<u>Comparative Biokinetics of Radiogallium and Radioindium in Mice</u>

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Radiopharmaceutical preparations of radiogallium and radioindium have
proved useful in nuclear medicine. Since both elements have many similar
properties, it is not clear which one may be preferable. Both elements are
members of Group III in the periodic table and thus have similar chemical
properties. Isotopes of the two elements also have similar nuclear decay
properties. (Slide [1]) Gallium-68 and indium-113m have relatively short
half-lifes and both have relatively high energy gamma emissions. Gallium-67
and indium-111 have longer half-lifes and their gamma emissions are in the
mid-energy range. Both gallium and indium have been found to bind to plasma
proteins, principally transferrin, immediately after intravenous injection
as ions in strongly acidic solution. Because of their similar chemical and
physical properties, knowledge of the relative biokinetic behaviors is
important in evaluating and comparing the two radionuclides so that the best
one for a particular purpose may be selected. As long as the exact bio-
chemical and physiological properties of the radioions and the biologically
labeled molecules remain unknown, an alternate approach using compartmental
modelling may be helpful.

Seven- to eight-week-old CF1-strain mice weighing 25 to 30 grams were
used in the determination of tissue distribution. An appropriate amount of
carrier-free radiogallium or radioindium chloride in 0.1 ml of solution at
∿ pH 2 was administered intravenously to anaesthetized mice. (Slide [2])
Data from 9 tissues were collected at time points of 15 minutes up to 5 days

for indium and 6 days for gallium. Tissue samples were removed and weighed after sacrifice by exsanguination; the radioactivity was assayed as % of injected, by counting against an injection standard. At least three mice were taken for each time point. These experimental data were then used in the compartmental modelling analysis.

(Slide [3]) In constructing the compartmental models, the mixable blood pool is considered as a composite compartment consisting of the blood and the extracellular space related to each tissue. The experimentally measured activity in each tissue (or the observable compartment, S) is a sum of the activity in the intracellular plus the related extracellular compartment. The equilibrium rates between the blood and the extracellular space are large and account for the fast initial clearance in the blood. Since this fast component does not provide much information for the kinetic study; the equilibrium between blood and the extracellular space is considered to be instantaneous. The exchange of the radionuclides between the mixable blood pool and the intracellular compartment is given by the rate constant k_{ij} which is defined in the next slide.

(Slide [4]) shows the linear differential equation which describes the kinetics for issue compartment i. k_{ij} is the time invariant rate constant defined as the fraction of tracer in compartment j transferred to compartment i in unit time. For example, in our compartmental model, k_{i1} is the transfer rate constant from the blood compartment 1 to tissue compartment i. For the tissue compartment which only exchanges with the blood compartment, the rate of change in the compartment is given by the amount transferred in from the blood compartment minus the amount returned to the blood. For excretory organs, the amount for excretion is further subtracted.

We have applied the SAAM 27 program of Berman, et al. at NIH to the compartmental model analysis. The program was used to solve the kinetic differential equations for all the organs simultaneously. The rate constants k_{ij} are determined such that the model gives the best fit to the experimental tissue distribution data.

This slide [5] shows the linear compartmental model for the blood clearance. The model for gallium shows higher total exchange rates between the blood and the sum of all tissues than those in the indium model. The excretion rate constant for gallium is also higher than that of indium. This may be due to stronger binding of the indium-labeled protein. The results from the compartmental model show a faster blood clearance for gallium and are in good agreement with the experimental data.

This slide [6] shows the linear compartmental model proposed for the biokinetic distribution of radiogallium and radioindium in mice. Pathways of direct exchange are assumed between the mixable blood pool and the organs of interest as indicated. Since an undetectable amount of activity is found in the gallbladder, we have assumed no transfer of the radionuclides from the liver to the intestine. Based on this model, the SAAM 27 program was applied to determine the rate constants k_{ij} for the best fit to the experimental data during the period observed. The results are shown in the next slide [7].

There is more information on this slide than anyone can absorb during this presentation. I will be happy to provide a copy of the results to anyone who is interested afterward. At present, I would only point out some general features and then move on to examine some parts of the model in a bit more detail.

The common feature in the model for gallium and indium is the slow tissue uptake of the radionuclides from the blood by the heart, lungs and uterus with negligibly small return rates during the period observed. The liver uptake from blood is faster than for the organs just mentioned for both radionuclides and the return rate is negligibly small. Two-directional exchange of the radionuclides is found for blood/spleen and blood/stomach. However, the exchange rate constants are higher for gallium.

Comparative excretion kinetics are shown here. (Slide [8]) The higher rate constant from blood to the kidneys for gallium results in a faster initial uptake than for indium. The concurrent higher kidney excretion rate constant for gallium is responsible for the maximum kidney concentration occurring at about 3 hours after injection, much earlier than the approximately 30 hours for indium. The higher excretion rate constant combined with the faster blood clearance curve results in a kidney concentration lower for gallium than for indium.

Both the transfer rate from blood to the intestine and the intestinal excretion rate are high for gallium with little transfer from the intestine back to the blood. Slower two-directional rate constants between blood and the intestines are indicated for indium. The undetected intestinal excretion for indium seems to be similar to that found in human studies. The results of the linear models show the maximum concentration for gallium in the intestine to occur at about 3 hours compared to about 18 hours for indium. The intestinal concentration for indium is about 1-1/2 times higher than that of gallium between 1-5 days.

This slide [9] shows the kidney-to-blood and intestine-to-blood ratios predicted by the compartmental model and compared to the experimental data.

The compartmental models show that the kidney-to-blood ratio for gallium increases rapidly to 25 in about 6 hours and remains constant up to about 6 days, however, for indium, the ratio increases more slowly up to ∿ 140 in 5 days. The intestine-to-blood ratio for gallium increases rapidly to a maximum of about 10 in 6 hours, decreases to about 7 in 1-1/2 days, and remains constant for the remainder of the observation period. For indium, the ratio increases more slowly to about 7 in 2-1/2 days and remains constant up to the 5 days observed.

The next slide [10] shows the comparison between the kinetics of gallium and indium in liver and spleen in our compartmental model study. The blood-to-liver rate constants are about the same and the return rate constants are negligibly small for both radionuclides. This suggests a similar transfer mechanism of the two radionuclides from blood to the liver. The tissue distribution curves for both radionuclides are similar in shape. However, the liver concentration for indium is higher than that for gallium by about 1-1/2 times due to a higher blood concentration. The blood-to-spleen rate constants for both radionuclides are small compared to the return rate constants. The resultant spleen concentration is higher for indium than for gallium.

The tissue-to-blood ratios for liver and spleen are shown in the next slide [11]. Due to the similar biokinetics demonstrated in the last slide, the liver-to-blood ratios are similar for both radionuclides even though the liver concentration is higher for gallium. The ratios increase to about 10 in 1-1/2 days and to about 40 in 5 days. The compartmental model shows a higher spleen-to-blood ratio for gallium initially with a rapid increase to about 3.5 in 6 hours, and a slower increase to 10 in 2-1/2 days. The ratio for indium has a slower and more uniform increase up to about 10 in 2-1/2 days.
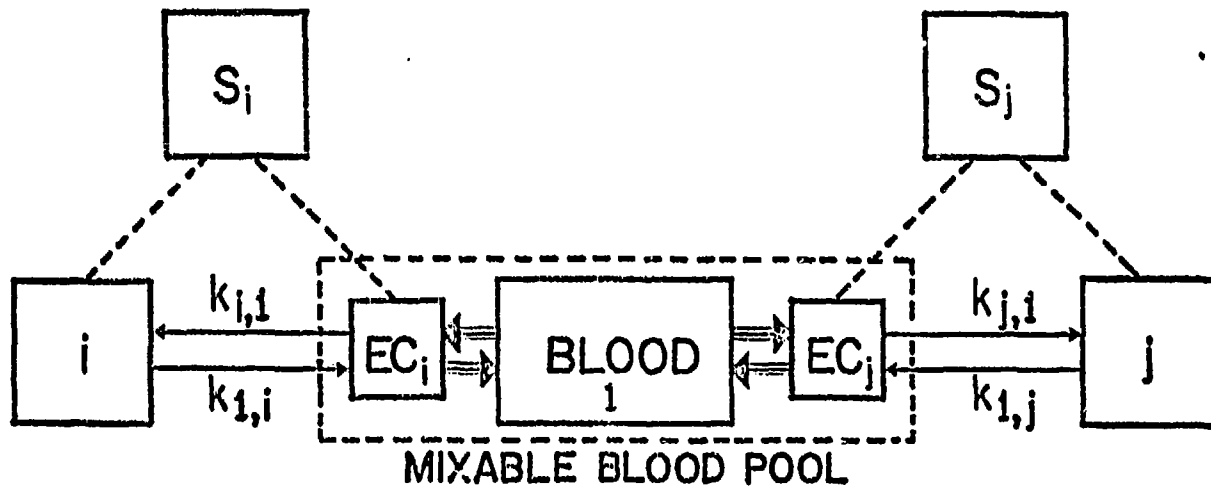
After 2-1/2 days the ratios for both radionuclides are similar and increase to about 20 in 5 days. The kinetics for other tissue compartments can be described similarly. However, due to time limitation, they will not be presented here.

The biokinetics of radionuclides in animals depends on the physical and physiological state of the subject under study. Biokinetic changes during pregnancy have been investigated for gallium and indium and will be presented at the World Federation meeting in September.

In conclusion, we have compared the biokinetics of radiogallium and radioindium in normal mice using the compartmental modelling analysis. The rate constants obtained provide useful information in understanding the physiological and biochemical kinetics of radionuclides in the intact object. A comparison of the compartmental models for gallium and indium reveals the similarities and differences between the biokinetics of the two radionuclides. Furthermore, the results provide valuable information and guidance for human studies and clinical use.

PHYSICAL CHARACTERISTICS OF *Ga & *In

RADIO-NUCLIDE	HALF-LIFE (HRS)	MODE OF DECAY	PRINCIPAL GAMMA RADIATIONS (Kev)	ABUNDANCE (%)
$_{31}Ga^{68}$	1.13	β^+(88%) EC (12%)	511	176
$_{49}In^{113m}$	1.67	IT	393	64
$_{31}Ga^{67}$	78	EC	93 184 296 388	40 24 22 7
$_{49}In^{III}$	68	EC	173 247	89 94

% INJECTED DOSE PER GRAM FOR GALLIUM

HOURS AFTER I.V. INJECTION

- ■ Kidney
- ◆ Liver
- o Spleen
- ✳ Uterus
- ✱ Stomach
- ● Intestine
- ✕ Lung
- ▲ Heart
- ● Blood

% INJECTED DOSE PER GRAM FOR INDIUM

HOURS AFTER I.V. INJECTION

$\boxed{\text{i}}$	TISSUE COMPARTMENT i
$\boxed{\text{EC}_i}$	EXTRACELLULAR COMPARTMENT OF i
$\boxed{\text{S}_i}$	OBSERVABLE COMPARTMENT OF i $\left(\ \boxed{\text{i}}\ +\ \boxed{\text{EC}_i}\ \right)$
$\Longrightarrow$	FAST EQUILIBRIUM RATE
$\xrightarrow{k_{i,j}}$	LINEAR TRANSFER RATE

LINEAR KINETICS FOR TISSUE COMPARTMENT i

$$\frac{df_i}{dt} = k_{i,1}f_1 - k_{1,i}f_i - \underbrace{[k_{10,i}f_i]}_{\text{excretion}}$$

f_i : amount of tracer in comp. i

$k_{i,j}$: time invariant rate constant
(Fraction of tracer in comp. j transferred
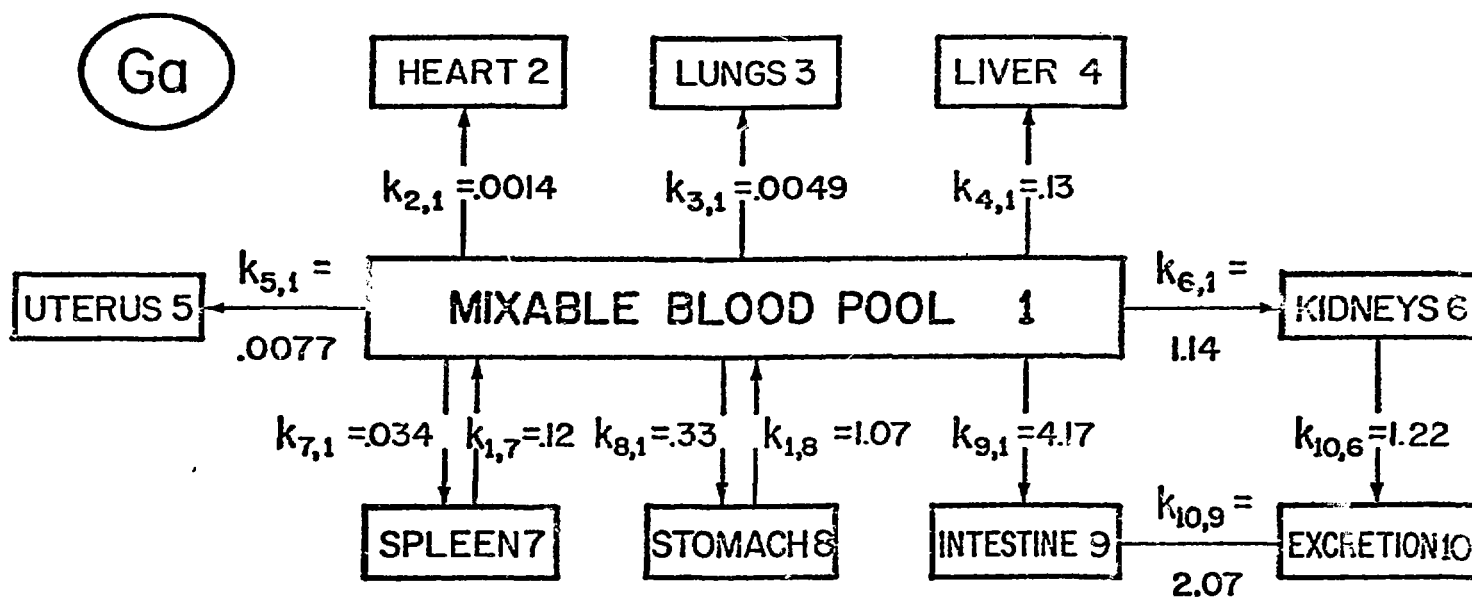to comp. i per unit time)

LINEAR COMPARTMENT MODEL IN MICE

BLOOD CURVES IN MICE

x Ga   Exp. Data
⊙ In
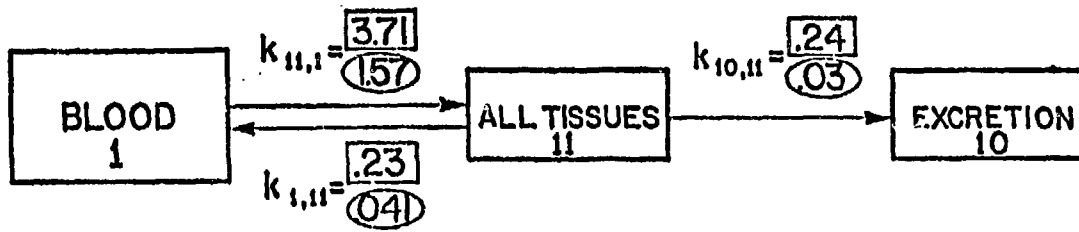
—   Ga   Linear Comp. Model
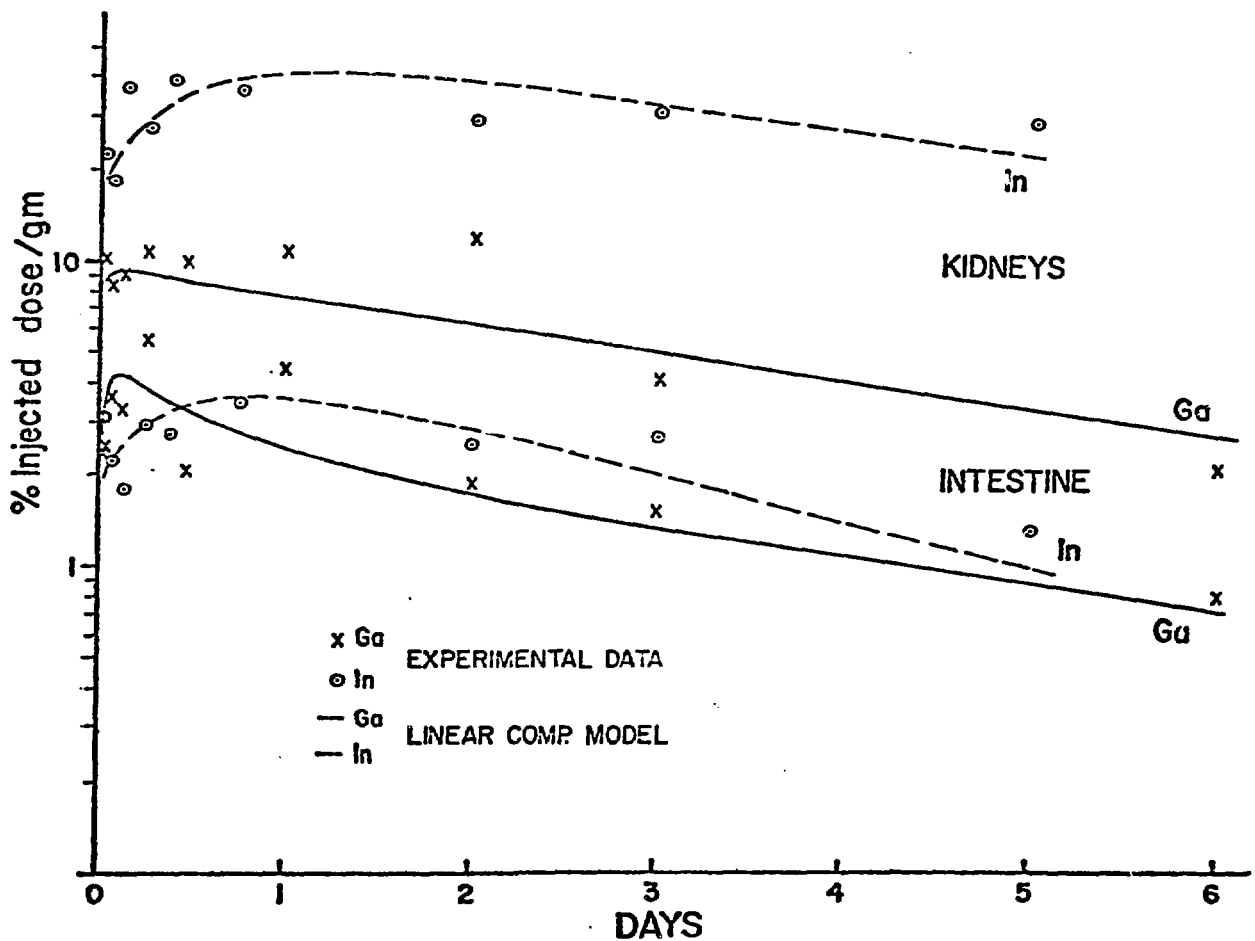····· In
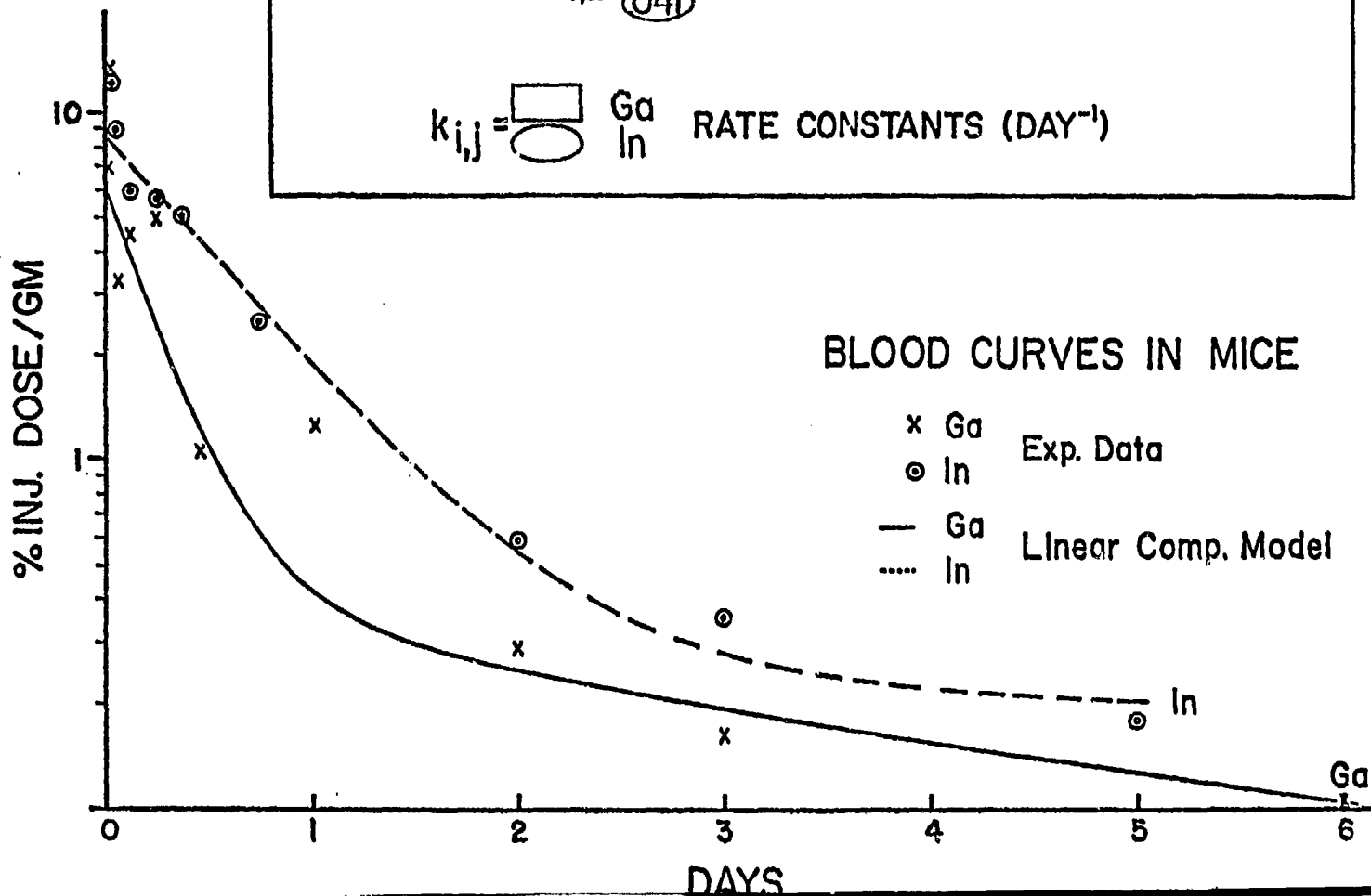
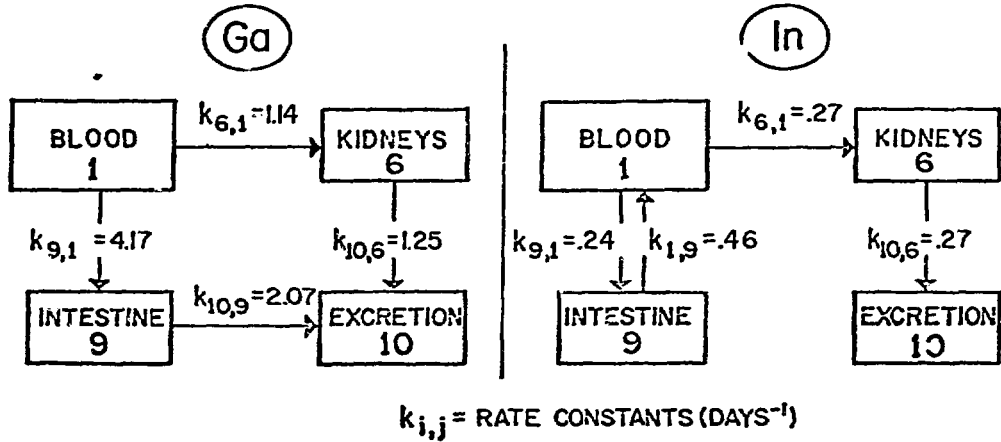# LINEAR COMPARTMENT MODEL OF *Ga AND *In IN MICE
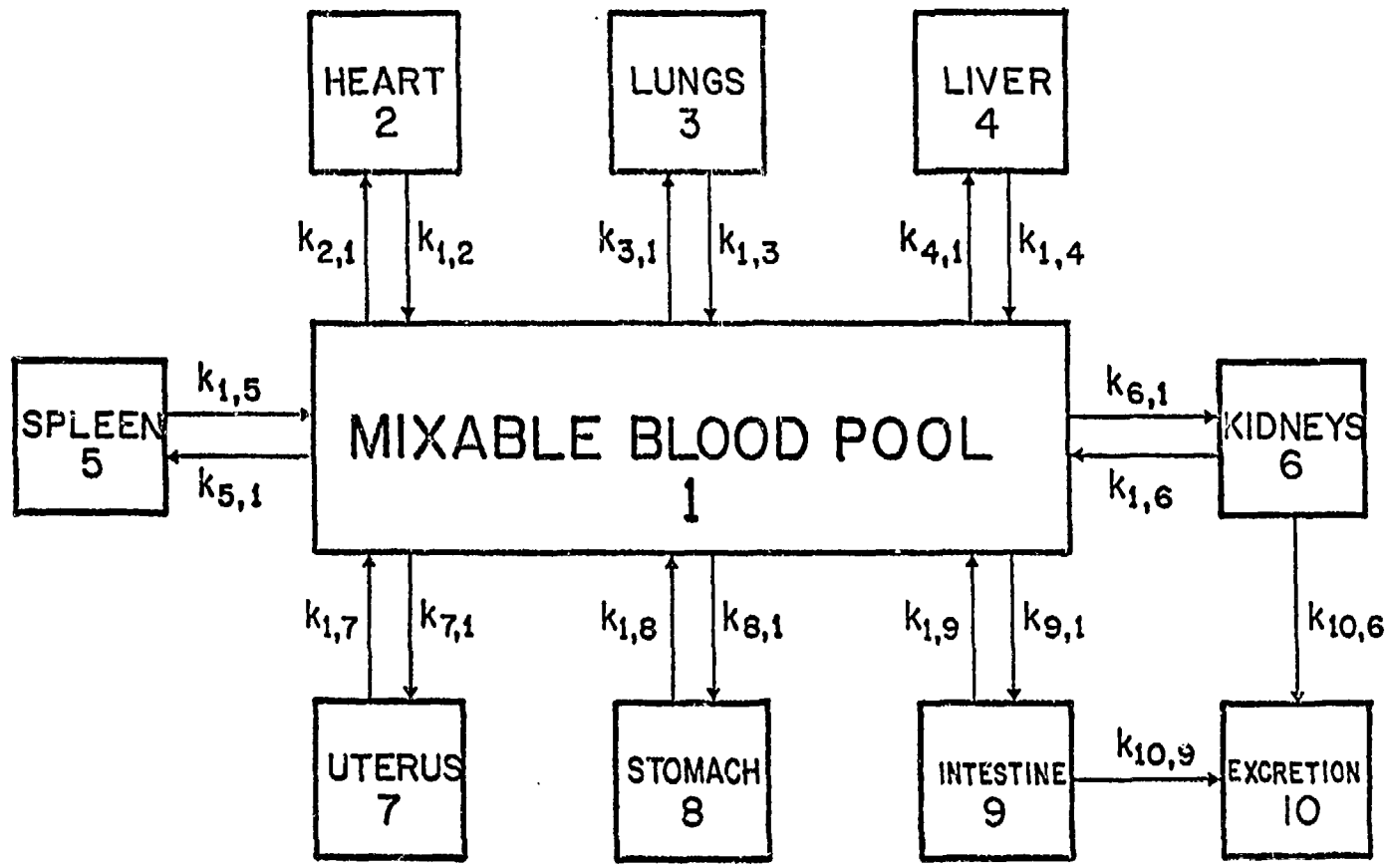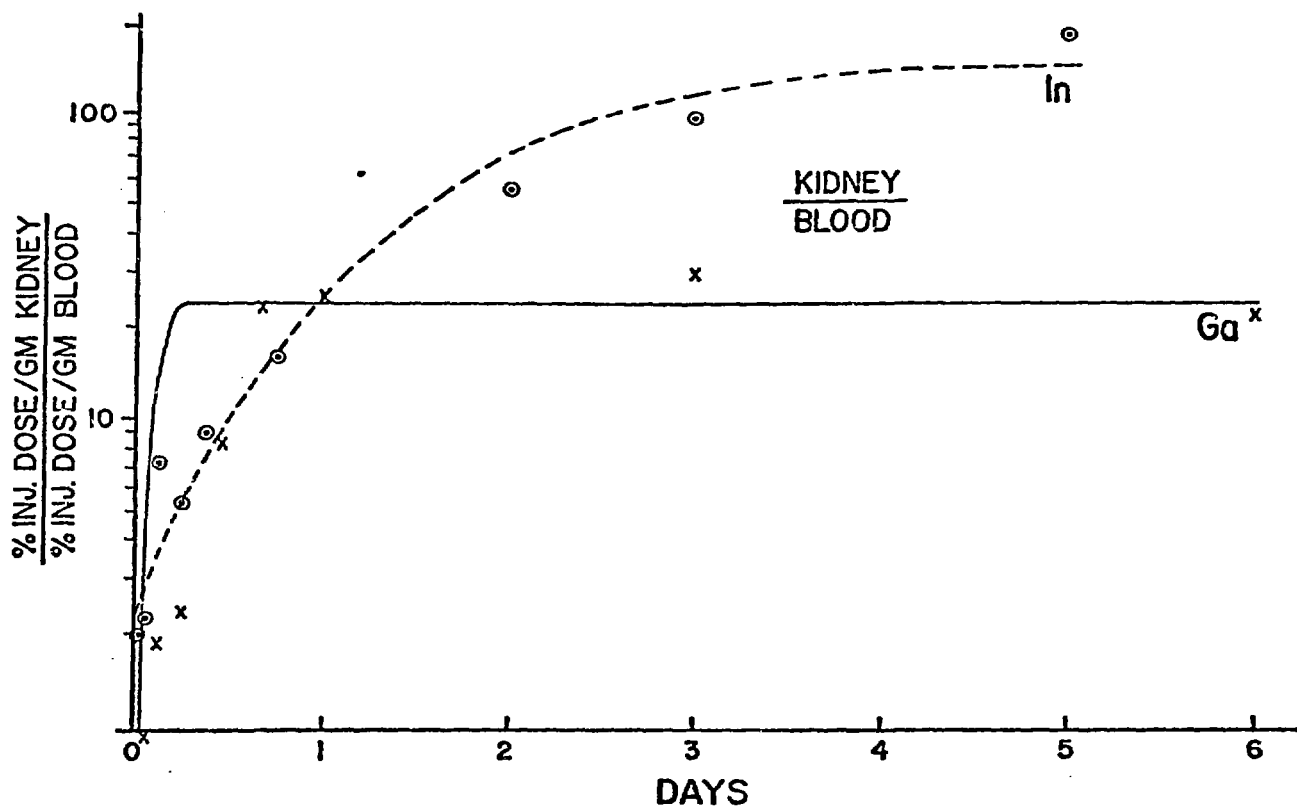
LINEAR COMPARTMENTAL MODEL IN MICE
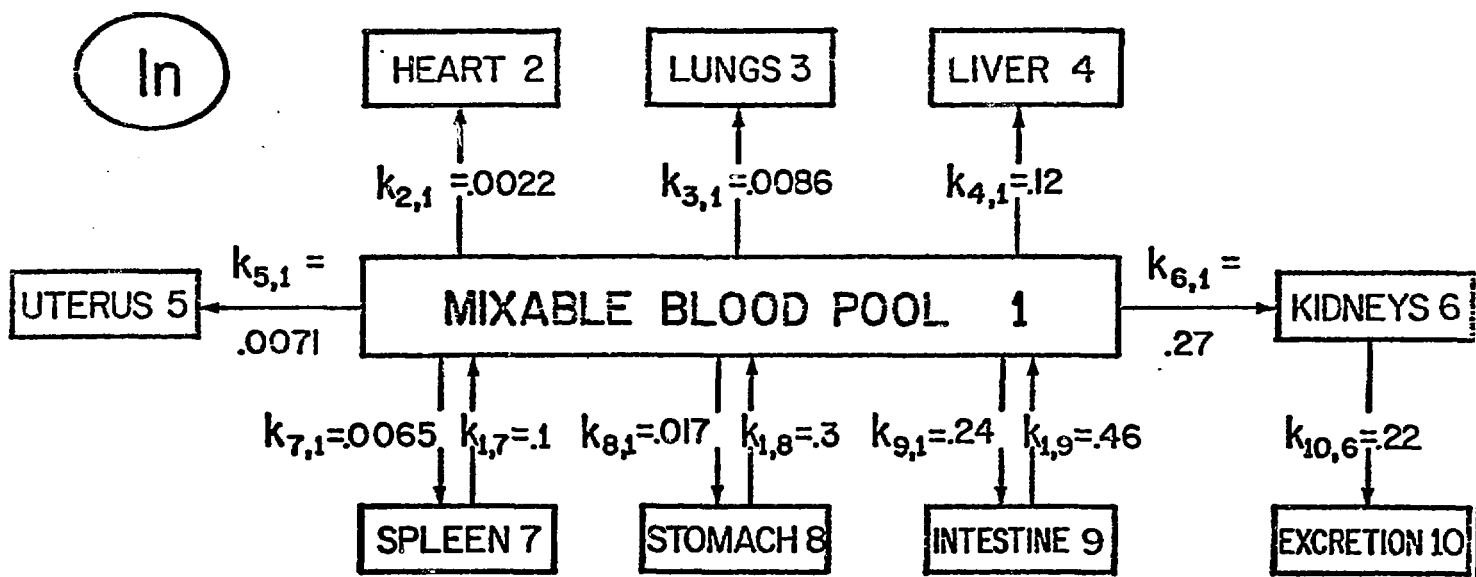
$k_{i,j}$: Rate constants (Day^{-1})

Models best fit exp. data between 0-5 days
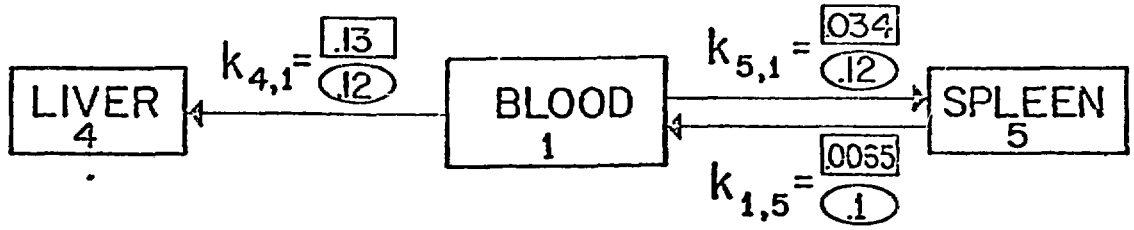
LINEAR COMPARTMENT MODELS IN MICE

KIDNEY / BLOOD

In

Ga

INTESTINE / BLOOD

Ga

In

x	Ga	EXP. DATA
⊙	In	
——	Ga	LINEAR COMP. MODEL
- - -	In	

LINEAR COMPARTMENT MODELS IN MICE

$k_{4,1} = \dfrac{\boxed{.13}}{.12}$ $k_{5,1} = \dfrac{\boxed{.034}}{.12}$

LIVER 4   BLOOD 1   SPLEEN 5

$k_{1,5} = \dfrac{\boxed{.0055}}{.1}$

$k_{i,j} = \dfrac{\square}{\bigcirc} \begin{array}{l} Ga \\ In \end{array}$ Rate Constants (Day⁻¹)

LIVER

In

Ga

% INJ. DOSE/GM

SPLEEN

In

Ga

x   Ga   Exp. Data
⊙   In

——   Ga   Linear Comp. Model
- - -   In

DAYS