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Use of an Analogue Computer in Studies of Strontium and Calcium Metabolism in Man*

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Although strontium is not normally a significant body component, its metabolism is currently of great interest because of its similarity to calcium metabolism and because of the hazards or potential hazards of strontium isotopes as fallout constituents. The data to be discussed here are part of a study being described in greater detail elsewhere (1) and which was undertaken to help quantify the degrees of similarity and difference between the behavior of calcium and strontium. The analogue computer described in the preceding paper (2) was used in the analysis of the data.

Briefly, the experiments involved injecting tracer doses of Ca^{47} and Sr^{85} intravenously in six adult patients. Subsequent measurements included determination of activity concentrations in blood samples and in urine and feces specimens. Retention in the body was measured with a whole-body counter employing an 8-inch diameter NaI (Tl) crystal in a room shielded with 6 inches of steel on all sides. Data were taken over a period of 30 days but the present analysis considers only the first ten days.

The method of analysis used is based upon the usual assumptions made concerning the relationships between the behavior of radioactive tracers and their stable counterparts in steady-state compartmented systems (3,4,5). In lieu, however, of solving the differential equations which relate the tracer behavior to the system parameters, the analogue computer provides a direct analogy of the compartmental model assumed. When analogue values are found such that the curves generated by the computer satisfactorily fit the data, it is assumed that this model represents at least a possible configuration of

the system parameters. It must be appreciated, however, that usually there is a considerable range of model values (sizes of compartments and rates of flow between compartments) which will generate equally satisfactory, if not almost indistinguishable, fits to the data. Sometimes the choice can be resolved by applying other restrictions to the system; sometimes a least squares fit, obtainable by digital methods[1], has to be used.

It is not appropriate here to attempt to review the extensive literature on strontium and calcium metabolism, but it may be mentioned that any model used for comparing the metabolism of these elements should conform to certain established facts in addition to providing fits for the data at hand. Because it has been established, for example, that in a great many respects the metabolisms of calcium and strontium are similar, it is desirable to establish a model which will generate fits for both sets of data with minimal differences. On the other hand, one point of difference, known from prior work and supported by the present data, is that the plasma clearance by urinary excretion is about three times as great for strontium as it is for calcium.

The problem, then, is to establish a model which generates satisfactory fits for the calcium plasma and whole-body data simultaneously, and with minimal adjustment of the system parameter values also to fit the strontium plasma and whole-body curves simultaneously.

The calcium and strontium plasma data and the fits generated by the analogue computer using the model discussed below are shown in Fig. 1. The upper set of data points is for Ca^{47}, the lower for Sr^{85} concentrations, with both normalized relative to the first data point, which was taken at 30 minutes after injection.

Fig. 2 shows the plasma and whole-body data and curves generated by the computer corresponding to intermediate inaccessible compartments, as well as those fitted to the data. The upper photograph (A) depicts the Sr^{85} results, the lower one (B) the Ca^{47} results.

Fig. 3 compares the biological model and its electrical analogue used in generating the above fits. The compartment sizes are given relative to the size of compartment I, and flow rates are expressed as fractions of I per day.

As indicated by the syringe and needle in the diagram, the initial injection of radioactivity is into compartment I, which is also designated "plasma." Actually, the first experimental point, to which the other data are normalized, corresponds to dilution in an apparent distribution "space" of 0.33 gram of calcium, which is slightly large for the plasma calcium content and indicates that some extravascular calcium is included in this compartment. The arrow out of compartment I indicates urinary excretion, with the clearance rate for strontium being about twice that for calcium.

Although good fits could be obtained with the values in the model being the same for calcium and strontium, except for the urinary excretion rate, for the best fit, it was necessary also to manipulate the relative size of compartment II, as is indicated by giving this compartment a value 2.16 for calcium and 1.88 for strontium.

The dashed line enclosing compartments III and IV indicate that both of these are regarded as being in bone.

In the electrical analogue it will be noted that only a resistor connects compartment I with compartment II, representing equal flow rates in the opposing directions between these compartments. There is only one-way flow in the rest of the model, however, and to simulate this kind of transfer, operational amplifiers are used as one-way pumps. In the computer, resistor 32A is ganged with resistor 32B so that one dial setting adjusts both resistors at once and insures their being equal within the precision of the components. The circuit is such that if R32A = R32B, the current into capacitor III through R32B equals that out of capacitor II through R32A, so that each current is determined only

by the voltage on capacitor II independently of that on capacitor III, thus simulating one-way flow from compartment II to compartment III, and so on. The lower portion of the electrical diagram in Fig. 3 illustrates the use of operational amplifiers as multipliers and as an adder for generating the whole-body curves. Because the plasma and other compartment curves are in units of specific activity, whereas the whole-body data are in units of total activity, it is necessary to multiply each compartment by a factor corresponding to its mass to adjust the units before [redacted] addition. For an as-yet undetermined reason, it was found to be necessary to use a relatively larger factor for compartment IV than for the other compartments in fitting the whole-body curves. If the size of compartment IV were adjusted to correspond to this factor, the plasma curve could not be made to fit. The turnover time for compartment IV in the model used is given by $\frac{S}{\rho} = \frac{13.5}{.458} = 29.5$ days, and that for the other bone compartment, III, is only 1.6 days. These are rather fast turnover rates for bone, and presumably there are one or more much more slowly exchanging compartments in the bone which are not accounted for in this model, but the inclusion of which would be necessary to give simultaneous fits for both the plasma and the whole-body data.

Another reason for assuming that a large, very slowly exchanging compartment has been omitted is that the total size of the four calcium compartments combined is only 17 times that of compartment I. Since compartment I represents only some 0.33 gram of calcium, a total of only 6 to 10 grams of calcium is accounted for in this model, indicating that in the first ten days after injection of labeled calcium, only about one per cent of the

calcium in the body participates in the calcium exchange processes. Similar interpretation of Bauer's (7) data gives a correspondingly low result for the amount of calcium involved in the rapid exchange processes. It is, of course, also known that detectable amounts of activity do become fixed in bone during the period considered, but the rate at which this occurs is too slow to have an apparent effect on the model system presented.

References

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Footnote

[1]In the discussion which followed this paper it was pointed out that Uffer and Sheppard (6) have described a method for using an analogue computer to obtain a least-squares fit.

Figure Captions

Negative No.

1. Plasma calcium (A) and strontium (B) data points and corresponding curves generated by the analogue model shown in Fig. 3 for compartment I. (The data points have been retouched for clarity.) 4-361-62

2. A. Data points and curves representing relative specific activities of Sr^{85} in the model shown in Fig. 3. Curves labeled A, B, C and D correspond to compartments I, II, III and IV, respectively, and curve E is the whole-body curve. The data for the whole-body counts are in units of total retained activity, normalized so that the time zero point coincides with that of the other curves.

   B. Corresponding data points and curves for Ca^{45} using the same model system. 4-362-62

3. Four-compartment model used in analysis of calcium and strontium kinetics.

   A. Biological model. 4-442-62

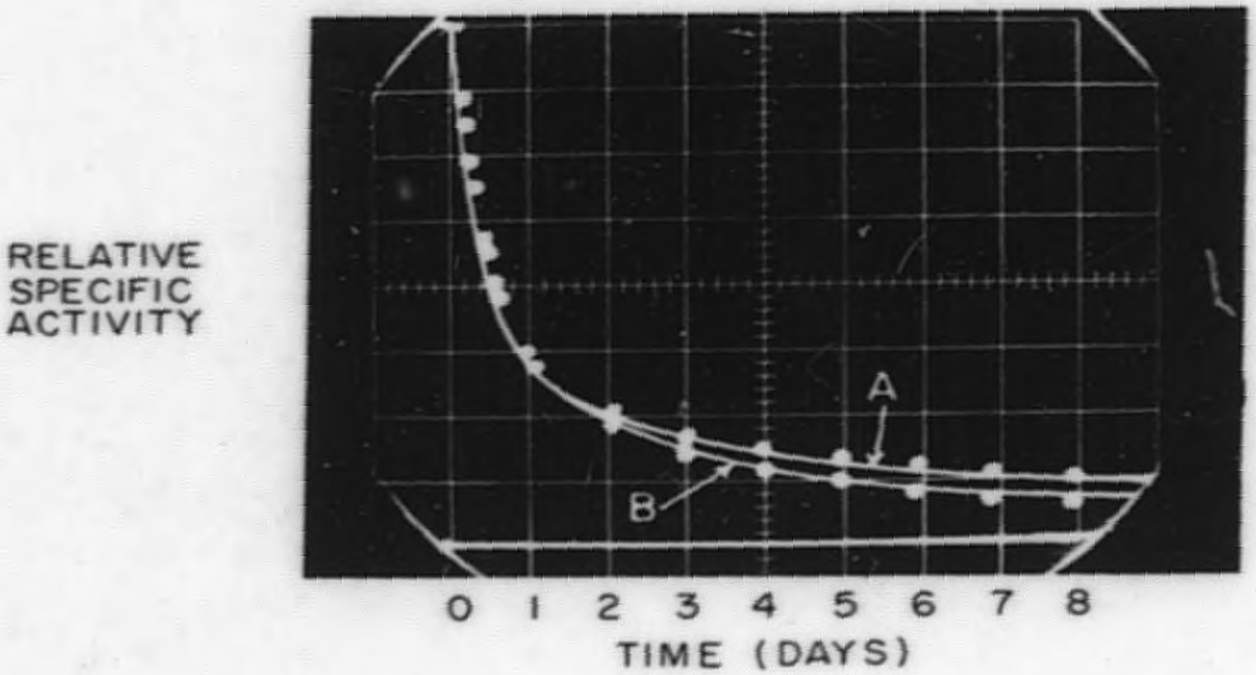
   Initial injection is into compartment I. The numbers within the boxes indicate compartment size relative to that of compartment I. Two values are given for compartment II because for the best fit, the size of this compartment for strontium was smaller than for calcium. The numbers opposite the ρ's indicate flow rates in units of fractions of I per day.

Negative No.

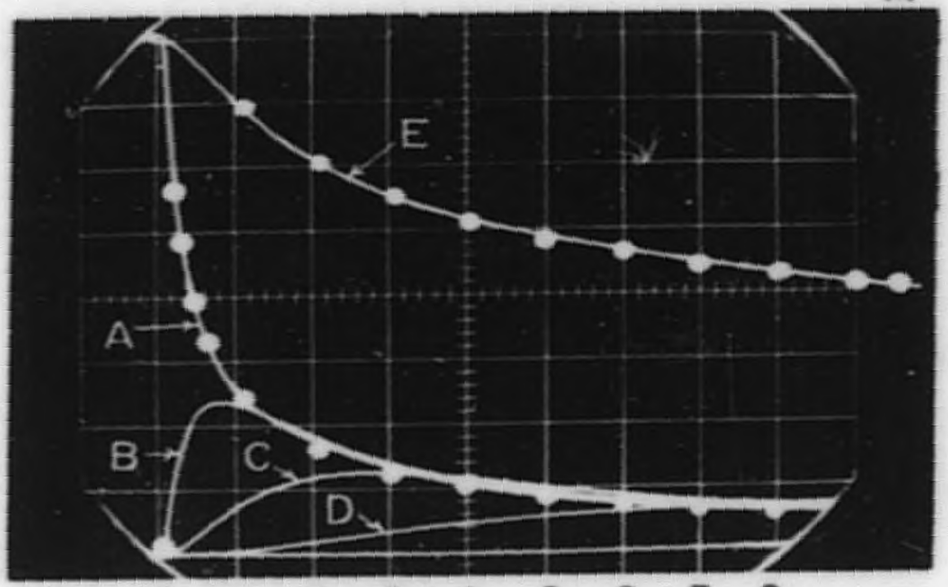
B. Electrical model. 4-441-62

V and S indicate a source and switch for simulating the initial injection. Compartment sizes are represented by capacitor values and rates of flow by the reciprocals of the resistor values. The large triangles represent triads of operational amplifiers, providing for isolation and summing of the input voltages. The smaller triangles in the lower diagram represent single operational amplifiers as used in generating the whole-body curves.

Combined: 4-443-62



A

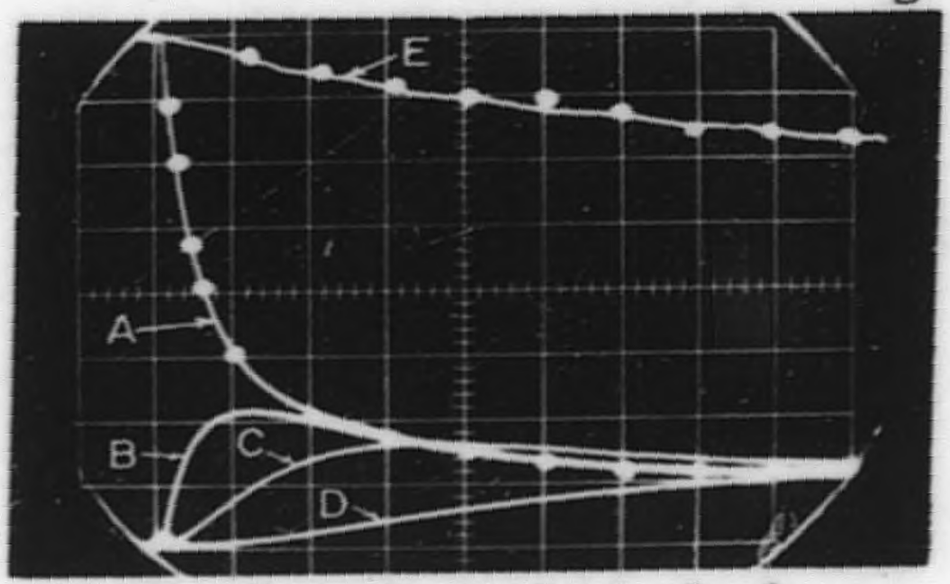


RELATIVE SPECIFIC ACTIVITY

0 1 2 3 4 5 6 7 8

TIME (DAYS)

B



RELATIVE SPECIFIC ACTIVITY

0 1 2 3 4 5 6 7 8

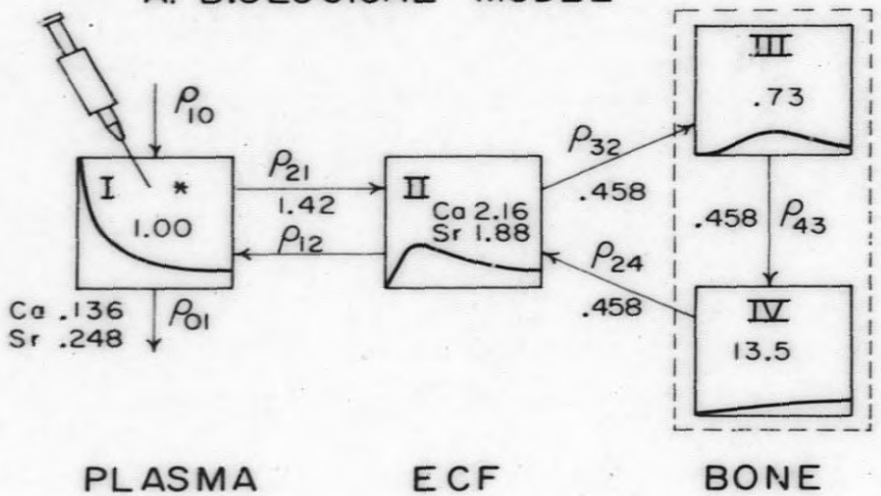
TIME (DAYS)

12

BNL NE3 4 562 62 - FIG 2

CALCIUM AND STRONTIUM KINETICS

A. BIOLOGICAL MODEL



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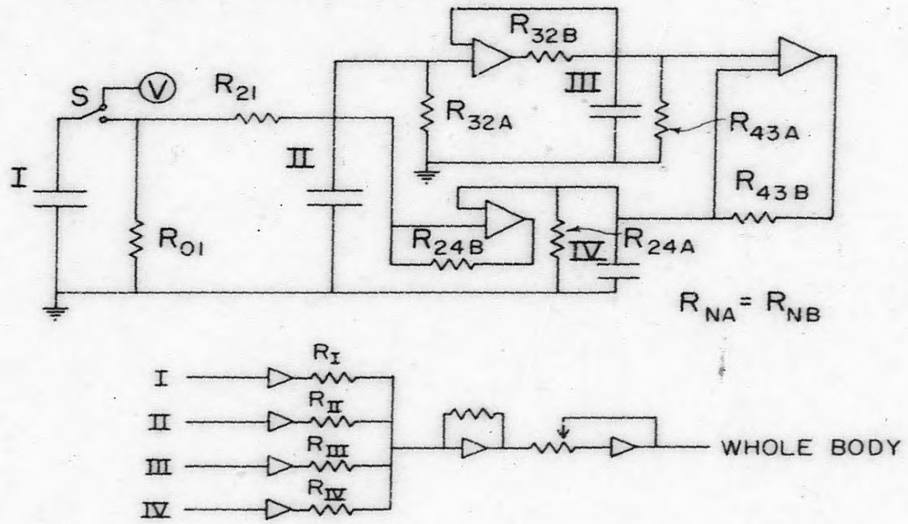
B. ELECTRICAL ANALOGUE



CALCIUM AND STRONTIUM KINETICS

BNL No. No. 4-4414-6

CALCIUM AND STRONTIUM KINETICS

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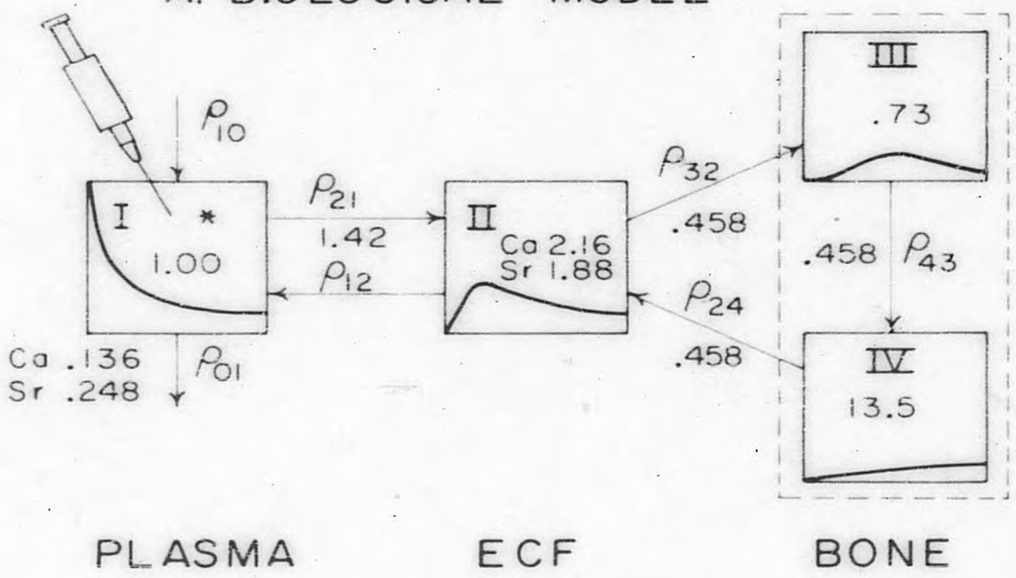

B. ELECTRICAL ANALOGUE