As part of a program devoted to studying the accumulation of metallic ions by mammalian skeletal tissue, it was decided to investigate the uptake of yttrium by rats. Although this element is encountered but rarely in biochemical investigations, its behavior in the body has become important since its discovery as one of the major products of nuclear fission [1]. Radioactive isotopes of yttrium have been reported to be removed rapidly from the blood and deposited in bone, where the element remains for very long periods of time [2, 3]. The same general behavior has been noted for radioisotopes of the alkaline earth elements and for members of the lanthanide and actinide rare earth series. However, on the basis of radioautographs, two fundamentally different modes of bone deposition have been reported. Sr\textsuperscript{90} seems to be deposited more or less uniformly throughout cortical bone, in close association with bone salt. Yttrium, on the other hand, appears to be laid down in the osteoid matrix [4, 5]. By providing Sr in the drinking water, a level of as high as 5 per cent Sr in the bone ash can be attained with mice [6].

In view of these observations, it seemed desirable to learn whether or not yttrium and, by inference perhaps, the lanthanide elements are as avid "bone seekers" as strontium has proved to be. Radioactive yttrium was not applied in the present experiments, in order to avoid possible disturbance of normal osteoblast and osteoclast cellular activity by irradiation.

**Materials and Methods**

Thirty young, white, male rats, ranging in weight from 50 to 75 g, were injected intraperitoneally every 2 days with an aqueous solution of reagent grade yttrium chloride (20 mg. of Y\textsuperscript{+++} per ml.). The dosage was 60 mg. per kilo of body weight and the pH of the solution was 6.4. In addition, ten additional rats were given single intraperitoneal injections

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ranging in dosage from 1 to 20 mg. A control group of thirty young male rats was maintained on the same diet (Rockland rat pellets), each animal being weighed on the same days that injections were made. The injections were terminated at various intervals and each animal was sacrificed 1 day after the last injection. Both femurs were removed, cleaned of soft tissue, and ashed at 600° overnight. The ends of each femur were then clipped off about 2 mm. below the epiphyseal junction and pooled, and the mixture was analyzed independently of the shaft.

The yttrium content of the ash was obtained by dissolving the sample in 1 N HCl, adding a predetermined amount of aqueous ammonium chloride containing lanthanum nitrate as a spectrographic internal standard, and lyophilizing the mixture to a dry powder. A few mg. of this powder were then burned in a direct current arc and the relative intensities of the yttrium and lanthanum emission lines (Y 3242.3 A and La 3249.5 A, respectively) were measured. Details of this general spectrographic technique are to be published elsewhere. The lower limit for detection of yttrium was 80 parts per million. The standard deviation for a single determination was 7.4 per cent.

Results

The period of injections extended for more than 5 months, during which time no fatalities were observed. The greatest number of injections given to a single animal was 83. At autopsy, many rats which had received more than twenty injections showed abdominal trauma and intestinal adhesions. However, no nodules of precipitated yttrium salts were found in the abdominal cavity; hence absorption of most of the administered YC13 may be assumed. This assumption was strengthened by analyzing the liver, kidney, spleen, and lungs of several of the animals. The yttrium content of the ash of these organs ranged from 1000 to 10,000 p.p.m.1 The growth curves for the treated animals did not differ significantly from that for the untreated control animals. Chronic systemic toxic effects, under these conditions at least, were not obvious.

Fig. 1 presents the amount of yttrium in the ashed bone ends as a function of the mg. of Y+++ administered to the animals. Yttrium was not detectable in twelve cases; i.e., they contained less than 80 p.p.m.

Fig. 2 presents the ratio of bone end content to bone shaft content as a function of total dosage of Y+++ If this scatter diagram embodies a

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1 It is interesting to note that these organs are part of the reticuloendothelial system. Particles of insoluble materials of colloidal size, such as hydrated yttrium oxides which may precipitate at the pH of serum, would be removed from the circulation by phagocytic cells in these tissues.
linear relationship between the two variables (an assumption which, it must be admitted, is not fully justified by the somewhat meager data at hand), then the straight line indicated is the best possible fit. The location and slope of this regression line were computed by the method of least squares (7).

Fig. 1. Deposition of yttrium in bone as a function of total dosage. The shaded region is an area of uncertainty. Twelve rats, whose total dosages were under 40 mg., showed less than 80 p.p.m. in the femur ends.

Fig. 2. Distribution of yttrium within the femur as a function of total dosage.

DISCUSSION

Perhaps the first observation to be made is that macro amounts of yttrium did not accumulate in bone. Although total dosages as large as 936 mg. were administered, the amount of yttrium in the bone ash never exceeded 330 p.p.m. For similar dosages of strontium, the uptake is greater by about a 100-fold (6). The bone burden of yttrium did not increase linearly with increasing dosage. An attempt to fit a straight line to the data of Fig. 1, when plotted on semilogarithmic cross-section paper, was also unsuccessful, indicating that a simple exponential type of function, such as is found in surface adsorption phenomena, could not describe the behavior adequately.

Fig. 1 suggests the following interpretation. If less than about 50 mg. of $^{111}$Y are given by intraperitoneal injection, the cations are deposited in the bone by a mechanism whose details are unknown at present, but
which becomes overloaded or flooded at higher dosage levels. When the bone is burdened with 150 to 200 p.p.m. of yttrium, further accumulation becomes more difficult, possibly because a second process of slower rate achieves dominance. Speculations on the nature of these processes have been made previously (8).

The tendency for yttrium to become uniformly distributed throughout the femur as the injections continued and the animals grew older is illustrated by Fig. 2. Although the percentage of yttrium in the spongy femur ends may be twice that in the compact bone shaft during the early stages, the ratio approaches unity with the passage of time. The gradual decrease in the avidity of trabecular bone (the femur ends) for yttrium may possibly be related to the decrease in osteoblast activity at the epiphyses as the animals attained maturity and the rate of new bone formation diminished.

Finally, it may be appropriate to voice an opinion concerning studies of the skeletal uptake of ions in which radioisotopes are employed. One must differentiate between results obtained with carrier-free radioisotopes (in which the actual number of atoms administered is very small) and experiments in which microgram to mg. amounts of a stable isotope are tagged with a few microcuries of the radioactive species. For example, from the tenacious retention of carrier-free Y³⁹ by bone (2, 3) one might be tempted to classify the element as a "bone seeker" in the same sense that strontium and lead are considered. The results reported herein show that such a conclusion is unwarranted. It seems likely that skeletal tissue is capable of withdrawing almost any metallic cation from circulating blood and of "fixing" small numbers of these atoms with a permanence which depends partly upon the rates of normal bone formation and resorption. However, the attainment of concentrations in bone which are several orders of magnitude greater than these "ordinary" levels is probably restricted to a much smaller number of elements.

**SUMMARY**

The accumulation of non-radioactive yttrium in the bones of growing rats was studied. YCl₃ was administered intraperitoneally every 2 days, the greatest number of injections being 83. Analyses of the ashed femur ends and shafts were made by an emission spectrographic technique.

Chronic systemic toxic effects were not obvious. Large amounts of yttrium did not accumulate: the level never exceeded 330 p.p.m. parts of bone ash, about one-hundredth the uptake of strontium after similar dosages.

After the bone was burdened with 150 to 200 p.p.m. of yttrium (ap-
proximately 50 mg. injected), further accumulation became more difficult, possibly because a second process of slower rate achieved dominance.

The ratio of the amount of yttrium in spongy bone to that in compact bone approaches 1 with the passage of time.

It is concluded that yttrium is not a "bone seeker" of the same degree as strontium and lead.

BIBLIOGRAPHY