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# NAVAL MEDICAL RESEARCH INSTITUTE *and* U.S. NAVAL HOSPITAL



BIOLOGICAL STUDIES OF ANTIMONY COMPOUNDS CONTAINING RADIOACTIVE ISOTOPES; III. THE BLOOD-TISSUE EXCHANGE AND EXCRETION OF ANTIMONY IN HUMANS GIVEN A SINGLE DOSE OF TARTAR EMETIC

Research Project X-635

Report No. 1

NAVAL MEDICAL RESEARCH INSTITUTE  
AND  
U. S. NAVAL HOSPITAL  
NATIONAL NAVAL MEDICAL CENTER  
BETHESDA, MARYLAND

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BIOLOGICAL STUDIES OF ANTIMONY COMPOUNDS CONTAINING RADIOACTIVE  
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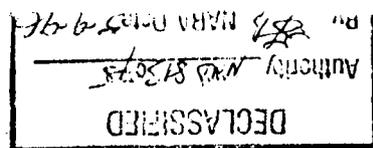
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SUMMARY AND CONCLUSIONS

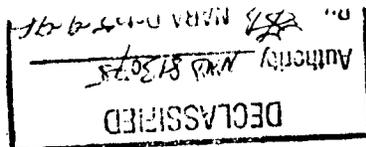
1. Two patients each received a single injection of tartar emetic (0.8 mg. Sb/kg.) synthesized from radioactive antimony.
2. The time-concentration curves of antimony in whole blood and in the blood fractions indicate that the concentration of antimony in the blood was reduced within one hour to 50 per cent and after 13 hours, to 10 per cent of its initial value following injection.
3. The curves obtained for total excreted antimony over a period of about 650 hours have demonstrated that by 500 hours 50 per cent of the initial dose has been excreted in the urine and about 3 per cent in the feces. It is also estimated from the excretion curves that ultimately about 90 per cent of the initial dose will be excreted via the kidneys and the remainder in the feces.
4. Comparison of the rate of elimination of antimony from the blood with the rate of its excretion in urine and feces makes possible a prediction of the relative rate of exchange by the body as a whole.

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5. External measurements using a Geiger counter over regions adjacent to organs has enabled gross estimates of the degree of anti-mony accumulation by various organs within the body; these results are comparable with those from chemical analytical procedures. The technic offers a unique advantage in not requiring biopsy and chemical manipulation of the sample, and its further refinement should permit useful clinical application.



## BACKGROUND

Recent studies in this laboratory (1,2,3) and those by Brady and co-workers (4,5) at the National Institute of Health, have clearly established radioantimony as a practical labeling agent for quantitative assay of the blood and tissue distributions of antimonial drugs in animals. The present report describes what is believed to have been the first use of radioantimony in studies on man.

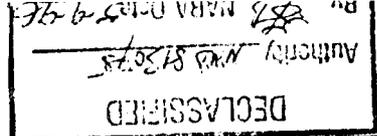
Use of the radioactive isotope of antimony incorporated into tartar emetic made possible two kinds of measurements:

1. The concentration of antimony in the blood and blood fractions in successive samples down to the order of 0.01 microgram per gram of samples and similar determinations on total excretion.
2. In vivo estimation of accumulation of antimony in the liver, muscles, brain and thyroid, etc., by placing a Geiger counter externally over the appropriate body areas and recording the radioactivity emitted.

## PROCEDURE

Two ambulatory male patients at the U. S. Naval Hospital, Bethesda, Maryland, volunteered as subjects. One patient, B-1, age 20, had been admitted some three months previously with diagnosis of filariasis involving the testicles. Examinations had been negative for microfilaria. This patient had received a course of antimony as fuadin at a base hospital several months previous to this admission.

A single dose (.71 mg. Sb/kg.) of tartar emetic, synthesized from radioactive antimony and tested for toxicity and pyrogens in rabbits, was given i.v. (7.5 mg. Sb/cc. in 0.85% NaCl) to patient B-1 at 1330, 22 August 1945. Venous blood samples were drawn (from the arm opposite to that used for injection) at time intervals up to 120 hours. From each sample two Van Allen hematocrit tubes were filled and a 1cc. aliquot of the blood was taken; the remaining blood was then centrifuged to obtain samples of red cells and plasma. The concentration of antimony in red cells was corrected to that for 1 cc. of blood by multiplying the apparent concentration by the hematocrit value and the red cell specific gravity (assumed to be 1.090 gm/cc.). Plasma antimony concentration was corrected for hematocrit by the factor (100 - %RBC) and the value added to that of the corrected red cell concentration. This summated value was used as a check against the antimony concentrations obtained by independent measurement on the whole blood.



Daily collections of the entire output of urine and feces were made for the next 25 days. Geiger counter measurements were made on 1 cc. aliquots of the urine and on 1 gm. samples of the dried and pulverized feces.

Essentially the same procedure was carried out with patient B-2, except, that the latter was not consistent in the collection of the excrement; thus, the estimate of the total excretion is not as satisfactory.

Analysis of the blood and excrement curves was effected graphically from the plots of the logarithm of concentration or of amount vs. time. By this means it was possible to compare quantitatively the ratio of elimination between the blood and excrement. Additional deductions are also possible.

External estimates on residual antimony contained in the various body organs at times after the injection were made by placing a Geiger counter over the areas regarded to be in juxtaposition to the organs. The technic employed no collimation or other type of heavy shielding and was used only in an exploratory manner. The results must, therefore, be regarded as purely demonstrative of the general application of the method and not as a satisfactory quantitative measure.

## RESULTS

The concentration of antimony in the blood following the injection was found to decrease exponentially with time (fig. 1); thus, in both patients it had dropped to 50 per cent of its initial value by the end of one hour and to 10 per cent by about 13 hours. At this latter time the concentration in both patients was approximately 0.1 microgram of antimony per cubic centimeter of blood.

Logarithmic analysis of these curves yields empirical equations in which the concentration at any time may be represented as a sum of decaying exponentials and their coefficients. Thus, in general, the concentrations  $C$  at any time  $t$ , in hours after the injection, is given by the equation:

$$C(t) = C_0 e^{-b_0 t} + C_1 e^{-b_1 t} + \dots + C_n e^{-b_n t} \quad (1)$$

where  $b_0, b_1, b_2, \dots, b_n$  is a decay constant; the numerical values of the  $C$ 's and  $b$ 's (table 1) for patients B-1 and B-2 may be substituted into the equation.

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Table 1.- Values for coefficients and exponential decay terms for curves of elimination of antimony from the blood by patients B-1 and B-2

Subscript	B-1		B-2	
	C	b	C	b
0	0.2319	4.062	-	-
1	0.5600	1.065	0.768	1.245
2	0.2730	0.392	0.098	0.288
3	0.0820	0.053	0.185	0.0912
4	0.0831	0.007	0.049	0.007

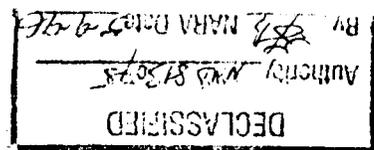
The information contained in the table allows certain inferences to be drawn regarding the elimination of antimony from the blood in the two patients studied. At zero time, for example,  $e^{-bt} = 1$  and, thus, the summated values of the C's =  $(C_0 + C_1 + \dots C_n)$  are 1.230 and 1.110 micrograms per cubic centimeter of blood for B-1 and B-2 respectively. Since this concentration is far lower than could result from dilution by the blood volume, it is evident that the concentration has been reduced by such factors as dilution with the extravascular aqueous volume of the body, and rapid removal by the liver and kidney.

An analysis of the rates at which antimony disappears from the blood may be obtained by differentiation of the equation (1) after substitution of the numerical values. By this means one may compare rates of loss from the blood stream in the two patients at various times (table 2).

Table 2.- Rates of loss of antimony from blood at various times after injection

Time (hr.)	$\mu\text{ gm/cc/hr.}$	
	Patient B-1	Patient B-2
0	1.6500	1.001
1	0.2985	0.313
10	0.0052	0.0087
50	0.0007	0.0004

From such a comparison it is apparent that the rates of elimination of antimony from the blood stream were reasonably similar in the two patients.



The whole blood values were in fair agreement with those calculated from summation of the corrected plasma and red cell measurements (fig. 1,2), although, as might be expected, there was greater deviation toward the terminal portions of the curves.

The concentration of antimony within the red cells maintained a fairly constant ratio of about five times that in the plasma (table 3); this may be taken as evidence that a state of dynamic equilibrium exists between the cell and plasma, and that it is one which appears dependent upon the concentration gradient.

Table 3.- Comparison of antimony concentration in red cells with that in plasma

	Time (hr.) after injection											
	0.25	0.50	1.0	2.0	4.0	8.0	19.0	24.0	48.0	72.5	93.0	120.0
	Concentration in $\mu$ gm. Sb/cc. whole blood											
Red cells	.730	.592	.449	.289	.175	.108	.078	.059	.028	.025	.022	-
Plasma	.148	.099	.049	.053	.019	.017	.009	.015	.006	.006	.008	-
RBC/plasma	4.93	6.00	9.25	5.44	9.15	6.46	9.01	4.10	4.86	4.32	2.57	

Analysis of the antimony eliminated via the urine and feces was based on graphical methods similar to those employed for blood. However, it was necessary to compute an asymptotic level respectively for urine and for feces and then to analyze graphically the plot, logarithm (asymptotic amount minus increment amount) vs. time. The asymptotes were approximated using the assumption that 100 per cent of the injected antimony would ultimately be excreted and that the ratio of amounts excreted via urine as compared with feces would not change greatly after the last measured values at 692 hours. Thus, at the latter time, 54 per cent of the initial dose had been eliminated via the urine and 8 per cent in the feces. At an asymptotic value of 100 per cent excreted  $54/62 = 87$  per cent would, therefore, have been eliminated by the kidney and 13 per cent via the feces. Since the urinary excretion rate, however, was still somewhat more rapid at 700 hours than that via the feces the asymptote for urinary excretion was chosen as 90 per cent and that for feces, 10 per cent of the initial dose.

Analysis of the curves for urinary and fecal antimony for patient B-1 (fig. 3) gave an expression also typified by equation (1), but containing only three decaying terms (table 4) rather than four and five as found in the blood curves. Incidentally, it should be noted

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in table 3 that the coefficients are not in units of concentration but in units of amount A, expressed as a per cent of the initial dose. The units of b are again in reciprocal hours.

Table 4.- Coefficients A and decay constants b for time curves of antimony excreted via urine and feces from patient B-1

Subscript	Urine		Feces	
	A(%)	b	A(%)	b
0	10.3	.0893	2.55	0.1137
1	24.8	.0049	0.68	0.0157
2	54.9	.0006	6.80	0.0017

The graphic origin of the curve of antimony from feces has been taken from 28 hours rather than from the time of injection. This displacement is presumed to be primarily a function of the physical rate of movement of the intestinal bolus, since no bowel movement occurred in this patient during the initial interm prior to this time.

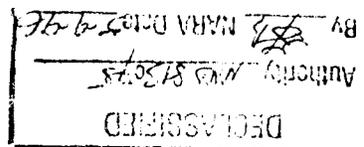
In general the curves of excretion indicate that by 500 hours 50 per cent of the initial dose has been excreted via the urine, and 3 per cent via the feces.

From the equation for amount excreted as a function of time, it is again feasible to differentiate the expression to obtain the rate. This gives a very useful value since one may then compare blood elimination with whole body excretion rates and draw certain inferences therefrom.

For example, in patient B-1, at 50 hours after injection the blood was losing antimony at a rate of  $7.11 \times 10^{-4}$  micrograms per hour per cc. of blood. At this same time the total kidney output was 101.7 micrograms per hour. If loss from the intestine is neglected, this gives a minimum kidney blood flow of

$$\frac{101.7}{7.11 \times 10^{-4}} = x \frac{1}{60} = 2.384 \text{ liters/min.}, \text{ which is low because it}$$

assumes 100 per cent efficiency in kidney filtrations. However, this apparent value for flow will be even lower at all times when other organs besides the kidney are actually accumulating antimony. Thus, at zero time a similar computation for kidney flow gives the ridiculous figure of 7.15 cc/min., which is merely evidence that accumulation in body organs is occurring very rapidly at that time.



Elimination through the feces is a complicating factor here, since it is not certain what proportion of the antimony in the bowel has been secreted via the bile from accumulated deposits within the liver.

In general, however, it appears that the accumulation curve of the body as a whole is predictable as the difference between blood loss and excretory loss (kidney plus feces). Such a curve may in fact be constructed from the data presented in this paper.

The results of the external measurements, using Geiger counters over the body areas in juxtaposition to the various organs, were but roughly quantitative and are presented here only in part (table 5). They serve to illustrate the order of difference which obtains in the antimony accumulated at different points in the body.

Table 5.- Estimations of antimony content of organs as determined by externally detectable radioactivity (patient B-1)\*

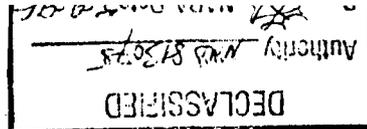
Organ	Microgram equivalents of antimony at various times				
	168 hr.	13 days	20 days	23 days	30 days
Thyroid	9.6	18.1	8.9	7.1	6.1
Gall bladder	42.1	42.8	50.2	44.9	24.2
Liver	40.0	47.7	39.2	31.1	26.2
Leg	3.6	2.5	2.5	3.7	3.1
Cranium, parietal region		2.5			

\* Similar estimates were obtained on patient B-2.

Despite its present crudity, the method does present intriguing possibilities for application to clinical studies. It is of interest to note, moreover, that the relative concentrations of antimony in liver as compared with peripheral tissues, such as muscle and brain, are very similar to those obtained from chemical analysis (see appendix).

#### COMMENT

The present results are in the nature of preliminary findings whose purpose has been chiefly to demonstrate the technics which may



be applied to problems of exchange when an accurate quantitative analysis and the time course of the exchange are both adequately known.

A final word should be offered regarding any possibilities of damage by radiation during this type of treatment. The dose given was estimated to be well below the toxic level even at sites of highest concentration where it appeared possible that up to 3r/da. maximum might be received. As an empirical check, blood studies were made both before and at several times after the treatment. However, no changes were observed either in the differential count or the red and white cell counts subsequent to the treatment. Basal metabolism measurements, taken two weeks after the treatment, were normal and no adverse symptoms of significance were observed during the entire period of the study.

#### ACKNOWLEDGMENTS

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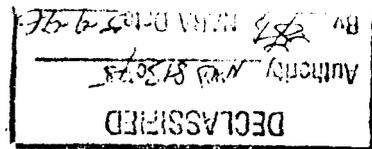
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## Appendix

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25 October 1945

## REPORT OF ANTIMONY ANALYSIS ON HUMAN AUTOPSY TISSUE

The tests were run at the request of Lt. Colonel F. R. Dieuaide, MC, AUS, on samples obtained at autopsy from a patient at Harmon General Hospital, Longview, Texas.

The patient was being treated for schistosomiasis and had received 0.274 gm. of antimony in the form of tartar emetic in the 16 days immediately preceding his accidental death.

Antimony was determined by Maren's modification of Webster's method, and at least three determinations were run on each tissue. The formaldehyde preservative was negative for antimony.

<u>Tissue</u>	<u>Micrograms antimony/gram formalized tissue</u>	<u>Average</u>
Liver	12.3	11.6
	10.9	
	11.9	
	11.5	
Heart	3.1	2.4
	2.1	
	1.5	
	2.5	
	2.8	
Kidney	2.6	2.5
	2.4	
	2.4	
Brain	0.93	0.95
	0.97	
	0.96	

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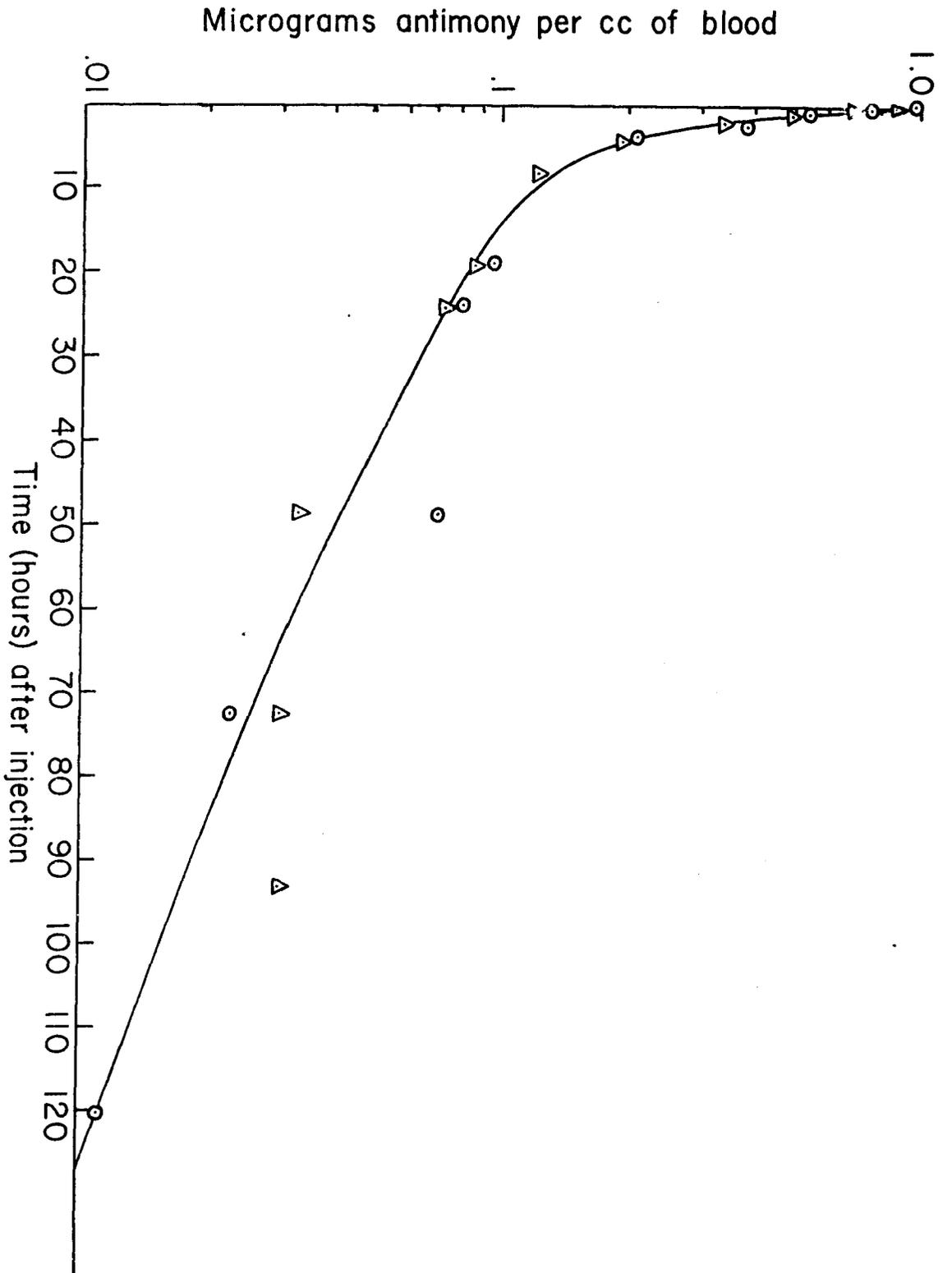


Figure 1.- Concentration of antimony in whole blood  $\circ$  and sum of corrected blood fractions (red cells + plasma)  $\Delta$ ; free-hand smoothing of semilog plot. Patient B-1.

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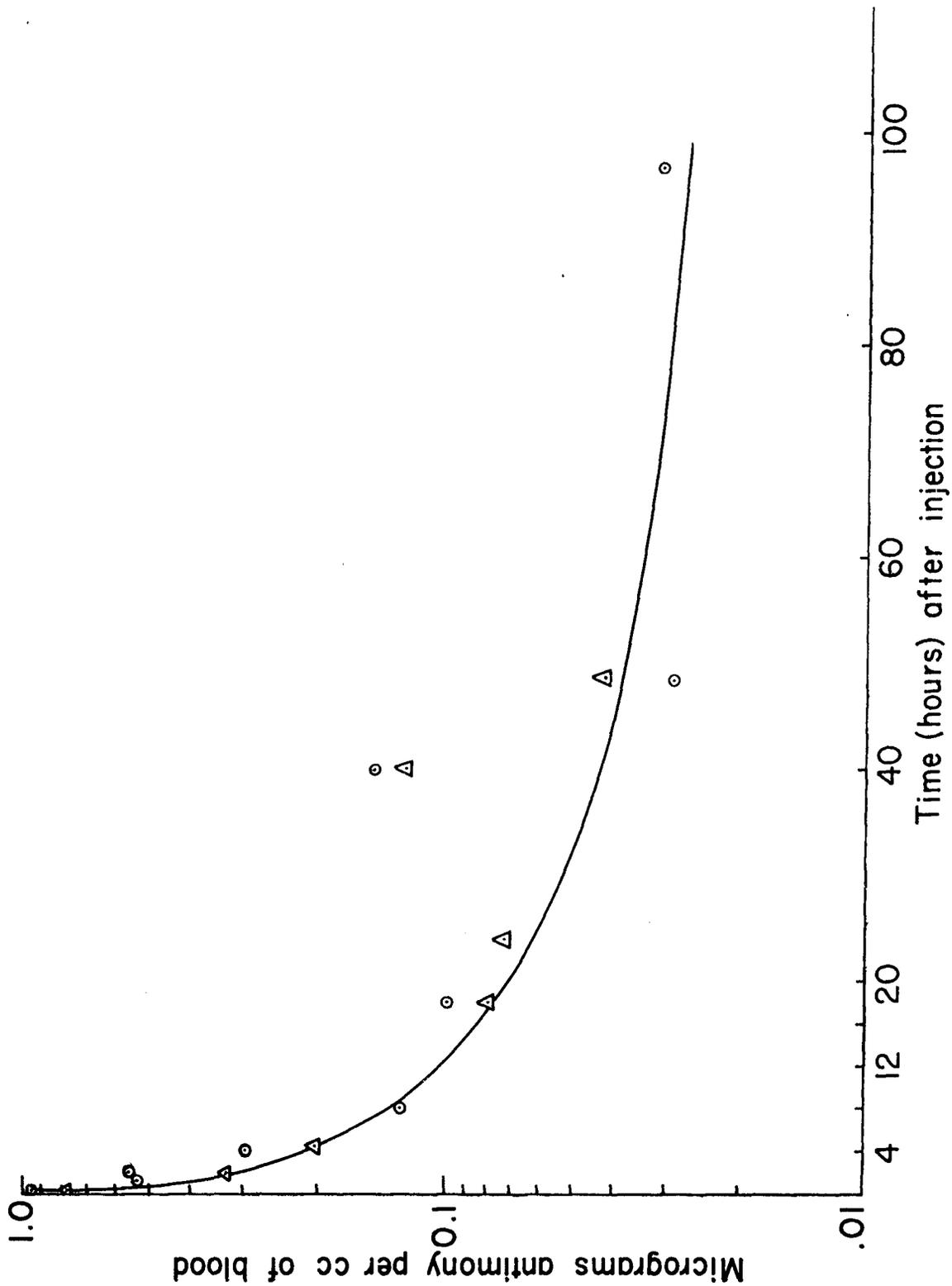


Figure 2.- Concentration of antimony in whole blood  $\circ$  and sum of corrected blood fractions (red cells + plasma)  $\Delta$ ; free - hand smoothing of semilog plot. Patient B-2.

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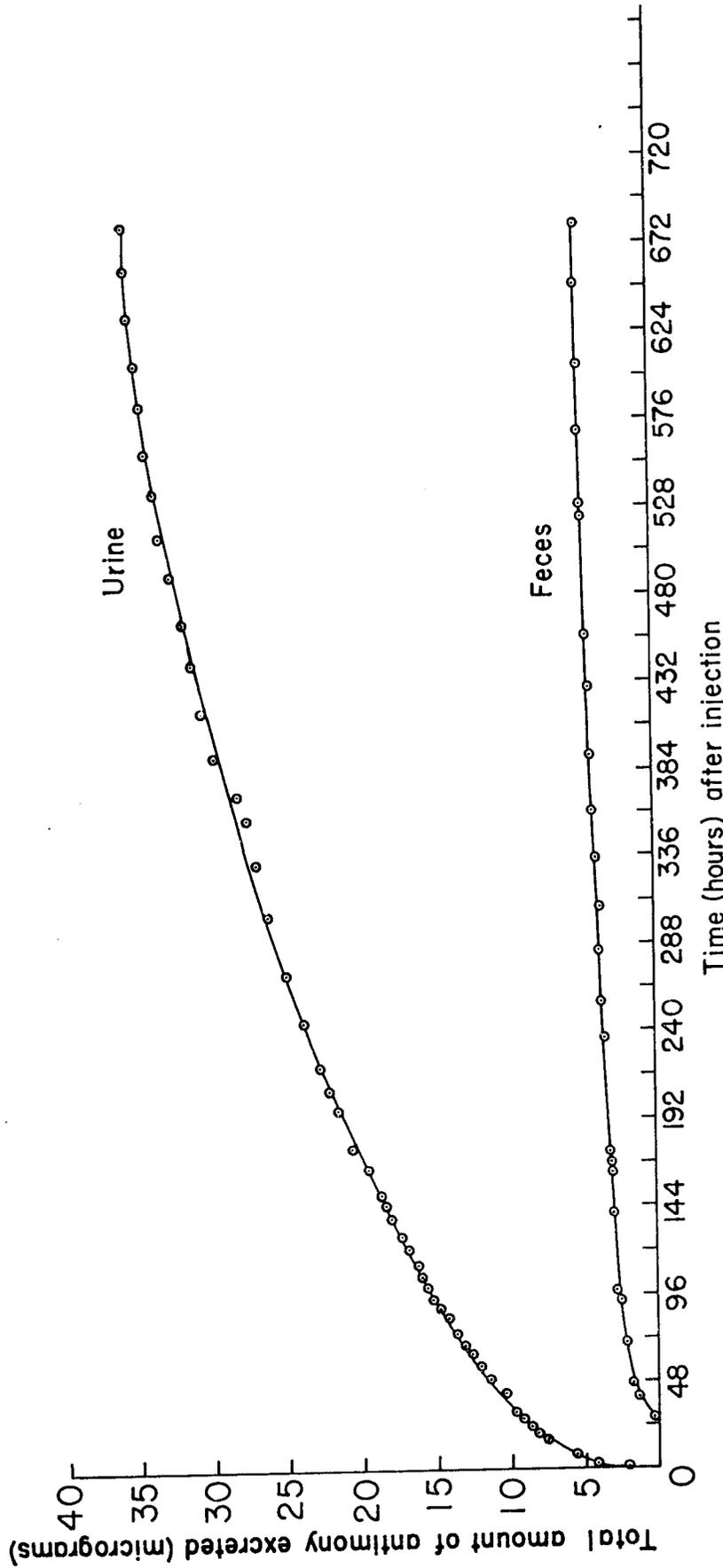


Figure 3.- Increment amount of antimony excreted via urine and feces by patient B-1. (Dose - 65.8 mgm. Sb.)