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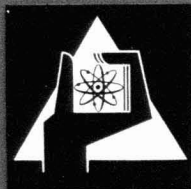
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Toxicology: Radioactive Metals

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## TOXICOLOGY: RADIOACTIVE METALS<sup>1,2</sup>

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### INTRODUCTION

The toxicity of internally deposited radioactive metals (<sup>238</sup>U probably being the single exception) to the living organism is a result of the emitted ionizing radiations. Therefore this subject would qualify as a special chapter of radiobiology. However, investigations utilizing internal emitters have contributed little to the elucidation of radiobiological problems. This is due to the fact that temporal and spatial dose distributions produced by internal radiation cannot be controlled to the same extent as distributions can be with external radiation sources. Hence, the influence of several parameters, which are essential for a radiobiological analysis, can only be determined with difficulty. Correspondingly, the desire for answers to practical problems rather than fundamental radiobiology initiated the very intensive and detailed studies on the toxicity of radionuclides during the last two decades. There is no need to stress the immense practical importance of evaluating the potential hazard for man of radionuclides, and the determination of their maximal permissible concentrations (MPC) in the human body, in water, and in the air. It does not seem practical to limit this review only to the toxicity of radiometals in the strict definition of this word; a deeper understanding of the metabolic behavior of radiometals in general, which in turn depends on various factors, is a necessary prerequisite for other than a purely phenomenological treatise and especially for MPC calculations.

The present survey is essentially restricted to the work published in 1960 and 1961; for earlier work, reference is made to the comprehensive reviews of Chen *et al.* (38), Foreman (54), and Thompson (152). A separation into paragraphs dealing with individual radiometals is adopted. This, however, unavoidably leads to the impression of a casuistic and accidental treatment, due to the relatively short period of time covered. In order to counteract this tendency, general considerations and several relevant and generally valid questions are discussed at the outset making it possible to locate more specialized work within a wider frame.

<sup>1</sup> The survey of the literature pertaining to this review was concluded in March, 1962.

<sup>2</sup> Abbreviations used in this chapter include: BADE (2:2'-bis-[di(carboxylmethyl)amino]-diethylether); DF (discrimination factor); DTPA (diethylenetriaminepentaacetic acid); \*ICRP (International Committee of Radiological Protection); LET (linear energy transfer); MPC (maximal permissible concentrations); OR (observed ratio); TTHA (triethylenetetraaminehexaacetic acid); \*EDTA (ethylenediaminetetraacetic acid).

## GENERAL CONSIDERATIONS

Screening investigations on distribution and excretion patterns of radiometals can be regarded as completed now that the rarer and (from a practical viewpoint) less important elements have been included. In summarizing this work it would seem tempting to classify radiometals by their metabolic behavior as related to their chemical qualities, and their place in the periodical system. Such analyses [e.g., Durbin (45)] reveal only a limited correlation. Although the far-reaching analogies between the metabolism of elements in certain main groups (e.g., alkaline metals, alkaline earths or lanthanides) are very well known, these, however, are not found for elements of other groups or subgroups. In view of the relatively numerous exceptions, a tentative attempt to correlate the metabolic behavior of radiometals to their valency does not appear convincing.

The behavior of a given radiometal in the organism can ultimately be explained by certain chemical, particularly coordination-chemical, and ion exchange processes. Attempts to specify these purely general and formal considerations have progressed only slowly, and many results are not yet free of ambiguities and contradictions. The causes are primarily methodical ones: The classical procedures of separation and purification of defined biochemical fractions from tissues and body fluids usually entail drastic changes of pH, or make use of substances with coordination tendencies or adsorbing qualities. Hence, the preservation of the original biochemical distribution pattern is not assured. Especially with carrier-free radionuclides possessing a stronger tendency to form radiocolloids, the danger of artifacts arises. Further, the value of *in vitro* investigations of relatively simple models ought not to be overestimated. The difficulties of transferring the obtained results to the complex biological milieu, for which a multitude of competing reaction partners is characteristic, are self-evident.

Returning to the problem of metabolism of chemically related elements, present interest is concentrated on elaborating finer quantitative differences in the behavior of element-pairs (e.g., Sr—Ca or Cs—K) and on investigations of the mechanisms which are responsible for biological discrimination. A summary of the present situation in respect to these questions and definition of the nomenclature used is given by Comar & Wasserman (41). These authors stress the practical importance of the so-called OR (observed ratio) of the pair Sr—Ca for the assessment of the radiation hazard and prediction of the radio-contaminant level in the human population. The OR is defined as

$$\text{OR}_{\text{sample-precursor}} = \frac{\text{Sr/Ca in sample}}{\text{Sr/Ca in precursor}} .$$

The term discrimination factor (DF) applies to a particular physiological process which is responsible for the differential behavior of an element-pair, and is linked to the OR by

$$\text{OR} = \prod_{i=1}^n (\text{DF})_i .$$

The conditions for a valid application of DF- and OR-values are discussed in a general way by Kornberg (74); theoretical as well as experimental evidence indicates that variations of discrimination may occur. This applies to Cs—K even more than to Sr—Ca. Summarizing, Kornberg recommends that  $^{90}\text{Sr}$  contamination be reported in terms of ratios as well as absolute concentration units.

An exact mathematical formulation of retention and excretion of a radionuclide in long-term experiments is of great practical importance in so far as it is requisite for the calculation of MPC values. Furthermore, such a formulation admits the possibility of estimating the body burden from measured excretion rates and, under certain conditions, the time of incorporation of the radionuclide. Direct observations on man must be preferred to experiments with animals, a consequence of the greatly different behavior of certain radiometals in different species and the resulting uncertainty in the extrapolation of animal data to man. The retention and excretion functions are generally given in a multiple exponential formulation because simple exponential functions are only very rarely sufficient:

$$R_t \text{ or } E_t = \sum_{i=1}^n a_i \exp(-b_i t)$$

or approximated as power law:

$$R_t \text{ or } E_t = ct^{-d}$$

where  $R_t$  is the amount of radiometal retained after  $t$  days,  $E_t$  the excretion rate at day  $t$ , while  $a_i$ ,  $b_i$ ,  $c$  and  $d$  are constants;  $a_i$  and  $c$  are usually given as percentage of the dose administered. While a power function doubtlessly has the advantage of simplicity, it has only formal meaning. A multiple exponential formulation is preferable, however, because it affords the possibility of correlating real physiological compartments or processes with the mathematical terms of the function, thus attaching biological significance to them.

Early screening tests concerned with the metabolism of radiometals were usually restricted to a single administration of the nuclide. During the last few years, however, interest has shifted to experimental arrangements in which the radiometal is given continuously and its build-up in different organs is observed. This procedure has made possible evaluations of MPC values which naturally are more reliable than data based on a single administration of the radionuclide. Investigations of this type may also entail more or less drastic future revisions of the present recommendations of the ICRP (International Committee of Radiological Protection).

From the practical point of view, and taking into consideration all past experiences, the ingestion and inhalation of radiometals are the main routes for their entry into the body. That our knowledge about the fate of inhaled radiometals is scanty, especially quantitatively, is partly caused by the difficulties of experimental techniques, and partly because the multitude of physical, chemical, and physiological factors which can influence the deposi-

tion and retention of inhaled particles. Concerning the physical parameters other than their density, which determine the extent of deposition the size of the particles plays a decisive role according to Morrow (101). The dominating influence on particles of diameter more than  $0.5 \mu$  is gravitational settling; for particles of less than  $0.1 \mu$  diameter, impacts from Brownian motion dominate; whereas, in the intermediate range of  $0.1$ – $0.5 \mu$  stable aerosols are formed and a relatively small percentage are subject to deposition in the respiratory tract. Modifying factors (i.e., coagulation of submicroscopic particles, their role as condensation centers, and thermal effects) add to the difficulties which have to be dealt with before the extent of deposition can be quantitatively predicted or mathematically formulated. This is additionally complicated by the fact that the number of deposited particles depends upon purely physiological factors, such as tidal volume and respiratory frequency. Those factors which are responsible for the further fate of the deposited aerosols and also for elimination mechanisms (e.g., lung clearance due to the activity of ciliated epithelial cells, phagocytosis, lymphatic drainage, as well as final solubilization and subsequent absorption of particles) are discussed by Casarett (22). The experimental deposition data, as given in a review of investigations with different aerosols [Bair (3)] are in good agreement with theoretical expectations; namely, that the fraction of material deposited after inhalation is largest with particles of approximately  $2 \mu$  diameter and smallest at  $0.3 \mu$ . According to Bair (3) the experimental data do lend some credence to the basic assumptions of the ICRP recommendations. That is, in the standard man 75 per cent of the dust he breathes will be deposited in the whole respiratory tract and approximately one third in its lower parts. The retention is usually represented by a sum of several exponential terms with half-times of a few days through several hundred days. This signifies, at least in principle, the action of different clearance mechanisms. The preponderance of one or another particular mechanism depends of course on the kind and chemical composition of the inhaled particles. It should be mentioned, however, that the observed retention is not necessarily related to the properties of the compounds in pure solutions. Thus, inhaled AgI is rapidly absorbed from the lungs, although it is only weakly soluble in water [Willard & Bair (169)]. Also, Bair (3) in agreement with Stannard (146) points out the accumulation of inhaled insoluble radiometals in tracheobronchial lymph nodes, a fact which may gain importance for evaluations of the MPC. However, considerably more information about the pathological consequences of a localized lymphatic deposition will be needed to assess its importance. An unexpected observation of possibly more general significance was made by Cember *et al.* (37) in experiments with mice to which  $\text{Ba}^{32}\text{SO}_4$  and  $\text{Ba}^{137}\text{SO}_4$  had been given. An interaction between radiation level and lung burden seemed to exist insofar as the lung clearance was decelerated with application of lower specific activity, i.e., higher lung burden. This could mean that the lung hazard is an inverse function of the specific activity of the inhaled aerosol.

Whereas formerly, often tacitly, the assumption was made that the metabolic behavior of internally deposited radiometals is independent of the radioactivity level over a wide range, more recent investigations have shown that this is not necessarily true. Especially in the skeleton, deposition of toxic amounts of radioactivity seem to impair elimination processes. Investigations pursuing the influence of external radiation on the metabolism of internal emitters are bearing upon these questions and are not without practical importance; for example, a nuclear disaster resulting in simultaneous exposure to external and internal irradiation.

To date, the acute LD<sub>50</sub> has been determined for most of the practically important radiometals, and the qualitative aspects of radiotoxicity have been treated rather exhaustively. Henceforth, we should find the "center of gravity" of toxicological studies shifting toward investigations in which the practically encountered types of incorporation (like continuous ingestion or inhalation) occur, as well as the quantitative elucidation of long-term effects. Of special interest—also in regard to MPC evaluations—is the question of dose relationship and of a threshold dose. Probably the most comprehensive experimental material bearing on this question is due to Finkel (49), who investigated the incidence of lymphatic tumors and osteosarcomas after injection of mice with single doses of <sup>90</sup>Sr. The essential result can be summarized as follows: a plot of the response versus the dose injected ( $\mu\text{c/g}$ ) does not show a linear relationship, and indicates that the existence of a threshold dose is quite possible. It is thought that doses below this threshold do not produce tumors, which is in accord with more general theoretical considerations about carcinogenesis by Brues (17). The impossibility of obtaining more precise conclusions can be explained statistically. Another difficulty in interpretation comes from the fact that the radiation doses accumulated depend not only on the amount of the activity administered but, also, on the lifetime of the experimental animals. The lifetime of the animals depends in turn on the amount of the radiometal given. Archer & Carroll (2) proposed to allow for this by plotting the response against the  $\mu\text{c-days/g}$  amounts of activity. However, as was pointed out by Finkel (50), this is an oversimplification of the problem insofar as it equates the radiation dose accumulated during the lifetime to the actual radiation dose for the induction of a tumor (or any other disease); of course, this cannot be the case. Even if in favorable cases it should be possible to separate morbidity from mortality (i.e., true incidence of disease from its apparent incidence at death), it still would be very difficult, if at all possible, to determine exactly the duration of the real time of latency and the amount of "wasted" radiation. Further complications of this problem arise from the fact that in the higher dose region the frequency of tumors decreases despite increasing doses. This means that at high doses the cell killing effectiveness of the radiation dominates. Since the dose rate may constitute a decisive factor in the induction of radiation damage, a final complication is introduced by the fact that the dose rate usually decreases because of the radioactive decay, or the

excretion of an internal emitter or both. For this same reason it is not possible to predict the consequences of chronic exposure from single dose data; actual experimentation is needed. This is even more so since chronic exposure, compared to the administration of a single dose, not only results in a different temporal dose distribution but also in a more uniform spatial distribution of radiation doses. For small animals, whose organs are smaller than the mean range of the emitted radiation, this factor may be neglected; not, however, for larger species and man. For this reason alone experiments with animals larger than small rodents would be required. A series of experiments with dogs have been initiated, but clear-cut results are yet to be obtained. It remains to mention that the temporal distribution of the radiation dose seems to have different importance for radiations with different LET; as was pointed out by Moskalev (102) on review of experimental data with various radionuclides, the recovery processes are less efficient after  $\alpha$  irradiation compared to  $\beta$  and  $\gamma$  irradiation.

A quantitative analysis of radiotoxicity requires a determination of the radiation doses which accumulates in the organs after administration of a given amount of radionuclides. For this, knowledge of the retention functions as well as the microscopic distribution in the organ under scrutiny is needed, as dose calculations on the basis of average organ concentrations lead only very rarely to realistic estimates. This applies primarily to deposition in the lungs after inhalation exposure as well as to distribution patterns of most radiometals in the skeleton, which in autoradiographs show a pronounced nonuniform and spotty deposition. The nonuniformity-factor will in such calculations be more important the smaller the range of the emitted particles, that is with soft  $\beta$  or  $\alpha$  emitters. A detailed mathematical treatment of dose calculations is given by Björnerstedt & Engström (14), with special consideration of the inhomogenous distribution, to the critically interesting case of  $^{90}\text{Sr}$  deposition in bone. A different and very promising approach, which is attributed to Hoecker & Roofe (64) and Spiers (142) and has the advantage of directness, was recently taken up by Hindmarsh *et al.* (63) and Rowland & Marshall (128). It is based on the counting of  $\alpha$  tracks in autoradiographs or the photometry of blackening in thick section autoradiographs. Another direct dosimetric method is the use of Schulman-Etzel dosimeters consisting of small-volume silver phosphate glass for direct measurements of the radiation dose delivered to the organs. This method is discussed in detail by Hayes *et al.* (61). It appears questionable, however, whether dose measurements by implantation of such dosimeters can gain wider importance, apart from certain problems such as the irradiation burden of the intestinal tract after ingestion of a nonabsorbable radionuclide [Nold *et al.* (107)]. It is obvious that computations or measurements of radiation doses lead to considerably higher values, if the spotty distribution of radioactivity is taken into account, than under assumption of a uniform distribution. However, the influence of nonuniformity of the dose distribution in regard to the pathological sequelae has not finally been cleared up. In other words, it is



still arguable whether a defined portion of the bone (or another organ) rather than the total bone has to be regarded as the critical organ.

A treatise of radiotoxicity would be incomplete if possibilities of therapeutic treatment were not mentioned. Effective measures can in the present state of our knowledge only consist in attempts to prohibit or reverse those chemical reactions which are responsible for the deposition of a radiometal. Of the numerous basic possibilities of achieving an intensification of excretion (chelating agents, isotopic dilution, and action on physiological functions) the use of chelators still appears to be the most promising. The physiochemical foundations and the factors which are relevant for the effectiveness of a chelating agent have already been discussed in detail by Schubert (133), and recently in a revised and more general form by Heller & Catsch (62). A survey of recent experimental results has been given by Catsch (26). Whereas until recently EDTA (ethylenediaminetetraacetic acid) was practically the only compound for which experimental data and clinical experiences were available, interest during the last few years has been concentrated on the considerably more efficient DTPA (diethylenetriaminepentaacetic acid) and other related synthetic polyaminopolycarboxylic acids. The reason for the superiority of DTPA is to be found in the fact that the ratio of the chelate stability constant for the metal ion to be removed to that for calcium (the essential endogenous competing cation) reaches higher values than for EDTA. The stability of the Ca-chelates is principally greater than for the Sr-chelates in all chelators investigated so far, and therefore their effectiveness for Sr removal is only minimal even under optimal conditions. Hence, the most promising approach in this case is probably a combination of measures or pharmaceuticals with different modes of action. One possible way of improving the effectiveness of chelating agents in delayed treatment, which is generally less efficient than early treatment, is opened up by pilot experiments with esterified polyamino acids [Catsch (25, 26)]. It is thought that the higher effect of the esters is brought about by their ability to permeate cellular membranes.

#### INDIVIDUAL RADIOMETALS

*Transuranic elements.*—The metabolic behavior of  $^{241}\text{Am}$  in rats shows a close similarity to that of  $^{239}\text{Pu}$ , but also certain differences [Taylor *et al.* (150)]: faster removal of  $^{241}\text{Am}$  from the liver and reduced initial deposition in the skeleton. The retention of both of these radionuclides by the femur observed over a period of 600 days can be represented by simple exponential functions which read for  $^{241}\text{Am}$ :  $R_t = 1.9 \exp(-0.00043t)$  and for  $^{239}\text{Pu}$ :  $R_t = 2.8 \exp(-0.00052t)$ . The fecal/urinary excretion ratio of  $^{241}\text{Am}$  and  $^{239}\text{Pu}$  is smaller than unity only on the first day, but later reaches values between six and nine. At the site of highest  $^{241}\text{Am}$  deposition in the femur, namely the "active band" of the metaphysis, the dose rates (as determined by an autoradiographic technique) on the second day after administration of  $0.0033 \mu\text{g}$  are a minimum of 21 rads per day, a maximum of 362 rads per

day, and on the average 138 rads per day. If the pronounced nonuniformity of the microscopic distribution is not taken into account in calculating the dosage, one obtains the completely unrealistic figure of 6.1 rads per day. In comparison to the results of Taylor *et al.* (150) a considerably faster removal of  $^{239}\text{Pu}$  from the skeleton was observed by Buldakov & Moskalev (19):  $R_t = 50.6 \exp(-0.0013t)$ . While fractionated administration of  $^{239}\text{Pu}$  does not influence its skeletal retention, a clear but inexplicable difference is found in the liver:  $R_t = 4.36 \exp(-0.0036t)$  for a single dose and  $R_t = 3.34 \exp(-0.0144t) + 0.66$  or  $R_t = 3.3t^{-.43}$  respectively for a fractionated dose. The investigations by Rysina (130) into the behavior of  $^{239}\text{Pu}$  in dogs are not evaluable quantitatively. By and large, however, they confirm the previously found slower clearance from the liver in comparison to small rodents. About 20 per cent of an inhaled  $^{239}\text{PuO}_2$  aerosol with a mean particle size of  $0.2 \mu$  was retained by the lungs of mice [Bair *et al.* (6)]. The clearance from the lungs correspond to  $R_t = 70 \exp(-0.23t) + 25 \exp(-0.034t) + 4 \exp(-0.0015t)$ . The largest quantity of translocated  $^{239}\text{Pu}$  was accumulated in the skeleton, about 0.3 per cent of the total dose. Assuming a uniform distribution of  $^{239}\text{Pu}$  in the lungs—which actually is not the case—the accumulated radiation dose is computed as 550 rads in 70 days after deposition of  $0.02 \mu\text{c}$ . Using these experimental data the MPC for man is computed as  $1.6 \cdot 10^{-10} \mu\text{c}/\text{cc}$  air compared to the value of  $4 \cdot 10^{-11} \mu\text{c}/\text{cc}$  recommended by the ICRP. After exposure of two dogs to a  $^{239}\text{PuO}_2$  aerosol with a geometric mean particle size of  $0.6 \mu$ , 75 per cent of the inhaled aerosol was found in the lungs and 20 per cent thereof in the upper respiratory tract [Bair *et al.* (4)]. The daily excretion can be described by a power law where—a characteristic of inhalation exposure—the fecal excretion is about two orders of magnitude higher than the urinary excretion. The whole body retention is represented by  $R_t = 47 \exp(-0.12t) + 4 \exp(-0.028t) + 49 \exp(-0.00048t)$  and  $R_t = 25 \exp(-0.23t) + 8 \exp(-0.046t) + 67 \exp(-0.00039t)$  respectively. It is important that at later times the  $^{239}\text{Pu}$  concentrations in the lungs are lower than those in the bronchial and mediastinal lymph nodes. The question of the critical organ cannot be answered yet, as on one hand the pathological sequelae of the lymphatic drainage are not known; and on the other hand, the comparison with the average concentration in the lungs may be misleading in that it does not allow for the localization of  $^{239}\text{Pu}$  in “hot spots.” Tissue analysis from a  $^{239}\text{Pu}$ -process operator whose death resulted from an overdose of external radiation, and who had been exposed to  $^{239}\text{Pu}$  for approximately six years via inhalation, was performed by Foreman *et al.* (56). A total body burden of about  $0.018 \mu\text{c}$  was estimated. It is noteworthy that the  $^{239}\text{Pu}$  concentrations of the pulmonary lymph nodes exceeded markedly those of the other organs.

Concerning the kind and site of  $^{239}\text{Pu}$  binding in bone, according to Tseveleva (156) about 90 per cent can be found in the organic fraction extracted by trichloroacetic acid and the bulk of this in the collagen. This result is not convincing, however, for those reasons discussed earlier, and is in con-

tradition to the affinity of  $^{239}\text{Pu}$  to the bone mineral which was found by Foreman (55). A determination by Twente & Jee (157) of the  $^{239}\text{Pu}$  concentration in the bone using a microdensitometric technique showed satisfactory agreement with the usual method of counting  $\alpha$  tracks. On a beagle injected with  $2.85 \mu\text{c}/\text{kg}$ , endosteal surface deposits of  $1.6 \cdot 10^{-5} \mu\mu\text{c per } \mu^2$  were found after 92 days and the corresponding dose rates delivered to bone tissue and marrow cells were 40–60 rads/day. The autoradiographic distribution of  $^{239}\text{Pu}$  in the skeleton was investigated very thoroughly by Jee & Arnold (69) and related to radiographic and histopathological changes in early and delayed stages of poisoning. It was found that bone lesions can be of direct as well as of an indirect nature. Certain changes like the death of osteocytes and the plugging of Haversian canals can be explained by a disrupted blood supply [Jee & Arnold (67)]. The impairment of bone function is also revealed by a reduced uptake of  $^{32}\text{P}$ ,  $^{45}\text{Ca}$ , and  $^{14}\text{C}$ -labelled glycine into the epiphysis of the rat femur [Yelkina & Tseveleva (170)]. Jee & Arnold (68) further investigated the hitherto neglected microscopic distribution of  $^{239}\text{Pu}$  and the induced pathological changes in jaws and teeth; osteogenic sarcomas occurred in the jaws but not in the dental tissue. The marked retention of  $^{239}\text{Pu}$  by the liver of dogs manifests itself not only in morphological changes but also in functional changes, as for instance the production of bile [Fedorovsky (48)].

Concerning the dependence of  $^{239}\text{Pu}$  toxicity upon the dose rate, Moskalev *et al.* (104) report that single doses are significantly more effective than fractionated ones in the induction of hematological reactions, and the reduction of life-span of rats. The induction of osteosarcomas, however, does not appear to be affected by these two different kinds of application, in contrast to  $\beta$  emitters like  $^{90}\text{Sr}$  or  $^{144}\text{Ce}$ .

$^{239}\text{Pu}$  administered orally is well known to be absorbed only slightly, and hence the intestinal tract is thought to be the critical organ in this case. However, investigations by Sullivan *et al.* (149) showed that following oral administration of  $^{239}\text{PuO}_2$  to rats, even after doses as high as  $230 \mu\text{c}/\text{g}$  and because of insufficient penetration of the  $\alpha$  particles, only superficial epithelial damage occurred, and conspicuous toxicity or mortality were absent. Hence, the gastrointestinal tract in this case seems to be of secondary importance for determinations of the MPC. The histopathological changes in the respiratory tract of mice after intratracheal administration of  $^{239}\text{PuO}_2$  were studied by Temple *et al.* (151). An increased frequency of papillary adenomas was observed only in animals having received  $0.1 \mu\text{c}$  but not after smaller or higher doses. This result is compatible with the well-known fact that after excessive amounts of radiation, cell killing surpasses carcinogenesis.  $^{239}\text{Pu}$  deposition was considered responsible for the development of 3 malignant pulmonary tumors at 100 and 400 days after exposure when the calculated radiation dose was 2300 and 4000 rads respectively.

The high effectiveness of DTPA could be confirmed for  $^{241}\text{Am}$  removal from rats [Sowby & Taylor (139)]. Investigations in comparison to early ad-

ministration of DTPA show mobilization of smaller quantities of  $^{239}\text{Pu}$  if the chelator is administered after a delay; delayed administration is still sufficient, however, from a therapeutic point of view [Smith *et al.* (138)]. It is pointed out that DTPA not only increases urinary but also fecal excretion, and that the effectiveness of DTPA remains observable for several days after cessation of treatment. This is in accord with an *in vitro* study by Lindenbaum & Schubert (91) who found an increased amount of  $^{239}\text{Pu}$  in ultrafiltrates of tissue homogenates several days after administration of DTPA. According to Smith *et al.* (138) these experimental findings show that a certain amount of DTPA does penetrate the membrane of liver cells, and that the sustained action is due to the intracellular DTPA concentration—a possibility discussed earlier by Catsch *et al.* (24, 26, 29) in analyses of their results with  $^{144}\text{Ce}$ . The effectiveness of DTPA is markedly reduced for  $^{239}\text{Pu}$  administered in a colloidal form compared to monomeric  $^{239}\text{Pu}$  [Schubert *et al.* (134)]. Belayev (10) investigated the effectiveness of 1,2-diaminocyclohexanetetraacetic acid in rats which seems to be comparable to the effectiveness of EDTA, i.e. considerably lower than that of DTPA. The efficiencies of EDTA and DTPA were compared by Norwood (108) in 6 persons which had been contaminated by exposure to  $^{239}\text{Pu}$  over a period of three to eight years. EDTA intensified the urinary  $^{239}\text{Pu}$  excretion by a factor of approximately 10, DTPA by a factor of 40 to 100. However the fecal excretion (which was not investigated systematically) was also increased by DTPA. This, in connection with the observations on experimental animals mentioned above, demonstrates that determination of urinary excretion only leads to an underestimation of the DTPA effectiveness. In the case of a  $^{239}\text{Pu}$  deposition which was thoroughly investigated by Sanders (132), EDTA was practically ineffective. Orally administered  $^{239}\text{Pu}$  is absorbed in very small fractions; in spite of this, an attempt to impede its absorption should be made in view of the high toxicity of  $^{239}\text{Pu}$ . Cation-exchange resins have been shown to be effective in this respect, but only if administered shortly after the entry of  $^{239}\text{Pu}$  [Belayev (11)].

*Thorium.*—Stover *et al.* (147) studied the metabolic behavior of intravenously injected carrier-free  $^{228}\text{Th}$ -citrate in beagles. The plasma concentration was found to drop rather quickly. The excretion was measured through 1300 days. Initially the urinary excretion is much higher than the fecal, but after several years the two are about equal. The total daily excretion can be represented by

$$E_t = 11.3 \exp(-1.4t) + 0.35 \exp(-0.071t) + 0.021 \exp(-0.0011t).$$

About 80 per cent of  $^{228}\text{Th}$  is retained by the skeleton, the remainder by the soft tissues, particularly the liver from which it is eliminated faster than from the bone. Estimated from soft tissue and skeletal data, the retention can be represented by  $R_t = 18 \exp(-0.0010t) + 69 \exp(-0.00014t)$ . An essentially equal distribution pattern is found for  $^{234}\text{Th}$  in rats, while an isotopic dilution leads to the formation of colloidal aggregates in the blood and to a

pronounced deposition in liver and spleen [Catsch & Tocchini-Valentini (36), Fried & Schubert (57)]. The microscopic distribution of  $^{228}\text{Th}$  in dental tissues as well as its effect upon blood vessels of cortical bone is comparable to that of  $^{239}\text{Pu}$  [Jee & Arnold (67–69)]. Catsch & Tocchini-Valentini (36) found an increased removal of  $^{234}\text{Th}$  by DTPA compared to EDTA, while the 10-dentate triethylenetetraaminehexaacetic acid was even more effective. As all chelating agents investigated so far show a very strong reduction of their effectiveness on isotopic dilution of  $^{234}\text{Th}$  [Catsch & Tocchini-Valentini (36), Fried & Schubert (57)], hopes for their effectiveness on old deposits of thorotrast ( $\text{ThO}_2$ ) must be regarded as very low even under optimal conditions.

In recent years repeated reports about late damage after diagnostical administration of thorotrast have appeared. A new case has recently been communicated by Baserga *et al.* (9): This was a bile duct carcinoma of the liver which appeared 14 years after injection of thorotrast into a cavity of a liver abscess. Thorotrast deposits were found on autopsy in liver, spleen, lymph nodes, bone marrow, and, to a lesser extent, in the testes. The latter observation deserves to be noted insofar as some deposition of thorotrast in ovaries was also demonstrated in animals by Matthes & Kriegel (98). Hence, the possibility of genetic damage should at least be considered. Baserga *et al.* (9) give an extensive bibliography and a compilation of 36 known cases of malignancy in man following administration of thorotrast. The fact of the carcinogenic action of thorotrast, and its relation to the radioactivity of  $^{232}\text{Th}$  and decay products thereof can hardly be doubted. The incidence of damages, however, is difficult to estimate from casuistic observations. An increased value must, therefore, be attributed to investigations of nonselected groups of persons. The status of 35 patients with a mean retention time of thorotrast of about 15 years has been determined by Looney (94). Disregarding the occurrence of one or possibly two rare hepatic tumors of mesodermal origin, there were relatively few deleterious effects directly attributable to thorotrast administration in these patients. In order to evaluate the real frequencies of thorotrast induced damage, coordinated follow-up studies on a broad scale are needed.

*Polonium.*— $^{210}\text{Po}$  has been the subject of intensive research during the last decade; among other radionuclides, the toxicology of  $^{210}\text{Po}$  is one of the most thoroughly investigated. The more recent publications on  $^{210}\text{Po}$  are concerned with very specialized aspects. In summarizing these experimental findings, it must be noted that it is yet questionable whether the disturbances observed in  $^{210}\text{Po}$  poisoned animals—hypoxemic states [Bezin (12)], electrocardiographic changes [Moroz & Grozdov (100)], alterations of the kidney function [Poluboyarinoва (117)], and of the cortical activity of suprarenals [Chuchukalo (40)]—are really pathogenically relevant symptoms and not unspecific responses of secondary importance. Hematological and histopathological investigations by Mikhailovich & Erleksova (99) and Petrovich (116) yielded no new insights. Corresponding to the strong affinity of  $^{210}\text{Po}$

for kidneys, the reduction of SH-groups (which can also be demonstrated in other organs) is most pronounced in the kidneys [Zotova (17)]. Histological changes of the nervous system in the chronic state of poisoning are mainly in the sympathetic extramural ganglia, as observed by Lebedev (81). Within the last few years intensification of  $^{210}\text{Po}$  excretion by chelating agents possessing SH-groups has been demonstrated. In addition to a marked fecal excretion of  $^{210}\text{Po}$ , a prolongation of the mean survival time after administration of sodium diethyldithiocarbamate has now been observed by Krivchenkova (79).

*Rare Earths and Yttrium.*—Retention and excretion of carrier-free  $^{144}\text{Ce}$  in rats over a period of 60 days was studied by Slouka (136). The diminution of  $^{144}\text{Ce}$  content in blood can be represented by a sum of 3 exponential terms. The coefficients of these exponentials are in good agreement with ones derived earlier by Catsch *et al.* (31). The retention in liver and kidneys is represented by simple exponential functions  $R_l = 53.3 \exp(-0.13t)$  and  $R_k = 2.4 \exp(-0.067t)$  respectively, while the  $^{144}\text{Ce}$  content of the skeleton remains nearly constant. The retention in the whole body has an effective half-time of about 142 days. The fecal excretion is 10 times higher on the average than the urinary excretion. According to Catsch (24), the retention by the liver of rats follows an exponential law with a half-time of 7 days only up to the 30th day; thereafter the excretion rate drops markedly. In explanation of this at least 2 liver compartments, responding in parallel toward chelating agents, are assumed. The distribution of carrier-free  $^{144}\text{Ce}$  in rats shows a marked dependence on sex. In male rats, as compared to females, a lower deposition is observed in the liver and higher concentrations in the kidneys and skeleton [Catsch (24, 25)]. The subcellular distribution of  $^{144}\text{Ce}$  was studied by Catsch *et al.* (29). Disregarding the first days after administration, the distribution of  $^{144}\text{Ce}$  among the intracellular fractions (cytoplasm > mitochondria > microsomes > nuclei) remains essentially constant. The decrease in absorption of intraperitoneally applied  $^{144}\text{Ce}$  with increasing pH of the injected solution, or after isotopic dilution with  $\text{CeCl}_3$ , is explained by the formation of radiocolloids or colloidal aggregates which are absorbed poorly [Spode & Gensicke (145)]. Isotopic dilution of  $^{91}\text{Y}$  also results in a change of the distribution pattern, especially in a marked deposition in the reticuloendothelial organs [Gensicke & Spode (59)]. The metabolic behavior of  $^{152}\text{Sm}$  is generally equal to that of the lighter lanthanides [Spode & Gensicke (144)]. The placental transfer of  $^{144}\text{Ce}$  and  $^{91}\text{Y}$  is considerably lower than that of  $^{90}\text{Sr}$  and  $^{137}\text{Cs}$  [Kriegel *et al.* (75, 77, 78, 79)].

After inhalation exposure of rats to an aerosol of  $^{144}\text{CeCl}_3$  with a mean particle size of  $1 \mu$ , approximately 10 per cent of the amount initially deposited in the lungs was absorbed [Buldakov *et al.* (20)]. In the course of investigations on the deposition of fall-out fission products in human lungs,  $^{144}\text{Ce}$  concentrations in pulmonary lymph nodes were found to exceed the concentration in the lungs by one to two orders of magnitude [Liebscher *et al.* (87)]. Numerous experimental data on the biological behavior of radioyttrium have been reviewed by Ramsden (119). Of special interest are investigations into

the affinity of  $^{90,91}\text{Y}$  for chemically defined body constituents. Regarding the state of Y in the blood, numerous experiments utilizing paper electrophoresis are found to yield rather contradictory results. It is generally agreed, however, that a variable fraction of the radionuclide applied to the paper remains immobile on the spot of application. Apart from this, binding of Y by  $\gamma$  and  $\beta$  globulins, and by phospholipids as well as low molecular weight plasma constituents is claimed to have been found. In all likelihood the immobile fraction is formed by binding of Y to cellulose. Hence the affinities mentioned could be considered partially as artifacts. Other methods, such as pressure filtration, equilibrium dialysis [Rosoff (126)] and especially density gradient electrophoresis [Ekman *et al.* (46)] established a pronounced affinity of  $^{91}\text{Y}$  as well as of  $^{144}\text{Ce}$ ,  $^{147}\text{Pm}$ , and  $^{169}\text{Yb}$  to albumins, while binding by globulins was not confirmed.

Razumovsky & Torchinskaya's (120) discovery of  $^{144}\text{Ce}$  deposition in the collagen fraction of bone appears questionable for methodological reasons and is in contradiction with reports by Jowsey *et al.* (70). The latter authors showed by *in vitro* and autoradiographic investigations that deposition of  $^{91}\text{Y}$  and radioactive lanthanides occur mainly in the bone mineral, a localization on highly mineralized quiescent or resorbing bone surfaces being characteristic. According to Neuman *et al.* (106), the preferential deposition of  $^{91}\text{Y}$  on resorption cavities is due to an elevated concentration of hydrogen and citrate ions. These ions are produced locally by the osteoclasts.

The superior effectiveness of 2:2'-bis-[di(carboxymethyl)amino]-diethylether (BADE) and particularly DTPA (compared to EDTA) in removing internally deposited  $^{144}\text{Ce}$  and  $^{91}\text{Y}$  observed by Catsch *et al.* (24, 26, 31, 32) was confirmed by Razumovsky *et al.* (120, 121, 122), Tregubenko *et al.* (155). In addition, the first authors were able to show for *in vivo* and *in vitro* conditions an almost equal effectiveness of DTPA and BADE on the skeleton in delayed treatment in contrast to early administration. The dependence of DTPA effectiveness on time and mode of administration was thoroughly investigated by Catsch (24). The most important result is that only a few doses of DTPA are sufficient to remove that fraction of  $^{144}\text{Ce}$  from the body which is subject to mobilization. In view of the relatively frequent contamination of wounds, the observation of DTPA-accelerated absorption of  $^{144}\text{Ce}$  from intramuscular depots is of practical importance [Catsch & Kiefer (30)]. Catsch & Schindewolf-Jordan (34, 35) tested the effectiveness of several new chelating agents. With the exception of triethylenetetraaminehexaacetic acid (TTHA) all of them proved to be inferior to DTPA. TTHA showed, if administered early, a significantly higher skeletal effectiveness than DTPA with  $^{144}\text{Ce}$  and  $^{91}\text{Y}$ .

The amount of  $^{91}\text{Y}$  absorbed in the intestinal tract does not exceed 0.05 per cent. The  $\beta$  radiation of orally administered  $^{91}\text{Y}$  is sufficiently penetrating to damage the intestinal tract which dominates the clinical picture. The  $\text{LD}_{50}$  for rats is 17  $\mu\text{g/g}$  according to Sullivan *et al.* (149) and the mean survival time 8 days. Severe pathological changes were confined to the cecum

and the colon owing to longer retention of intestinal contents in these parts of the digestive tract. The radiation doses after ingestion of the LD<sub>50</sub> are 1150 rads to the small intestine, 2800 rads to the ascending colon, and 4700 rads to the descending colon; these doses are computed with the formula given by Thompson & Hollis (153). Nold *et al.* (107) executed direct dose measurements by implantation of Schulman-Etzel dosimeters in various parts of the digestive tract in dogs and goats after administration of <sup>90</sup>Y. The results agreed exceptionally well with the computed doses. It was estimated that the maximum permissible dose of 300 mrad would be delivered by a dose of 4  $\mu$ c in dogs and 17  $\mu$ c in goats. These values are reduced by diarrhea by a factor of 2 to 4, and increased in constipated animals by a factor of 3 to 7. By extrapolation to man one obtains as maximum permissible intake 4  $\mu$ c of <sup>90</sup>Y which compares to 3.1  $\mu$ c recommended by the National Bureau of Standards Handbook.

*Alkaline Earths.*—The retention of <sup>90</sup>Sr in the skeleton of rats determined over a period of 600 days can be represented by  $R_t = 39 \exp(-0.0106t) + 0.23 \exp(-0.00102t)$  [Moskalev (103)]. The <sup>90</sup>Sr concentration displays a considerably faster decrease owing to accretion of new bone. No differences are found in the retention of several dosages of <sup>90</sup>Sr varying between 1 and 1000  $\mu$ c per animal. This is contradicted by Ray & Lyon (123) who find a reduction in the mobilization of stable Sr administered prior to a single dose of 3  $\mu$ c <sup>90</sup>Sr/g, as well as abolition of the protective effectiveness of a phosphorus-deficient diet. It may be concluded that the presence of viable bone cells and an adequate blood circulation are necessary for the excretion of radiostrontium from the bone, and that these factors will be impaired by high radiation doses. The retention of <sup>85</sup>Sr by the skeleton of dogs (which follows a power law) shows a marked dependence on the age of the animals [Glad *et al.* (60)]: with increasing age the exponent  $d$  increases while the coefficient  $c$  decreases. According to Parfenov (115), the skeletal concentration of <sup>90</sup>Sr in dogs can be represented by simple exponential functions; the half-time of the exponentials, however, is widely variable (between 665 and 2100 days) for different bones.

The question is yet to be resolved whether mobilization due to the osteoclastic activity or an exchange process is responsible for the persistent but slow loss of alkaline earths from the skeleton. Rowland (127) attempted to find an answer from autoradiographic investigations after dogs had received <sup>226</sup>Ra by the multiple injection technique. He concludes that an exchange process is probably the dominating mode of action on diffusely deposited <sup>226</sup>Ra as well as in hot spots. From a comparison of specific activities in bone and blood plasma, it is concluded that there is no significant discrimination against <sup>226</sup>Ra in favor of Ca in transfer from blood to bone.

Following incorporation of <sup>90</sup>Sr in liver, spleen, and kidneys of rabbits a pronounced surplus of <sup>90</sup>Y was shown to exist [Lloyd (93)]. This suggests translocation of the decay product formed in the body. Hence, dose calculations for these parenchymatous organs, based on the assumption of radioactive equilibrium, will give an underestimation by a factor of at least 10.



Nevertheless, the skeleton accumulates considerably higher radiation doses, and, therefore, is still the critical organ.

Jee & Arnold (68) investigated the microlocalization of  $^{90}\text{Sr}$  and  $^{226}\text{Ra}$  in teeth in comparison to the radioactive actinides. They found distinct differences, such as the penetration of the alkaline earths into the dentine while the actinides are concentrated on the surface. A characteristic of all bone-seeking radiometals is the spotty concentration in zones of active calcification.

According to Bishop *et al.* (13), the total daily excretion rate of  $^{85}\text{Sr}$  in man after intravenous injection follows the equation  $E_t = 16.5 \exp(-0.41t) + 4.7 \exp(-0.16t) + 0.20 \exp(-0.014t)$ . The urinary excretion is strongly dominating during the first days; later urinary and fecal rates become nearly equal. For the assessment of body burdens as a function of the activity ( $U$ ) excreted in the urine over 24 hours the following relation holds:  $R = 0.06 + 0.65 U^{1/3}$ . The validity of this formula was confirmed by Rundo & Williams (129) in a case of accidental inhalation exposure to  $^{90}\text{SrCO}_3$  for which excretion and activity as measured by a whole body counter were determined. Systematic research on enrichment of  $^{90}\text{Sr}$  in the human skeleton from fall-out has been continued by Kulp *et al.* (80). In the years 1958 and 1959 the average content was  $0.3 \mu\mu\text{c}$  per g Ca, and for adults was independent of age. For children one year of age, a mean value of  $2.1 \mu\mu\text{c}$  per g. Ca was found.

In three cases of  $^{226}\text{Ra}$ -poisoning the microscopic distribution of  $\alpha$  tracks in the long bones was found to depend upon the age at which the patient acquired the burden [Lloyd (92)]. In the patient who ingested  $^{226}\text{Ra}$  at the age of 17 most of the activity was found in the subperiosteal layer. The activity of the hot spots accounted for 12 per cent of activity of the whole bone-section; in those patients who acquired  $^{226}\text{Ra}$  at 32 and 47 years, the hot spots amounted to only 3 per cent. The nonuniformity factor, defined as the ratio of the highest concentration to the average concentration (assuming uniform distribution), varies in the range of 13 to 40. Supposing identical distribution of  $^{90}\text{Sr}$ , the nonuniformity factor could have a maximum value of six because of the longer range of the  $\beta$  particles. The terminal dose rates delivered to the lacunae are computed as 5 to 18 rads per day using the formula of Spiers (142).

The transfer of radiostrontium from mother to fetus was investigated with small rodents by Holmberg *et al.* (65) and Kriegel (75). A maximum transfer was found when the radionuclide was administered during the last days of gestation. Special mention may be made of the pronounced mobilization of  $^{90}\text{Sr}$  from the bones of lactating rats [Kriegel & Neumann (76)].  $^{90}\text{Sr}$  is discriminated against Ca by a factor of 12 on transfer from the mother's diet to the human fetus [Kulp *et al.* (80)].

A more detailed discussion of the numerous papers which deal with physiological discrimination of alkaline earths and their basic mechanisms would exceed the scope of the present review. It may suffice to summarize briefly their main results. The  $^{85}\text{Sr}/^{226}\text{Ra}$  ratio for dogs is 0.83 in bones, 0.8 in feces, and 1.83 in urine [Glad *et al.* (60)]. The tubular reabsorption of  $^{226}\text{Ra}$  in dogs compared to  $^{85}\text{Sr}$  and  $^{45}\text{Ca}$  decreases in the order: Ca, Sr, Ra; whereas,

the ultrafiltrable fraction of the plasma behaves in the opposite fashion [Hursh *et al.* (66)]. Essentially the same results are obtained by Della Rosa *et al.* (43) in investigations on the renal excretion of  $^{85}\text{Sr}$  and  $^{45}\text{Ca}$  by dogs. The renal discrimination against  $^{85}\text{Sr}$  in man varies between 2.8 and 4.4 [Barnes *et al.* (8), Bishop *et al.* (13)]. Garner *et al.* (58) compared the metabolism of  $^{140}\text{Ba}$ ,  $^{89}\text{Sr}$ , and  $^{45}\text{Ca}$  in lactating cows and found marked differences. The most important contribution in over-all discrimination in the passage from diet to milk is the absorptive discrimination. The determination of several OR- and DF-values for cattle by Buldakov & Burov (18) yields no essentially new results or aspects above the earlier work of Comar & Wasserman (41). Close agreement exists over the  $\text{OR}_{\text{milk-diet}}$  between lactating animals and man [Lough *et al.* (95)]. The  $\text{OR}_{\text{milk-diet}}$  of cows and goats is 0.12, and does not depend on the dietary Ca-level [Comar *et al.* (42)].

Investigations into the basic mechanisms of intestinal absorptive discrimination do not yet yield a clear-cut picture [Lengemann & Comar (84), Palmer & Thompson (114), Wasserman (166)]. Similar discrepancies are found in investigations of the Sr/Ca discrimination on transfer from blood to bone [Lengemann (82), Likins *et al.* (88, 89), Samachson & Lederer (131)]. In connection with Kornberg's criticism of the OR concept (74), work by Thompson & Palmer (154) deserves special attention. They followed the build up of  $^{90}\text{Sr}$  and  $^{45}\text{Ca}$  in the skeleton of rats during chronic ingestion of the radionuclides. Sr/Ca discrimination is found to decrease in magnitude as the dietary Ca-level increases. Furthermore the  $\text{OR}_{\text{bone-diet}}$  depends upon time as the retention of  $^{45}\text{Ca}$  decreases when the Ca-supply is increased, while the rate of  $^{90}\text{Sr}$ -removal from the bone remains practically constant. A correlation of Sr/Ca discrimination with age and dietary Ca- and P-levels was found by Wasserman & Comar (167). Stover *et al.* (148) reported the failure of a dog to discriminate between  $^{90}\text{Sr}$  and Ca given orally.

The absorption of  $^{90}\text{Sr}$  from the digestive tract is enhanced by whole-body X-irradiation with doses of 200 r and higher [Lengemann (83)]. This effect is more pronounced for young rats than for mature animals. The influence of the irradiation could be due to an increased permeability as well as a slower rate of transit through the irradiated intestinal tract [Lengemann & Comar (85)]. After local irradiation of an extremity with 2000 r an inhibition of accretion and an increase of the exchangeable fraction of bone is observed [Cohn (39)].

Some work has been devoted to functional or morphological disturbances in  $^{90}\text{Sr}$ -poisoned animals. That these symptoms are pathogenically relevant, however, appears to be questionable. These changes are: enhanced urinary excretion of Dische positive compounds [Uspenskaya (159)], disturbances of DNA-metabolism of the liver [Uspenskaya (160)], glomerular-tubular disturbances of the kidneys [Poluboyarinova (118)], damage of the intestinal tract [Lebedev (81)], alterations of the cardio-vascular functions [Korchemkin (73)], and of conditioned reflex activity [Aleksyeva *et al.* (1), Klimova *et al.* (71)]. Less well known is the fact that a pronounced bone-seeker like radiostrontium may produce tumors in the soft tissue adjacent to bone.

Sissons & Vaughan (135) describe squamous carcinomas of the external auditory meatus following injection of newly-born rabbits with  $0.5 \mu\text{c} \text{ }^{90}\text{Sr/g}$ . However, in rabbits injected with 0.2 to  $1.0 \mu\text{c/g}$  at the age of one year no ear tumors are found. Impediment of bone growth was observed by Macpherson (96) on weanling rabbits following injection of  $0.6 \mu\text{c} \text{ }^{90}\text{Sr/g}$ . Doses of  $0.1 \mu\text{c/g}$  remained practically without effect, i.e., no significant stunting of growth is observed. It is difficult to decide whether direct radiation, or a general metabolic effect in the course of radiation sickness, is the more important factor impairing bone growth.

Finkel *et al.* (53) investigated the dependence of the  $^{90}\text{Sr}$ -toxicity on the administration pattern. CF1 mice received intraperitoneally a total of 0.25, 0.5, or  $1 \mu\text{c/g}$ , either as a single dose (S), or once a week for 5 weeks (F5), or 5 times a week for 4 weeks (F20). Concerning the induction of osteosarcomas, S was decidedly more effective than F5 or F20. For the induction of lymphomas, however, the influence of the dose rate obviously depends on the total dose given. The order of effectiveness after administration of  $1 \mu\text{c/g}$  is  $S > F5 > F20$ , after  $0.5 \mu\text{c/g}$   $S = F5 > F20$ , and after  $0.25 \mu\text{c/g}$   $S < F5 = F20$ . These findings are not very amenable to interpretation. It may be concluded that at least two processes are involved in the radiation induction of lymphatic tumors. One process may be a direct response of the irradiated tissue, and the other an abscopal effect. The effectiveness of an initially high dose-rate, produced by a single dose, is also confirmed for the induction of osteogenic tumors from investigations on the consequences of continuous ingestion of  $^{90}\text{Sr}$  by CF1 mice [Finkel *et al.* (51)]. These mice were fed with  $10 \mu\text{c}$  per g of dietary Ca from the day of conception onwards. Osteosarcomas appear much later and in smaller numbers than anticipated on the basis of experience with single parenteral doses. It also turned out that very young mice are not more sensitive to the carcinogenic effect of radiation. The true incidence of osteosarcomas may be quite different from its apparent incidence at death, as has been already pointed out. In order to elucidate this question, Finkel *et al.* (52) investigated by use of serial roentgenographs the frequency of osteosarcomas following single parenteral doses of  $^{90}\text{Sr}$  (approximately  $1 \mu\text{c/g}$ ) in CF1 and CBA mice. A difference in response between the two strains was observed which is not easily explicable: The average number of four tumors per mouse is about equal for both strains but the curve representing the cumulative incidence in CBA mice lags behind the CF1 curve by approximately 60 days. The earliest roentgenographic diagnosis of an osteosarcoma was made in a CF1 mouse on the 98th day, in a CBA mouse on the 180th day. The tumor-rate (defined as the rate of appearance per 100 mouse-days) reaches a plateau, although the total energy absorbed is continuously increasing. Hence, it is concluded that the total accumulated radiation dose is less important than the radiation delivered during the first days. It is suggested tentatively that at a rate of 150 rads per day irradiation for only one day is sufficient to give rise to the development of osteogenic neoplasms. Obviously these findings complicate the determination of the dose-effect relationship and the threshold dose.

Numerous investigations are devoted to the problem of removing internally deposited radiostrontium from the body. To a certain extent, earlier findings have been confirmed, but also new conclusions and starting points have been reached. Carlquist & Nelson (21) find a reduction of the skeletal  $^{90}\text{Sr}$ -deposition by stable Sr-compounds administered prior to or simultaneously with  $^{90}\text{Sr}$ , while Ca-salts have a negative or no effect. This is in contradiction with Spencer *et al.* (140, 141) who observe markedly enhanced urinary excretion of  $^{85}\text{Sr}$  after infusion or oral administration of Ca-gluconate to man. Seemingly the pseudoisotopic carrier-effect of Ca is confined to a very narrow dose region. This was observed earlier by Catsch & Melchinger (33) and would explain the discrepancy mentioned above. Also in disagreement with Spencer *et al.* (141), who found enhanced  $^{85}\text{Sr}$ -excretion by man after oral administration of ammonium chloride, are investigations by Della Rosa *et al.* (43). These authors could not observe an effect of ammonium chloride on dogs whereas an increased  $^{85}\text{Sr}$ -excretion took place after alkalosis had been induced by sodium bicarbonate. Similarly, Walser *et al.* (165) found enhanced urinary excretion after intravenous infusion of sodium sulfate. The mechanism by which sodium sulfate promotes the intensified excretion of  $^{85}\text{Sr}$  is not fully understood. Concerning the action of sodium or potassium rhodizonate, the positive results claimed by Lindenbaum (90) could not be reproduced by Dooronbekov *et al.* (44) nor by Volf (162). A chelating compound which is active, if only weakly, is BADE. Its effectiveness can be potentiated by combination with a different principle of action: isotopic dilution [Catsch (27, 28)]. The administration of the  $\text{Na}_2\text{Sr}$ -chelate, instead of the ordinary  $\text{Na}_2\text{Ca}$ -chelate or of the  $\text{Na}_2$ -salt, results in a reduction of skeletal deposition of  $^{85}\text{Sr}$  to about one half. This should be one of the strongest effects which have been achieved with early treatment. The amount of  $^{85}\text{Sr}$  which can be mobilized by delayed treatment with  $\text{Na}_2\text{Sr}$ -BADE is practically zero. In the same way the increased effectiveness of  $\text{CaNa}$ -citrate over that of the  $\text{Na}$ -compound can be understood [Ogawa *et al.* (109)]. For fundamental reasons, it appears unlikely that a major success in removal of radiostrontium already fixed in the bone can be achieved solely by application of chelators. Therefore, the observations of Knizhnikov (72) deserve close attention and should be confirmed as soon as possible: Namely, the chronic feeding of nontoxic amounts of sodium fluoride to mice and dogs results not only in a reduced deposition of  $^{90}\text{Sr}$  but also in an accelerated elimination of  $^{90}\text{Sr}$  already deposited. Ogawa *et al.* (110) found enhanced excretion of  $^{90}\text{Sr}$  from mice after administration of tetracycline. They attributed this action to the chelating properties of the compound. This explanation, however, appears to be questionable. According to Richards *et al.* (124) tetracycline does not seem to influence the initial deposition, but to effect an accelerated mobilization from the bone. To what extent this is connected with the action of tetracycline on skeletal growth remains to be shown, as does the question of effectiveness with other animal species. The attempt to increase the transfer-rate of radiostrontium from the blood into intestine, and to block its intestinal reabsorption by oral administration of

barium sulfate or other agents, has yielded only a weak and hardly satisfactory effect [Volf (163, 164)]. The acceleration of Sr-elimination from bone by a phosphorus-deficient diet has been known for some time. It was assumed, however, that such diets are only poorly tolerated and lead to marked histological changes of the skeleton. Van Putten (161) demonstrated, however, that effective phosphorus-deficient diets were tolerated relatively well and lead to a convincing reduction of the radiotoxicity of  $^{90}\text{Sr}$  in mice. In this connection an observation by Uchiyama & Ukita (158) should be mentioned: a single oral dose of aluminium citrate promoted a markedly intensified excretion of  $^{90}\text{Sr}$  injected parenterally into mice. This is explained by precipitation of phosphorus in the intestinal tract.

#### MISCELLANEOUS METALS

The retention of inhaled  $^{192}\text{Ir}$  aerosol in rats was studied by Casarett *et al.* (23). The major fraction of the aerosol, with a mean particle size of  $0.7\ \mu$ , was retained by the upper parts of the respiratory tract. This is in contradiction to results with other radiometals. There is no readily apparent explanation for this discrepancy. The  $^{192}\text{Ir}$  load of the upper parts of the respiratory tract is rapidly removed via the gastrointestinal tract. For this reason, together with the low absorption of  $^{192}\text{Ir}$ , the digestive tract is the critical organ.

By autoradiographic studies Nelson *et al.* (105) observed very pronounced and rapid appearance of  $^{137}\text{Cs}$  in the cartilage. Although the myocardium accumulates  $^{137}\text{Cs}$  to the same extent as the skeletal muscle, it does not retain  $^{137}\text{Cs}$  for longer periods of time as does the skeletal muscle. Wasserman & Comar (168) investigated the influence of dietary K-levels on the retention of chronically ingested  $^{137}\text{Cs}$  in rats. The maximum effect observed was a two-fold reduction of  $^{137}\text{Cs}$ -retention in response to a ninefold elevation of dietary K-concentration. As has been emphasized above, the OR in the case of the element pair Cs-K is not of major importance. This can be seen from the variation of the  $\text{OR}_{\text{muscle-diet}}$  between 1 and 5.3, depending on the K-content of the diet. A sizable placental transfer of  $^{137}\text{Cs}$  was to be expected and could experimentally be shown to take place in small rodents, especially during the last days of gestation [Kriegel *et al.* (78)]. A significant enhancement of  $^{137}\text{Cs}$ -excretion is effected by  $\text{NaHCO}_3$ ,  $\text{Na}_2\text{SO}_4$ ,  $\text{Na}_2\text{HPO}_4$  and  $\text{NaH}_2\text{PO}_4$  [Ogawa *et al.* (113)], the active mechanism has yet to be elucidated. Oral administration of a carbonic anhydrase inhibitor (diamox) for long periods of time reduces the body content of  $^{134}\text{Cs}$  by about 20 per cent [Richmond & Furchner (125)]. Following an accidental ingestion of 4 mc  $^{137}\text{Cs}$  by a technician, only unspecific and slight impairment of health was observed [Fateyeva *et al.* (47)].

The intestinal absorption of  $^{114m}\text{In}$  is about 0.5 per cent in rats. Following different routes of administration of the radiometal, the highest concentrations were found in the kidneys, spleen, liver and salivary glands. A bioassay method is presented which allows an estimate of the body burden to be made from urinary excretion data [Smith *et al.* (137)].

The enteral absorption of  $^{106}\text{Ru}$  depends on its chemical form; in rabbits it amounts to 10 to 15 per cent for nitrosyl derivates, and approximately 3 per cent for the chloride and the dioxide. However, the subsequent distribution of the absorbed fraction was identical for all compounds, the kidneys showing the highest concentrations [Bruce & Carr (15)]. The half-time of retained  $^{106}\text{Ru}$ , administered as nitrosyl-trinitrate, is 1.6 days for the first 10 days and increases to 7 weeks thereafter. The retention of the serial doses in the case of a chronic oral exposure is somewhat less than after a single dose [Bruce & Carr (16)]. After inhalation of an  $^{106}\text{RuO}_2$  aerosol with a mean particle size of  $0.33 \mu$ , about 24 per cent of the particles is deposited in the lungs of mice. The retention of the fraction deposited is represented by  $R_t = 83 \exp(-0.1t) + 15 \exp(-0.024t) + 2 \exp(-0.003t)$ . This means that essentially the same conditions prevail as those following inhalation of a  $^{239}\text{PuO}_2$  aerosol. It is noteworthy that relatively higher concentrations are observed in ovaries and adrenals compared to the lungs. Assuming the lungs as the critical organ, a MPC of  $1.3 \cdot 10^{-9} \mu\text{c}/\text{cc}$  air is obtained from the values given above [Bair *et al.* (5)]. This compares with  $6 \cdot 10^{-9} \mu\text{c}/\text{cc}$  which is the value recommended by the ICRP. From investigations of the pathological sequelae of  $^{106}\text{Ru}$  inhalation, no consistent picture can yet be derived [Temple *et al.* (151)]. Administration of EDTA or condensed phosphates proved to be ineffective in mobilizing internally deposited  $^{106}\text{Ru}$  [Spode & Gensicke (143)].

The influence of various compounds on the retention and excretion of  $^{96}\text{Zr}$  in mice and rats was tested by Ogawa *et al.* (111, 112). CaNa-citrate, EDTA, tetracycline, and small doses of stable carrier promoted a slight enhancement of the urinary excretion.

Although  $^{65}\text{Zn}$ , produced by the addition reaction of neutrons with  $^{64}\text{Zn}$ , is not a fission product, it is of major practical importance as a biospheric contaminant. Its presence in cyclotron workers is caused by the absorption of deuterons in  $^{63}\text{Cu}$  contained in the cyclotron. Ballou & Thompson (7) studied in detail the validity of MPC values given by the ICRP for this radionuclide. The retention of  $^{65}\text{Zn}$  injected intravenously into rats is found to be representable by a sum of three exponential terms. The highest concentrations of  $^{65}\text{Zn}$  were found in hair, bone and prostate of the rats. 10 to 20 per cent of the nuclide is found to be absorbed from the digestive tract. After chronic feeding of  $^{65}\text{Zn}$ , steady state concentrations were observed long before the end of the feeding period. The agreement between the build-up values observed and those predicted is fairly good. The MPC values calculated for water from single and chronic administration data are also in satisfactory agreement with each other. These values, however, are higher for most organs than those given by the ICRP recommendations. Special attention should be devoted to very young organisms in view of the enhanced intestinal absorption and the relatively high placental transfer of  $^{65}\text{Zn}$ . Significant changes of uptake and distribution of orally administered  $^{65}\text{Zn}$  in mice were found after whole body X-irradiation [Matsui *et al.* (97)].

Despite its wide distribution,  $^{60}\text{Co}$  has received only little attention in the past. Recently, a considerable number of papers by Soviet authors (86) have

been devoted to its behavior and toxicity. Investigations with rats and rabbits indicate a variation in enteral absorption of between 13 and 33 per cent. Concentration in liver and kidneys is found to exceed that in all other organs. Excretion is preferably urinary. The steady state concentration following chronic feeding is reached relatively rapidly (approximately after 0.5–2 months). The experimentally found dependence of the equilibrium concentration on concentration level of the diet is regarded as a carrier effect, the preparation being used having a relatively low specific activity. The steady state retention  $R_{\infty}$  of  $^{60}\text{Co}$  obeys the relation  $R_{\infty} = 6.25a^{0.5}$  where  $a$  is the amount of activity given per day. In investigations concerned with radiotoxicity, rabbits received oral dosages of 1.25 and 12.5  $\mu\text{c}/\text{kg}$ . These are quantities 100 and 1000 times, respectively, higher than those for water contained in the ICRP recommendations. Most prominent in the clinical picture are disturbances of erythropoiesis and lymphopoiesis. Especially following the higher dosage, a marked hyporegenerative anemia and a constant absolute lymphopenia develop. Disturbances in the case of the lower dosage are only observable when a functional stress is applied. The radiation doses are computed as 0.1 and 0.61 rep per day, respectively, for  $\beta$  irradiation of the liver, and 0.24 and 1.16 r per day, respectively, for  $\gamma$  irradiation of the whole body.

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