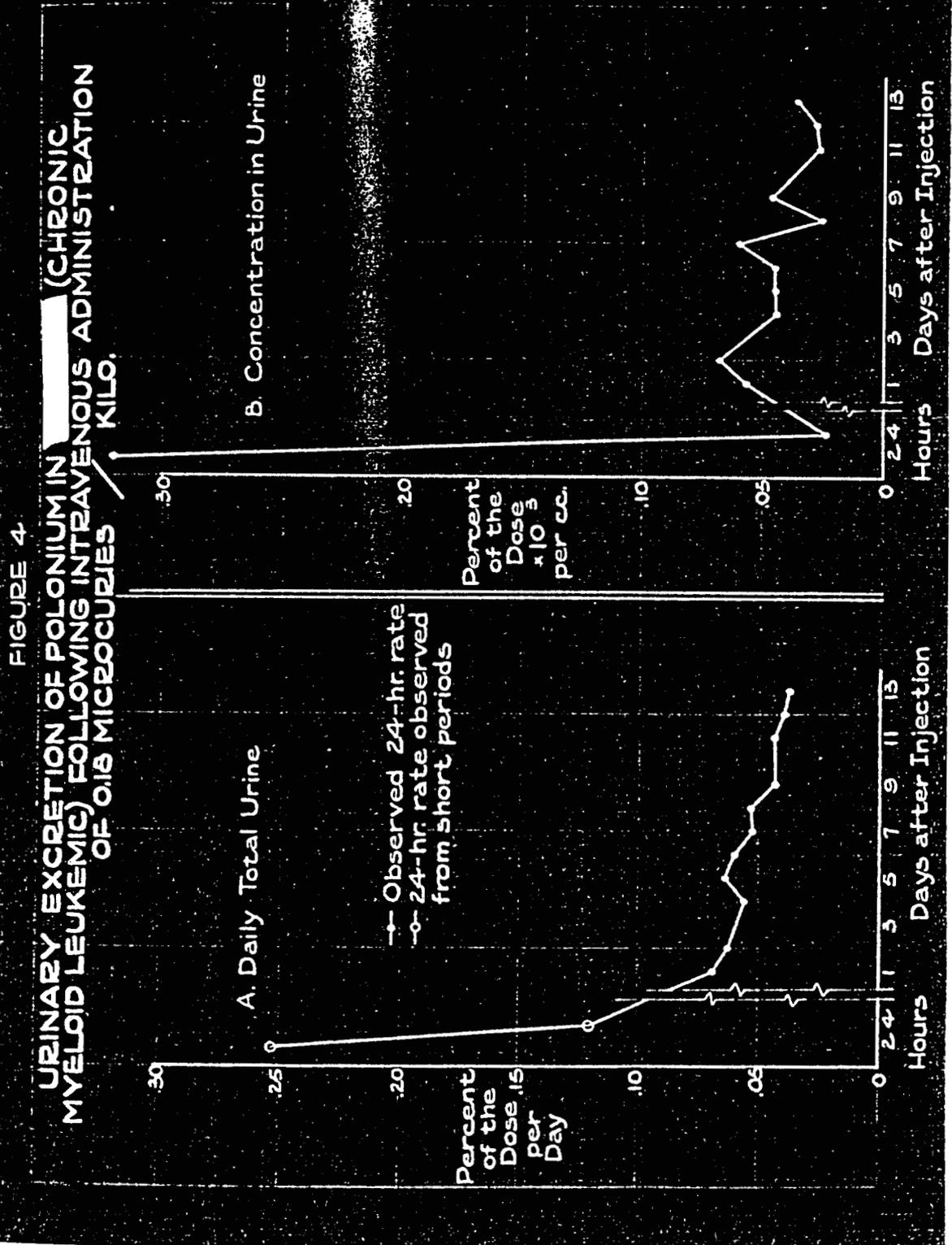
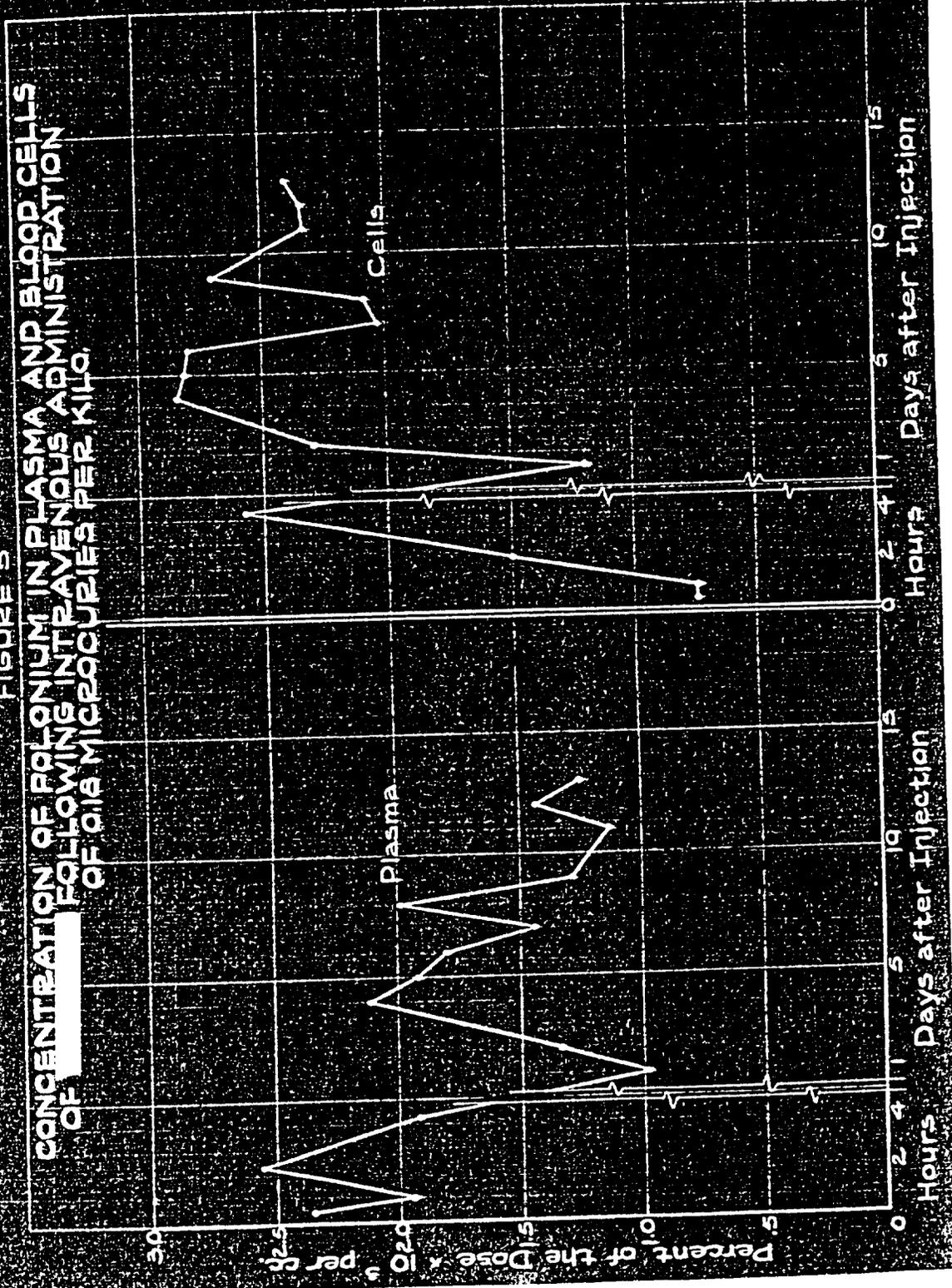


FIGURE 6
CONCENTRATION OF POLONIUM IN PLASMA AND BLOOD CELLS
FOLLOWING INTRAVENOUS ADMINISTRATION
OF 0.18 MICROCURIES PER KILO



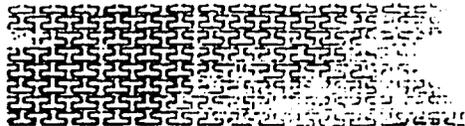
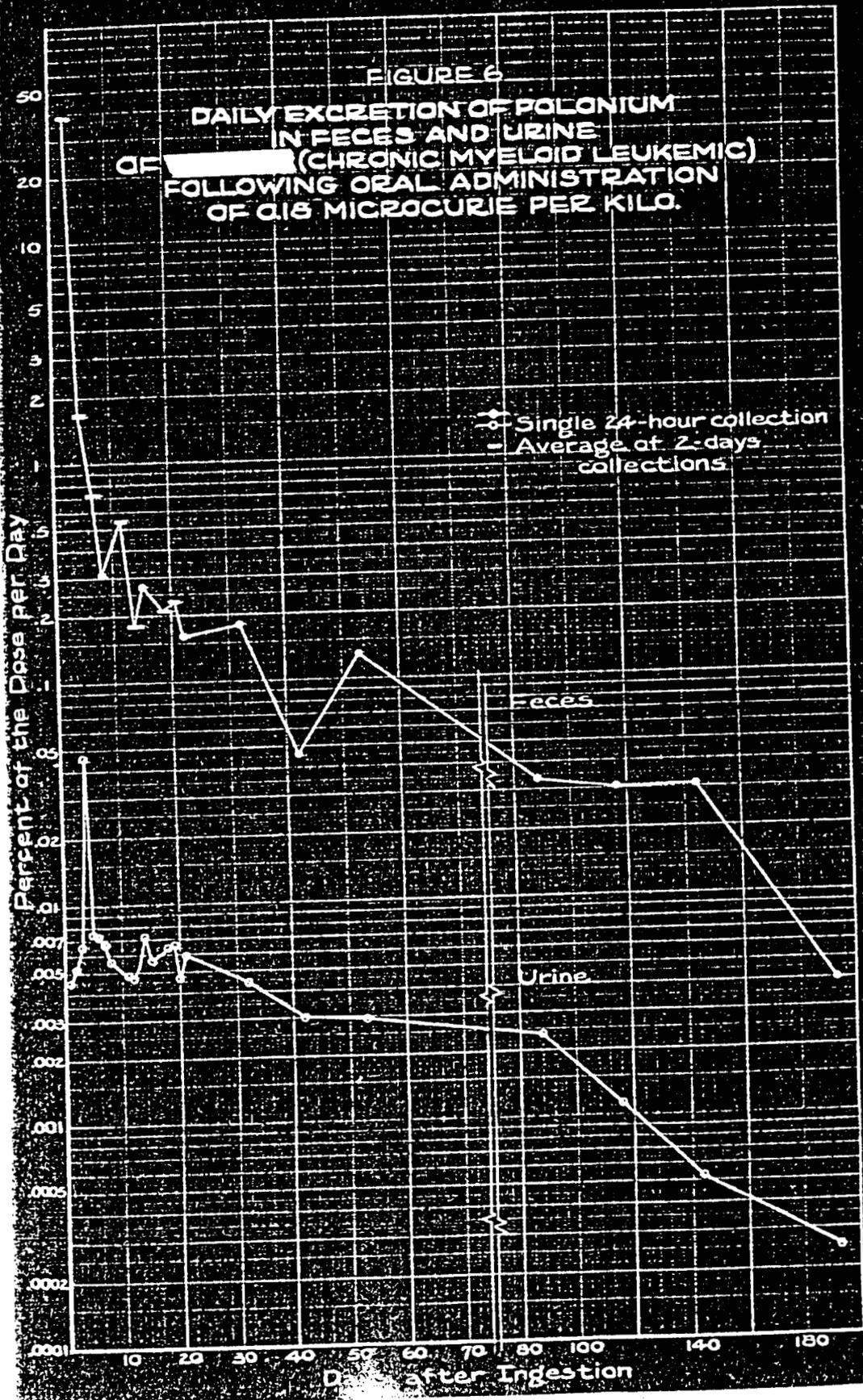


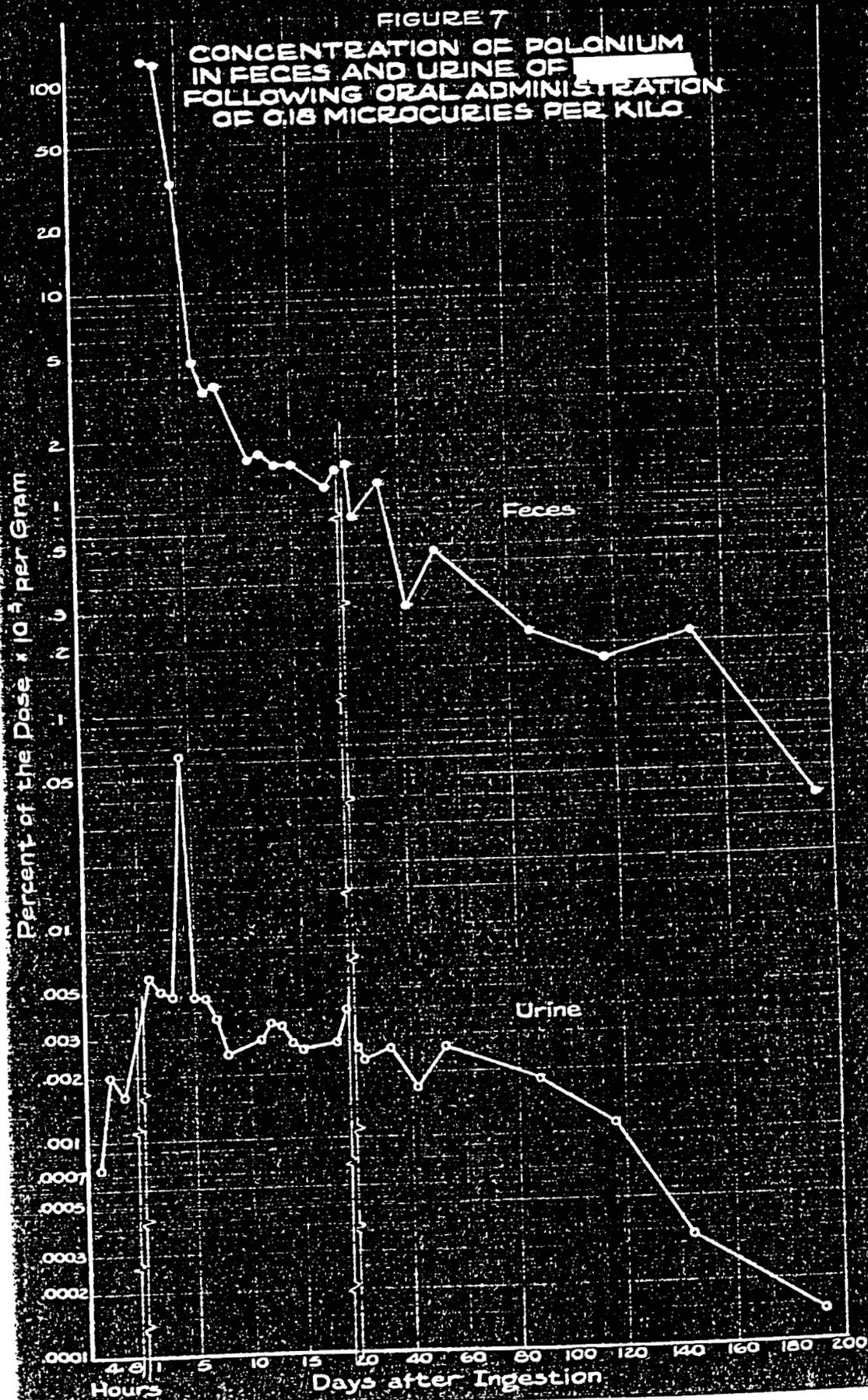
Table 3.

Percent of the dose in blood, urine and feces of (chronic myeloid leukemia) after oral administration of 0.193 microcurie of polonium chloride per kilogram of body weight.

3a. Excretion

Time after ingestion	% of dose excreted in Feces	% of dose excreted in Urine	Concentration	
			% of dose/gm. Feces x10 ³	% of dose/cc. Urine x10 ⁵
0 - 3 1/2 hrs.		.00020		.075
2 1/2 - 4 1/2 hrs.		.00032		.20
6 1/2 - 7 hrs.		.00035		.16
7 - 24 hrs.		.0037		.58
1 day	.00065	.0045 (total)	.0036	
2	40.1	.0058	126.2	.50
3	36.4	.0066	122.3	.47
4	--	.045	---	6.4
5	5.35 (42 hr.)	.0074	32.7	.47
6	1.35	.0073	4.7	.46
7	.118	.0067	3.4	.37
8	.321	.0056	3.6	.25
11	.901	.0048	1.6	.29
12	.171	.0047	1.7	.35
13	---	.0053	---	.34
14	.367 (48 hr.)	.0071	1.5	.28
15	.272	.0057	1.5	.26
16	.135	.0064	1.15	.28
17	.284	.0065	1.41	.40
18	.260	.0047	1.48	.26
21	.207	.0059	1.32	.24
22	.162	.0058	.83	.23
23	.181	.0044	1.20	.26
24	.045	.0030	.31	.17
25	.129	.00295	.56	.26
26	.037	.00235	.23	.18
116	.031	.00115	.17	.11
124	.032	.00052	.22	.03
133	.004	.00025	.04	.01
287	.003	.00020	.01	.01



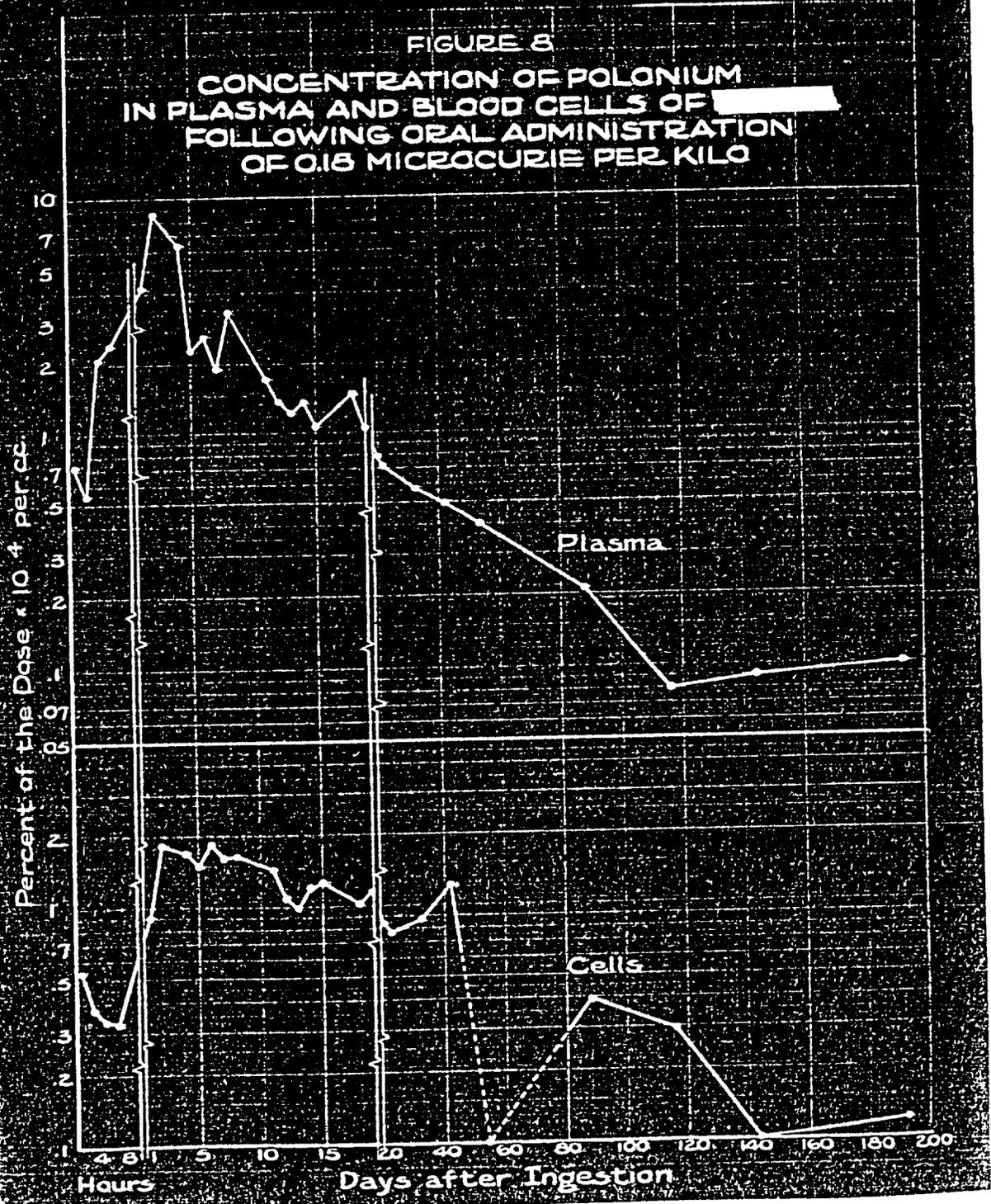


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Table 3, continued

3 b. Concentration in blood.

Time after ingestion	% of dose per cc. x 10 ⁴ in		
	Whole blood	Plasma	cells
1 hour	.6	.72	.54
3 hour	.5	.54	.38
5 hour	1.3	2.06	.34
7 hour		2.39	.33
26 hour	2.6	4.22	.92
2 days	5.3	8.55	1.84
4	4.2	6.32	1.72
5	1.9	2.28	1.50
6	2.2	2.57	1.84
7	1.8	1.88	1.52
8	2.6	3.28	1.66
11	1.6	1.68	1.46
12	1.2	1.74	1.10
13	1.1	1.21	1.00
14	1.3	1.33	1.22
15	1.1	1.05	1.27
18	1.3	1.45	1.02
19	1.1	1.03	1.15
20	.80	.78	.84
21	.84	.84	.85
22	.75	.71	.79
32	.71	.57	.89
42	.83	.49	1.22
54	.26	.40	.10
88	---	.21	.39
116	1.4	.08	.19
144	.09	.09	.09
193	.11	.10	.12
228	.07	.03	.06



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