CONF-770673--1

BIOKINETICS OF Tl-201 IN MICE AFTER INTRAVENOUS AND ORAL ADMINISTRATION OF TlCl

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Presented at the Society of Nuclear Medicine 24th Annual Meeting
23 June 1977

McCormick Place, Chicago

DISCLAIMER

The high myocardial concentration and fast blood pool clearance of Tl-201 are useful features in myocardial imaging for the detection of myocardial infarction and transient ischemia. However, considerations of the high absorbed doses in organs such as kidneys and intestines have been the main concern in its applications. In this paper we will present a study of the biokinetics of Tl-201 in mice after intravenous and oral administrations. A simple compartment model is proposed in the analysis. It is hoped that the results will provide information on the physiological and biochemical kinetics of Tl-201 to serve as a guide in the collection of critical data to be used for the construction of a human model.

Seven- to eight-week-old CF1-strain female mice weighing 25-30 gms were used in the tissue distribuiton study. The appropriate amount of carrier-free Tl-201 in 0.1 ml of TlCl solution was administered to fasting mice. Data were collected at time points of 1/2 minute up to 7 days after i.v. and oral administration. After sacrifice by exsanguination, organs and tissue samples were removed and weighed; the radioactivity was counted against a standard to correct for physical decay and the % injected dose was determined. At least three mice were taken for each time point.

The first slide (1) shows the tissue distribution curves of Tl-201 in mice after the i.v. injection. Three distinct groups are evident. The blood curve shows a fast initial clearance rate with a half-time of less than 1/2 minute and levels off to a half-time of about 1-1/2 days after 5 hours following the injection. Kidney concentration is highest among all tissues and maintains a kidney-to-blood ratio of about 350. All other organs show a fast initial uptake to about 90% of maximum within one minute. After 5 hours following injection, all show a constant disappearance rate with half-time of about

1-1/2 days and the tissue-to-blood ratios cluster between 20 to 50. Data from the oral administration show a fast initial uptake in the liver and wall of the small intestine and slower uptake in all other organs. From 5 hours after administration, distribution curves of all organs exhibit characteristics similar to those of the i.v. injection.

The next slide (2) shows comparison of the heart-to-blood and heart-to-lung ratios from the i.v. and oral administrations. In the i.v. injection, the heart-to-blood and heart-to-lung ratios of 60 and 2 respectively are maximal at about one hour. In the oral administration, they maintain a broad maximum between 1 and 5 hours and are about 26 and 1.6 respectively.

In the next slide (3), we see that the heart-to-liver ratio is about 3 at 1 hour after i.v. injection and maintain a broad maximum of about 1.3 between 1 and 5 hours after oral administration. The heart-to-muscle ratio is about 7 at 1 hour after i.v. injection and decrease from about 4 to 2 between 1 and 5 hours after oral administration. The high ratios in this and the last slide are important factors in the success of Tl-201 in myocardial imaging.

The next slide (4) shows the blood curve of Tl-201 in mice after i.v. injection. The dashed curve is a least square fit to the experimental data using a sum of three exponentials. The first component gives a disappearance half-time of less than 1/2 minute and can be considered to be due to the fast equilibrium rates between the blood and the extracellular space in the tissue. Since this fast component does not provide much information to the kinetic study, we will consider the equilibrium between blood and the extracellular space to be instantaneous. A least square fit using a sum of two exponentials gives a blood concentration of about 2% of the injected dose/gm at zero time.

To construct a compartment model, we considered the mixable blood pool as a composite compartment consisting of the blood and the extracellular space

related to each organ. The experimentally measured activity is a sum of that in the intracellular and that in the related extracellular compartment. The exchange of Tl-201 between the mixable blood pool and the intracellular compartment of the tissue are given by the rate constants λ's.

The next slide (5) shows a simple compartment model proposed for the Tl-201 biokinetics in mice. Pathways of direct exchange are assumed between the mixable blood pool and the organs: heart, lung, liver, spleen, stomach, kidney and the intestinal walls. Excretion of Tl-201 is assumed to be carried out by the urine and feces. We have applied the Simulation, Analysis and Modeling program (also known as SAAM) which is developed at the National Institute of Health to the compartment model analysis. The tissue distribution data from both the i.v. and oral administrations are used to determine the rates constants λ's in the model.

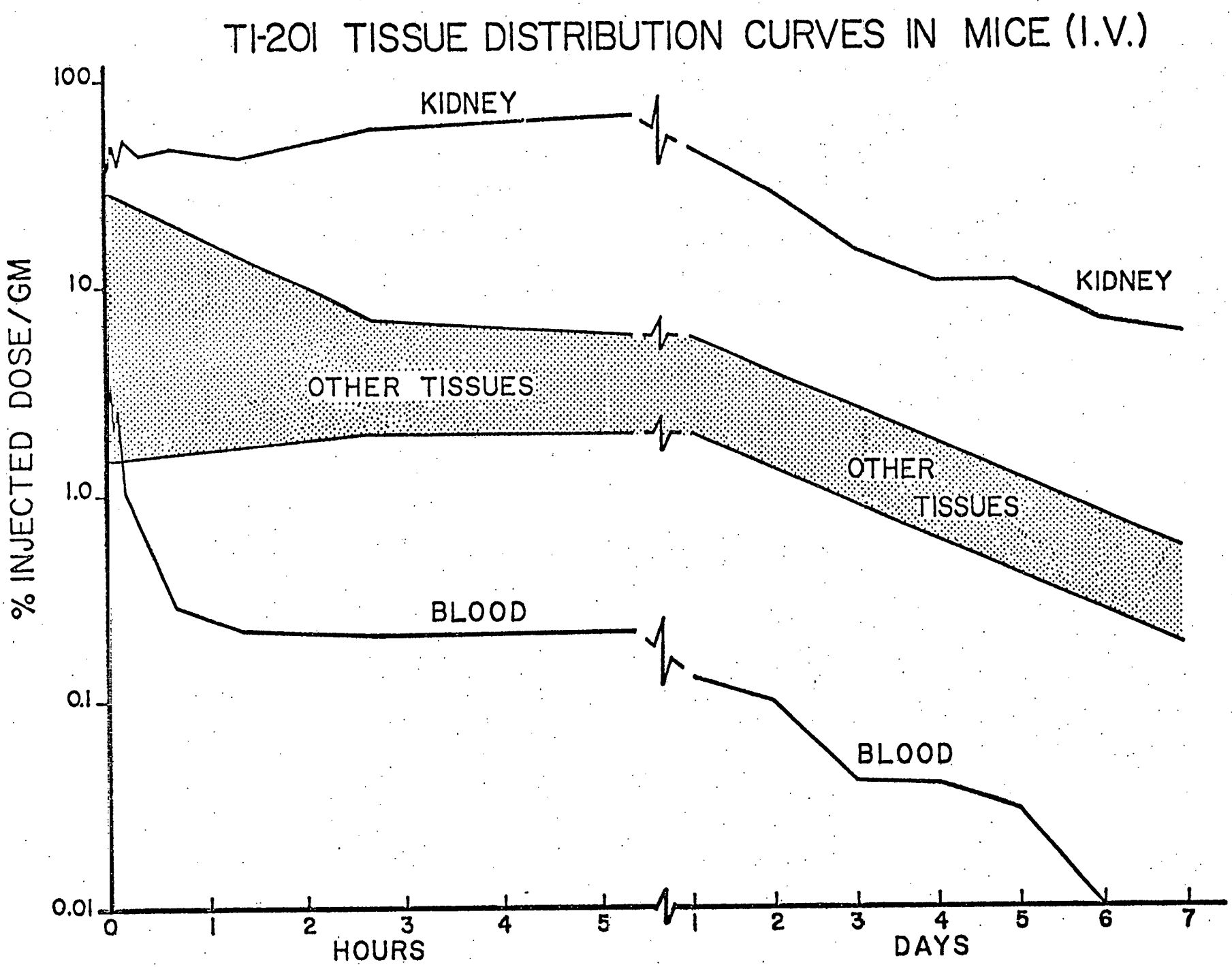
In the next slide (6) we show a comparison between the experimental data (shown with different symbols) and the results from the compartment model calculation (shown in solid and dashed lines) for the digestive system after i.v. injection. Similar agreement has also been found for other organs and for all organs after oral administration. The tissue distribution curves calculated from the compartment model can be integrated to obtain the residence time of Tl-201 in the organs. The results are shown in the next slide (7).

The absorbed dose can be obtained by correcting the tissue distribution curves for physical decay before integration and multiplying by the S factor determined by the MIRD Committee. Since all tissue distribution curves are similar in shape, the residence time will be approximately proportional to the fractional cumulated activity in the organ per unit of administered activity. Hence the cumulated activity in the kidney is about the same as that in the

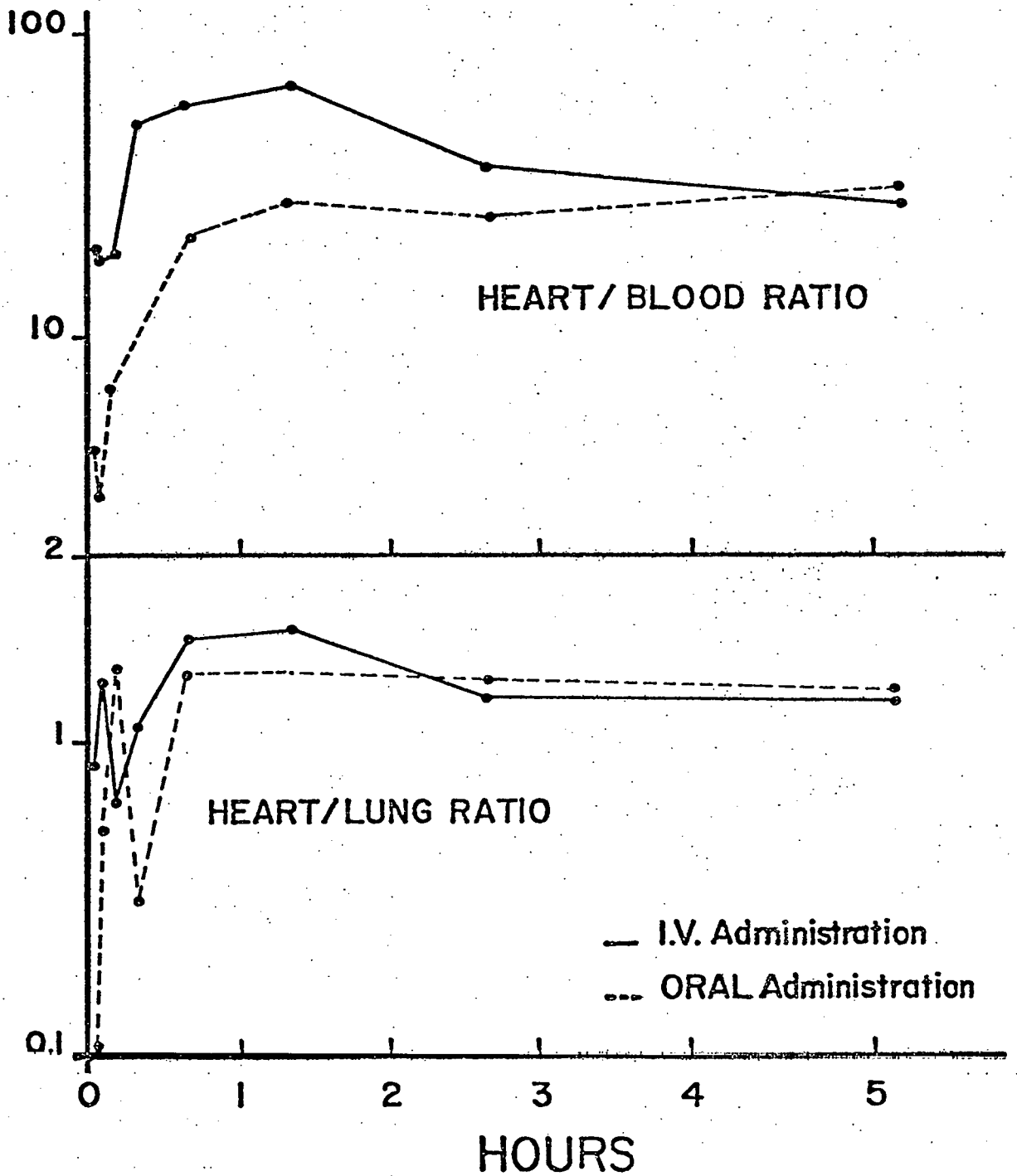
entire intestines plus content and is about four times that in the liver. It is also noted that the residence time for all organs from the oral administration is about 75% of that from the i.v. injection suggesting a decrease in absorbed dose for all organs following oral administration.

The rate constants obtained from the compartment model analysis are useful in understanding the physiological and biochemical kinetics of Tl-201 in the intact subject, valuable information which would be difficult to obtain from other means. A list of these rate constants and their respective fractional standard deviations are given in the distributed hand-out. For example, the rate constant from blood to kidney is about twice the return rate and this coupled with the small rate constant to the urinary excretion gives rise to the high concentration of activity observed in the kidney data. The high rate constants between the intestinal walls and intestinal contents suggest that two-directional exchange of Tl-201 between them. Recently it has been shown that the uptake of Tl-201 in humans after exercising is very high in the thigh muscle and very low in the liver. Such changes in the uptake can be accounted for by appropriate changes in the corresponding rate constants.

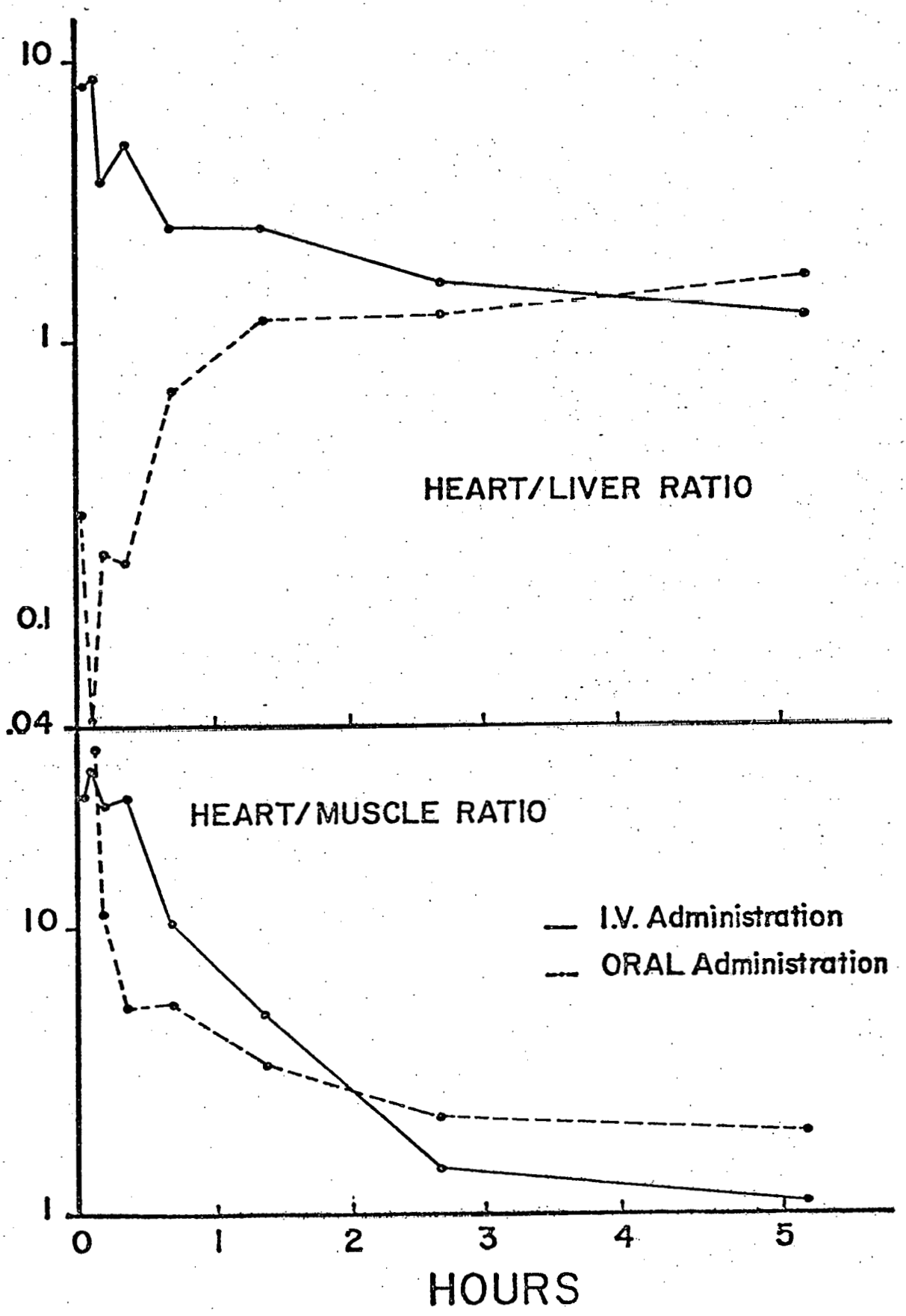
In conclusion, we have studied the biokinetics of Tl-201 in mice after i.v. and oral administrations. A compartment model analysis was applied with good results and provided valuable information on the physiological and biochemical kinetics of Tl-201 as well as a more accurate calculation of absorbed dose in the organs. In the future, we plan to use this compartment model developed with mice as a guideline for collecting critical data in human studies. Human tissue distribution data are scarce and incomplete because of the difficulties attendant to their collection. We hope to be able to construct a reasonably complete human compartmental model from such meager data by using information obtained in the mouse model as a guide.


TI-201 TISSUE DISTRIBUTION CURVES IN MICE (I.V.)
% INJECTED DOSE/GM
100
10
1.0
0.1
0.01
KIDNEY
KIDNEY
OTHER TISSUES
OTHER TISSUES
BLOOD
BLOOD
0
1
2
3
4
5
1
2
3
4
5
6
7
HOURS
DAYS

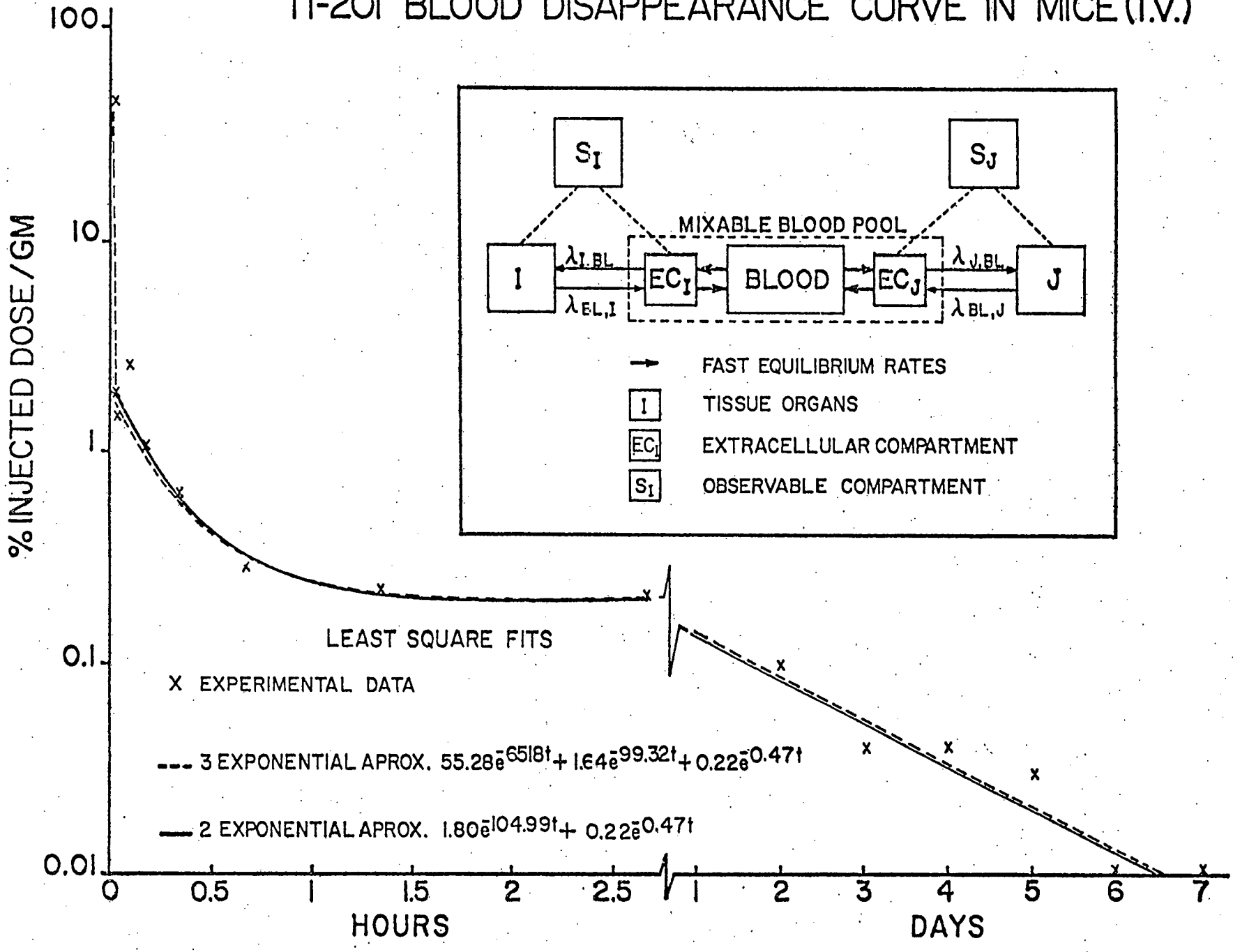
TI-201 TISSUE DISTRIBUTION



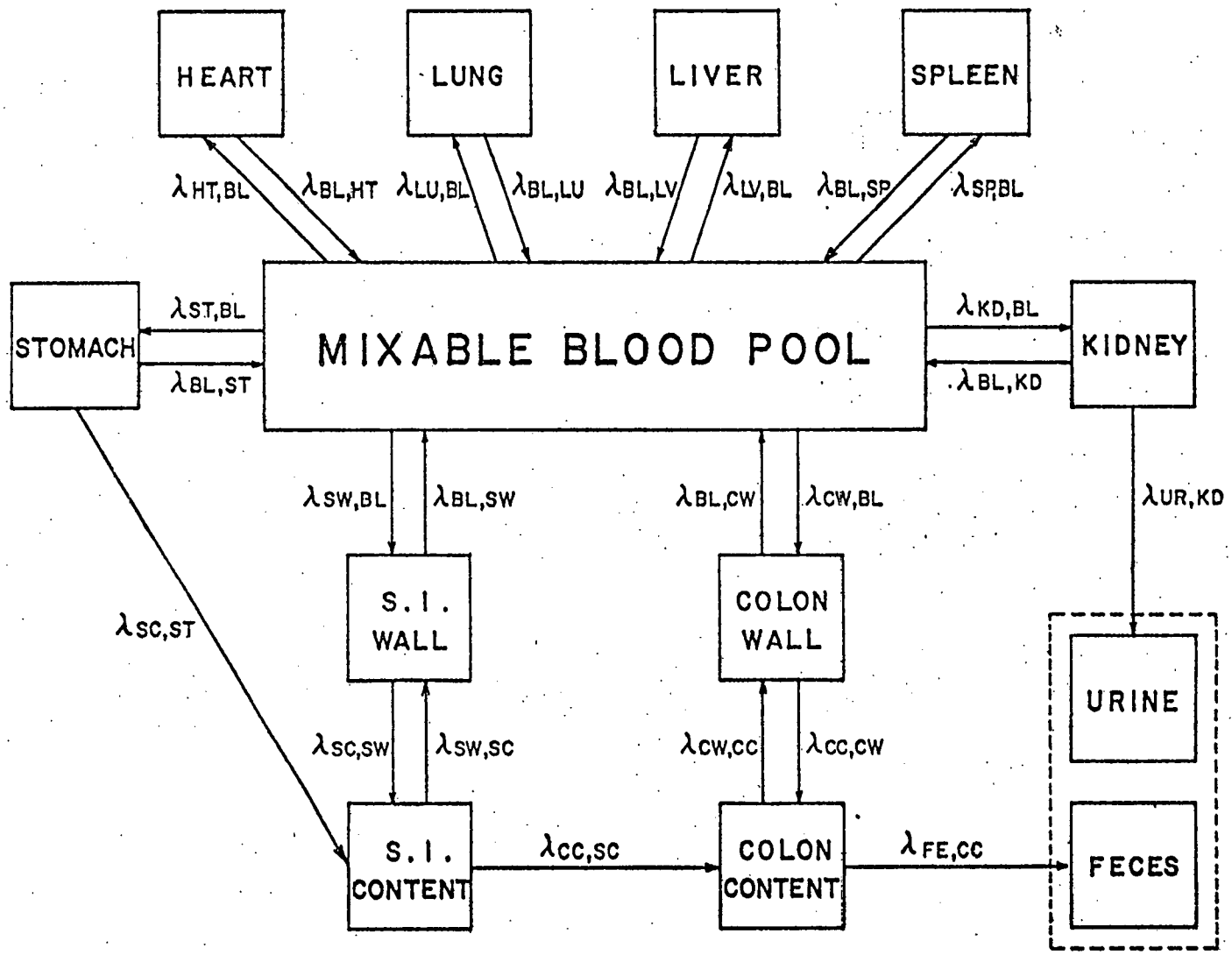
TI-201 TISSUE DISTRIBUTION



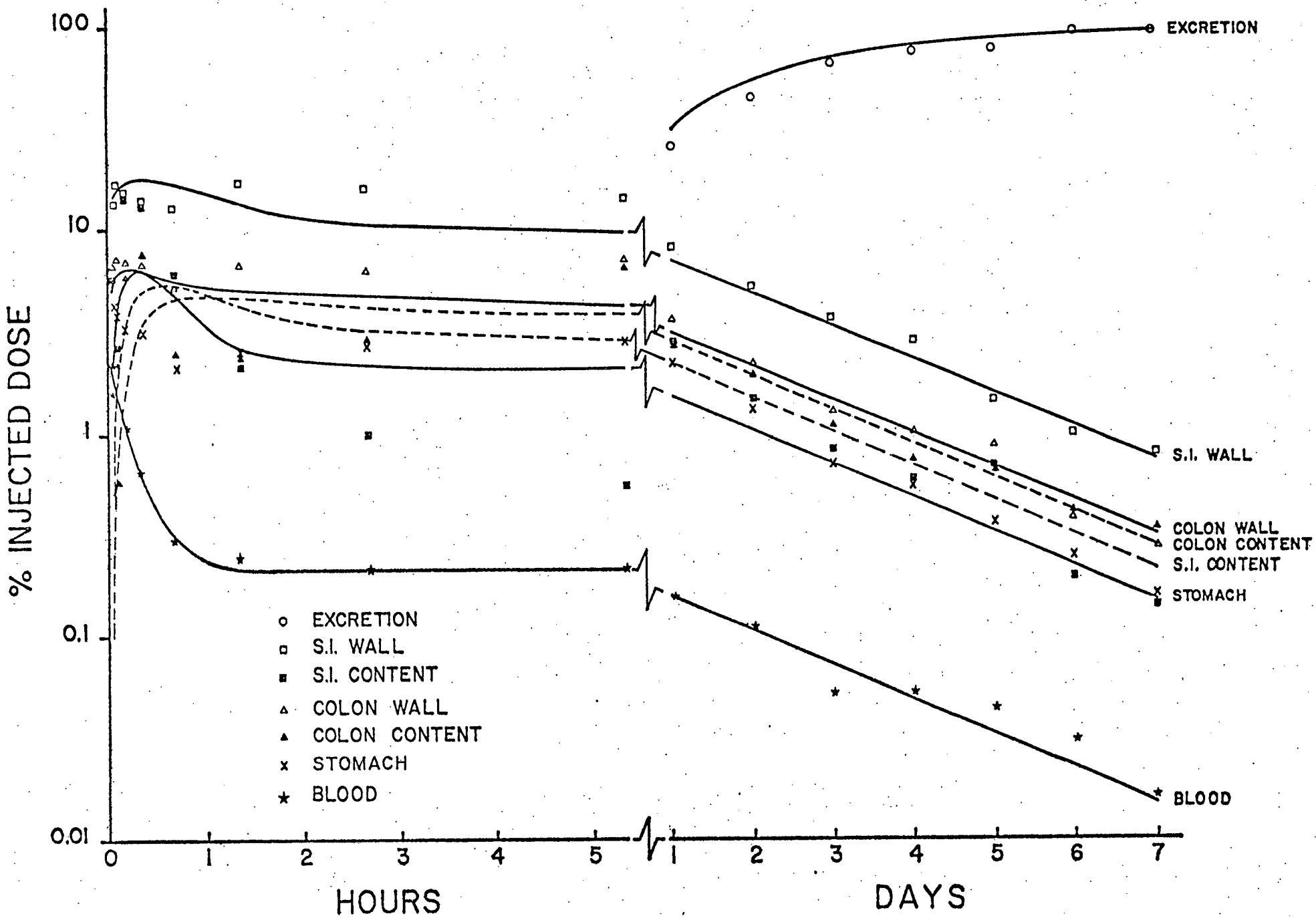
TI-201 BLOOD DISAPPEARANCE CURVE IN MICE (I.V.)



COMPARTMENT MODEL FOR TI-201 BIOKINETICS IN MICE



BIOKINETICS FOR TI-201 IN MICE (I.V.)



ORGANS	RESIDENCE TIME FOR TI-201 (HR)	
	I. V.	ORAL
HEART	0.46	0.34
LUNG	0.86	0.63
LIVER	4.12	3.02
SPLEEN	0.47	0.34
KIDNEY	13.44	9.90
STOMACH	1.38	1.34
S.I. WALL	6.56	5.07
S.I. CONTENT	1.92	1.51
COLON WALL	2.83	2.08
COLON CONTENT	2.49	1.84

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PARAMETERS FOR COMPARTMENT MODEL OF Tl-201 IN MICE

I ← J		RATE CONSTANTS	
		$\lambda_{I,J}$ (HR^{-1})	FSD ($SD/\lambda_{I,J}$)
HEART	BLOOD	0.04	0.27
BLOOD	HEART	1.37	1.20
LUNG	BLOOD	0.001	0.45
BLOOD	LUNG	0.015	0.45
LIVER	BLOOD	0.40	0.26
BLOOD	LIVER	0.75	0.28
SPLEEN	BLOOD	0.03	0.29
BLOOD	SPLEEN	0.53	0.32
KIDNEY	BLOOD	0.68	0.21
BLOOD	KIDNEY	0.35	0.22
URINE	KIDNEY	2×10^{-4}	2.34
STOMACH	BLOOD	0.61	0.08
BLOOD	STOMACH	1.71	0.18
S.I. CONTENT	STOMACH	1.33	0.19
S.I. WALL	BLOOD	1.27	0.25
BLOOD	S.I. WALL	1.84	0.21
S.I. CONTENT	S.I. WALL	7.88	0.76
S.I. WALL	S.I. CONTENT	24.36	0.68
COLON CONTENT	S.I. CONTENT	10^{-5}	1.77
COLON WALL	BLOOD	0.52	0.22
BLOOD	COLON WALL	1.01	0.30
COLON CONTENT	COLON WALL	4.31	0.39
COLON WALL	COLON CONTENT	4.01	0.45
FECES	COLON CONTENT	0.40	0.13