THE DEPOSITION OF ^{91}Y IN RABBIT BONES.

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KNOWLEDGE of the metabolism of yttrium is urgently required because radioactive yttrium isotopes are themselves important fission products, and also one, ^{90}Y, is produced by the radioactive decay of ^{90}Sr. It is known that the greater part of any yttrium reaching the blood stream is concentrated in the skeleton, and that the deposition of tracer doses of radioactive yttrium in bone differs both in localization and mechanism from that of certain other bone-seeking elements, notably strontium and phosphorus (Vaughan, Kidman and Tutt, 1952; Macdonald, Nusbaum, Alexander, Ezmerlian, Spain and Round, 1952). The present paper describes observations on the distribution of ^{91}Y in the skeleton of rabbits of different ages at varying periods after a single intravenous injection.

EXPERIMENTAL

Rabbits of the same stock as those used in previous experiments (Kidman, Tutt and Vaughan, 1950; Tutt, Kidman, Rayner and Vaughan, 1952) were fed on a diet of oats, hay and cabbage. They were given a single intravenous injection of ^{91}Y as YCl_3 in doses varying from 12 to 500 μc. according to the length of the experiment. Only traces of carrier were present in the solution, which was kept acid (pH 1–3) to prevent adsorption on glass or formation of colloids. Three groups of animals of different ages were used :

(i) Of 18 rabbits aged 5–7 weeks 3 were killed 10 minutes, 24 hours, 9 days, 8 weeks, 16 weeks and 24 weeks after injection. The urinary and faecal excretion of ^{91}Y was estimated for 5 days before the animals in the last group were killed.

(ii) Twelve rabbits aged 3–4 months were killed in groups of 3, 10 minutes, 24 hours, 9 days and 21 days after injection.

(iii) Two rabbits a year old were killed 10 minutes and 9 days after injection respectively.

Immediately after death the bones were removed as previously described. (Kidman, Rayner, Tutt and Vaughan, 1952 ; Tutt *et al.*, 1952). The right femur and usually the right tibia were used for the preparation of autoradiographs ; one or both tibia-fibula, and both humeri, were used for the determination of yttrium retention in different parts of the bone in animals aged 5–7 weeks and 3–4 months. The bones were divided into epiphysis, epiphyseal plate, metaphysis and diaphysis in animals killed at intervals up to 8 weeks after injection. After that time they were divided into " ends " and diaphysis only. Figures for the tibia-fibula only are given ; those for the humerus followed the same pattern. The yttrium content of the scapula, pelvic girdle, radius and ulna and left femur was determined separately, and that for the " rest of the bone " together since it was difficult to clean and therefore to weigh the bones with any accuracy. In order to obtain a figure for the total percentage of injected yttrium in the skeleton, the figure obtained for the left femur was doubled and a calculated figure added to represent the tibia and humerus content. The amount of isotope present is expressed throughout as a percentage of the injected dose, and the weight of bone is also given, since in younger animals the growth dilution factor is considerable. It must be remembered, however, in interpreting the Tables that although the percentage retained in

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any two bones may be the same, the concentration of isotope may be different. The percentage retained is related to the initial uptake, but the growth dilution factor varies from bone to bone. A statistical analysis of the results was carried out, taking into consideration the interaction of percentage retention and gain in weight.

Autoradiographs.

Autoradiographs were prepared from sections of bone as previously described (Kidman *et al.*, 1952), all sections being embedded in perspex prepared from methyl methacrylate monomer. Exposure was regulated to give a satisfactory macroscopic picture. Degrees of blackening in different autoradiographs cannot be compared, although differences in different parts of one autoradiograph are significant. Sections of normal bone containing no radioactive isotope were exposed as controls and were always negative.

Estimation of ^{91}Y.

Estimation of ^{91}Y in the bones was carried out as described for similar experiments with radioactive strontium. (Kidman *et al.*, 1950 ; Tutt *et al.*, 1952).

RESULTS.

Autoradiographs.

Autoradiographs prepared from the long bones showed two types of reaction, localized and diffuse. The picture was unaffected by the size of the dose within the range given.

Localized reactions were found in young animals in the following sites immediately after injection : (*i*) a strong reaction in the region of the lower edge of the epiphyseal plate which extended down less strongly into the metaphyseal trabeculae ; (*ii*) a narrow band above the epiphyseal and beneath the articular cartilage ; (*iii*) a fine line outlining bony trabeculae and the whole of the periosteal and endosteal surface of the bone which was possibly more intense on the periosteal surface of the metaphysis ; (*iv*) irregular streaks and dots throughout the diaphysis (Fig. 1 and 7). In the weanling rabbits 9 days after injection there was wide separation of the two bands adjacent to the epiphyseal plate, the lower one appearing only as a series of dots on the lower end of the metaphyseal trabeculae. The other localized reactions appeared unaltered (Fig. 2). Eight and 16 weeks after injection in the young rabbits there was still a heavy localized reaction in the bony trabeculae in the centre of the epiphysis. The speckling in the shaft was still present, and at varying points dependent on the rate of growth of the bone there was an area of strong reaction at some distance from the epiphysis in the diaphysis. This point appeared to correspond to the lower end of the metaphysis at the time of injection, and is presumably due to incorporation of the most lateral trabeculae in the diaphysis (Fig. 3). The periosteal and endosteal lines were less clearly defined. The picture was unchanged 6 months after injection (Fig. 4). Changes of the same order but less marked were seen in autoradiographs from the bones of rabbits 3–4 months old (Fig. 5). Bones from animals a year old immediately after injection showed a clear outlining of all bony trabeculae, of periosteal and endosteal surfaces and speckling throughout the diaphysis and all bony trabeculae (Fig. 6).

Diffuse reaction.—At all ages there was a faint diffuse reaction throughout mineralized bone immediately after injection. This diffuse reaction was still present six months after injection in all bone which was formed before the injection. It was also present in the diaphysis on the metaphyseal side of the localized points already described extending with decreasing intensity towards the epiphysis. A diffuse reaction in the metaphyseal trabeculae was present but visible only microscopically. A more definite diffuse reaction was apparent in spongy bone external to that showing a localized reaction in the epiphysis.

Chemical Analysis.

(a) 5–7-*week-old rabbits.*

Total retention in the skeleton 10 minutes after injection, expressed as percentage of the injected dose, was 43·8 ± 4·3, after 24 hours it was 75·0 ± 2·3, after 9 days 75·8 ± 0·5 ; it then fell extremely slowly, being still 59·5 ± 3·2 six months after the injection (Table I). The average daily excretion in the urine six months after injection was 0·07 per cent, and in the faeces 0·02 per cent of the injected dose.

TABLE I.—*Mean Values for* ^{91}Y (*Expressed as Percentage of the Injected Dose*) *Retained in the Skeleton of Rabbits Killed at Varying Time Intervals after Injection* (3 *Rabbits in each Group*).

Time after injection.	*Age at time of injection.* 5–7 weeks.	3–4 months.
10 minutes	43·8±4·3*	30·3±0·7
24 hours	75·0±2·3	53·2±4·0
9 days	75·8±0·5	71·7±7·9
21 "	—	66·8±2·4
8 weeks	70·0±1·4	
16 "	65·1±4·3	
24 "	59·5±3·2	

* S.E. $\sqrt{\frac{\Sigma(x - \bar{x})^2}{n(n-1)}}$ · x = individual observation. $\bar{x}$ = means of observations. n = number of observations in group.

DESCRIPTION OF PLATES.

Autoradiographs prepared from sections of lower end of femur of rabbits 5–7 weeks old at time of injection with ^{91}Y. (*All* × 3.)

FIG. 1.—10 minutes after injection (100 μc./kg.). Note (*a*) intense localized reaction beneath the epiphyseal plate ; (*b*) speckled reaction in the diaphysis ; (*c*) narrow periosteal and endosteal lines.

FIG. 2.—9 days after injection (100 μc./kg.). Note (*a*) intense localized reaction is now at extreme lower end of metaphyseal trabeculae.

FIG. 3.—8 weeks after injection (200 μc./kg.). Note (*a*) loss of reaction in the metaphysis : (*b*) two localized areas of reaction in diaphysis presumed to be remains of lateral metaphyseal trabeculae at time of injection incorporated in the diaphysis ; (*c*) persistence of localized reaction in centre of epiphysis ; (*d*) faint reaction in diaphysis in areas of new bone formation.

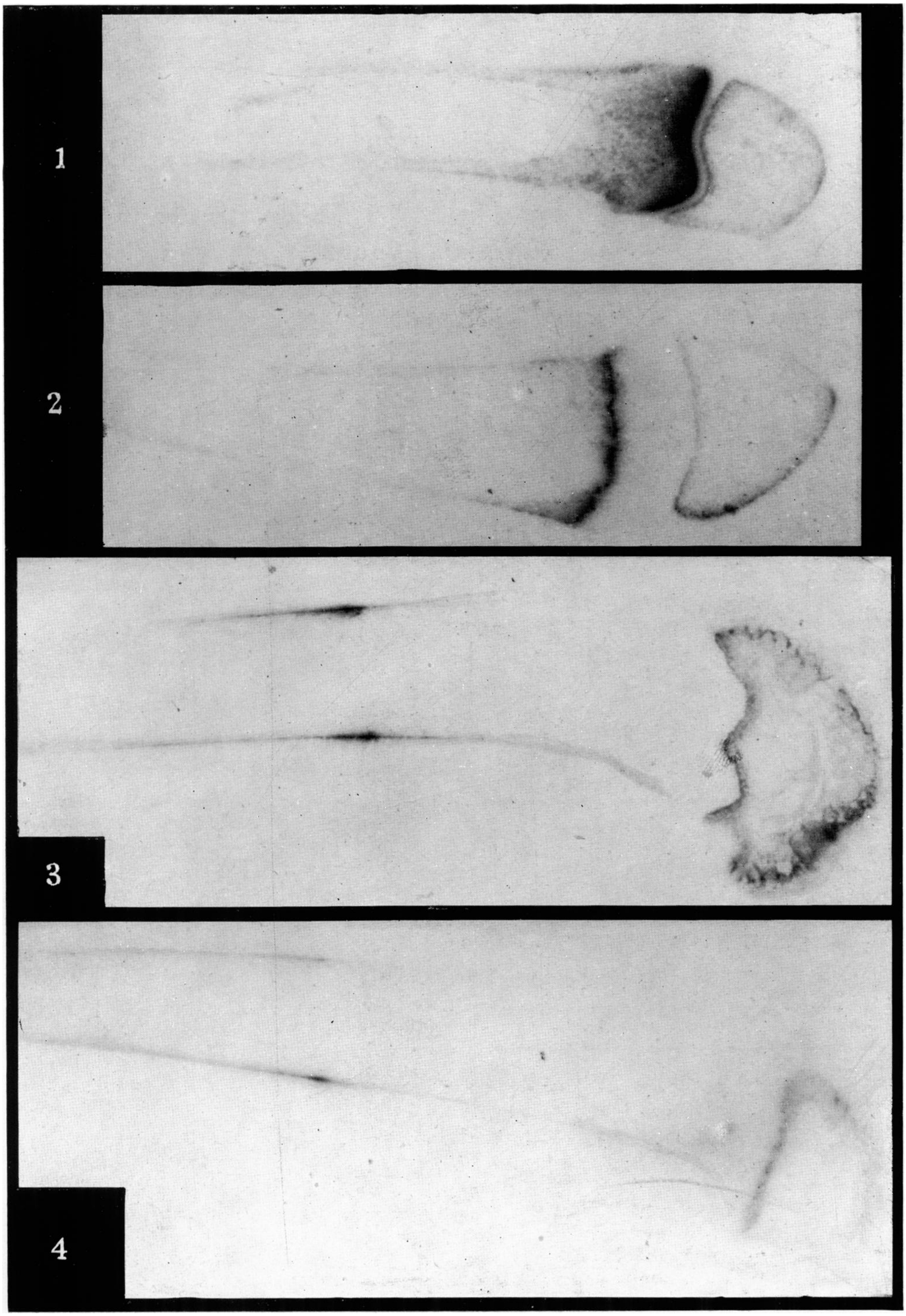
FIG. 4.—24 weeks after injection (500 μc./kg.). Note diffuse reaction throughout diaphysis and epiphysis.

Autoradiographs prepared from sections of lower end of femur of older rabbits after an injection of ^{91}Y.

FIG. 5.—3–4-month-old rabbit killed 21 days after injection (180 μc./kg.). Note (*a*) persistence of localized reaction in the metaphysis ; (*b*) outlining of periosteum and endosteum. (× 3.)

FIG. 6.—12-month-old rabbit killed 10 minutes after injection (100 μc./kg.). Note (*a*) outlining of trabeculae and of periosteal and endosteal surface of bone ; (*b*) speckling in shaft and trabeculae. (× 3.)

FIG. 7.—High-power view of autoradiograph of cortical bone, showing localized reaction giving speckling against a background of diffuse reaction. (× 100.)



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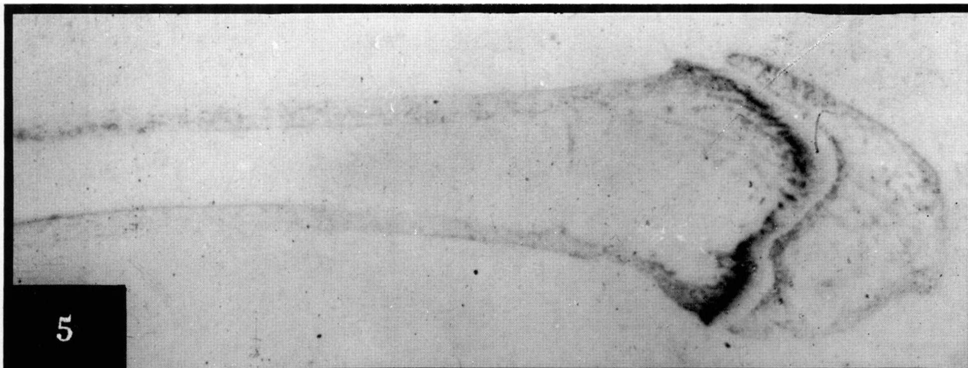

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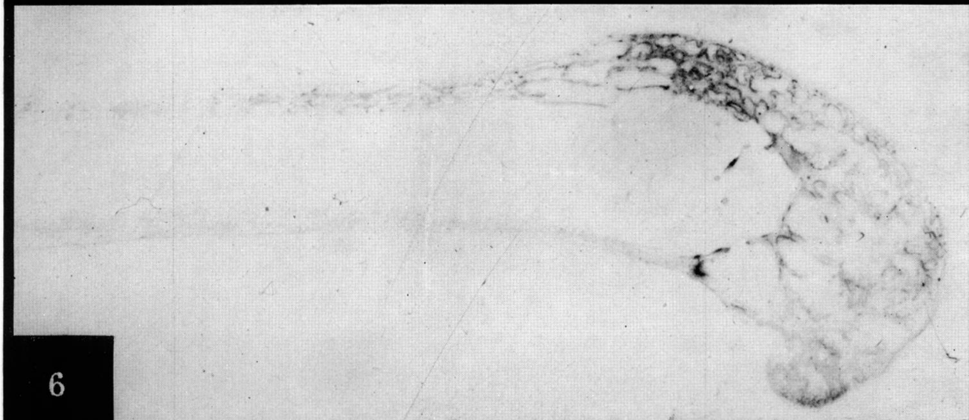

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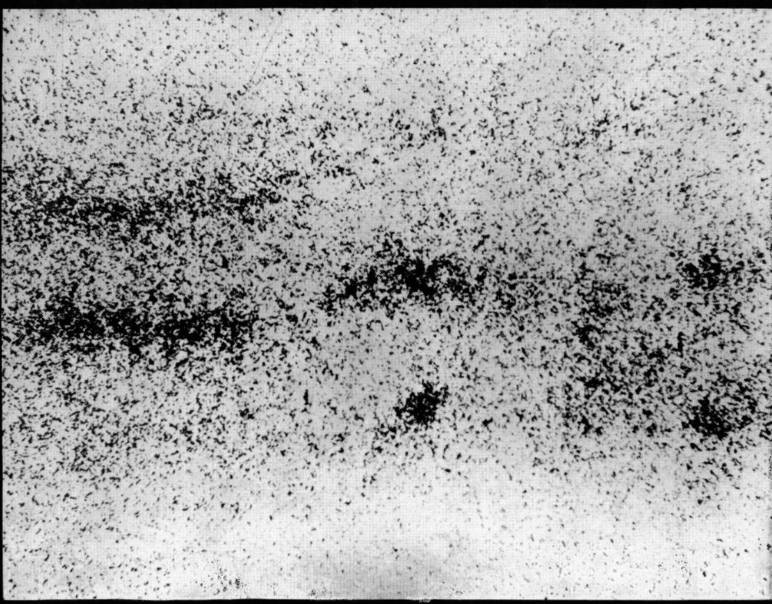

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TABLE II.—*Weights of Bones and Percentages of Injected ^{91}Y Retained at Different Times after Injection in 5–7-Week-old Rabbits. (Mean of 3 Bones at each Point).*

Time after injection.	Femur.		Radius-Ulna.		Scapula.		Pelvic Girdle.		"Rest of Bone."	
	Weight (g.).	Per cent.	Weight (g.).	Per cent.	Weight (g.).	Per cent.	Weight (g.).	Per cent.	Weight (g.).	Per cent.
10 minutes	4·45±0·18	4·51±0·44	1·73±0·12	1·58±0·14	1·18±0·14	1·16±0·02	2·63±0·10	2·89±0·18	41·0±1·5	27·55±3·42
24 hours	5·47±0·27	10·04±0·61	2·23±0·22	3·81±0·21	1·50± —	2·52±0·10	3·30±0·15	6·25±0·06	47·3±2·3	38·58±0·82
9 days	6·77±0·20	8·84±0·23	2·60±0·06	2·72±0·11	1·95±0·17	2·07±0·09	4·48±0·07	5·47±0·22	57·7±4·1	45·15±1·00
8 weeks	10·37±0·44	7·43±0·21	3·36±0·13	2·45±0·11	3·18±0·19	1·94±0·06	7·19±0·83	4·85±0·20	92·3±3·9	43·50±1·42
16 ,,	12·67±0·67	6·40±0·33	4·00± —	2·78±0·56	3·50±0·29	1·70±0·08	8·50±0·29	3·38±0·63	105·0±2·6	41·64±3·47
24 ,,	11·83±0·44	6·43±0·18	4·50± —	2·36±0·07	4·67±0·44	1·62±0·03	8·83±0·17	3·99±0·12	113·7±1·8	36·30±2·85

TABLE III.—*Weights of Portions of Tibia-fibulas and Percentages of ^{91}Y Retained at Different Times after Injection in 5–7-Week-old Rabbits.*

Time after injection.	Epiphysis.		Epiphyseal Plate.		Metaphysis.		Diaphysis.	
	Weight (g.).	Per cent.	Weight (g.).	Per cent.	Weight (g.).	Per cent.	Weight (g.).	Per cent.
10 minutes	0·162±0·007	0·39±0·01	0·144±0·015	0·64±0·04	0·220±0·013	0·59±0·13	0·298±0·012	0·33±0·02
24 hours	0·167±0·011	0·58±0·05	0·177±0·013	1·79±0·06	0·251±0·012	1·21±0·08	0·370±0·013	0·49±0·02
9 days	0·261±0·027	0·55±0·05	0·246±0·011	0·64±0·03	0·374±0·022	1·57±0·20	0·557±0·031	0·71±0·06
8 weeks	0·323±0·004	0·53± —	0·344±0·009	0·46±0·01	0·463±0·054	0·52±0·04	1·097±0·084	1·32±0·08

TABLE V.—*Weights of Bones and Percentages of Injected ^{91}Y Retained at Different Times after Injection in 3–4-Month-old Rabbits. (Mean of 3 Bones at Each Point).*

Time after injection.	Femur.		Radius-Ulna.		Scapula.		Pelvic Girdle.		"Rest of Bone."	
	Weight (g.).	Per cent.	Weight (g.).	Per cent.	Weight (g.).	Per cent.	Weight (g.).	Per cent.	Weight (g.).	Per cent.
10 minutes	11·8±0·2	3·29±0·24	4·3±0·3	1·36±0·04	3·7±0·2	0·97±0·05	8·3±0·3	2·16±0·10	95·3±2·4	17·82±1·04
24 hours	10·7±0·9	6·80±0·92	3·7±0·2	2·21±0·17	3·7±0·3	1·70±0·06	8·0±0·6	4·15±0·33	87·7±3·4	29·36±1·56
9 days	11·7±0·7	8·52±1·33	4·5±0·3	3·01±0·22	3·8±0·3	2·33±0·26	8·5±0·8	5·93±0·61	97·3±4·3	40·31±4·00
21 ,,	13·3±0·3	7·05±0·39	5·0±0·8	2·75±0·31	4·3±0·4	2·34±0·12	9·5±0·5	4·90±0·32	110·0±5·0	41·19±1·54

TABLE VI.—*Weights of Portions of Tibia-fibulas and Percentages of ^{91}Y Retained at Different Times after Injection in 3–4-Month-old Rabbits.*

Time after injection.	Epiphysis.		Epiphyseal Plate.		Metaphysis.		Diaphysis.	
	Weight (g.).	Per cent.	Weight (g).	Per cent.	Weight (g.).	Per cent.	Weight (g.).	Per cent.
10 minutes	0·348±0·033	0·16±0·02	0·373±0·022	0·58±0·11	0·580±0·088	0·42±0·52	1·294±0·155	0·40±0·07
24 hours	0·319±0·331	0·29±0·04	0·352±0·020	1·18±0·09	0·483±0·034	0·82±0·07	1·182±0·081	0·73±0·07
9 days	0·351±0·045	0·56±0·20	0·391±0·014	1·06±0·17	0·512±0·070	1·14±0·22	1·264±0·078	0·90±0·09
21 ,,	0·330±0·021	0·27±0·03	0·479±0·021	0·68±0·10	0·556±0·037	0·70±0·08	1·661±0·109	0·83±0·08

Different bones.—The percentage of the injected dose retained in different bones directly after injection was roughly proportional to their initial weight (Table II). Uptake in the femur, radius, ulna, pelvic girdle and scapula reached its maximum 24 hours after injection, while in the " rest of bone " the highest figure was found 9 days after injection. There was then a slow fall in all bones except for an apparent rise at six months in the pelvic girdle. Unless such a result is confirmed on repetition its significance is doubtful. With this exception the downward trend may be regarded as significant, since although any particular difference observed may not be significant, the accumulation of several may ; thus for the femur, although neither the decrease from 24 hours to 9 days nor that from 9 days to 8 weeks is significant, the total decrease from 24 hours to 8 weeks is significant, showing that the apparent downward trend is genuine. The pattern of retention is then the same in the long and flat bones examined separately. In one or more of the bones included in " rest of bone " this pattern would appear to be different.

Different parts of the same bone.—Chemical analysis of retention in different parts of the bone showed that in all parts there was an increase in the percentage retained between 10 minutes and 24 hours after injection. Thereafter the percentage in the epiphysis was unchanged, that in the diaphysis increased, and that in the epiphyseal plate and metaphysis decreased up to 8 weeks after the injection (Table III). These differences were highly significant ; thus the percentages found 24 hours and 8 weeks after the injection were 0·49 and 1·32 respectively in the diaphysis, and 1·79 and 0·46 respectively in the epiphyseal plate. Analysis of " ends " and diaphysis six months after injection showed the diaphysis still contained 1·34 per cent of the injected dose, while the " ends " contained 1·02 per cent compared with 3·57 per cent at 24 hours (Table IV).

TABLE IV.—*Weights of " Ends " and Diaphysis of Tibia-fibulas and Percentages of* ^{91}Y *Retained at Different Times after Injection in 5–7-Week-old Rabbits.*

Time after injection.	" Ends."		Diaphysis.	
	Weight (g.).	Per cent.	Weight (g.).	Per cent.
10 minutes	$0·526 \pm 0·016$	$1·62 \pm 0·10$	$0·298 \pm 0·012$	$0·33 \pm 0·02$
24 hours	$0·596 \pm 0·033$	$3·57 \pm 0·12$	$0·370 \pm 0·013$	$0·49 \pm 0·02$
9 days	$0·881 \pm 0·042$	$2·76 \pm 0·26$	$0·557 \pm 0·031$	$0·71 \pm 0·06$
8 weeks	$1·130 \pm 0·058$	$1·52 \pm 0·26$	$1·097 \pm 0·084$	$1·32 \pm 0·08$
16 "	$1·236 \pm 0·059$	$1·12 \pm 0·06$	$1·618 \pm 0·166$	$1·21 \pm 0·13$
24 "	$1·329 \pm 0·034$	$1·02 \pm 0·03$	$1·763 \pm 0·052$	$1·34 \pm 0·04$

(b) 3–4-*month-old rabbits.*

Total retention in the skeleton expressed as percentage of the injected dose was $30·3 \pm 0·7$ 10 minutes after injection, $53·2 \pm 4·0$ after 24 hours, $71·7 \pm 7·9$ after 9 days, and $66·8 \pm 2·4$ after 21 days (Table I).

Different bones.—The maximum retention in all bones was found 9 days after injection. Except in the femur, the increase between 24 hours and 9 days was significant. Twenty-one days after injection there was no significant decrease. The pattern of retention was the same both in the long and flat bones examined separately and in the " rest of bone " (Table V).

Different parts of the same bone.—Analysis of the retention in different parts of the bone shows that the differences at different times, although not as dramatic as in younger animals, were significant at certain time intervals (Table VI). Thus there was a rise in the percentage of yttrium in all parts of the bone between 10 minutes and 24 hours after the injection. The epiphysis showed a further rise from 0·29 per cent 24 hours after injection to 0·56 per cent at 9 days, followed by a fall to 0·27 per cent at 8 weeks. The percentage in the plate decreased significantly from 1·18 at 24 hours to 0·68 at 9 days ; that in the metaphysis showed a rise from 0·82 at 24 hours to 1·14 at 9 days, and then a fall to 0·70 at 21 days. The percentage in the diaphysis did not rise or fall significantly between 24 hours and 8 weeks after the injection, the value remaining between 0·73 and 0·83.

DISCUSSION.

The chemical and autoradiographic results recorded here confirm previous observations (Vaughan *et al.*, 1952 ; Kidman, Tutt and Vaughan, 1951) that the uptake of radioactive yttrium in tracer doses by the rabbit's skeleton is extremely rapid at all ages, A rather higher percentage of the yttrium injected is taken up than of radioactive strontium, although if given in other than tracer amounts bone appears more avid for strontium (Macdonald *et al.*, 1952). The yttrium appears to be retained longer than the strontium, and to be less affected in its uptake by age. The higher uptake affects all parts of the bone in young animals. The fact that excretion of ^{91}Y in urine and faeces is lower at both 9 days and at 6 months (Kidman *et al.*, 1951) after injection than that of ^{90}Sr is compatible with this higher retention.

The significant point which arises from analysis of the yttrium content in different whole bones is that in the 5–7-week-old group the rate of uptake in the " rest of bone " is slower than in the separate bones examined. This effect is not apparent in the 3–4-month-old group. It is not yet known whether all or part only of the bones included in " rest of bone " are responsible for this phenomenon, nor whether it is the yttrium lost from the other bones or from the soft tissues between 24 hours and 9 days after injection that is taken up by the " rest of bones."

The autoradiographic studies suggest that as in the case of strontium (Kidman *et al.*, 1952) and phosphorus (Leblond, Wilkinson, Belanger and Robichon, 1950) ^{91}Y given in a tracer dose is deposited in bone in two ways, giving respectively a heavy localized reaction and a diffuse reaction. The latter may well be due to adsorption on bone salt or protein surfaces (Tutt *et al.*, 1952 ; Kidman *et al.*, 1952). Bone formed after injection, both in the shaft and in the epiphysis, also shows a diffuse reaction. As the length of new bone formed is considerable in some cases, this is presumably due to uptake from the blood stream of ^{91}Y released in the normal process of resorption or from the soft tissues. This secondary uptake has been observed in 24-hour-old rabbits following a single injection of ^{90}Sr, but is much less definite in 5–7-week-old rabbits given ^{90}Sr (personal observations, unpublished). Presumably the element in bone that takes up ^{91}Y takes it up more readily and when in a lower concentration in the blood than that which takes up ^{90}Sr. This secondary uptake together with considerable retention in the epiphysis may to a large extent account for the maintenance of a high total retention in the skeleton after resorption of the metaphyseal trabeculae containing the isotope laid down at the time of injection. If yttrium were to form a complex with some component of the connective tissue of bone as has been suggested (Hamilton, 1947 ; Copp, Hamilton, Jones, Thompson and Cremer, 1952), this may account for its continued retention, since the metabolic turnover of bone collagen is extremely slow (Perrone and Slack, 1951). It is, however, necessary to postulate a difference in the connective tissue in different sites, since yttrium is taken up in concentration by rapidly growing bone tissue beneath the epiphyseal plate giving a strong localized reaction, but not by active bone tissue beneath the endosteum and periosteum (Fell, 1931–32). The narrow line along the entire periosteal and endosteal surfaces of bone immediately following injection is possibly due to deposition of ^{91}Y in periosteum and endosteum, while the speckling in mineralised bone may depend on deposition in some element of connective tissue around Haversian systems in a manner similar to that following the injection of americium (Scott, Axelrod, Fisher, Crowley and Hamilton, 1948) and curium (Scott, Axelrod and Hamilton, 1949). That only certain systems are affected may be due to the fact that in bones as in other organs only a proportion of the vessels is patent at any one time, and the isotope is taken up in relation to those vessels which are patent when the blood level is high.

SUMMARY.

Chemical and autoradiographic studies show that the deposition of ^{91}Y in the bones of rabbits of different ages following a single intravenous injection of a carrier-free tracer dose is extremely rapid. Retention is greater, rather more persistent and less affected by age than that of strontium. Excretion in both urine and faeces is rather less than that of strontium.

^{91}Y appears to be concentrated (*i*) in the site of active bone growth beneath the epiphysis but not beneath the endosteum or periosteum, suggesting differences in the character of the connective tissue of bone in the two sites ; (*ii*) in a patchy way in the shaft presumably in association with the connective tissue around blood-vessels.

New bone in young animals formed months after the original injection contains traces of ^{91}Y, presumably due to the capacity of some element in bone to complex with ^{91}Y present in extremely low levels in the blood as a result of normal processes of resorption.

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A copy of the statistical analysis can be obtained on request. The conclusions are embodied in the text.

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