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describing the plasma concentration is very nearly equal to the value of the exponent in the time derivative of the expression for the retention of these elements.

IV. The Retention and Plasma Clearance of the Alkaline Earths by Human Beings

R. E. Rowland

Having noted that the first derivatives of the equations describing the retention of alkaline earths in dogs are very closely related to the functions describing the plasma clearance of these elements, we inquire whether this relationship might also hold for the human being. The literature was searched for data describing the retention and plasma clearance in human beings of intravenously injected alkaline earth isotopes. These data are discussed below, grouped according to the element studied.

Calcium-45

Several authors have published data describing the removal of Ca^{45} from human plasma following intravenous injection.(8-11) These data are plotted in Fig. 12 expressed in units of per cent dose per mg Ca. The data of Bronner and Harris(11) were plotted in their paper transformed to a body weight of 35.6 kg. These have been transformed back to the original weight of the 21-year old male subject, 51.4 kg, by multiplying their data by the ratio of weights, 35.6/51.4. Also included in Fig. 12 are unpublished data from our Laboratory(13) describing the clearance of Ca^{45} from a 51-year old male radium patient, (Case BM).

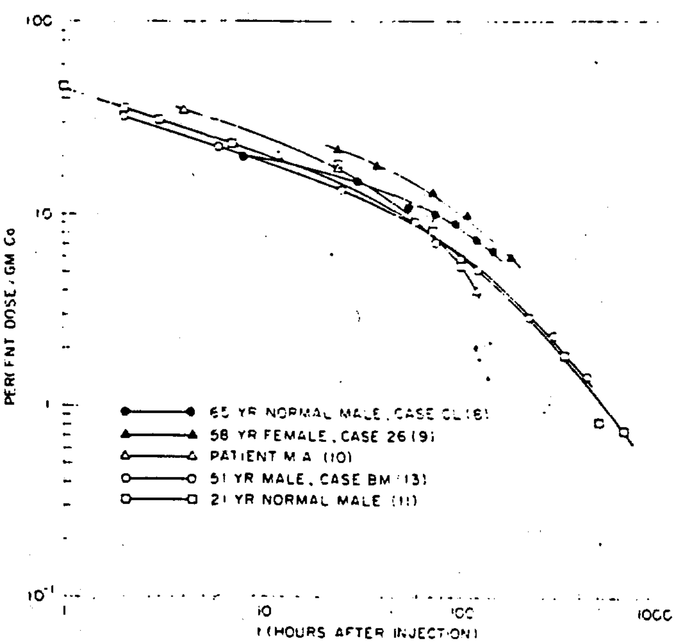

Fig 12 A summary of the plasma clearance of Ca^{45} for five human cases, following intravenous injection of this isotope.

It will be noted from this figure that these plasma clearance curves do not become definite straight lines, indicative of a power function, during the time over which observations have been made. It appears as if plasma clearance would have to be followed out to about 2000 hours (83 days) to prove definitely that such a behavior did or did not exist. However, if one defines the best straight line between 220 hours and 672 hours for the combined data from references 11 and 13, it appears to have a slope approximately equal to $t^{-1.2}$.

The best data found for the retention of Ca^{45} in a human subject are those of Bronner et al.,(12) who calculated the retention in a 21-year old male (same case as reference above) for 60 days from excreta studies. These are plotted in Fig. 13 and may be described by a power function

$$R = 0.96\ t^{-0.12}.$$

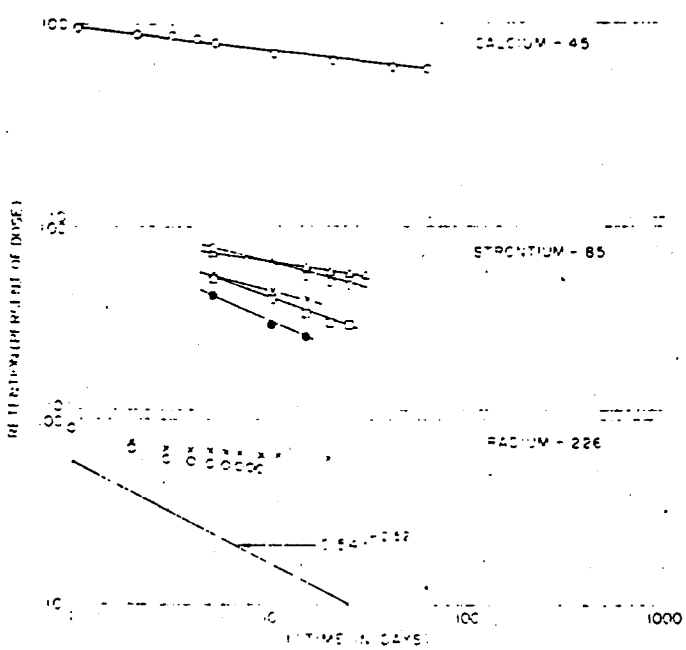

Fig. 13
The retention of calcium, strontium, and radium in human patients. The calcium data are from Bronner et al.;(12) the strontium data from Van Dilla et al.;(16) the two radium cases from Seil et al.(18) In all of these cases the retention was calculated from excreta measurements. Also plotted is the power function for the retention of radium from the observations of the Elgin State Hospital cases.(19)

From the derivative of this expression, one expects a plasma clearance described by $t^{-1.12}$, a value perhaps not greatly different from the value mentioned above, $t^{-1.2}$. While these seem to be in fair agreement, they certainly cannot be used to illustrate the equality of the first derivative of the retention equation to the slope of the plasma clearance equation.

Strontium

The removal of strontium from the plasma of human patients has been described by several authors. In Fig. 14 average values for these different groups given intravenous Sr^{85} are plotted. Two of these sets of data were kindly supplied by Dr. H. Spencer;(14,15) the third is from the work of Van Dilla et al.(16)

Also plotted in Fig. 14 is the disappearance of stable strontium from the plasma of a 40-year old, 85-kg male subject, following the injection of

100 mg Sr as SrCl. This study by Harrison et al.[17] indicates quite effectively that this larger quantity of stable strontium is cleared from the plasma at the same rate as the much smaller isotopic tracers.

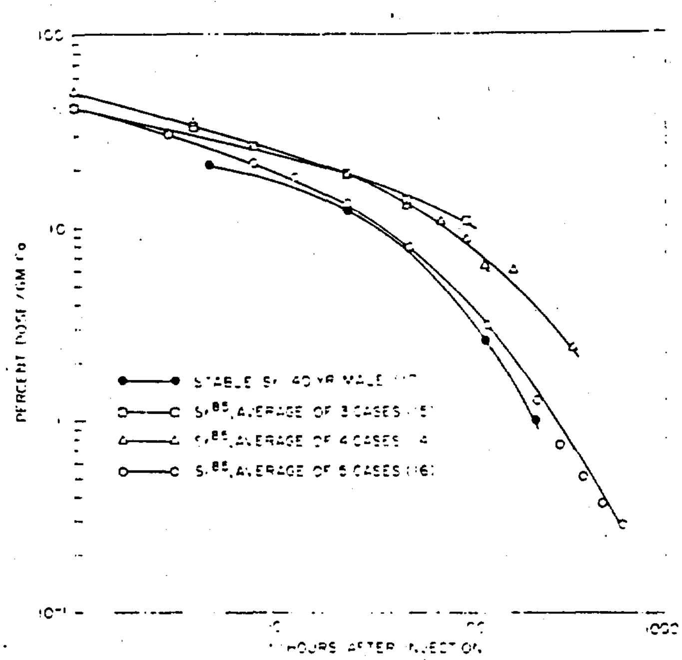

Fig. 14 Plasma concentrations following intravenous injection of strontium in human patients.

The data of Van Dilla et al.,[16] which extend out to 600 hours, seem to be approaching a straight line of slope $t^{-1.5}$, but data are needed for longer periods to verify this.

The retention of Sr^{85} in these five cases was measured during the period from 5 to 15 days, and in one case, 30 days after injection by measurement of total Sr^{85} excreted. In Fig. 13 the retention for each of these cases is plotted; each case seems to be described by a straight line over this interval, but the slopes differ from $t^{-0.16}$ to $t^{-0.44}$.

A study of the terminal distributions of Ca^{45} and Sr^{85}, as described by Schulert et al.[20] in a series of ten terminal patients who survived $\frac{1}{8}$ to 124 days after administration of the tracers, shows that a considerable fraction of the injected dose remains in the soft tissues many weeks after injection. Table 11, based on their published data, expresses the fraction of the retained dose found in the soft tissues of each patient.

Table 11

Percentage of retained calcium and strontium tracers in the soft tissues of terminal patients after intravenous administration

Patient	H.H.	S.K.	S.J.	C.C.	J.Z.	G.B.	S.G.	T.M.	A.W.	M.S.
Survival, days,	$\frac{1}{8}$	2	3	3	6	18	30	39	65	124
Ca^{45}	52	40	34	42	35	28	7.9	7.2	1.5	4.5
Sr^{85}	63	40	55	41	38	35	5.7	5.2	5	0.6

This high tissue fraction of the retained burden in man is in marked contrast to the situation in the dog. Glad et al.[1] described a double tracer experiment with Sr^{85} and Ra^{226} in which a beagle was sacrificed 8 days after an injection of the two isotopes. At that time only 2.7% of the retained Sr^{85} and 7% of the retained Ra^{226} was in the soft tissues. This might account for some of the observed differences between the two species. Perhaps one should not look for power-law behavior in the plasma clearance rate until almost all of the body burden is deposited within the skeleton. If this were the case, then the expected relationship between the retention and plasma clearance rate would only be valid for a skeletally-bound isotope.

Thus it appears that the most interesting data describing the retention and plasma clearance of these isotopes will be found after the first 100 days. No such data are available for humans.

Radium

Radium is the isotope with which human beings have had the most experience, and it is on this experience that we base a good part of our knowledge of the effects of bone-seeking radioisotopes on man. Yet, nowhere in the literature are there any data describing the clearance of this element from human plasma.*

The retention of radium in human beings has been based on the measurements of the Elgin State Hospital patients;(19) from them has been obtained the well-known expression for their retention of radium,

$$R = 0.54\ t^{-0.52}$$

which is plotted in Fig. 13.

Recently, Marinelli et al.(22) have described the retention and excretion of Ra^{226} from a young adult male who accidently inhaled $RaSO_4$. Their retention data, after the first 100 days, are described by a power function with $t^{-0.78}$, while the excretion is found to follow a power function with $t^{-1.78}$. These data, covering a period of 6.5 years, show definitely the relationship between the retention function and its differential, the excretion function, but only after the isotope had transferred from the lung to the skeleton.

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* Aub et al.(21) measured the radium in the blood of a dial painter who was receiving medication in attempt to release radium from the skeleton. The woman had painted watch dials for a seven-year period, and at the time of treatment, seven years later, retained 18 μc of radium. If this had been a case of intravenous injections, the power function $R = 0.54\ t^{-0.52}$ would predict a retention of three quarters of one per cent of the injected dose ten years later. Assuming the mid-point of the exposure period as the equivalent time of injection, the injected dose would have been 2400 μc. If radium is cleared from the plasma in a manner similar to Sr^{90}, the plasma values will be described by the equation $P_t = 38\ t^{-1.5}$ per cent of dose/g Ca. Using this function the plasma activity is calculated to be 0.21×10^{-12} c/cc of blood ten years after injection. The measured values were about 1×10^{-12} c/cc blood, a factor of five greater than the predicted value. Since the medication was shown to increase the daily elimination of radium by factors of 3 to 6, this measured value may be interpreted as being remarkably close to the value predicted by a power-function behavior of the plasma concentration.

It should be noted that Marinelli et al.[23] in a description of the elimination of radium from several patients following accidental inhalation, pointed out that not all of their measured body burdens could be assigned to the skeleton or lung, so that a significant fraction of the measured radium might be in the soft tissues. This was based on the asumption that only skeletal radium released radon, and that this release was 70% of the total found. Later work of Mays et al.[24] has shown that shortly after acquisition, about 90% of canine skeletal radon is released. If this is also true for the human being, the increased radon release implies even more soft tissue radium than Marinelli had estimated and lends considerable weight to his suggestion.

One set of data is available in the literature describing the early retention of Ra^{226} following intravenous injection of this element. In 1915 Seil, Viol, and Gordon[18] described the retention of radium in a 23-year old male, following intravenous administration of 100 μc Ra^{226}. They measured the total excreta (and incidentally found a fecal to urinary ratio of about 10:1) and based their retention on this. They repeated this study on the same individual two moths later, and two sets of retention data are plotted in Fig. 13.

The curves plotted from their data can be seen to be similar in slope to that obtained for Ca^{45}; the data of Seil actually fit a power function with $t^{-0.11}$ in one case, and $t^{-0.16}$ in the other, while the Ca^{45} data are described by $t^{-0.12}$. These data contradict the Elgin patients' power function, as can be seen in Fig. 13, yet we must recall that this power function was essentially determined by the retention at 20 years and the known dose, but not on the basis of any data within the first few weeks.

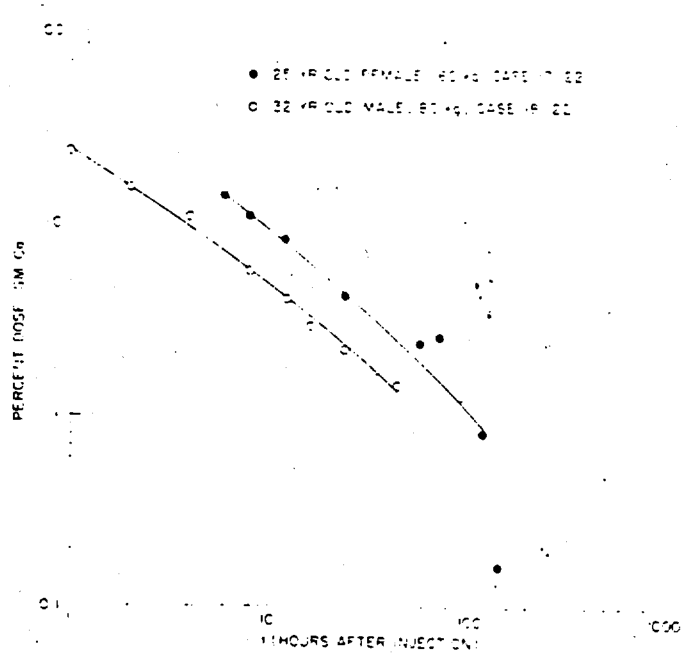

Fig. 15 Plasma concentrations following intravenous injection of Ba^{140} in human patients.

Barium

Here the only published study discovered is that of Bauer,[25] which describes the plasma clearance of Ba^{140} following an intravenous injection of $BaCl_2$ in a 25-year old woman. Bauer also kindly supplied the plasma values for a normal 32-year old male (Case 18 in the above reference). These are plotted in Fig. 15. It can be seen that plasma measurements would have to be taken for a much longer time in order to determine whether or not a power law fits.

Summary

From this review of the retention and plasma clearance of intravenously injected tracers of the alkaline earth family, it becomes apparent that the power law formulation for the retention of these elements is valid for the dog, and that the differential of this expression has the same slope as the power law describing the plasma concentration of the tracer. In the human, however, the data seem to indicate that these relationships do not hold during the first few weeks following intravenous administration of an alkaline earth tracer. It is suggested that after the first three or four months a power law probably will describe the retention, and that its derivative, also a power law, will describe the plasma concentration or excretion function.

The lack of agreement at early times may, in part, be due to the fact that the body burden is not entirely a skeletal burden. A power law should probably be expected to describe only the loss of activity from the skeleton. Yet to be resolved is the basic question: can the retention of all of these alkaline earth elements in the human being be described by power functions with constant slope. (i.e., constant value of the exponent, b), such as is the case for the dog, or is b a function of the isotope employed?

References

1. Glad, B. W., C. W. Mays, and W. Fisher. Semiannual Progress Report, Radiobiological Laboratory, Coll. Med., Univ. Utah (Sept. 30, 1959) pp. 44-51.

2. Maletskos, C. J., A study of the dynamics of calcium metabolism in dogs. Ph.D. thesis, Massachusetts Institute of Technology (1954).

3. Jowsey, J., R. E. Rowland, J. H. Marshall, and F. C. McLean. Unpublished data.

4. Mays, C. W., D. H. Taysum, and W. Fisher. Annual Progress Report, Radiobiology Laboratory, Coll. Med., Univ. Utah (March 31, 1958) pp. 139-146

5. Van Dilla, M. A., B. J. Stover, R. L. Floyd, D. R. Atherton, and D. H. Taysum. Radium (Ra^{226}) and Radon (Rn^{222}) metabolism in dogs. Radiation Research 8 417-437 (1958).

6. Kornberg, H. A. On the passage of pairs of elements through food chains. HW-60127 (May 1959).

7. Stover, B. J., and D. R. Atherton. Metabolism of Sr^{90} in adult beagle dogs. Proc. Soc. Exptl. Biol. Med. 99 201-205 (1958).

8. Heaney, R. P., and G. D. Whedon. Radiocalcium studies of bone formation rate in human metabolic bone disease. J. Clin. Endocrinol. and Metabolism 18 1246-67 (1958).

9. Bauer, G. C. H., A. Carlson and B. Lindquist. Bone salt metabolism in humans studied by means of radiocalcium. Act. Med. Scand. 158 143-150 (1957).

10. Bellin, J., and D. Laszlo. Metabolism and removal of Ca^{45} in man. Science 117 331 (1953).

11. Bronner, F., and R. S. Harris. Absorption and metabolism of calcium in human beings, studied with calcium-45. Ann. N.Y. Acad. Sci. 64 314-325 (1956).

12. Bronner. F., R. S. Harris, C. J. Maletskos, and C. E. Benda. Studies in calcium metabolism. The fate of intravenously injected radiocalcium in human beings. J. Clin. Invest. 35 78-88 (1956).

13. Marshall, J. H., R. E. Rowland and R. J. Hasterlik. Unpublished data.

14. Spencer, H., M. Brothers, E. Berger, H. E. Hart and D. Laszlo. Strontium-85 metabolism in man and effect of calcium on strontium excretion. Proc. Soc. Exptl. Biol. Med. 91 155-157 (1956).

15. Spencer, H., J. Samachson, B. Kabakow and D. Laszlo. Factors modifying radiostrontium excretion in man. J. Clin. Sci. 17 291-301 (1958).

16. Van Dilla, M. A., S. Wallach, and J. S. Arnold. Sr^{85} tracer studies in humans. Semiannual Progress Report, Radiobiological Laboratory, Coll. Med., Univ. Utah (Sept. 30, 1956) pp. 48-58.

17. Harrison, G. E., W. A. Raymond and H. C. Tretheway. The metabolism of strontium in man, paper No. 2. AERE-SPAR-2 (July 1955).

18. Seil, H. A., C. H. Viol and M. A. Gordon. The elimination of soluble radium salts taken intravenously and per os. Radium 5 40-44 (1915).

19. Norris, W. P., T. W. Speckman and P. F. Gustafson. Studies of the metabolism of radium in man. Am. J. Roentgenol., Rad. Therapy and Nuclear Med. 73 785-802 (1955).

20. Schulert, A. R., E. A. Peets, D. Laszlo, H. Spencer, M. Charles and J. Samachson. Comparative metabolism of strontium and calcium in man. Intern. J. Appl. Radiation and Isotopes 4 144-153 (1959).

21. Aub, J. C., R. D. Evans, D. M. Gallagher, and D. M. Tibbetts. Effects of treatment on radium and calcium metabolism in the human body. Ann. Intern. Med. 11 1443-1463 (1938).

22. Marinelli, L. D., H. F. Lucas, P. F. Gustafson and C. E. Miller. Excretion and retention of Ra^{226} in humans: A 2312-day follow-up of a single inhalation case. Argonne National Laboratory Radiological Physics Division Semiannual Report, July through December, 1958, ANL-5967, pp. 54-57.

23. Marinelli, L. D., W. P. Norris, P. F. Gustafson, and T. W. Speckman. Transport of radium sulfate from the lung and its elimination from the human body following single accidental exposures. Radiology 61 903-913 (1953).

24. Mays, C. W., M. A. Van Dilla, R. L. Floyd, and J. S. Arnold. Radon retention in radium-injected beagles. Radiation Research 8 480-489 (1958).

25. Bauer, G. C. H., A. Carlson and B. Lindquist. Metabolism of Ba^{140} in man. Acta Orth. Scand. 26 241-254 (1957).