6-3-1958

Retention and Excretion of Radionuclides of the Alkali Metals by Five Mammalian Species

Chester R. Richmond

Follow this and additional works at: https://digitalrepository.unm.edu/biol_etds

Part of the [Biology Commons](#)

Recommended Citation

Richmond, Chester R.. "Retention and Excretion of Radionuclides of the Alkali Metals by Five Mammalian Species." (1958).
https://digitalrepository.unm.edu/biol_etds/288

This Dissertation is brought to you for free and open access by the Electronic Theses and Dissertations at UNM Digital Repository. It has been accepted for inclusion in Biology ETDs by an authorized administrator of UNM Digital Repository. For more information, please contact disc@unm.edu.

UNIVERSITY OF NEW MEXICO-UNIVERSITY LIBRARIES

A14429 096186

378.789
Un31Ori
1958
cop.2

RETENTION
AND
EXCRETION OF
RADIONUCLIDE

—

RICHMOND

378.789

Un31Ori

1958

cop.2

THE LIBRARY
UNIVERSITY OF NEW MEXICO

Call No.

378.789
Un3lOri
1958
cop.2

Accession
Number

235595

1891

Chapman Bond

EX-100 ON FILE

UNIVERSITY OF NEW MEXICO LIBRARY

MANUSCRIPT THESES

Unpublished theses submitted for the Master's and Doctor's degrees and deposited in the University of New Mexico Library are open for inspection, but are to be used only with due regard to the rights of the authors. Bibliographical references may be noted, but passages may be copied only with the permission of the authors, and proper credit must be given in subsequent written or published work. Extensive copying or publication of the thesis in whole or in part requires also the consent of the Dean of the Graduate School of the University of New Mexico.

This thesis byChester R. Richmond.....
has been used by the following persons, whose signatures attest their acceptance of the above restrictions.

A Library which borrows this thesis for use by its patrons is expected to secure the signature of each user.

NAME AND ADDRESS

DATE

UNIVERSITY OF NEW MEXICO

Unpublished work submitted for publication in the University of New Mexico Library is open for inspection, but not to be used without the written consent of the author. The University of New Mexico Library is not responsible for the use of the work by the author or by any other person. The University of New Mexico Library is not responsible for the use of the work by the author or by any other person.

This thesis by _____ has been used in the following manner: _____ acceptance of the above statement. A library which borrows this thesis from the University of New Mexico is expected to return the original to the University.

DATE

NAME AND ADDRESS

RETENTION AND EXCRETION OF RADIONUCLIDES OF
THE ALKALI METALS BY FIVE MAMMALIAN SPECIES

By

Chester R. Richmond

A Thesis

Submitted in Partial Fulfillment of the
Requirements for the Degree of
Doctor of Philosophy in Biology

The University of New Mexico
1958

This dissertation, directed and approved by the candidate's committee, has been accepted by the Graduate Committee of the University of New Mexico in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

DEAN

DATE

Committee

CHAIRMAN

This dissertation, directed and approved by the candidate's committee, has been accepted by the Graduate Committee of the University of New Mexico in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

[Signature]
Chairman

[Signature]
June 3, 1957

Committee

[Signature]
Chairman

[Signature]

378,789
Un310ri
1958
cop. 2

ABSTRACT

Large-volume liquid-scintillation counters were used to measure in vivo the biological half-time ($BT_{1/2}$), whole-body retention, and excretion of several gamma-emitting alkali-metal radionuclides in five species of animals.

Tracer amounts of the radionuclides were administered to mice, rats, monkeys, dogs, and men by oral, intraperitoneal, or intravenous administration. Radioactivity levels in the excreta were determined at subsequent intervals and the whole-body retention was followed, where possible, until the retained body burden fell to 1.0 to 0.1 per cent of the administered dose.

The logarithms of the retention and excretion levels were plotted as functions of time after administration, and standard first-order kinetics were applied to determine the biological half-times and retention equations. Whole-body retention curves were best fitted by a single or multiple-component exponential function of the form

$$R = a_1 e^{-k_1 t} + a_2 e^{-k_2 t} + \dots a_n e^{-k_n t}$$

where $a_1, a_2, \dots, a_n$ are the intercept constants; $k_1, k_2, \dots, k_n$ are the rate constants; and R is the whole-body retention at time t . Values for the $BT_{1/2}$ of K^{42} in the mouse, rat, and dog were 1.3, 4.0, and 8.0 days, respectively. Respective values for Na^{22} in the mouse, rat, monkey, dog, and man were 1.7, 2.9, 7.5, 9.5, and 11.0 days; for Rb^{86} , 3.8, 8.6, 15.0, 20.0, and 80.0 days; and for Cs^{134} and Cs^{137} , 1.2, 6.5, 19.0, 25.0, and 110.0 days. Calculations based on these data suggest a reduction in the maximum permissible concentrations of radiocesium and radiorubidium in air, food, and water.

A first approximation for an interspecies correlation between $BT_{1/2}$ and body surface area of the form

$$BT_{1/2} = k(SA)^b$$

where k and b are constants was demonstrated for the radionuclides investigated. Data on the naturally occurring K^{40} in laboratory animals and on the distribution of Group I radionuclides in various tissues of the rat were also obtained.

ACKNOWLEDGMENTS

The author sincerely acknowledges the contributions made to this study by members of Group H-4 of the Los Alamos Scientific Laboratory. The enthusiastic interest and suggestions of Wright H. Langham, who initiated the problem, were particularly helpful. E. C. Anderson and J. E. Furchner contributed to the mathematical treatment of the data. W. J. Eversole gave valuable advice and encouragement. K. T. Woodward, W. Stedman, and R. Price provided technical assistance. The members of the Health Division who served as volunteers during the problem deserve special thanks.

The radioactive potassium used in this work was prepared by members of Group P-2 of the Los Alamos Scientific Laboratory; all other radionuclides were obtained from the Oak Ridge National Laboratory.

C. Clayton Hoff and William J. Koster of The University of New Mexico and W. H. Langham graciously donated their valuable time and technical counsel in the preparation of this document.

CONTENTS

	Page
Abstract	2
Acknowledgments	4
Chapter 1 Introduction	9
Chapter 2 Materials and Methods	20
2.1 Alkali-Metal Radionuclides	20
2.2 The Los Alamos Small Animal Counter	23
2.3 The Los Alamos Human Counter	26
2.4 Tissue Distribution Studies	27
2.5 Retention and Excretion Studies	28
Chapter 3 Results	36
3.1 Tissue Distribution Studies	36
3.2 Retention and Excretion of Alkali-Metal Isotopes	38
3.3 Retention and Excretion of Na ²²	40
3.4 Retention and Excretion of K ⁴²	44
3.5 Natural K ⁴⁰ and Potassium in Laboratory Animals	45
3.6 Retention and Excretion of Rb ⁸⁶	46
3.7 Retention and Excretion of Cs ¹³⁴ and Cs ¹³⁷	49
Chapter 4 Discussion	52
4.1 Physiological Significance of the Alkali Metals	52
4.2 Sodium Metabolism	55
4.3 Potassium Metabolism	62
4.4 Natural K ⁴⁰ and Total Body Potassium in Laboratory Animals	66
4.5 Rubidium Metabolism	67
4.6 Cesium Metabolism	70
4.7 Interspecies Correlations	76
Chapter 5 Summary and Conclusions	79
Bibliography	82

TABLES

	Page
Table 1 Distribution of Na ²² in the Rat after Intraperitoneal Administration	101
Table 2 Distribution of Rb ⁸⁶ in the Rat after Intraperitoneal Administration	102
Table 3 Distribution of Cs ¹³⁴ in the Rat after Intraperitoneal Administration	103
Table 4 Parameters for the Retention of K ⁴² in the Mouse, Rat, and Dog	104
Table 5 Potassium Content and K ⁴⁰ Gamma-Ray Activity of Adult Beagle Hounds	105
Table 6 Potassium Content and K ⁴⁰ Gamma-Ray Activity of Adult Male Rhesus Monkeys	106
Table 7 Potassium Content of Various Species of Laboratory Animals	107
Table 8 Fractions of Total Disintegrations in the Body Represented by the Components of the Retention Curves for the Alkali-Metal Radionuclides	108

ILLUSTRATIONS

Figure 1 Liquid-scintillation gamma-ray detector	109
Figure 2 Los Alamos small animal counter	110
Figure 3 Los Alamos human counter	111
Figure 4 Counting equipment used for dogs and monkeys	112
Figure 5 Graphic presentation of procedure for separating exponential functions from a composite retention equation	113

Figure 6	Retention and excretion of Na^{22} by mice following oral administration	114
Figure 7	Retention and excretion of Na^{22} by mice following intraperitoneal administration	115
Figure 8	Effect of low-sodium diet on the retention of Na^{22} by mice following intraperitoneal administration	116
Figure 9	Retention and excretion of Na^{22} by rats following oral administration	117
Figure 10	Retention of Na^{22} by rats following intraperitoneal administration	118
Figure 11	Retention and excretion of Na^{22} by monkeys following intravenous administration	119
Figure 12	Retention and excretion of Na^{22} by dogs following intravenous administration	120
Figure 13	Retention and excretion of Na^{22} by men following oral administration	121
Figure 14	Retention and excretion of Rb^{86} by mice following oral administration	122
Figure 15	Retention and excretion of Rb^{86} by mice following intraperitoneal administration	123
Figure 16	Retention and excretion of Rb^{86} by rats following oral administration	124
Figure 17	Retention and excretion of Rb^{86} by rats following intraperitoneal administration	125
Figure 18	Retention and excretion of Rb^{86} by monkeys following intravenous administration	126
Figure 19	Retention and excretion of Rb^{86} by dogs following intravenous administration	127
Figure 20	Retention and excretion of Rb^{86} by men following oral administration	128

Figure 21	Retention and excretion of Cs^{134} by mice following oral administration	129
Figure 22	Retention and excretion of Cs^{134} by mice following intraperitoneal administration	130
Figure 23	Retention and excretion of Cs^{134} by rats following oral administration	131
Figure 24	Retention and excretion of Cs^{134} by rats following intraperitoneal administration	132
Figure 25	Retention and excretion of Cs^{134} by monkeys following intravenous administration	133
Figure 26	Retention and excretion of Cs^{134} by dogs following intravenous administration	134
Figure 27	Retention and excretion of Cs^{134} and Cs^{137} by men following oral administration	135
Figure 28	Pattern of Na^{22} retention in five species of animals	136
Figure 29	Pattern of Rb^{86} retention in five species of animals	137
Figure 30	Pattern of Cs^{134} and Cs^{137} retention in five species of animals	138
Figure 31	Relationship between $\text{BT}_{1/2}$ and surface area for Na^{22} , Rb^{86} , Cs^{134} , and Cs^{137} in five species of animals	139

CHAPTER 1

INTRODUCTION

The potential hazard of an internally deposited radionuclide depends on its physical half-life, on the characteristics of the emitted radiation, and on its bodily assimilation, distribution, retention, and excretion.

The need for excretion and retention data for the calculation of maximum permissible concentrations (MPC) of radioactivity in food, air, and water prompted Hamilton and co-workers to begin, in 1942, systematic studies of the metabolism of radionuclides in rats (Hamilton, 1943, 1947, 1948a, 1948b, 1949; Scott et al., 1947). These co-workers devoted special attention to the heaviest elements and to the products of nuclear fission. Because of the large number of nuclides that had to be considered, the researchers attempted to correlate metabolic properties with position of the elements in the Periodic Table. The retention data were obtained by comparing the tissue

distribution of the radionuclides in serially sacrificed animals. This early work still provides the only data available on some radionuclides.

Excretion analyses are used also to assess the retention of radionuclides in animals (Sheline et al., 1943; Hamilton, 1948b; Burch et al., 1955; Zipser et al., 1953; Threefoot, Burch and Ray, 1955; Weeks and Oakley, 1954). This method, however, involves considerable error and is limited in many instances by the low level of radioactivity in the samples of excreta. In addition, biological losses through other routes (i.e., lungs and skin) are not included in excretion analyses which are restricted to samples of urine, or in some cases, of urine and feces.

Although more than 20 years have passed since radioisotopes were first administered to human beings (Hamilton and Stone, 1937; Hamilton, 1938; Hevesy, 1942), relatively little information on retention and excretion has been reported and data for many of the radionuclides are still fragmentary. Some of the nuclides studied were:

H^3	Pinson, 1951
Na^{22}	Threefoot et al., 1949; Veall et al., 1955
Na^{24}	Hevesy, 1942; Arons et al., 1954; Burch et al., 1948
P^{32}	Lawrence et al., 1939; Erf, 1941

Cl ³⁶	Ray et al., 1952; Ray et al., 1954
K ⁴²	Hevesy, 1942; Arons et al., 1954; Ray et al., 1955; Kilpatrick et al., 1956; Tyor and Eldridge, 1956
Sr ⁸⁵	Spencer et al., 1956; Hasterlick et al., 1956
Rb ⁸⁶	Threefoot et al., 1954; Ray et al., 1955; Kilpatrick et al., 1956; Tyor and Eldridge, 1956
Sr ⁸⁹	Harrison et al., 1955
I ¹³¹	Hamilton and Soley, 1940; Hamilton, 1942
Cs ¹³⁴	Woodward, Richmond, and Langham, 1956
Po ²¹⁰	Fink, 1950
Ra ²²⁶	Norris et al., 1955
Pu ²³⁹	Langham et al., 1950

Few human excretion or retention studies were of sufficient duration to explore fully the rate processes involved.

Retention (or excretion) rates of specific radionuclides by man are often not available so that it is commonly necessary to use data collected from experimental animals. Extrapolations of animal data to man are subject to considerable criticism, and probably justifiably so because of the variations among species. Familiar examples of species variability are the differences in erythrocyte concentration of sodium and potassium and the ability of some animals to synthesize their own Vitamin C. Hood and Comar (1953a) reported significant differences in the excretion of Cs¹³⁷ between ruminants, as represented by cattle and sheep, and

animals with a single-chambered stomach as found in rats and mice. Recently, significant differences in the metabolism of Po^{210} were reported by Stannard and Smith (1957) who found that man was more nearly similar to the rat or mouse than to the rabbit or dog. Until adequate experimental data are collected from human subjects, the practice of extrapolation from laboratory animals to man will remain a "necessary evil." If good interspecies correlation can be established, they will provide a better basis for extrapolation.

As the elimination of a radioactive material from an organism is commonly thought to be exponential, a constant rate can be assigned to the process. That is, the amount lost is a constant percentage of that remaining as shown by the exponential equation

$$N_t = N_o e^{-kt}$$

where N_o is the number of atoms present at time zero, N_t is the number of atoms present at any time t , and k is the rate constant representing the fractional rate of change. The term biological half-life or biological half-time, as commonly used, refers to the time interval necessary for an organism to eliminate one-half of an introduced material. The symbols $T_{1/2}$, T_{50} , T_e , T_b , $E_{1/2}$, and $B_{1/2}$ are used. In

some instances, the term is applied to specific organs and tissues and not to the entire organism. The symbol $BT_{1/2}$ will be used in this report to represent the time necessary for an animal to lose the first half of its initial body burden by all routes of elimination, regardless of the method of administration.

The average time a nuclide remains in an organism can be expressed as the reciprocal of the rate of elimination. The relationship between half-time, rate of elimination, and average time is shown by the expression

$$\tau = \frac{1}{k} = \frac{BT_{1/2}}{0.693}$$

where τ is the average or mean time, k is the elimination rate constant, and $BT_{1/2}$ is the time required to lose one-half of the original amount. The term effective half-life is sometimes encountered in calculations of MPC values of radionuclides in air, food, and water. The effective half-time takes into account biological and physical half-life of the radionuclide and is shown by the expression

$$T = \frac{T_b \cdot T_r}{T_b + T_r}$$

where T_b is the biological half-time, T_r is the radiological

or physical half-life, and T is the effective half-time. It can be seen from the above relationship that a material with a large T_b value and a small T_r value would have a comparatively small T value.

Considerable confusion exists in the literature relevant to the meaning and designation of biological half-time. Some workers refer to the concentration one-half ($C_{1/2}$) of a tracer material as the time required for it to reach one-half the concentration existing at equilibrium in any body fluid, tissue, organ, or specific compartment (Threefoot et al., 1949). Thus, a $C_{1/2}$ value for a given radionuclide can be measured in the cerebrospinal fluid, hepatic parenchyma, or plasma. Occasionally the plasma $C_{1/2}$ value is reported as the $BT_{1/2}$ of the material investigated. In some instances this is erroneous. For example, it is not possible to trace potassium adequately by sampling an extracellular compartment such as plasma. Changes in the extracellular compartment do not adequately reflect changes in the major potassium compartment which is intracellular (Threefoot, Ray, and Burch, 1955). In addition, one cannot always relate loss of activity from the plasma to the whole-body loss via the kidney and gut, as many materials enter the intracellular compartment from the plasma somewhat rapidly and are subsequently lost via the common routes of excretion. Changes in the volume of the

extracellular compartment will change the concentration of a contained radionuclide. For example, a hypothetical doubling of the volume of the extracellular compartment could cause an apparent decrease by one-half in the concentration of a material contained therein, without effecting a change in the total amount of the material in the organism.

Threefoot et al. (1949) used the term urinary elimination one-half ($U_{1/2}$) to define the time required to eliminate one-half of a tracer material from the body via the urine. The presently existing $BT_{1/2}$ values for many radionuclides were obtained from experimental work in which the $U_{1/2}$ was the measured parameter. A $U_{1/2}$ value can be used as the $BT_{1/2}$ if excretion is entirely urinary and exponential.

The concept of $BT_{1/2}$, which assumes that excretion is a simple exponential function of time, is embodied in the calculation of values for MPC's for air, food, and water in the National Bureau of Standards Handbook No. 52 (1953) and in the recommendations of the International Commission on Radiological Protection (1955). Simple exponential excretion implies that, once a radioactive material enters an organism, either it is retained in a single anatomical or physiological compartment or the rate of loss from one of several compartments controls the over-all excretion rate. In many cases experimental data indicate that these

implications are not strictly true, even for material which at first seems to be excreted as a simple exponential function of time.

The over-all retention or excretion pattern of a radio-nuclide very commonly is a composite of several exponential functions of time rather than a single exponential rate (Woodward, Richmond, and Langham, 1956; Langham, 1956; Rosenthal, 1956; Langham, 1957). For example, Comar and Wasserman (1956) show that the over-all excretion process can be described by the following relationship:

$$U = U_1 e^{-k_1 t} + U_2 e^{-k_2 t} + \dots U_n e^{-k_n t}$$

The general equation for each rate process given above is

$$U = U_0 e^{-[(0.693/T_{1/2})t]}$$

where U is the excretion rate (fraction of injected dose per day) by the given rate process at time t , U_0 is the same as above but at zero time, and $T_{1/2}$ is the half-time (days) of the given rate process. Unfortunately, few experiments concerned with these parameters were of sufficient duration to explore fully the possibility of rate changes with respect to time after administration. It is known that the excretion rate of plutonium continues to change over a period of five years. The excretion rate for this material is

conveniently expressed as a power function of the type

$$Y = at^{-c}$$

where Y is the excretion rate (fraction of the injected dose excreted per day), t is the time after exposure (days), and a and c are constants. The data can also be expressed as a multiple-exponential rate function; the choice of expression depends on the specific application of the data (Langham, 1956).

The increasing use of radioactive materials in industry, research, and medicine helped promote the construction of detectors capable of measuring small amounts of radioactivity in accidentally exposed individuals. Large ionization chambers, sufficiently sensitive to measure the natural gamma-ray activity of the human body, are in use by several investigators (Burch and Spiers, 1953; Rundo, 1955; Sievert, 1956). Miller and Marinelli (1956) used a sodium iodide crystal to detect whole-body gamma-ray activity. This apparatus has spectrometric properties which permit the identification of the radionuclides detected. Several detectors, composed of Geiger-Müller tubes placed in several arrangements around the subject, are used to study exchangeable sodium (Veall et al., 1955; Fowler, 1957; Martin et al., 1957). Bradley et al. (1956) suggested the possibility of

counting radionuclides of rubidium, potassium, iodine, and chromium in humans by using whole-body Geiger-Müller counters. Bremsstrahlung measurements with external counters have been proposed also for distribution studies of pure beta-emitting radionuclides in the human body (Mehl, 1956). Many of these methods of detection, however, are somewhat inefficient from the standpoint of long counting times and desirable counting rates. Several similar counters, using Geiger-Müller tubes, are used to detect the whole-body gamma-ray activity of small animals (Arnott and Fossey, 1952; Campbell et al., 1956).

The development of various sizes of whole-body liquid-scintillation counters for in vivo counting (Reines et al., 1953; Van Dilla et al., 1954; Anderson et al., 1956; Woodward, Richmond, and Langham, 1956) provides a rapid approach to the study of the excretion and retention of gamma-emitting radionuclides by several species, including man. Because of the characteristics of the large-volume liquid-scintillation detectors, it is possible to administer very small amounts of radionuclides to experimental animals and still obtain very high in vivo counting rates. By employing the in vivo counting technique, the retention process can be followed in the same group of animals until the radionuclide is no longer detectable. Such studies can be made on humans without

administering more than 0.1 to 0.01 of a maximum permissible body burden.

The primary purpose of this study was to determine by means of the in vivo counting methods the retention and excretion of several gamma-emitting radioisotopes of the alkali metals in mice, rats, dogs, monkeys, and man, as part of a general program to reinvestigate the metabolism of the more common gamma-emitting radionuclides. From such data interspecific correlations can be attempted, and possibly some common metabolic parameter established. In any event, the results provide much needed data on retention and excretion of radioisotopes by man.

CHAPTER 2

MATERIALS AND METHODS

2.1 Alkali-Metal Radionuclides

The Group I elements of the Periodic Table occur in the following order: lithium, sodium, potassium, rubidium, cesium, and francium. In terms of chemical behavior, these elements may be separated into two categories with the division between sodium and potassium. Potassium, rubidium, and cesium display similar physiochemical properties which differ only quantitatively. With the exception of lithium and francium, radionuclides suitable for tracer studies are available for all the alkali metals.

Normal sodium consists of but one nuclide, Na^{23} ; however, artificially produced species with mass numbers 22 and 24 are available. The longer-lived species, Na^{22} , has a physical half-life of 2.6 years and is produced by cyclotron bombardment using the $\text{Mg}^{24}(\text{d}, \alpha)\text{Na}^{22}$ reaction. Na^{22} decays to stable Ne^{22} by positron emission and K-capture

(orbital electron capture). The positron emission accounts for about 90 per cent of the disintegrations and has a maximum energy of 0.54 million electron volt (Mev); an accompanying 0.51 Mev annihilation gamma radiation is also present (Laslett, 1937). A 1.27 Mev gamma ray is associated with the K-capture (Sullivan, 1957). The shorter-lived species, Na^{24} , is not widely used because of its short physical half-life (15 hours).

Normal potassium contains two stable nuclides, K^{39} and K^{41} , with relative abundances of 93.3 and 6.6 per cent, and a naturally radioactive species, K^{40} , which is only present to the extent of 0.012 per cent (Suttle and Libby, 1955). K^{40} decays to stable Ca^{40} by the emission of a 1.35 Mev negatron or to stable Ar^{40} by K-capture. A 1.46 Mev gamma ray is associated with the K-capture; this represents approximately 10 per cent of the disintegrations (Hollander et al., 1953). However, K^{40} , which has a physical half-life of 1.25×10^9 years (Suttle and Libby, 1955), is not used in tracer studies because of its small percentage abundance.

An artificially radioactive species, K^{42} , can be produced by the $\text{K}^{41}(\text{n}, \gamma)\text{K}^{42}$ reaction. Its use in tracer studies is seriously limited, however, because of its very short (12.4 hours) physical half-life. K^{42} emits two high energy negatrons as it decays to stable Ca^{42} . One negatron

represents about 18 per cent of the total disintegrations, has a maximum energy of 1.98 Mev, and is associated with a 1.53 Mev gamma ray. The other accounts for about 82 per cent of the total disintegrations and has a maximum energy of 3.54 Mev (Sullivan, 1957).

Naturally occurring rubidium is a mixture of stable Rb^{85} and weakly radioactive Rb^{87} , with percentage abundances of 72.2 and 27.8. The artificially radioactive species, Rb^{86} , is produced by the $\text{Rb}^{85}(\text{n},\gamma)\text{Rb}^{86}$ reaction and has a physical half-life of 18.7 days (Emery et al., 1955). It decays to stable Sr^{86} with the emission of a 1.80 Mev negatron, or a 0.72 Mev negatron which is followed by a 1.08 Mev gamma ray (Hollander et al., 1953). The gamma ray occurs in approximately 8.4 per cent of the total disintegrations (Emery et al., 1955).

The naturally occurring species of cesium is Cs^{133} . There are also several artificially radioactive species, the most important being Cs^{134} , which is produced by the $\text{Cs}^{133}(\text{n},\gamma)\text{Cs}^{134}$ reaction. Cesium-134, with a physical half-life of 2.3 years, decays to stable Ba^{134} by the emission of two negatrons of 0.66 and 0.09 Mev, with relative abundances of roughly 75 and 25 per cent. These in turn give rise to a cascade of gamma rays with recognizable energies of 0.568, 0.602, and 0.794 Mev (Elliot and Bell, 1947).

Cesium-137 is of considerable contemporary interest because it is a fission product of high yield and has a physical half-life of 26.6 years (Wiles and Tomlinson, 1955). It has been incorporated into the biosphere and is presently measurable in plants and animals (Anderson et al., 1957). Cesium-137 disintegrates to Ba^{137} with the emission of two negatrons; about 10 per cent have a maximum energy of 1.2 Mev and about 90 per cent have a maximum energy of 0.5 Mev. The lower-energy negatron is followed by a gamma ray of 0.66 Mev (Hollander et al., 1953).

It is apparent from the radioactive decay schemes that fairly energetic gamma rays are emitted from all the alkali-metal radionuclides. At present, the in vivo whole-body counting technique is limited to the use of radionuclides that emit gamma rays with energies greater than 0.3 Mev in sufficient abundance to give desirable counting efficiencies.

2.2 The Los Alamos Small Animal Counter

The liquid-scintillation counter used to measure the gamma ray activities of small animals has also been called the "Arm Counter," as it was originally designed to accommodate the forearm of a man. A modification of this counter has been used to measure radioactivities in dogs (Van Dilla et al., 1954).

A schematic representation of the detector and the electronic circuits are shown in Fig. 1. The over-all length of the detector is $27\frac{1}{4}$ in.; the diameter, $16\frac{3}{4}$ in. The central cavity measures $14\frac{1}{4}$ in. in length and $4\frac{1}{4}$ in. in diameter and accommodates small laboratory animals such as rats, mice, and guinea pigs. Six photomultiplier tubes (DuMont 6292) are mounted at one end of the detector. These are placed at equal distances in a circle with a radius of $4\frac{1}{2}$ in. from the center of the detector. The cathode surfaces of the phototubes are directed into the scintillator solution, and leakage from the tank is prevented by O-ring seals. The tank containing the scintillator solution is almost entirely surrounded by an outer tank containing mercury which provides $1\frac{1}{2}$ in. of shielding. The effect of the mercury shielding on the integral background of the detector was reported by Van Dilla et al. (1954).

The scintillator solution is composed of 4 grams per liter of terphenyl and 0.1 gram per liter of 2,2'-p-phenylene-bis (5-phenyloxazole) (POPOP) dissolved in reagent-grade toluene. The total volume of the tank is 35.3 liters. A coating of anatase TiO_2 in an epoxy resin protects the inner walls of the scintillation tank from the chemical action of the scintillator solution and provides light reflectance.

The scintillation process begins with the deposition of

energy, from the Compton scattering of the gamma rays, in the scintillator solution. After a series of energy transfers, the secondary solute, POPOP, emits its characteristic spectrum of photons. The photons are then converted to an electrical pulse at the photocathode of the photomultiplier tube (Hayes, 1956). Light collection efficiency of the photomultiplier tubes is significantly enhanced by reflectance from the wall of the scintillator tank.

After the electrical pulses are multiplied, they are amplified, sorted, and scaled by electronic components. Sorting is accomplished in the small animal counter by a single-channel analyzing system. The counter functions as a single-channel gamma-ray spectrometer. Figure 2 shows the detector, resting on a welded iron carriage, and its associated electronic equipment.

Integral pulse-height spectra for background and gamma radiations of several energies were measured with the small animal counter. The discriminator settings (with high voltage supply adjusted to 1050 volts) that afforded the best counting statistics, as indicated by the ratio of sample squared to background count (S^2/B), for the alkali-metal isotopes were found to be 7.5 and 40.0 volts. Loevinger and Berman (1951) showed the importance of the S^2/B ratio as an efficiency criterion for radioactivity counting. As the

counting sensitivity is dependent upon this ratio, the high counting rates of the liquid-scintillation counters become extremely advantageous.

The counter was stable to 0.5 per cent of the background counting rate over a period of 1 hour. A 3 per cent random deviation about the mean was measured over a 23 day period. Significant coincidence losses were not observed until counting rates exceeded 2×10^4 counts per second (cps). Most of the animals measured in the small animal counter had initial whole-body activities below 10^4 cps. The minimum gamma-ray energy detectable was about 0.3 Mev, and the counting efficiency for hard gamma rays (~ 1.5 Mev) was about 50 per cent. The sensitivity of the counter was such that 10^{-9} gamma-ray curie could be measured in a small animal to a precision of 3 per cent in 200 seconds of counting time.

2.3 The Los Alamos Human Counter

The characteristics of the human counter (Fig. 3) were reported in detail by Anderson et al. (1956). The principal differences other than size from the small animal counter are the radial arrangement of 108 photomultiplier tubes around the scintillator tank, the use of 4 in. of lead shielding, and the use of a dual-channel electronic system. The energy resolution of the detector is adequate to permit the

simultaneous determination of Cs^{137} (0.66 Mev) and K^{40} (1.46 Mev) gamma rays. Anderson et al. (1956) stated that "its ultimate sensitivity is 0.0005 microcurie (μc) of gamma activity [20 disintegrations per second (dps)] for only 100 seconds of counting time." The natural K^{40} radioactivity of man, which corresponds to about 0.013 μc as gamma rays, can be measured to a precision of better than 5 per cent in less than 2 minutes of counting time with this instrument.

2.4 Tissue Distribution Studies

Distribution of Na^{22} , Rb^{86} , and Cs^{134} in the tissues of the rat was determined at 1, 5, 12, and 20 days after intraperitoneal administration. Six male Sprague-Dawley rats were used for each determination. The quantities of the radionuclides administered were calculated from previously determined whole-body retention data so that the animals in each group would have approximately equal whole-body activities at sacrifice ($\sim 10^4$ cps). The radionuclides were given intraperitoneally as a neutral solution of the chloride, and 30 μc was the maximum dose administered. All groups that received the same radionuclide were injected at one time. The animals were housed in standard wire-bottomed laboratory cages and allowed Purina chow and water ad libitum.

The whole-body gamma-ray activity was determined just

prior to sacrifice by counting each animal in the small animal counter (Fig. 2). At sacrifice each animal was weighed and 8 to 10 ml of blood withdrawn, under ether anesthesia, by cardiac puncture with a heparinized syringe. The thoracic and abdominal cavities were opened and the animal was perfused with saline (~ 30 ml) to remove residual blood from the tissues. The entire viscera and skin were removed and aliquots of muscle and bone were obtained by removing one gastrocnemius muscle and both femurs. The remainder of the carcass and the skin, liver, gastrointestinal tract, lungs, and other tissues were assayed for gamma-ray activity under replicate geometric conditions in the small animal counter.

Blood samples were centrifuged at 2300 rpm for 20 minutes. The hematocrits were recorded and aliquots of the plasma were removed for radioassay. After washing the erythrocytes twice with normal saline, sufficient distilled water was added to replace the serum. Aliquots of the plasma and the laked erythrocytes were counted for 200 seconds, and the gamma-ray activity was expressed as per cent of the whole-body activity measured at the time of sacrifice.

2.5 Retention and Excretion Studies

Groups of 6 male Sprague-Dawley rats and 12 female CF₁ mice were given single doses of Na²², K⁴², Rb⁸⁶, and Cs¹³⁴.

Average weights of the rats and mice at the time of administration were 250 and 25 grams, respectively. Rats were given $\sim 0.4 \mu\text{c}$ and mice $\sim 0.2 \mu\text{c}$ of activity as the chloride in neutral solution. Each radionuclide was studied in both species following intraperitoneal and oral administration. Animals that received the radionuclides orally were fasted 18 hours prior to administration.

All animals were placed in standard metabolism cages, and urine and feces were collected daily until the activity excreted per day dropped essentially to the limits of detection. The dietary regimen consisted of Purina chow and water ad libitum, except for one group in which the mice were fed a low sodium diet, 3 milliequivalents (meq) sodium per 100 grams food, for 21 days after the administration of Na^{22} . Periodic weighing of all animals showed no difference between experimental and control animals.

The whole-body gamma-ray activity of the individual animals was determined immediately after administration of the radionuclides and periodically thereafter by in vivo counting. Each rat was placed in a 3-1/4 in. diameter cardboard container (Seal-Rite water-tight food container), trimmed to measure 4-1/2 in. in length. A perforated cover was firmly attached by tape to ensure confinement of the animal. The container was then inserted into a flexible,

thin-walled polyethylene sleeve, and both were inserted into the detector. The sleeve, shown with the counter in Fig. 2, protected the interior of the detector from possible contamination. The procedure for counting mice was essentially the same as that for rats; however, each carton was 3-7/8 in. long and held 2 mice. The shorter carton restricted the movements of the pair of animals during the radioassay.

Excreta samples were collected at 24 hour intervals. At the end of each collection period, the metabolism cages and funnels were rinsed several times with water. The rinse water and the urine sample were collected in 8 ounce polyethylene bottles, and (to ensure duplication of the counting geometry) enough water was added to the collection to make the total volume of the sample approximately that of the animal. Because of their somewhat low activity fecal samples were collected and counted in small waxed cups. Standards of each radionuclide were prepared by pipetting into polyethylene bottles an amount of the activity equivalent to that administered to the animals. Each bottle contained a quantity of water which approximated the average weight of the animals in the experimental group. The counting cartons and the standards used for the rats and mice are shown with the counter in Fig. 2. Similar samples, containing no radioactivity, were prepared and used as phantoms for background

determinations.

Mature male rhesus monkeys (Macaca mulatta, average weight 4.1 kg) and beagle hounds (average weight 11.0 kg) were given $\sim 1 \mu\text{c}$ amounts of the radionuclides via oral and intravenous administration. Each experimental group usually consisted of 4 animals. Intravenous administration of the radionuclide was via the cephalic vein of the dog and the saphenous vein of the monkey. All oral doses were administered through a small-bore polyethylene tube inserted into the gastric lumen. A two-way stopcock permitted immediate rinsing of the syringe and tube directly into the stomach.

The animals were housed separately in metabolism cages throughout most of the experiment. Water was allowed ad libitum, and a standard portion of dog or monkey diet was offered daily.

The experimental design used for the dog and monkey retention and excretion studies was similar to that used for the rats and mice. All radioassays were made in vivo by the human counter (Fig. 3). Figure 4 shows a beagle hound in the cardboard container used to restrain the dogs and monkeys and to protect the detector from possible contamination during the radioassay. Standards, phantoms, urine, and feces were counted in 5 gallon polyethylene bottles, with enough water added to approximate the average

weight of animals of the groups.

All samples were routinely counted for 200 seconds until the radioactivity levels were less than 50 cps. The counting time of samples of low activity was increased sufficiently so that the error contributed by the radioassay was less than 3 per cent. The standard deviation can be computed with good accuracy for strongly radioactive samples simply by taking the square root of the total number of counts:

$$\sigma = \sqrt{N}$$

For relatively weak samples, the background counting rate contributes appreciably to the statistical error. The combined error is expressed as the square root of the sums of the individual errors:

$$\sigma_{a-b} = \sqrt{N_a + N_b} \quad (1)$$

where σ_{a-b} is the standard deviation due to sample and background, N_a is the number of counts for the sample, and N_b is the number of counts for the background. Since $N = rt$, where r is the counting rate and t is time, the expression becomes:

$$t\sigma_{a-b} = \sqrt{r_a t + r_b t}$$

or

$$t\sigma_{a-b} = \sqrt{(r_a + r_b) t} \quad (2)$$

To obtain a desired σ_{a-b} of 3 per cent (with a background counting rate of 270 cps), a sample with an activity of 30 cps should be counted for ~ 400 seconds.

In the human studies, healthy male laboratory personnel, in groups of 3 or 4, were given $\sim 1 \mu\text{c}$ amounts of the radionuclides as the chloride in neutral solution. The subjects were fasted overnight and the dose was administered orally in 100 ml of water. An additional 100 ml of water, used to rinse the container, was also ingested. A licensed physician supervised the administration of radioactive materials.

The subjects were assayed immediately after ingestion of the radionuclide and at intervals thereafter in a manner similar to that used for the dogs and monkeys. In this case, however, standards of each radionuclide were prepared by pipetting an amount of the isotope equivalent to that ingested into polyethylene bottles containing 1 gallon of water. Twenty-four hour excreta samples were collected, diluted to 1 gallon in polyethylene bottles, and counted in the human counter in a fixed geometry with respect to the standard.

As the human counter was sufficiently sensitive to detect Cs^{137} and natural K^{40} in large animals, the monkeys, dogs, and men were counted to measure their natural K^{40} activities before the radionuclides were administered. Monkeys and dogs were thoroughly washed and dried to remove

surface contamination, and men were required to remove street attire and put on clean pajamas and booties, prior to being counted. From these measurements it was possible to calculate the whole-body potassium content of each animal from the known K^{40} content (0.012 per cent, Suttle and Libby, 1955) of normal potassium.

The natural K^{40} activity was also measured in each of the following species of laboratory animals: weanling mice; rats, after the removal of hair with a depilatory; and rabbits that had been thoroughly washed to remove surface contamination. Measurements were made by counting a several-pound sample of animals of each species after they were sacrificed. The counting efficiency for K^{40} was determined for each group by counting a similar weight of KCl under the same geometric counting conditions used for the animals.

The following relationships were used to determine the whole-body retention of the various radionuclides from the in vivo gamma-ray activities measured in the scintillation counters:

$$WBRT_x = \frac{WBt_x / (St_x / St_o)}{WBt_o} \quad (3)$$

or

$$WBRT_x = \frac{WBt_x / St_x}{WBt_o / St_o} \quad (4)$$

where

WBt_x = whole-body retention at time t_x in cps

WBt_x = whole-body activity at time t_x in cps

WBt_0 = whole-body activity at time t_0 in cps

St_x = standard activity at time t_x in cps

St_0 = standard activity at time t_0 in cps

For radionuclides with long physical half-lives (i.e., negligible decay during the experimental period), the whole-body retention at any time, t_x , is merely WBt_x/WBt_0 (Eq. 3). For radionuclides which decay during the experimental period, the ratio St_x/St_0 in Eq. 3 will correct the whole-body activity at any time, WBt_x , for physical decay.

For ease in calculations, the ratio of the body activity to the standard at any time, t_x , was divided by the ratio of the body activity to the standard at time zero, t_0 , to obtain the whole-body retention corrected for physical decay of the radionuclide at any time, t_x (Eq. 4).

The whole-body retention and excretion values were plotted (dependent variable per cent) as a function of time (independent variable days) on semilogarithmic paper.

CHAPTER 3

RESULTS

3.1 Tissue Distribution Studies

Distribution of Na^{22} in the tissues of the rat is shown in Table 1. Quantitatively, the skin, muscle, bone, gastrointestinal tract, and blood were the major tissues for Na^{22} accumulation. The relative skeletal burden increased until on the twentieth day it accounted for ~ 31 per cent of the body burden. Little change was seen in the plasma Na^{22} activity relative to that of the whole body over the 20 day period.

The data in Table 2 show that the muscle, skin, liver, and gastrointestinal tract had the larger amounts of Rb^{86} at all times after administration. The muscle mass contained almost two-thirds the entire body burden. Approximately 4 per cent of the body activity was contained in the skeleton at all times. The fraction of the body burden contained by each organ remained constant over the 20 day

period. The testes, brain, and plasma contained peak Rb^{86} concentrations sometime between 1 and 5 days; all other tissues probably reached their peak activities during the first 24 hours after administration. The Rb^{86} activity found in the muscle mass was about 16 times greater than that of the skeleton. Throughout the study the activity in the liver remained about one-sixth that of the muscle mass.

Distribution of Cs^{134} in the tissues of the rat is shown in Table 3. Muscle, skin, gastrointestinal tract, and liver were the tissues with largest cesium depositions shortly after administration. The muscle mass contained about 80 per cent of the total body burden at 5, 12, and 20 days after administration. Except for the first day, the muscle, skin, heart, lungs, testes, and brain contained relatively constant fractions of the total body burden at time of sacrifice. Bone, gastrointestinal tract, spleen, liver, kidney, and plasma contained diminishing fractions of the body activity at the four sampling periods. Erythrocytes contained more Cs^{134} than the plasma some time after the first day. On day 1 the liver activity represented one-seventh that of the muscle mass; however, on days 5, 12, and 20 this activity was about one-thirtieth that of the muscle mass.

3.2 Retention and Excretion of Alkali-Metal Isotopes

The retention and excretion data for the various radio-nuclides were best expressed in most cases as multiple-component rate functions of the form

$$R = a_1 e^{-k_1 t} + a_2 e^{-k_2 t} + \dots a_n e^{-k_n t}$$

in which $a_1, a_2, \dots a_n, k_1, k_2, \dots k_n$ are the intercept and rate constants, respectively, of the individual or first-order components of the composite retention or elimination process. The value of k was determined from the retention data by the expression

$$k = \frac{0.693}{T_{1/2}}$$

where $T_{1/2}$ is the half-time of retention of the specific component. The parameter k , the rate constant, represents the fractional amount of the substance which is lost per unit time from a specific compartment. When t is expressed in days, the units of k are fraction per day. In some instances, single exponential functions best described the retention and excretion processes.

The values of the intercept constants and half-times were determined from the data by the standard kinetic approach (Zilversmit, Entenman, and Fishler, 1943; Solomon, 1949;

Kamen, 1951).

Figure 5 illustrates the procedure used to separate the individual components of a multiple-component rate function. Experimental data were plotted on semilogarithmic paper and the curve that gave the best fit by inspection was drawn. The method of least squares was then used to determine the equation of the best-fitting line for the linear portion of the curve between 22 and 57 days. The equation was then solved for the $T_{1/2}$ ($y = 50$) and the y intercept ($t = 0$). Differences between corresponding ordinates of the original retention curve and the extrapolated line (shaded area in Fig. 5a) were plotted in Fig. 5b and again a smooth curve was fitted to the data. The method of least squares was used to fit the line to the linear portion of the curve between 3 and 12 days. Once again the ordinates bounding the shaded area in Fig. 5b were subtracted from one another and the new data were plotted in Fig. 5c. Because the resulting curve, representing the final component, is a straight line, the kinetic analysis is considered complete. In practice, the shaded areas are plotted on expanded scales for greater accuracy in the process of subtracting ordinates.

The shaded area in Fig. 5a is actually the contribution of components A and B added to component C. Thus the composite retention process shown in Fig. 5 can be represented

by the sums of its individual components:

$$R = 48.5 e^{-1.3860t} + 36.0 e^{-0.2887t} + 15.5 e^{-0.1066t}$$

The biological half-time ($BT_{1/2}$) as used in this dissertation represents the average time necessary for a group of animals to lose the first half of their initial body burden by all routes of elimination, regardless of the method of administration. It should be recognized, however, that the significant portion of the retention curve (from the internal-hazard standpoint) may be represented by the longest-lived component, which could accumulate a larger fraction of the radionuclide during chronic exposure.

3.3 Retention and Excretion of Na^{22}

The whole-body retention of Na^{22} in the mouse after oral administration is shown in Fig. 6. Each point represents the mean value for six pairs of mice; one standard deviation is shown for several of the mean values. A multi-component rate function, composed of three individual exponential functions with half-times of 1.5, 2.5, and 45.0 days, best fits the retention data. The $BT_{1/2}$ was 1.7 days. Urinary and fecal excretion curves were exponential and parallel until the time excreta samples no longer contained measurable activity.

The general formula for excretion by a single exponential rate is given by the expression

$$U = U_0 e^{-[(0.693/T_{1/2})t]}$$

where U is the excretion rate (μc per 24 hours) by a given rate process at time t , U_0 is the excretion rate (same units as U) at time zero, and $T_{1/2}$ is the half-time (days) of the rate process. The μc activity, Q , that will be lost by a single exponential process (Comar and Wasserman, 1956) is given, therefore, by the expression

$$Q = \int_0^{\infty} U_0 e^{-[(0.693/T_{1/2})t]} dt$$

and

$$Q = \frac{U_0 T_{1/2}}{0.693}$$

When the values of U_0 and $T_{1/2}$ from the excretion curves in Fig. 6 were substituted in the above equation, the loss of Na^{22} via the urine and feces was calculated as 84 and 16 per cent, respectively. This calculation assumes that the entire burden is lost by these routes as single exponential processes. This assumption is valid because the slope of the retention curve does not change appreciably until most (~ 90 per cent) of the Na^{22} atoms are lost from the animal. For chronic exposures, however, one cannot ignore the

slow-moving component.

Figure 7 shows the total retention and excretion of Na^{22} after intraperitoneal administration to mice. The $\text{BT}_{1/2}$ for the group was 1.5 days and the half-times of the contributing components were 1.2, 2.8, and 22.0 days. The ratio of urinary to fecal radioactivity (U/F) was about 5.5, suggesting that approximately 82 per cent of the Na^{22} was lost via renal excretion.

The effect of restricted Na^{23} intake on the retention of Na^{22} in mice after intraperitoneal injection is shown in Fig. 8. The half-time of the Na^{22} , during the 3 weeks of low Na^{23} intake, was about 60 days. After the animals were returned to normal ad libitum Purina chow feeding, the retention curve dropped very rapidly. Three exponential rates contributed to the multiple-component function that described the retention curve after the data were normalized to 100 per cent retention at 21 days. The total body retention was best represented by the equation

$$R = 92.9 e^{-0.5331t} + 5.5 e^{-0.0866t} + 1.6 e^{-0.0015t}$$

(The slowest-moving component had a half-time of 136 days and represented 1.6 per cent of the body burden at zero time.

Figure 9 illustrates the retention of Na^{22} in rats

after oral administration. Three components with half-times of 2.5, 6.0, and 105.0 days formed the composite retention curve. The $BT_{1/2}$ for the group was 2.9 days. Urinary and fecal excretion curves were roughly parallel and showed that about 90 per cent of Na^{22} was lost via the urine and 10 per cent via the feces. A comparison of Figs. 9 and 10 shows the difference in retention of Na^{22} after oral and intraperitoneal administration to rats. The $BT_{1/2}$ of Na^{22} after intraperitoneal administration was 2.8 days, and half-times of 1.8, 4.7, and 105.0 days were associated with the three components of the retention curve.

Figure 11 illustrates the retention of Na^{22} in a group of 4 monkeys following intravenous injection. The $BT_{1/2}$ was 7.5 days and the half-times of the individual components were 5.5, 9.0, and 120.0 days. Both the urinary and fecal excretion curves, which were fitted by the method of least squares, were simple exponentials over the period studied. (Comparisons of the areas under the curves, assuming no further rate changes, showed that approximately 9 times more activity was lost via the urine than via the feces.

Following intravenous injection, the average rate function for Na^{22} in 4 beagles was composed of three components with half-times of 7.5, 10.0, and 205.0 days (Fig. 12). The $BT_{1/2}$ for the group was 9.5 days. Urinary excretion exceeded

fecal excretion by a factor of 2.5 at zero time and remained constant for at least 40 days. Thus, approximately 60 per cent of the Na^{22} excreted was lost via the urine.

Figure 13 shows the average body retention and urinary excretion levels for 3 people following a single oral dose of Na^{22} . The mean $\text{BT}_{1/2}$ for the group was 11.0 days, but after approximately three half-lives the rate of loss decreased. Eventually, a very slow-moving component was evident. Three components with half-lives of 8.5, 13.5, and 445.0 days contributed to the retention process.

The method of least squares was used to fit a line to the mean urinary excretion values for the group. Approximately 99 per cent of the administered dose would be lost via the urine, assuming the urinary excretion rate follows a simple exponential function. Radioassay of fecal samples showed Na^{22} loss by this route to be negligible.

3.4 Retention and Excretion of K^{42}

Table 4 summarizes the parameters which were measured in connection with whole-body retention studies of K^{42} in mice, rats, and dogs. Because of the short physical half-life of K^{42} , studies were carried out over a period of only 3 to 4 days and no measurements were made in monkeys or men.

Following oral administration to both rats and mice, the

composite retention curve consisted of two exponential components, whereas only one exponential rate of change was evident following intraperitoneal or intravenous administration. The $BT_{1/2}$ value for dogs was obtained by extrapolating the retention curve to the 50 per cent level, as the K^{42} activity in the animals was not detectable after 3-1/2 days because of radiological decay. Calculations showed that approximately 82 per cent of the K^{42} was lost via the urine from both the rat and the mouse following intraperitoneal administration. The estimated renal excretion of K^{42} by the dog was 75 per cent.

3.5 Natural K^{40} and Potassium in Laboratory Animals

Data on the natural K^{40} and total-body potassium content of 24 beagle hounds are shown in Table 5. The counting efficiency of K^{40} as a function of sample mass was determined by counting KCl samples of different weights. The mean K^{40} activity was 7.1 dps per kilogram after correction for background and sample mass.

The following equation was used to convert the gamma-ray activity (dps) to milliequivalents of potassium per kilogram of body weight:

$$K \text{ (meq/kg)} = \frac{\text{dps } K^{40} / \text{kg}}{(0.039)(2.97)}$$

where 0.039 is the milliequivalent weight (in grams) of potassium, and 2.97 is the number of gamma rays emitted per second from 1 gram of natural potassium. The potassium content of males was slightly, although not significantly, higher than that of females. The mean potassium content for the 24 animals was 61.6 meq/kg.

The average K^{40} gamma-ray activity for a group of 21 male monkeys was 8.9 dps/kg, which was equivalent to 77 meq/kg body weight. These data are shown in Table 6.

The natural K^{40} gamma-ray activity averaged 8.7, 9.6, and 6.7 dps/kg for the mouse, rat, and rabbit, respectively. Table 7 shows the potassium content of several species of animals reported in the literature, as well as values found in this study. The K^{40} in vivo counting technique was used also to determine the total body potassium content of man and a value of 49 meq/kg was obtained (Anderson et al., 1957).

3.6 Retention and Excretion of Rb^{86}

Retention and excretion of Rb^{86} by mice following oral administration is shown in Fig. 14. Each point represents the average of 6 pairs of mice. The $BT_{1/2}$ was 3.8 days. The urinary and fecal excretion curves were exponential over the period during which activities were measurable.

Calculations showed that about 76 per cent of the administered dose was eliminated in the urine, provided excretion remained exponential.

Two components with half-times of 1.2 and 3.7 days composed the total retention curve shown for mice following intraperitoneal administration in Fig. 15. The $BT_{1/2}$ for the group was 2.7 days. Assuming continued exponential excretion, the elimination of Rb^{86} via the kidneys was estimated as approximately 83 per cent of the administered dose.

The average $BT_{1/2}$ of Rb^{86} in rats following oral administration (Fig. 16) was 8.6 days. Half-times of 3.5 and 11.5 days were measured for the two components of the total retention curve and the kidney was the major route of excretion. Following intraperitoneal administration of Rb^{86} , the $BT_{1/2}$ was 7.5 days and the retention curve was composed of two components of 2.0 and 10.4 days. The urinary and fecal excretion curves following oral (Fig. 16) and intraperitoneal administration (Fig. 17) showed 2 rates of loss corresponding to the two components of the retention curve. This seemed to indicate that virtually 100 per cent of the Rb^{86} was absorbed from the gastrointestinal tract.

Fecal excretion of Rb^{86} by the monkey was greater than urinary excretion (Fig. 18). The half-time of both urinary and fecal elimination was 17 days, and the F/U ratio was

1.13. Assuming a continued exponential elimination rate, about 45 per cent of the Rb^{86} ultimately would be eliminated from the body via the kidneys. Following intravenous administration, the whole-body retention curve showed only one rate function, and the $\text{BT}_{1/2}$ for the 4 monkeys was 15 days.

Average retention and excretion values for 4 beagle hounds following intravenous injection of Rb^{86} are given in Fig. 19. All three curves were single exponential functions. The $\text{BT}_{1/2}$ for Rb^{86} was 20 days, and the kidney was the major excretory route. Assuming a continued exponential elimination function, approximately 85 per cent of the Rb^{86} would be lost ultimately in the urine and 15 per cent in the feces.

Figure 20 shows the average whole-body retention and urinary excretion of orally administered Rb^{86} for 3 men. The $\text{BT}_{1/2}$ for the group was 80 days, with a range of 70 to 94 days. Two components with half-times of 4 and 95 days formed the composite retention curve. At least two components also contributed to the urinary excretion curve. Radioassay of fecal samples at several times after administration showed that Rb^{86} loss via the feces was considerably less than via the urine. About 80 per cent of the Rb^{86} lost the first day was via the kidneys.

3.7 Retention and Excretion of Cs¹³⁴ and Cs¹³⁷

The data in Figs. 21 and 22 show that the retention and excretion curves of Cs¹³⁴ following oral and intraperitoneal administration to mice were similar. The $BT_{1/2}$ for the oral and intraperitoneal groups was 1.2 and 1.8 days, respectively. Following both modes of administration the retention curves were composites of three exponential functions with half-times of 0.5, 2.4, and 6.6 days. At least two exponential components contributed to the urinary and fecal excretion curves following both methods of administration.

The retention and excretion patterns of Cs¹³⁴ in the rat following oral and intraperitoneal administration also were similar (Figs. 23 and 24). The $BT_{1/2}$ for both groups was 6.5 days, and three exponential components contributed to the body-retention curve. Half-times of 0.8, 6.8, 13.5, and 1.5, 7.0, and 14.0 days were found following oral and intraperitoneal administration, respectively, and the urine was the major route of excretion.

Data showing the average retention and excretion of Cs¹³⁴ by 4 monkeys are given in Fig. 25. Following intravenous injection, a $BT_{1/2}$ of 19 days was obtained. The composite retention curve consisted of three components with half-times of 3.0, 23.0, and 40.5 days. At least two

components were observed for the urinary and fecal excretion curves. The long components of these curves were parallel and each had a half-time of 26.5 days. The relative amounts of Cs^{134} lost via these slower-moving components were calculated to be 61 and 39 per cent in the urine and feces, respectively.

The average retention and excretion data following intravenous administration of Cs^{134} to 4 beagle hounds are plotted in Fig. 26. The $\text{BT}_{1/2}$ was 25 days for the group. Exponential functions with half-times of 1.1, 27.0, and 43.5 days formed the composite retention curve. Most of the Cs^{134} was lost by renal excretion. The fecal excretion of cesium was considerably smaller in the dog than in the monkey.

Figure 27 shows the average retention and excretion of radiocesium for 4 men following oral administration. Two subjects received Cs^{134} and two received Cs^{137} . The average $\text{BT}_{1/2}$ for the group was 110 days and two components formed the composite retention curve. The bold symbols represent average retention values for 4 subjects, and the small symbols represent individual retention values. The slow-moving component ($T_{1/2} = 143$ days) and the fast-moving component ($T_{1/2} = 3$ days) correspond to 84 and 16 per cent of the total activity at zero time. One subject has been

counted periodically for 2 years, and two others have been counted for 14 months. Because a third component in the retention curve was found in other species, counting of available subjects is being continued.

CHAPTER 4

DISCUSSION

4.1 Physiological Significance of the Alkali Metals

General relationships are known to exist between the position of elements in the groups of the Periodic Table and their physiologic and metabolic properties. For example, the alkali-earth elements are considered to be primarily bone seekers, and the thyroid tissues are known to have an affinity for the halide elements (Baumann et al., 1956).

The first two members of the alkali metals, lithium and sodium, are strikingly different in their biochemical behavior as compared with potassium, rubidium, and cesium. It is generally accepted that lithium is distributed, somewhat like sodium, throughout the extracellular compartment of the body; however, potassium, rubidium, and cesium are ions of intracellular importance. Little is known about francium as all its known species have half-lives of less

than 30 minutes.

Sodium and potassium, although they follow very different metabolic pathways in animals, are the two alkali metals that are essential to biological systems. Their functions are mainly concerned with water and electrolyte balance. Biological interest in the metabolism of cesium and rubidium is a natural consequence of their close proximity to potassium in the Periodic Table.

The metabolic similarities of potassium, rubidium, and cesium have long been recognized. Ringer (1882) first observed that rubidium and, to a lesser extent, cesium had similar physiological effects on the contraction of the isolated frog heart. In 1922, Clark showed that rubidium could be substituted for potassium for the maintenance of the physiological activity of various isolated organs; cesium was an imperfect substitute. Loeb (1921) found that cesium ions could replace potassium ions in solutions required for the development of sea urchin eggs into swimming blastulae. It is of historical interest to mention that Loeb could not replace the potassium ions in these solutions with thorium or uranium ions from thorium chloride or uranium acetate. Some of his contemporary workers believed that the physiological action of potassium was due to its natural radioactivity and that other radioactive

materials could replace it in physiological reactions (Zwaademaker, 1920a). Zwaademaker (1918) stated, "It is the radioactivity of potassium which renders it indispensable for life." He also suggested that the radioactivity of this element was the possible cause of the heart beat and that the absence of a radioactive element in the kidney allowed the passage of sugar (Zwaademaker, 1920b). Some very recent work showed that K^{40} was not responsible for the physiological action of potassium (Vinogradov and Kovalevskii, 1957).

Follis (1943) demonstrated that the presence of either rubidium or cesium in low potassium diets prevented the appearance of typical histological lesions that normally occur owing to potassium depletion in rat tissues. Rubidium provided more protection than cesium. MacLeod and Snell (1948) showed that rubidium or cesium could replace potassium as an ion required for the growth of bacteria. Relman et al. (1957) demonstrated that more than half of the muscle potassium was replaced by rubidium or cesium when the latter were fed together with potassium to young rats. Their results suggested that the alkali metals accumulated in the muscle cells in a decreasing order of preference ranging from cesium to rubidium to potassium.

4.2 Sodium Metabolism

The sodium ion, which is widely distributed in the biosphere, is reported to be rapidly and completely absorbed from the gastrointestinal tracts of animals. Greenberg et al. (1940) showed that about 95 per cent of a Na^{24}Cl solution disappeared from the gastrointestinal tract of the rat within 1 hour of administration. Other workers showed that Na^{24} distribution was identical to Na^{22} distribution after 24 hours in the rat (Mannery and Bale, 1941). Hamilton (1938) reported that Na^{24} was completely absorbed by fasted human subjects within 3 hours of oral administration. Veall et al. (1955) found that Na^{24} was uniformly distributed throughout the human body 3 hours after oral ingestion. Human excretion data collected 24 hours after Na^{24} ingestion also indicated a rapid equilibrium of the ions with their miscible pools (Arons et al., 1954). They found the excretion of Na^{23} and Na^{24} to be parallel. Pommerenke and Hahn (1953) showed that radiosodium appeared in human milk 20 minutes after ingestion.

The similarity in the excretion curves after oral and intraperitoneal administration (Figs. 6 and 7) indicated complete gastrointestinal absorption of Na^{22} by mice. Excretion data for the rat and man also suggested complete absorption. Other experiments, which are being continued,

showed that the retention pattern of Na^{22} after oral administration to dogs was the same as that obtained after intravenous administration. This also suggested complete gastrointestinal absorption.

Greenberg et al. (1940) found that 20 per cent of administered Na^{24} was located in the skin, 20 per cent in muscle, 2.5 per cent in the liver, and 11 per cent in the plasma of rats. These values are in fair agreement with data shown in Table 1.

In human subjects, approximately 6 per cent of the Na^{22} was excreted by the kidneys during the first 24 hours (Fig. 13). This value is in good agreement with average values of 7.3 and 6.5 per cent given by others (Miller and Wilson, 1953; Arons et al., 1954). It is of interest to note the absence of fecal sodium in humans as some loss via this route occurs in the other species. Others found fecal loss of radiosodium to be negligible in humans (Miller and Wilson, 1953; Martin and Walker, 1957).

Threefoot et al. (1949) reported a drop in the serum Na^{22} concentration to one-half the initial level in an average time of 13.3 days for four normal subjects, whereas 28.8 days were required for one-half of the dose to be excreted in the urine. They stated that very likely the $\text{BT}_{1/2}$ was equal to the serum $\text{C}_{1/2}$ value of 13.3 days. The

serial decrease of serum Na^{22} activity in normal people was, in all probability, closely related to the serial changes in the whole-body retention as measured by the in vivo counting technique. The value of 29 days for the $\text{BT}_{1/2}$ of sodium in Handbook No. 52 (National Bureau of Standards, 1953) was obtained from the Threefoot data. Another value of 19 days given in Handbook No. 52 was a calculated value. Veall et al. (1955), who used an in vivo counting method, measured an 11 day $\text{BT}_{1/2}$ for radiosodium in man, which is the same value reported in the present study (Fig. 13). A personal communication from Veall has verified the slowly-moving component (Fig. 13) which represents about 0.2 per cent of the administered activity at zero time in adult subjects. Martin et al. (1957) measured the change in the body activity of Na^{22} with external Geiger-Müller counters and found the $\text{BT}_{1/2}$ to range from 17 to 31 days in a group of six hospital patients.

A family of retention curves for five species of animals is shown in Fig. 28. The curves show the retention pattern after oral administration for mice, rats, and men. The dogs and monkeys were injected intravenously. Other experiments showed that the retention pattern of orally and intravenously administered Na^{22} was similar in the dog. A body burden in the rat, dog, and man was 0.5 per cent of the initial dose 100 days after administration. In each

species, the sodium retention changed with time as the result of three exponential rates of loss: a relatively fast-moving component, which accounted for most of the initial burden; an intermediate component; and a slow-moving component, which represented a small fraction of the initial burden.

The amounts of the Na^{22} activity associated with each exponential component at zero time might represent fractions of the total sodium pool. If one assumes that Na^{22} mixes rapidly with and proportionally to the number of Na^{23} atoms in the various compartments of the pool, then the intercept values can be considered as being proportional to the amounts of Na^{23} in each fraction of the total pool.

If the Na^{22} atoms do not distribute in proportion to the number of Na^{23} atoms, the intercept values are not proportional to the fractions of the Na^{23} pool. Thus the compartment associated with the slowest-moving component of the retention curve might actually represent a relatively larger compartment in which the Na^{23} atoms did not reach equilibrium with the Na^{22} atoms. It is well known, for example, that approximately one-third of the total body sodium is in the skeleton, yet only 30 to 40 per cent of it is exchangeable with radiosodium (Kaltreider et al., 1941; Forbes and Perley, 1951; Stern et al., 1951; Edelman et al., (1954)).

Bergström["] (1955) showed that only 29 per cent of the bone sodium of the rat could be mobilized by several sodium depletion techniques. The mobilized portion came from the exchangeable sodium fraction. Since the exchangeable fraction represents the sodium that is actively participating in the metabolism of the organism, it is of greater physiological interest than the nonexchangeable fraction.

Sodium loss from the rat following intraperitoneal dialysis against ammonium chloride was found to be shared by extracellular, intracellular, and bone sodium; the respective contributions to the total loss were 52, 20, and 28 per cent (Bergström["], 1955). The three fractions of the total Na^{22} pool observed in this study could represent extracellular, intracellular, and bone sodium.

The components of the retention curves for all species (Fig. 28) indicate that sodium is lost from three compartments at three different rates. Dobson and Warner (1957) reported that the areas into which Na^{22} perfused might be overlapping regions, regions included one within another, or regions anatomically separated as different types of tissue. In addition, Zilversmit et al. (1943b) showed that a single exponential rate might represent the sum total of multiple rates and not a simple transfer of a material to or from a single tissue or phase.

Veall (1955) proposed that the body might be regarded as a single compartment system in relation to its external environment. If, as in his model, the body content of an electrolyte (i.e., sodium) is equal to Q meq, and the daily intake q is equal to the excretion rate, and N and N_0 are the number of atoms present at any time t and time zero, respectively, then the following relation exists:

$$N = N_0 e^{-[(q/Q)t]} = N_0 e^{-[(0.693/T_{1/2})t]}$$

The body in relation to its external environment can also be considered to be a multicompartment system. Thus the sodium ions may be thought of as being divided into three groups with different locations and exchange rates. One group is in a region (or regions), which we designate Compartment A, where the exchange rate is most rapid; the second group is in another region, Compartment B, where the exchange rate is less rapid; and the third group is in Compartment C, where the exchange rate is least rapid.

The area under a retention curve obtained following a single acute exposure to a given radionuclide is proportional to the number of atoms disintegrating in the organism. Likewise, the area under each exponential component of a composite curve and the disintegrations represented by it are in proportion. The areas under the components of a curve

of the type

$$R = a_1 e^{-k_1 t} + a_2 e^{-k_2 t} \quad (5)$$

can be calculated from the parameters a_1 , a_2 , k_1 , and k_2 . The equation which represents the total integrated area under each component is

$$A_1 = \int_0^{\infty} a_1 e^{-k_1 t} dt \quad (6)$$

or

$$A_1 = \frac{a_1}{k_1} (1 - e^{-k_1 t}) \quad (7)$$

and, because e^{-kt} is infinitely small at infinite time, Eq. 7 becomes

$$A_1 = \frac{a_1}{k_1} = x \text{ and } A_2 = \frac{a_2}{k_2} = y \quad (8)$$

It follows that the total area under the composite curve (Eq. 5) is

$$A = \frac{a_1}{k_1} + \frac{a_2}{k_2} = x + y \quad (9)$$

and

$$\frac{x}{x + y} \text{ and } \frac{y}{x + y} \quad (10)$$

are the fractions of the total area represented by each component.

Table 8 gives the fractions of the disintegrating atoms attributable to the various components of the retention curves for several radionuclides in five mammalian species. If one could relate the relative masses of the regions irradiated to the fractions of the total disintegrations given in Table 8, then radiation doses could be calculated. These data apply only to acute exposures. Component C of the sodium retention curves (1 per cent or less of the initial activity in all species) contributed a large fraction (10 to 27 per cent) to the total disintegrations because of its long half-time (Table 8). Presumably this component represented some phase of bone sodium metabolism.

4.3 Potassium Metabolism

Greenberg et al. showed in 1938 that approximately 90 per cent of a $K^{42}Cl$ solution was absorbed within 30 minutes after oral administration to fasted rats. They observed that the liver took up a greater fraction of the radio-potassium when it was administered orally than when it was injected intraperitoneally. Joseph et al. (1939) also reported the rapid absorption of $K^{42}Cl$; about 90 per cent of the dose was absorbed, primarily from the small intestine,

within 30 minutes after administration.

D'Silva and Neil (1951) found the distribution of K^{42} to be the same as that of normal potassium. Approximately 90 per cent of the $K^{42}Cl$ was removed from the intraperitoneal cavity within 5 minutes after injection. They reported, "It can be calculated that because of their favorable anatomical positions when the intraperitoneal route is used for injection, the liver and gut remove, by exchange, some 40 to 50 per cent of the active potassium injected during passage of the radioactive blood through these tissues for the first time." When the injection was given intravenously, however, the liver was least favorably situated for K^{42} uptake, as only a part of its blood supply was derived from blood rich in K^{42} . The portal venous blood had already traversed the gut where many of the K^{42} ions were removed. Levitt and Guadino (1949) reported a very rapid uptake of K^{42} by the visceral organs of the dog. The temporary elevation caused the specific activities of these organs to be higher than that of plasma.

Hamilton (1938) reported that K^{42} was completely absorbed by fasted human subjects after 5 hours. Hevesy in 1942 stated, "It is clearly shown that a very substantial part of the labeled potassium and thus all of the potassium taken in with the food interchanges with the potassium located in

the tissue cells in the course of some hours." The data of Arons et al. (1954) indicated a relatively rapid mixing of K^{42} with its miscible pools in humans, as the excretion rates of both radioactive and stable isotopes were parallel.

The difference between the number of components in the retention curves following oral and intraperitoneal administration for both the rat and mouse could not be explained (Table 4). The presence of two components after oral administration suggested that K^{42} was lost from several compartments at different rates. Consideration of the fraction of the total disintegrations attributable to each exponential component following oral administration showed that the fast-moving components represented only 2 per cent of the total (Table 8).

The whole-body retention pattern appeared to depend on the route of administration in the mouse and rat. Supporting work showed that the retention of K^{42} after oral administration to dogs was very similar to that reported for intravenous injection in Table 4.

The short physical half-life of K^{42} made it difficult to interpret these data (Table 4). For example, any additional rate change in the retention process would change the values of the parameters that describe the process for only 4 days.

Because K^{42} was not given to humans, an attempt was made to calculate the $BT_{1/2}$ of potassium in man from K^{40} intake and body content data. It was assumed that a single rate controlled the loss from the body. The data from animals indicated that this was a good approximation (Table 4). It was also assumed that skeletal muscle was the critical tissue; 98 per cent of the body potassium was in the critical tissue (Moore et al., 1956); the daily intake and body content of potassium was 2.6 grams and 0.19 per cent of the body weight, respectively (Anderson et al., 1957); and potassium was completely absorbed from the gastrointestinal tract.

When the required values were substituted in the equation employed for the calculation of a $BT_{1/2}$ (Handbook No. 52, National Bureau of Standards, 1953), a value of 35 days was obtained. The equation is

$$BT_{1/2} = \frac{0.69mc}{If_w}$$

where m is the muscle mass (3×10^4 gm); c is the concentration of potassium ($130/3 \times 10^4$ gm per gram) in m ; I is the intake of the element (2.6 gm per day); and f_w is the fraction of potassium reaching m by ingestion ($f_w = f_1 \times f_2$). In the last expression f_1 is the fraction going from the gastrointestinal tract to the blood, and f_2 is the fraction

in m of that in the entire body.

This calculation treats the whole body as a single compartment system in which the daily exchange with a constant pool is known. The retention of potassium at any time t is given by the expression

$$R = R_0 e^{-[(I/Q)t]} = R_0 e^{-[(0.693/T_{1/2})t]} = R_0 e^{-[kt]}$$

where I is the daily intake, and Q is the total amount of the element in the body.

A calculated $BT_{1/2}$ value of 33 days is given for potassium in Handbook No. 52 (National Bureau of Standards, 1953).

4.4 Natural K^{40} and Total Body Potassium in Laboratory Animals

The data in Tables 5 and 6 suggested that rhesus monkeys had more potassium per kilogram of gross body weight than beagle hounds. Total body potassium, when expressed in this manner, was shown to vary with age, sex, and the relative amounts of fat, muscle, and water in the body (Forbes and Lewis, 1956; Sagild, 1956; Woodward, Trujillo, Schuch, and Anderson, 1956). The significant difference between the potassium content of dogs and monkeys was probably related to the fat/muscle ratio for each species. Moore et al. (1956) reported that the body potassium content appeared to

be a proportionate function of the lean body mass.

Published data on the total potassium content of several animals were included in Table 7 for comparative purposes. In general, the values taken from the literature were slightly lower than those found in this study. It is interesting to note that the ratio of the potassium contents for the dog and monkey (M/D) taken from the literature was the same (1.25) as that found in this study. The blood, hair, and contents of the gastrointestinal tract were excluded from the chemical analyses in some of the studies; this partially explains the lower values found in the literature. The rabbits used were obviously obese (5 kg each) and had a relatively low potassium value (56.9 meq/kg); however, man had the lowest potassium content (about 50 meq/kg) and, consequently, the highest fat/muscle ratio of all the species studied. As little potassium is found outside the skeletal muscle mass (about 2 per cent), the potassium content of an animal is a good assessment of its lean muscle mass (Moore et al., 1956).

4.5 Rubidium Metabolism

The results of retention and excretion data indicated that Rb^{86} was completely absorbed from the gastrointestinal tract and, in turn, rapidly deposited in the tissues.

Hamilton (1948b) demonstrated the complete absorption of Rb^{86} in rats. Freedberg et al. (1952) showed that more than 90 per cent of intravenously administered Rb^{86} left the blood of dogs and men within 5 minutes. Zipser et al. (1953) demonstrated similar results for man.

Spectrographic analysis of animal tissues by Sheldon and Ramage (1931) and Bertrand and Bertrand (1946) showed that rubidium was present in most animal tissues in a range of 0.002 to 0.006 per cent of the dry-tissue weight. Despite its very small natural abundance, 1 part in 10^5 of potassium in the earth, about 2 parts of rubidium were found for every 10^3 parts of potassium in living tissues (Relman, 1956).

Tissue studies indicated that the absolute majority of the Rb^{86} ions was distributed to the skeletal muscle of the body. This distribution of the rubidium ion was reported in several species of animals (Sheldon and Ramage, 1931; Freedberg et al., 1952; Zipser and Freedberg, 1952; Love et al., 1954). In general, the distribution of rubidium, cesium, and potassium was similar, as all three ions were found in relatively high concentrations in erythrocytes, skin, muscle, and visceral organs, and in low concentrations in bone and plasma. On the first day after administration (Tables 2 and 3) the distribution of cesium and rubidium

was similar; however, a greater percentage of the cesium burden was found in the muscle mass at subsequent times. Apparently the small amount of rubidium in bone (Table 2) was not tenaciously bound because it remained constant, relative to the whole-body burden, over the 20 day period. Hamilton (1948b) reported that about 15 per cent of a dose of Rb^{86} was located in the bone mass and 41 per cent in the muscle mass 4 days after oral administration.

The similarity in the relative distribution of rubidium and potassium suggested to some workers the possibility of using radiorubidium to trace potassium metabolism. Several investigations, however, showed that despite the apparent similarities of these ions in erythrocyte metabolism, there was always a proportionately slower excretion of rubidium (Kilpatrick et al., 1956; Tyor and Eldridge, 1956; Love and Burch, 1953). Although the ions behaved similarly in some respects, each had its characteristic physiological behavior.

The retention curves for Rb^{86} in five species of animals (Fig. 29) were composed of one or two exponential components. Except for the dog and monkey, only oral data were plotted. The retention process in the mouse, monkey, and dog was expressed by one exponential; two rates were necessary to explain the loss from the rat and man. Subsequent studies showed that a single exponential rate described the loss of

Rb^{86} from the dog and monkey after oral administration. Apparently the turnover rates for the Rb^{86} -containing tissues of the dog and monkey were sufficiently similar to be measured as one rate by the whole-body counting method. In the composite processes, the contribution of the faster-moving component was very small with respect to the second component (Table 8). It accounted for less than 1 per cent of the total disintegrations in humans. From the standpoint of dosage calculations, the slow-moving component ($T_{1/2} = 98.5$ days) was the more important.

Few data concerning the $BT_{1/2}$ of rubidium in animals were available. Burch et al. (1955) reported that one-half of an intravenous dose of Rb^{86} was lost via the urine and feces of three people in 39 to 134 days. Despite the large range and small number of subjects, the mean time was surprisingly close to the average time of 80 days found in this study. Handbook No. 52 (National Bureau of Standards, 1953) gave a $BT_{1/2}$ of 13 days for Rb^{86} . This value was originally obtained from small animal data (Hamilton, 1948b).

4.6 Cesium Metabolism

The similarity of the excretory patterns after intravenous and oral administration of Cs^{134} to rats and mice verified the works of others (Hamilton, 1947; Weeks and

THE UNIVERSITY OF CHICAGO LIBRARY

 

CHICAGO LIBRARY

Oakley, 1954) who reported the complete gastrointestinal absorption of this ion. Retention and excretion data indicated that this was also true for the monkey, dog, and man.

The cesium ion, which has an abundance in the earth of 1 part in 10^6 parts of potassium, was first detected in animals in mammalian retinal tissue (Scott and Canaga, 1939). Since then it has been detected in soils, plants, and animals (Bertrand and Bertrand, 1949a; 1949b; 1949c). Its presence in animals at average concentrations of 3×10^{-3} per cent of dry tissue indicated that, relative to potassium, cesium was more abundant in living organisms than in the external environment (Relman, 1956).

Tissue studies indicated that Cs^{134} was mainly concentrated in the muscle mass of the rat, although it was distributed throughout all tissues, including bone. The radio-cesium content of the skeleton was very small, when expressed as per cent of the body burden, per gram of bone. Because the blood concentration was very low, the tissues accumulated cesium against a concentration gradient. Other investigators reported that the muscle mass was the largest storehouse for radiocesium (Hamilton, 1947; Hood and Comar, 1953a; Ballou and Thompson, 1957). Hamilton (1947) found that cesium distribution was similar after oral and intraperitoneal

administration.

The urinary and fecal excretion data obtained after oral administration of Cs^{134} to rats (Figs. 23 and 24) were similar to those reported by other workers (Scott et al., 1947; Hood and Comar, 1953a; Weeks and Oakley, 1954). Three-foot, Burch, and Ray (1955) found that one-half of an intravenously administered dose of Cs^{134} was lost in 17 to 39 days via the urine and feces of mongrel dogs. The mean value was in accord with the $\text{BT}_{1/2}$ of 25 days for dogs shown in Fig. 26.

The family of curves plotted in Fig. 30 shows the retention patterns of radiocesium in the mouse, rat, and man after oral administration and in the dog and monkey following intravenous injection. The expected third component for man was not apparent at the time of writing. These data showed that the time required to excrete one-half the initial activity did not give a good indication of the retention pattern. Since the human retention curve was composed of two components, the $\text{BT}_{1/2}$ value of 110 days was somewhat low with respect to dosage calculations. The slower-moving component had a half-time of 143 days and represented more than 99 per cent of the total disintegration (Table 8). Anderson et al. (1957) gave an estimate of 145 days for the $\text{BT}_{1/2}$ of Cs^{137} in chronically exposed

individuals. Ninety per cent or more of the total disintegrations that occurred in all species given radiocesium was contributed by components B and C (Table 8).

It is difficult to explain the fractionation of the radiocesium pool in terms of its distribution in the tissues. Perhaps the sum of several or all of the fractions represented cesium bound in soft tissues (mainly skeletal muscle) by more than one mechanism. Thus, each of the tissues would lose cesium at several different rates. Ballou and Thompson (1957) reported that 90 per cent of a Cs^{137} burden was in the muscle of rats 30 days after administration. The retention of cesium in muscle over a 200 day period was best described as the sum of two components with half-times of 8 and 16 days; this was closely approximated by a single exponential function with a half-time of 13 days. Most of the tissues showed similar components plus a very-short-lived one. The half-times of the three components which described the retention of Cs^{134} in rats in the present study were roughly 1, 7, and 14 days (Figs. 23 and 24). In addition, it was suggested (University of Tennessee, 1955) that cesium was bound in different ways by tissues such as muscle, liver, and kidney; one portion was not readily replaceable and was not changed by altering the potassium content of the diet.

Alternatively, the components of the cesium retention

curves may represent the exchange of radiocesium with stable cesium, or a similar element such as potassium, in three separate areas at three different rates.

If muscle is assumed to be the critical tissue, then the maximum permissible concentration of Cs^{137} in water, $(\text{MPC})_w$ can be calculated on the basis of an allowable dose of 300 mrem per week to this tissue. The usual calculation of an $(\text{MPC})_w$ employs the following equation (International Commission on Radiological Protection, 1955):

$$(\text{MPC})_w = \frac{(3.1 \times 10^{-4})(qf_2)}{(Tf_w)(1 - e^{-0.693 t/T})}$$

in which qf_2 is the permissible organ burden, T is the effective half-life (days) of the radionuclide in the critical organ, f_w is the fraction of the ingested radionuclide deposited in the critical organ, and t is the exposure time (days) which is taken as 25,000 days (70 years) for the life span of man. The rate of water consumption is taken as 2200 ml per day.

The presently recommended value for the $(\text{MPC})_w$ of Cs^{137} is $2 \times 10^{-3} \mu\text{c/ml}$ (International Commission on Radiological Protection, 1955). This value was obtained by using 17 and 0.48 for T and f_w , respectively, in the above equation; the T and f_w values were obtained from experiments done with

rats (Hamilton, 1948). On substitution of the effective half-time calculated from experimental data obtained from humans, the $(MPC)_w$ became $2 \times 10^{-4} \mu\text{c/ml}$. If, in addition, the value of f_w was changed to 0.80, the $(MPC)_w$ became 1.2×10^{-4} . Thus the $(MPC)_w$ requires reduction from the presently recommended value by a factor of 9 to 15, depending on the fraction of the Cs^{137} deposited in muscle. In all the above cases, a qf_2 value of 44.2 was used (International Commission on Radiological Protection, 1955).

Cesium-137 is a fission product of particular concern because of its long physical half-life, its high fission yield, and its reported presence in man and foodstuffs (Sievert et al., 1956; Booker, 1957; Anderson et al., 1957) as a result of world-wide contamination from nuclear weapons testing. It represents 18 per cent of the total fission product disintegrations 10 years after instantaneous fission (Hunter and Ballou, 1951).

Hood and Comar (1953b) calculated that 1 liter of milk produced 1 day after a cow was exposed to 20 mc of Cs^{137} would contain 80 per cent of the permissible human body burden; a pound of meat from the same cow killed 1 week after exposure would contain 30 per cent of the permissible body burden for humans. When one considers the complete assimilation and comparatively long retention of Cs^{137} by human beings,

it becomes apparent that large sources of food could be rendered unfit for human consumption as the result of an exposure to Cs^{137} .

4.7 Interspecies Correlations

The consistent increase in the $\text{BT}_{1/2}$ values in the retention curves for sodium, rubidium, and cesium in the mouse, rat, dog, monkey, and man (Figs. 28-30) suggested a relationship between $\text{BT}_{1/2}$ and species weight or $\text{BT}_{1/2}$ and body surface area. Plots of $\text{BT}_{1/2}$ as a function of the log of body weight were nonlinear and indicated a possible log-log relationship. Linear relationships were found when the logs of the $\text{BT}_{1/2}$ values were plotted against the logs of either gross body weight or body surface.

The lines of regression for $\text{BT}_{1/2}$ versus body surface (Fig. 31) were best represented by an equation of the type

$$\log y = k + b \log x$$

where y is the $\text{BT}_{1/2}$ in days, x is the body surface area in square meters, and k and b are the intercept and slope constants, respectively. $\text{BT}_{1/2}$ values taken from Handbook No. 52 (National Bureau of Standards, 1953) are shown for comparison. The regression equations, which were calculated by the method of least squares, were

$$\log y = 1.013 + 0.375 \log x \text{ (sodium)}$$

$$\log y = 1.570 + 0.498 \log x \text{ (rubidium)}$$

$$\log y = 1.729 + 0.767 \log x \text{ (cesium)}$$

Although species variations (i.e., high fecal excretion of Rb^{86} by monkeys and virtually no fecal excretion of Na^{22} by human subjects) were observed in this study, a first approximation for an interspecies correlation appeared to be justified from Fig. 31. Experiments in which Na^{22} , Rb^{86} , and Cs^{134} were given to dogs indicated that the $\text{BT}_{1/2}$ measured values were the same after oral or intravenous administration. Results of similar experiments in monkeys were inconclusive because the animals were immature and in a constantly changing metabolic state.

When the dog and monkey data were omitted from Fig. 31 and the regression equations recalculated for the mouse, rat, and man, the following equations were obtained:

$$\log y = 0.954 + 0.350 \log x \text{ (sodium)}$$

$$\log y = 1.755 + 0.575 \log x \text{ (rubidium)}$$

$$\log y = 1.864 + 0.825 \log x \text{ (cesium)}$$

The $\text{BT}_{1/2}$ values calculated from these sodium and rubidium

regression equations showed excellent agreement with the measured values. Values of 1.4, 4.8, and 118.0 days calculated for the mouse, rat, and man from the cesium regression equation compared reasonably well with measured values of 1.2, 6.5, and 110.0 days.

Stannard and Smith (1957) showed that the mouse, rat, and man were similar with respect to Po^{210} metabolism, whereas the dog was different. It is possible that similar species relationships occurred in the metabolism of radiorubidium and radiocesium in the present study; however, because some dietary factors other than the intake of the element being measured were shown to have varying effects on the retention of some radionuclides, one might expect variations such as those in Fig. 31 (Mraz and Patrick, 1957; Mraz et al., 1957). In addition, the time necessary for the initial body burden of a material to drop by a factor of 2 is not usually the same as the times required for the burden to drop by subsequent factors of 2.

It should be emphasized that the regression equations represent only a first approximation for an interspecies relationship among the animals used in this study. The relationship does not hold for ruminants, such as sheep and cattle, that excrete large amounts of Cs^{137} in the feces.

CHAPTER 5

SUMMARY AND CONCLUSIONS

Large-volume liquid-scintillation counters were used to measure the biological half-time ($BT_{1/2}$), whole-body retention, and excretion of Na^{22} , K^{42} , Rb^{86} , Cs^{134} , and Cs^{137} in five species of animals. Mice, rats, monkeys, dogs, and men were given 0.1 to 1.0 μc amounts of the radionuclides by oral, intraperitoneal, or intravenous administration. Radioactivity in the excreta was measured at subsequent 24 hour intervals, and the whole-body retention was followed by in vivo radioassay, where possible, until the retained body burden fell to 1.0 to 0.1 per cent of the administered dose.

The logarithms of the retention and excretion levels were plotted as functions of time after administration, and standard first-order kinetics were applied to determine the $BT_{1/2}$ values and retention equations. The $BT_{1/2}$, as used in this report, is the time required for the whole-body

activity to decrease by a factor of 2 owing to biological loss.

Tissue distribution of the radionuclides at various times after administration was studied in rats to help interpret the retention data.

From these studies, it may be concluded that:

(a) The whole-body retention curves for the radionuclides investigated were best fitted by a single or multiple-component exponential function of the form

$$R = a_1 e^{-k_1 t} + a_2 e^{-k_2 t} + \dots a_n e^{-k_n t}$$

where R is the whole-body retention at time t ; $a_1, a_2, \dots a_n$ and $k_1, k_2, \dots k_n$ are the intercept and rate constants, respectively.

(b) The fractions of the total disintegrations attributable to each component of the retention curve were proportional to a_n/k_n .

(c) Some variation among species occurred both in the major route of excretion and in the relative amounts lost by the different routes of excretion for a given radionuclide.

(d) The $BT_{1/2}$ values for radiorubidium and radiocesium in man are greater by a factor of 6 than those presently recommended by National and International Commissions on Radiological Protection.

(e) The maximum permissible concentration of Cs^{137} in water, as calculated from human retention data, was lower by a factor of 10 than presently recommended values.

(f) The relationship

$$\text{BT}_{1/2} = k(\text{SA})^b$$

where $\text{BT}_{1/2}$ is equal to the product of a constant and the surface area raised to a constant power, serves as a first approximation for an interspecies correlation for alkali-metal retention in the mouse, rat, monkey, dog, and man.

BIBLIOGRAPHY

1. Anderson, E. C., R. L. Schuch, W. R. Fisher, and W. H. Langham, 1957. Radioactivity of People and Foods. *Science*, 125(3261):1273-1278.
2. Anderson, E. C., R. L. Schuch, J. D. Perrings, and W. H. Langham, 1956. The Los Alamos Human Counter. *Nucleonics*, 14(1):26-29.
3. Arnott, D. G., and P. Fossey, 1952. Equipment for Studying the Distribution of Gamma-Active Radioisotopes in Small Animals. *J. Physiol.*, London, 118:18p-19p.
4. Arons, W. L., R. J. Vanderlinde, and A. K. Solomon, 1954. II. The Simultaneous Measurement of Exchangeable Body Sodium and Potassium Utilizing Ion Exchange Chromatography. *J. Clin. Invest.*, 33(7):1001-1007.
- . Ballou, J. E., and R. C. Thompson, 1957. The Long Term Retention of Cesium in the Rat following a Single Intraperitoneal Injection. Hanford Works Report HW-46150.

6. Baumann, E. J., N. Z. Searle, A. A. Yallow, E. Siegel, and S. M. Seidlin, 1956. Behavior of the Thyroid towards Elements of the Seventh Periodic Group. *Am. J. Physiol.*, 185(1):71-76.
7. Bergström, W. H., 1955. The Participation of Bone in Total Body Sodium Metabolism in the Rat. *J. Clin. Invest.*, 34(7):997-1004.
8. Bertrand, G., and D. Bertrand, 1946. Normal Existence of Rubidium in Animals. *Ann. Inst. Pasteur*, 72:805-809.
9. Bertrand, G., and D. Bertrand, 1949a. The Presence of Cesium in Arable Soil. *Compt. rend.*, 229:533-535.
10. Bertrand, G., and D. Bertrand, 1949b. Normal Existence of Cesium in Plants. *Compt. rend.*, 229:453-455.
11. Bertrand, G., and D. Bertrand, 1949c. Normal Existence of Cesium in Animals. *Compt. rend.*, 229:609-610.
12. Booker, D. V., 1957. Radio-cesium in Dried Milk. *Phys. in Med. Biol.*, 2(1):29-35.
13. Bradley, J. E. S., N. Veall, and F. Whiting, 1956. Whole Body Radioactivity Measurements as Applied to Clinical Tracer Studies. *Phys. in Med. Biol.*, 1(2):147-152.
14. Burch, G. E., S. A. Threefoot, and C. T. Ray, 1955. The Rate of Disappearance of Rb^{86} from the Plasma, the Biological Decay Rates of Rb^{86} , and the Applicability of Rb^{86}

- as a Tracer of Potassium in Man with and without Congestive Heart Failure. *J. Lab. Clin. Med.*, 45(3):371-394.
15. Burch, G. E., S. A. Threefoot, and P. B. Reaser, 1948. Some Aspects of Renal Excretion of Na^{24} by Normal Subjects and by Patients with Congestive Heart Failure. *Stanford Med. Bull.*, 6:81-87.
16. Burch, P. R. J., and F. W. Spiers, 1953. Measurement of the Radiation from the Human Body. *Nature*, 172(4377):519-521.
17. Campbell, R. M., D. P. Cuthbertson, C. M. Matthews, and A. S. McFarlane, 1956. Behavior of C^{14} - and I^{131} -Labeled Plasma Proteins of the Rat. *Intern. J. Appl. Radiation and Isotopes*, 1(1):66-84.
18. Clark, A. J., 1922. Mode of Action of Potassium upon Isolated Organs. *J. Pharmacol. Exptl. Therap.*, 18:423-427.
19. Comar, C. L., and R. H. Wasserman, 1956. Radioisotopes in the Study of Mineral Metabolism. In Bugher et al., eds., *Progress in Nuclear Energy, Series VI, Biological Sciences*. Pergamon Press Ltd., London. 1:153-196.
20. Dobson, E. L., and G. F. Warner, 1957. Measurement of Regional Sodium Turnover Rates and their Application to the Estimation of Regional Blood Flow. *Am. J. Physiol.*, 189(2):269-276.

21. D'Silva, J. L., and M. W. Neil, 1951. The Fate of Radioactive KCl Administered Intraperitoneally or Intravenously to Rats. *Biochem. J.*, 49(2):222-226.
22. Edelman, I. S., A. H. James, A. H. Baden, and F. D. Moore, 1954. Electrolyte Composition of Bone and the Penetration of Radiosodium and Deuterium Oxide into Dog and Human Bone. *J. Clin. Invest.*, 33(2):122-131.
23. Elliott, L. G., and R. E. Bell, 1947. Disintegration Scheme of 1.7-Year Cs¹³⁴. *Phys. Rev.*, 72:979-980.
24. Emery, E. W., J. E. S. Bradley, and N. Veall, 1955. Radiation Dosimetry of Rubidium-86. *Nature*, 175(4444):34.
25. Erf, L. A., 1941. Retention of Radiophosphorus in Whole and Aliquot Portions of Tissues of Patient Dead of Leukemia. *Proc. Soc. Exptl. Biol. Med.*, 47(2):287-289.
26. Fenn, W. O., T. R. Noonan, L. J. Mullins, and L. Haege, 1941. The Exchange of Radioactive Potassium with Body Potassium. *Am. J. Physiol.*, 135(1):149-163.
27. Fink, R. M., ed., 1950. Biological Studies with Polonium, Radium, and Plutonium. National Nuclear Energy Series Div. VI, Vol. 3. New York, McGraw-Hill Book Company, Inc., xvi and 411 pp.
28. Follis, R. H., 1943. Histological Effects in Rats Resulting from Adding Rubidium or Cesium to a Diet Deficient in Potassium. *Am. J. Physiol.*, 138(2):246-250.

- Physiol., 124(3):667-678.
36. Hamilton, J. G., 1942. The Use of Radioactive Tracers in Biology and Medicine. Radiology, 39(5):541-572.
 37. Hamilton, J. G., 1943. Metabolism of the Fission Products. Atomic Energy Commission Report MDDC-1000.
 38. Hamilton, J. G., 1947. The Metabolism of the Fission Products and the Heaviest Elements. Radiology, 49(3):325-343.
 39. Hamilton, J. G., 1948a. The Metabolic Properties of the Fission Products and Actinide Elements. Rev. Mod. Phys., 20(4):718-728.
 40. Hamilton, J. G., 1948b. The Metabolic Properties of Plutonium and Allied Materials. Univ. of Calif. Radiation Laboratory Report UCRL-98.
 41. Hamilton, J. G., 1949. The Metabolism of the Radioactive Elements Created by Nuclear Fission. New Eng. J. Med., 240(22):863-870.
 42. Hamilton, J. G., and M. H. Soley, 1940. Studies in Iodine Metabolism of the Thyroid Gland in situ by the Use of Radio-iodine in Normal Subjects and in Patients with Various Types of Goiter. Am. J. Physiol., 131(1):135-143.

43. Hamilton, J. G., and R. S. Stone, 1937. Excretion of Radiosodium following Intravenous Administration in Man. *Proc. Soc. Exptl. Biol. Med.*, 35(4):595-598.
44. Harrison, H. E., D. C. Darrow, and H. Yannet, 1936. Total Electrolyte Content of Animals and Its Probable Relation to Distribution of Body Water. *J. Biol. Chem.*, 113(2):515-529.
45. Harrison, G. E., W. H. A. Raymond, and H. C. Tretheway, 1955. The Metabolism of Strontium in Man. *Clin. Sci.*, 14(4):681-695.
46. Hasterlick, R. J., R. Druyan, and D. L. Fink, 1956. Studies on the Gross Metabolism of Strontium-85 in Man. *J. Lab. Clin. Med.*, 48(5):815-816.
47. Hayes, F. N., 1956. Liquid Scintillators: Attributes and Applications. *Intern. J. Appl. Radiation and Isotopes*, 1(1):46-50.
48. Heppel, L. A., and C. L. A. Schmidt, 1938. Studies on the Potassium Metabolism during Pregnancy, Lactation, and Growth. *Univ. Calif. (Berkeley) Publ. Physiol.*, 8:189-205.
49. Hevesy, G., 1942. Potassium Interchange in the Human Body. *Acta Physiol. Scand.*, 3:123-131.
50. Hollander, J. M., I. Pearlberg, and G. T. Seaborg, 1953. Table of the Isotopes. *Rev. Mod. Phys.*, 25:469-651.

51. Hood, S. L., and C. L. Comar, 1953a. Metabolism of Cesium¹³⁷ in Rats and Farm Animals. Arch. Biochem. Biophys., 45:423-433.
52. Hood, S. L., and C. L. Comar, 1953b. Metabolism of Cs¹³⁷ in Laboratory and Domestic Animals. Univ. of Tenn. Report ORO-91.
53. Hunter, H. F., and N. E. Ballou, 1951. Fission Product Decay Rates. Nucleonics, 9(5):C2-C7.
54. International Commission on Radiological Protection, 1955. Report of International Subcommittee II on Permissible Dose for Internal Radiation. Brit. J. Radiol., Suppl. 6:23.
55. Joseph, M., W. E. Cohn, and D. M. Greenberg, 1939. Studies in Mineral Metabolism with the Aid of Artificial Radioactive Isotopes. II. Absorption, Distribution, and Excretion of Potassium. J. Biol. Chem., 128(3):673-683.
56. Kaltreider, N. L., G. R. Meneely, J. R. Allen, and W. F. Bale, 1941. Determination of the Volume of the Extracellular Fluid of the Body with Radioactive Sodium. J. Exptl. Med., 74(6):569-590.
57. Kamen, Martin D., 1951. Radioactive Tracers in Biology. New York, Academic Press, Inc. xiv and 429 pp.

58. Kilpatrick, R., H. E. Renschler, D. S. Munro, and G. M. Wilson, 1956. A Comparison of the Distribution of K^{42} and Rb^{86} in Rabbit and Man. *J. Physiol.*, 133(1):194-201.
59. Langham, W. H., 1956. Determination of Internally Deposited Radioactive Isotopes from Excretion Analyses. *Am. Ind. Hyg. Assoc. Quart.*, 17(3):305-318.
60. Langham, W. H., 1957. Excretion Methods: The Application of Excretion Analyses to the Determination of Body Burden of Radioactive Isotopes. *Brit. J. Radiol.*, Suppl. 7:95-113.
61. Langham, W. H., S. H. Bassett, P. S. Harris, and R. E. Carter, 1950. Distribution and Excretion of Plutonium Administered Intravenously to Man. Los Alamos Scientific Laboratory Report LA-1151.
62. Laslett, L. J., 1937. A Long-Period Positron Activity: Na^{22} . *Phys. Rev.*, 52:529-530.
63. Lawrence, J. H., K. G. Scott, and L. W. Tuttle, 1939. Studies on Leukemia with the Aid of Radioactive Phosphorus. *New Intern. Clin.*, 3:33-58.
64. Levitt, M. F., and M. Gaudino, 1949. Use of Radioactive Isotopes to Measure Intracellular Cation Concentrations in the Normal Dog. *Am. J. Physiol.*, 159(1):67-72.

65. Loeb, R. F., 1921. Radioactivity and Physical Action of Potassium. *J. Gen. Physiol.*, 3(2):229-236.
66. Loevinger, R., and Mones Berman, 1951. Efficiency Criteria in Radioactivity Counting. *Nucleonics*, 9(1):26-39.
67. Love, W. D., and G. E. Burch, 1953. A Comparison of K^{42} , Rb^{86} , and Cs^{134} as Tracers of K in the Study of Cation Metabolism of Human Erythrocytes in vitro. *J. Lab. Clin. Med.*, 41(3):351-362.
68. Love, W. D., R. B. Romney, and G. E. Burch, 1954. A Comparison of the Distribution of Potassium and Exchangeable Rubidium in the Organs of the Dog, Using Rb^{86} . *Circulation Research*, 2(2):112-122.
69. MacLeod, R. A., and E. E. Snell, 1948. The Effect of Related Ions on the Potassium Requirement of Lactic Acid Bacteria. *J. Biol. Chem.*, 176(1):39-52.
70. Mannery, Jeanne, and W. F. Bale, 1941. The Penetration of Radioactive Sodium and Phosphorus into the Extra- and Intra-Cellular Phases of Tissue. *Am. J. Physiol.*, 132(1):215-231.
71. Martin, M. M., and G. Walker, 1957. Studies with Na^{22} . An Assessment of Sodium Balance and Distribution. *Metabolism, Clin. and Exptl.*, 6(5):466-478.

72. Martin, M. M., G. Walker, and M. Chapman, 1957. Sodium Balance Studied with Na^{22} and an External Counter for Measuring Whole-Body Radioactivity. *Lancet*, 272(6970):653-656.
73. Mehl, H. G., 1956. The Use of Bremsstrahlung for Investigating the Distribution of Pure Beta Sources in the Human Body. *Naturwissenschaften*, 43:310-311.
74. Miller, C. E., and L. D. Marinelli, 1956. Gamma-Ray Activity of Contemporary Man. *Science*, 124(3212):122-123.
75. Miller, H., and G. M. Wilson, 1953. The Measurement of Exchangeable Sodium in Man Using the Isotope Na^{24} . *Clin. Sci.*, 12(2):97-111.
76. Moore, F. D., J. D. McMurrey, H. V. Parker, and I. C. Magnus, 1956. Body Composition. Total Body Water and Electrolytes: Intravascular and Extravascular Phase Volumes. *Metabolism, Clin. and Exptl.*, 5(4):447-467.
77. Mraz, F. R., M. LeNoir, J. J. Pinajian, and H. Patrick, 1957. Influence of Potassium and Sodium on Uptake and Retention of Cesium-134 in Rats. *Arch. Biochem. Biophys.*, 66(1):177-182.
78. Mraz, F. R., and H. Patrick, 1957. Factors Influencing Excretory Patterns of Cesium-134, Potassium-42, and Rubidium-86 in Rats. *Proc. Soc. Exptl. Biol. Med.*,

- 94(2):409-412.
79. National Bureau of Standards Handbook No. 52, 1953. Maximum Permissible Amounts of Radioisotopes in the Human Body and Maximum Permissible Concentrations in Air and Water. U. S. Department of Commerce, Washington, D. C.
80. Noonan, T. R., W. O. Fenn, and L. Haege, 1941. The Distribution of Injected Radioactive Potassium in Rats. *Am. J. Physiol.*, 132(2):474-488.
81. Norris, W. R., T. W. Speckman, and P. F. Gustafson, 1955. Studies on the Metabolism of Radium in Man. *Am. J. Roentgenol.*, 73(5):785-802.
82. Pinson, E. A., 1951. The Body Absorption, Distribution, and Excretion of Tritium in Man and Animals. Los Alamos Scientific Laboratory Report LA-1218.
83. Pommerenke, W. T., and P. F. Hahn, 1953. Secretion of Radioactive Sodium in Human Milk. *Proc. Soc. Exptl. Biol. Med.*, 52(3):223-224.
84. Ray, C. T., G. E. Burch, and S. A. Threefoot, 1952. Biologic Decay Rates of Chloride in Normal and Diseased Man Determined with Long-Life Radiochloride, Cl^{36} . *J. Lab. Clin. Med.*, 39(5):673-696.
85. Ray, C. T., S. A. Threefoot, and G. E. Burch, 1954. Studies on the Excretion of Chloride by Man with and

- without Congestive Heart Failure, Using Long-Life Radiochloride, Cl^{36} . J. Lab. Clin. Med., 44(5):663-701.
86. Ray, C. T., S. A. Threefoot, and G. E. Burch, 1955. The Excretion of Radiorubidium, Rb^{86} , Radiopotassium, K^{42} , and Potassium, Sodium, and Chloride by Man with and without Congestive Heart Failure. J. Lab. Clin. Med., 45(3):408-430.
87. Reines, F., R. L. Schuch, C. L. Cowan, F. B. Harrison, E. C. Anderson, and F. N. Hayes, 1953. Determination of Total Body Radioactivity Using Liquid Scintillation Detectors. Nature, 172(4377):521-523.
88. Relman, A. S., 1956. The Physiological Behavior of Rubidium and Cesium in Relation to that of Potassium. Yale J. Biol. and Med., 29(3):248-262.
89. Relman, A. S., A. T. Lambie, B. A. Burrows, and A. M. Roy, 1957. Cation Accumulation by Muscle Tissue: The Displacement of Potassium by Rubidium and Cesium in the Living Animal. J. Clin. Invest., 36(8):1249-1256.
90. Ringer, S., 1882. An Investigation Regarding the Action of Rubidium and Cesium Salts Compared with the Action of Potassium Salts on the Ventricles of the Frog's Heart. J. Physiol., London, 4:370-379.
91. Rosenthal, H. L., 1956. Uptake and Turnover of Calcium-45 by the Guppy. Science, 124(3222):571-574.

92. Rundo, J., 1955. An Apparatus for the Measurement of Gamma-Radiation from the Human Body. *J. Sci. Instr.*, 32:379-384.
93. Sagild, U., 1956. Total Exchangeable Potassium in Normal Subjects with Special Reference to Changes with Age. *Scand. J. Clin. & Lab. Invest.*, 8(1):44-50.
94. Scott, G. H., and B. L. Canaga, 1939. Cesium in the Mammalian Retina. *Proc. Soc. Exptl. Biol. Med.*, 40(2):275-276.
95. Scott, K. G., R. Overstreet, L. Jacobson, J. G. Hamilton, J. Crowley, I. L. Chaikoff, C. Entenman, M. Fishler, A. J. Barber, and F. Loomis, 1947. The Metabolism of Carrier-Free Fission Products in the Rat. Atomic Energy Commission Report MDCC-1275
96. Sheldon, J. H., and H. Ramage, 1931. A Spectrographic Analysis of Human Tissues. *Biochem. J.*, 25(2):1608-1627.
97. Sheline, G. E., I. L. Chaikoff, H. B. Jones, and M. L. Montgomery, 1943. Studies on the Metabolism of Zinc with the Aid of its Radioactive Isotope. II. The Distribution of Administered Radioactive Zinc in the Tissues of Mice and Dogs. *J. Biol. Chem.*, 149(1):139-151.
98. Sievert, R. M., 1956. Investigations of the Gamma-Ray Activities of the Human Body. *Strahlentherapie*,

- 99(2):185-195.
99. Sievert, R. M., S. Gustafsson, and C. G. Rylander, 1956. Increase in Gamma-Radiation from Powdered Milk and Beef, 1953-1956. *Nature*, 178(4538):854-855.
 100. Shohl, A. T., 1939. Mineral Metabolism. New York, Reinhold Publishing Corporation. x and 384 pp.
 101. Solomon, A. K., 1949. Equations for Tracer Experiments. *J. Clin. Invest.*, 28(6):1297-1307.
 102. Spencer, H., M. Brothers, E. Berger, H. E. Hart, and D. Laszlo, 1956. Sr^{85} Metabolism in Man and Effect of Calcium on Strontium Retention. *Proc. Soc. Exptl. Biol. Med.*, 91(1):155-157.
 103. Stannard, J. N., and F. A. Smith, 1957. Species Differences in the Metabolism of Po^{210} . Univ. of Rochester Report UR-487.
 104. Stern, T. N., V. V. Cole, A. C. Bass, and R. R. Overman, 1951. Dynamic Aspects of Sodium Metabolism in Experimental Adrenal Insufficiency using Radioactive Sodium. *Am. J. Physiol.*, 164(2):437-449.
 105. Sullivan, W. H., 1957. Oak Ridge National Laboratory. Trilinear Chart of the Nuclides. U. S. Govt. Printing Office, Washington 25, D. C.
 106. Suttle, A. D., and W. F. Libby, 1955. Absolute Assay of Beta Radioactivity in Thick Solids. Application to

- Naturally Radioactive Potassium. Anal. Chem., 27(6):921-927.
107. Threefoot, S. A., G. E. Burch, and C. T. Ray, 1954. Studies of Excretion of Radiorubidium (Rb^{86}) and Potassium in Man with and without Congestive Heart Failure. J. Lab. Clin. Med., 44(6):941.
108. Threefoot, S. A., G. E. Burch, and C. T. Ray, 1955. The Biologic Decay Rates and Excretion of Radiocesium, Cs^{134} , with Evaluation as a Tracer of Potassium in Dogs. J. Lab. Clin. Med., 45(2):313-322.
109. Threefoot, S. A., G. E. Burch, and Paul Reaser, 1949. The Biologic Decay Periods of Sodium in Normal Man, in Patients with Congestive Heart Failure, and in Patients with the Nephrotic Syndrome. J. Lab. Clin. Med., 34(1):1-13.
110. Threefoot, S. A., C. T. Ray, and G. E. Burch, 1955. Study of the Use of Rb^{86} as a Tracer for the Measurement of Rb^{86} and K^{39} Space and Mass in Intact Man with and without Congestive Heart Failure. J. Lab. Clin. Med., 45(8):395-407.
111. Tyor, M. P., and J. S. Eldridge, 1956. A Comparison of the Metabolism of Rubidium-86 and Potassium-42 following Simultaneous Injection into Man. Am. J. Med. Sci., 232(2):186-193.

112. University of Tennessee, 1955. Agricultural Research Program (U. S. A. E. C.) Semi-Annual Progress Report ORO-145.
113. Van Dilla, M. A., R. L. Schuch, and E. C. Anderson, 1954. K-9: A Large 4π Gamma-Ray Detector. *Nucleonics*, 12(9):22-27.
114. Veall, N., 1955. Isotopes in Body Electrolyte Measurements. *Rec. trav. chim.*, 74:314-321.
115. Veall, N., H. J. Fisher, and J. E. S. Bradley, 1955. An Improved Method for Clinical Studies of Total Exchangeable Sodium. *Lancet*, 268(6861):419-422.
116. Vinogradov, A. P., and V. V. Kovalevskii, 1957. Biological Effects of K-40 Radioactivity on Animals. *Trans. Nuclear Science Abstracts. Doklady Akad. Nauk, S. S. S. R.*, 113:315-318.
117. Weeks, M. H., and W. D. Oakley, 1954. Gastro-intestinal Absorption, Distribution, and Retention of Cesium Fed Chronically in Various Forms to Rats. Hanford Works Report HW-35917.
118. White, H. I., and D. Rolf, 1954. Tissue Electrolytes in Normal and Adrenalectomized Rats. *Federation Proc.*, 13(1):164.
119. Wiles, D. M., and R. H. Tomlinson, 1955. Half-Life of Cesium-137. *Phys. Rev.*, 99:188.

120. Woodward, K. T., C. R. Richmond, and W. H. Langham, 1956. Measurement of Retention and Excretion of Radioisotopes of the Alkali Metals by Mice and Rats, Using an Annular Liquid Scintillation Counter. Proc. Health Physics Society meeting held at Ann Arbor, Michigan, 1:79-88.
121. Woodward, K. T., T. T. Trujillo, R. L. Schuch, and E. C. Anderson, 1956. Correlation of Total Body Potassium with Body-Water. Nature, 178(4524):97-98.
122. Zilversmit, D. B., C. Entenman, and M. C. Fishler, 1943. On the Calculation of "Turnover Time" and "Turnover Rate" from Experiments Involving the Use of Labeling Agents. J. Gen. Physiol., 26(3):325-331.
123. Zilversmit, D. B., C. Entenman, M. C. Fishler, and I. L. Chaikoff, 1943. The Turnover Rate of Phospholipids in the Plasma of the Dog as Measured with Radioactive Phosphorus. J. Gen. Physiol., 26(3):333-340.
124. Zipser, A., and A. S. Freedberg, 1952. The Distribution of Administered Radioactive Rubidium (Rb^{86}) in Normal and Neoplastic Tissues of Mice and Humans. Cancer Research, 12(12):867-870.
125. Zipser, A., H. B. Pinto, and A. S. Freedberg, 1953. Distribution and Turnover of Administered Rubidium (Rb^{86}) Carbonate in Blood and Urine of Man. J. Appl. Physiol., 5(7):317-322.

126. Zwaademaker, H., 1918. Importance of Radioactivity in Animal Life. Geneesk. Blader, 20:253-302.
127. Zwaademaker, H., 1920a. Physiological Radioactivity. J. Physiol., 53:273-289.
128. Zwaademaker, H., 1920b. Radioactivity and Life. Arch. Néerl. Physiol., 4:177-196.

TABLE 1. DISTRIBUTION OF Na²² IN THE RAT AFTER INTRAPERITONEAL ADMINISTRATION

Tissue	Per cent of whole-body burden at time of sacrifice					
	Day 1		Day 5		Day 12	
	$\bar{x}$	$\pm \sigma$	$\bar{x}$	$\pm \sigma$	$\bar{x}$	$\pm \sigma$
Muscle (2)	30.31	1.38	29.71	1.77	32.44	3.82
Bone (3)	16.70	0.62	17.80	1.58	21.15	1.70
Skin	20.00	0.52	25.30	0.88	20.26	0.34
G. I. Tract	10.40	0.50	10.60	1.02	9.53	0.60
Liver	2.11	0.24	1.91	0.84	1.82	0.84
Heart	0.13	0.12	0.20	0.07	0.15	0.06
Lungs	0.59	0.14	0.48	0.48	0.60	0.12
Spleen	0.15	0.06	0.13	0.06	0.12	0.08
Kidneys	0.81	0.22	0.89	0.08	0.67	0.02
Testes	1.27	0.08	1.21	0.10	0.93	0.07
Brain	0.71	0.05	0.61	0.05	0.54	0.07
Plasma	10.53	0.12	9.48	0.90	9.56	0.28
Erythrocytes (4)	0.35	----	0.85	0.66	-----	----

(1) $\bar{x} = \frac{\sum x}{n}$ and $\sigma = \sqrt{\frac{\sum x^2 - \frac{(\sum x)^2}{n}}{n-1}}$.

(2) 45 per cent of body weight.

(3) 8 per cent of body weight.

(4) Total blood volume assumed to be 6 per cent of body weight.

TABLE 3. DISTRIBUTION OF Cs¹³⁴ IN THE RAT AFTER INTRAPERITONEAL ADMINISTRATION

Tissue	Per cent of whole-body burden at time of sacrifice					
	Day 1	Day 5	Day 12	Day 20		
	$\bar{x} \pm \sigma$ (1)	$\bar{x} \pm \sigma$	$\bar{x} \pm \sigma$	$\bar{x} \pm \sigma$	$\bar{x} \pm \sigma$	
Muscle (2)	64.32 0.96	80.65 2.72	79.92 3.76	80.39 1.23		
Bone (3)	4.16 0.16	1.83 0.18	1.75 0.14	1.16 0.22		
Skin	9.74 1.02	5.54 0.16	4.85 0.52	5.02 0.50		
G. I. Tract	10.61 0.28	3.90 0.22	2.89 0.46	2.71 0.22		
Liver	9.36 0.20	3.22 0.42	2.40 0.33	2.08 0.13		
Heart	0.52 0.04	0.18 0.08	0.17 0.14	0.16 0.14		
Lungs	0.64 0.04	0.20 0.06	0.22 0.08	0.18 0.12		
Spleen	0.35 0.06	0.18 0.06	0.12 0.04	0.09 0.12		
Kidneys	1.72 0.11	0.68 0.06	0.54 0.06	0.49 0.04		
Testes	0.96 0.05	0.89 0.06	0.86 0.14	0.71 0.62		
Brain	0.20 0.02	0.19 0.04	0.24 0.04	0.18 0.02		
Plasma (4)	1.26 0.12	0.02 0.12	0.02 0.34	-----		
Erythrocytes (4)	0.67 0.12	0.40 0.06	0.74 0.20	0.26 0.12		

(1) $\bar{x} = \frac{\sum x}{n}$ and $\sigma = \sqrt{\frac{\sum x^2 - \frac{(\sum x)^2}{n}}{n-1}}$.

(2) 45 per cent of body weight.

(3) 8 per cent of body weight.

(4) Total blood volume assumed to be 6 per cent of body weight.

TABLE 5. POTASSIUM CONTENT AND K⁴⁰ GAMMA-RAY ACTIVITY OF ADULT BEAGLE HOUNDS

Body weight (kg)	Sex	K ⁴⁰ activity (dps/kg)	Body potassium (meq/kg)
15.6	Male	6.20	53.48
8.8	Male	6.97	60.12
11.8	Male	6.93	59.74
15.3	Male	6.29	54.24
12.5	Male	7.74	66.76
14.8	Male	8.09	69.79
13.5	Male	7.57	65.24
13.8	Male	7.74	66.76
12.9	Male	6.42	55.38
10.9	Male	7.43	64.10
11.6	Male	6.71	57.84
10.2	Male	7.06	60.88
11.6	Male	8.16	70.36
10.6	Male	7.08	61.07
10.5	Male	7.26	62.58
		$\bar{x} = 7.176$	$\bar{x} = 61.89$
		$\sigma^{(1)} = 0.616$	$\sigma = 5.32$
13.8	Female	7.10	61.26
9.7	Female	8.12	69.98
10.9	Female	6.11	52.72
11.8	Female	7.10	61.26
12.4	Female	6.99	60.31
12.4	Female	7.35	63.34
9.5	Female	7.17	61.82
10.9	Female	7.02	60.50
10.2	Female	6.84	59.98
		$\bar{x} = 7.089$	$\bar{x} = 61.13$
		$\sigma^{(1)} = 0.525$	$\sigma = 4.47$
Both		$\bar{x} = 7.144$	$\bar{x} = 61.60$
		$\sigma = 0.573$	$\sigma = 5.67$

$$(1) \quad \sigma = \sqrt{\frac{\sum x^2 - \sum x(\bar{x})}{n-1}}$$

TABLE 6. POTASSIUM CONTENT AND K⁴⁰ GAMMA-RAY ACTIVITY
OF ADULT MALE RHESUS MONKEYS

Body weight (kg)	K ⁴⁰ activity (dps/kg)	Body potassium (meq/kg)
4.32	8.45	72.82
3.75	6.86	59.17
4.09	9.52	82.12
4.43	10.76	92.74
4.09	9.08	78.32
4.20	12.74	109.81
4.09	5.76	49.69
5.68	10.32	88.95
7.27	7.94	68.46
10.45	8.18	70.55
9.32	8.16	70.36
8.86	9.88	85.15
7.27	9.17	79.08
7.16	9.17	79.08
7.61	7.96	68.65
7.84	10.65	91.79
9.20	6.25	53.86
6.93	9.26	79.84
9.32	9.06	78.14
7.27	9.57	82.50
7.27	9.19	79.27
$\bar{x} =$		$\bar{x} =$
8.95		77.16
$\sigma^{(1)} =$		$\sigma =$
1.58		13.56

$$(1) \quad \sigma = \sqrt{\frac{\sum x^2 - \sum x(\bar{x})}{n-1}}.$$

TABLE 7. POTASSIUM CONTENT OF VARIOUS SPECIES
OF LABORATORY ANIMALS

Species	Potassium content (meq/kg body weight)	Reference
Mouse	74.5	
Rat	82.4	
	74.4	118
	66.4	80
	62.5	48
Rabbit	56.9	
	82.9	26
Monkey	77.1	
	65.5	44
Dog	61.9	
	52.6	44
Man	49.0	1
	54.0	30
	48.0	30
	55.0	100
	47.0	76
	46.0	30

TABLE 8. FRACTIONS OF TOTAL DISINTEGRATIONS IN THE BODY REPRESENTED BY THE COMPONENTS OF THE RETENTION CURVES FOR THE ALKALI-METAL RADIONUCLIDES

Species	Route	Na ²²			K ⁴²		Rb ⁸⁶		Cs ¹³⁴ - Cs ¹³⁷		
		Component			Component		Component		Component		
		A	B	C	A	B	A	B	A	B	C
Mouse	Oral	0.69	0.21	0.10	0.02	0.98	1.00	-----	0.11	0.41	0.47
Mouse	I.P.	0.68	0.22	0.10	1.00	-----	0.13	0.87	0.06	0.41	0.53
Rat	Oral	0.52	0.22	0.26	0.02	0.98	0.07	0.93	0.02	0.32	0.66
Rat	I.P.	0.28	0.45	0.27	1.00	-----	0.05	0.95	0.04	0.25	0.71
Monkey	I.V.	0.39	0.43	0.17	-----	-----	1.00	-----	0.03	0.59	0.38
Dog	I.V.	0.42	0.43	0.15	1.00	-----	1.00	-----	0.0005	0.53	0.46
Man	Oral	0.34	0.56	0.10	-----	-----	0.006	0.994	0.004	0.996	(1)

(1) Two components assumed.

Fig. 1. Liquid-scintillation gamma-ray detector.

Fig. 2. Los Alamos small animal counter.

Fig. 3. Los Alamos human counter.

Fig. 4. Counting equipment used for dogs and monkeys.

Fig. 5. Graphic presentation of procedure for separating exponential functions from a composite retention equation.

Fig. 6. Retention and excretion of Na^{22} by mice following oral administration.

Fig. 7. Retention and excretion of Na^{22} by mice following intraperitoneal administration.

Fig. 8. Effect of low-sodium diet on the retention of Na^{22} by mice following intraperitoneal administration.

Fig. 9. Retention and excretion of Na^{22} by rats following oral administration.

Fig. 10. Retention of Na^{22} by rats following intraperitoneal administration.

Fig. 11. Retention and excretion of Na^{22} by monkeys following intravenous administration.

10A 107

100m 100m

10

Fig. 12. Retention and excretion of Na^{22} by dogs following intravenous administration.

Fig. 13. Retention and excretion of Na^{22} by men following oral administration.

Fig. 14. Retention and excretion of Rb^{86} by mice following oral administration.

Fig. 15. Retention and excretion of Rb^{86} by mice following intraperitoneal administration.

Fig. 16. Retention and excretion of Rb^{86} by rats following oral administration.

Fig. 17. Retention and excretion of Rb^{86} by rats following intraperitoneal administration.

Fig. 18. Retention and excretion of Rb^{86} by monkeys following intravenous administration.

Fig. 19. Retention and excretion of Rb^{86} by dogs following intravenous administration.

Fig. 20. Retention and excretion of Rb^{86} by men following oral administration.

Fig. 21. Retention and excretion of Cs^{134} by mice following oral administration.

100

Fig. 22. Retention and excretion of Cs^{134} by mice following intraperitoneal administration.

Fig. 23. Retention and excretion of ^{134}Cs by rats following oral administration.

Fig. 24. Retention and excretion of Cs^{134} by rats following intraperitoneal administration.

Fig. 25. Retention and excretion of Cs^{134} by monkeys following intravenous administration.

Fig. 26. Retention and excretion of Cs^{134} by dogs following intravenous administration.

Fig. 27. Retention and excretion of Cs^{134} and Cs^{137} by men following oral administration.

Fig. 28. Pattern of Na²² retention in five species of animals.

Fig. 29. Pattern of Rb^{86} retention in five species of animals.

Fig. 30. Pattern of Cs¹³⁴ and Cs¹³⁷ retention in five species of animals.

Fig. 31. Relationship between $BT_{1/2}$ and surface area for Na^{22} , Rb^{86} , Cs^{134} , and Cs^{137} in five species of animals.

Available Ground

100% COTTON FIBER

IMPORTANT!

Special care should be taken to prevent loss or damage of this volume. If lost or damaged, it must be paid for at the current rate of typing.

Date Due	
JAN 1 1 1963	
DEC 20 RECD	SEP 21 1967
JUN 1 1964	SEP 21 1967
JUN 1 RECD	
AUG 13 1965	DEC 4 1967
JUL 27 RECD	DEC 2 RECD
JAN 27 1966	JAN 1 1 1968
JAN 8 RECD	JAN 2 1968
AUG 14 1967	
AUG 14 RECD	

PRINTED IN U. S. A.