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EFFECT OF HIGH ^{131}I DOSES ON THE BONE UPTAKE AND RETENTION OF ^{90}Sr AND ^{90}Y

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Abstract

The uptake and retention of ^{90}Sr and ^{90}Y in mouse bones after injections of the two nuclides in equilibrium were examined after heavy thyroid irradiations from ^{131}I deposited in the glands. The radiation doses to the thyroid glands as well as the gross doses to the femurs and humeri of the mice were calculated. The radiation destruction of the thyroid tissues had no effect on the bone weights nor on the skeletal metabolism of ^{90}Sr. The uptake of ^{90}Y was, however, depressed after thyroidal irradiation but reached the same bone concentration as ^{90}Sr at about 30 days after the administration of the nuclides, i.e. at a time when the corresponding equilibrium between ^{90}Sr and ^{90}Y in the bones was reached in mice without a thyroidal irradiation.

Key words: Radiobiology; mice, high ^{131}I doses, ^{90}Sr–^{90}Y uptake, bone.

A reactor accident or a nuclear explosion giving rise to a release of radiostrontium available for human inhalation or ingestion in amounts that would constitute a non-negligible risk of bone tumors, would also imply a risk of massive radioiodine incorporations during the first weeks after the catastrophe. GREITZ & EDVARSON (10)have calculated that the consumption of milk from cattle grazing in 'fresh' fallout areas caused by atomic bombs would give rise to thyroid radiation doses that are 100 to 1000 times higher than those to the skeleton from bonedeposited radiostrontium. These dose differences would even be higher if fission products from reactor accidents were inhaled. Uptakes of tumorigenic amounts of radiostrontium in man would therefore correspond to a more or less total destruction of the thyroid gland by the thyroidal uptake of radioiodines.

The uptake and retention of radiostrontium in the skeleton is greatly dependent on the hormonal balance in the body. It would therefore be of interest to examine to what extent complete destruction of the thyroid gland would interfere with the incorporation and retention of strontium in bone. The destruction of thyroid tissue by high ^{131}I doses would depress the production of triiodothyronine (T_3), thyroxine (T_4), and calcitonin (CT) from the thyroidal C-cells, but it should not seriously affect the parathyroid gland or the production of parathyroid hormone (PTH).

Information about the effects of T_3 and T_4 depression on bone metabolism is scanty, but it is known that the thyroid hormones affect bone variously. Osteoporosis is a frequent finding in hyperthyroidism in man (2). The increased bone turnover in hyperthyroid patients is due to an increase in both bone resorption and bone formation, but the former, a consequence of elevated osteoclastic resorption, prevails (13). In this connection, thyroxine is known to elevate the activation frequency of mesenchymal cells in bone, i.e. causes increased differentiation of mesenchymal cells into osteoclasts and osteoblasts (8), and to stimulate directly the metabolic activity of bone cells, thus profoundly affecting the bone turnover (11). The housing of rats and mice in cold conditions activates the thyroidal function (20) and this activation has been suggested to be the main reason for the increased calcium and strontium release from the bones, as observed in cold-treated rats and mice (2, 23). Treatment with T_3 and T_4 reduced the retention of bone-bound ^{85}Sr in young mice (18) and stimulated bone resorption in cultured fetal rat bones (14).

MARKS (12) found that experimentally produced osteopetrosis provided evidence that C-cells are the source of

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an osteoblast-stimulating factor, related during periods of hypercalcemina, which has a net effect on bone, antagonistic to that of PTH. In other words CT would stimulate the incorporation of calcium (and strontium?) into bones, whereas PTH would act as a releasing factor. However, as pointed out by ATKINS & PEACOCK (1) the interaction between the two hormones is more complex than that, since it is recognized that thyroid hormones influence the responsiveness of bone cells to 1.25-dihydroxycholecalciferol, PTH and CT. The excess of thyroid hormones sensitizes (and deficiency blunts) the response of bone to PTH (4). DOBROSKOK et coll. (6) have shown that the combined effect of ^{45}Ca and PTH produced a significantly greater number of osteosarcomas in male rats than that found after ^{45}Ca alone. Still lower frequencies were recorded in cases where the ^{45}Ca-injections were combined with parathyroidectomies. The extra administration of PTH somewhat increased the ^{45}Ca concentration in the rat bones (and thus the radiation dose to the skeleton), but the authors concluded that the main cause of the tumor-promoting effect of the hormone was an endocrine regulatory disturbance of the metabolism in the bones.

The calcemic response to 1.25-dihydroxycholecalciferol declines in thyroidectomized rats and the fact that T_4 restores the normal response suggests that this phenomenon is due to a lack of this hormone and not to the lack of thyrocalcitonin (16).

No significant change in the bone uptake of ^{90}Sr—though well a depression of the ^{90}Y-uptake—was found by injecting ^{90}Sr in equilibrium with ^{90}Y to parathyroidectomized rats (19).

The present investigation was designed to examine in mice the effect on the skeletal uptake and retention of ^{90}Sr and ^{90}Y by (massive) irradiation of the thyroid glands from concurrently administered ^{131}I.

Material and Methods

Male C57Bl/S mice, 70 to 90 days old were maintained on an iodine-deficient diet for 14 days. They were treated according to the scheme presented in Table 1. The designation of the animal groups in Table 1 refers to the division of the investigation into two separate experiments, in the following called expt. A and expt. B. In expt. A, some animals still exhibited small remains of thyroid tissues in the lobal peripheries, as seen 180 days after the injection in spite of the high radiation doses to the gland. However, remaining fragments of thyroid tissues were seen only in a few cases and they were severely damaged and fibrotic, yet we could not à priori exclude some functional capacity of the remnant tissues. The expt. A was therefore repeated one year later with twice as high ^{131}I-doses. The second experiment is here called expt. B and great efforts were laid down to ensure identicality in management of the animals in the two experiments.

The iodine-deficient diet was replaced by a diet with normal iodine content (Astra-Ewos) after the treatments. The mice were kept under controlled temperature, humidity and light conditions throughout experiment. Water was supplied ad libitum. The radionuclides used were from the Radiochemical Centre, Amersham, England.

Table 1

Experimental design

Experiment group	No. of mice	Treatment	When examined (days post-treatment)
A-1	20	Controls	1, 5, 27, 180
A-2	20	370 kBq ^{90}Sr	
A-3	20	370 kBq ^{90}Sr+1.1 MBq ^{131}I	
B-1	20	Controls	1, 5, 27, 180
B-2	20	370 kBq ^{90}Sr	
B-3	20	370 kBq ^{90}Sr+2.2 MBq ^{131}I	1, 5, 27, 180

The radionuclides were injected intraperitoneally as $^{90}Sr(NO_3)_2$ and Na ^{131}I in saline. Five animals from each of the experimental groups were killed on the day of examination.

The measurement of thyroidal ^{131}I-content and dose determinations were described earlier (21). The measurement of ^{90}Sr and ^{90}Y in the mouse-bones was described by WALINDER & MÜLLER (22).

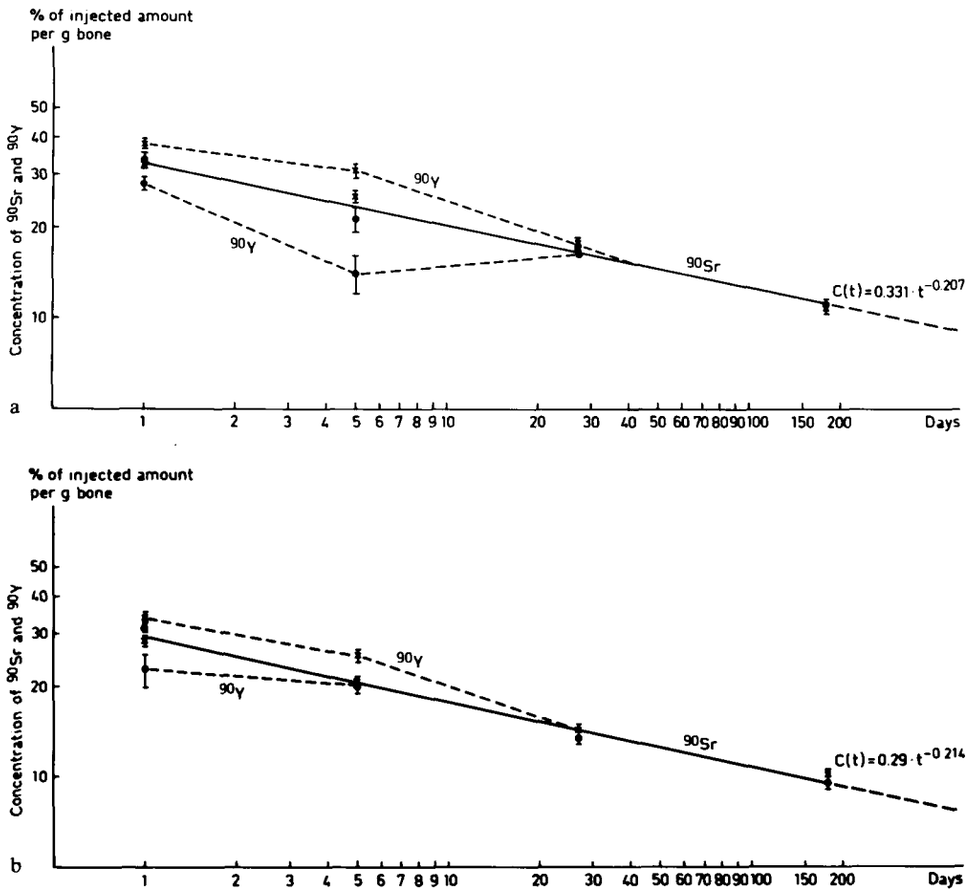
Calculation of β-doses to the femur. The effective ^{90}Sr and ^{90}Y doses have been calculated on the assumption that uptake and retention of the two nuclides in the femur were the same as those in the humeri as found by WALINDER & MÜLLER (22) for female C57Bl mice. The doses were determined in the femurs since they were the predominant sites of bone tumors (9). The reason why the uptakes and retentions were measured in the humeri and not in the femurs was that the humeri are smaller than the femurs and they can thus be measured in whole in the liquid scintillation counter whereas the femurs have to be divided into two parts to avoid unacceptable quenching and absorption of the scintillations. The results from the humeri measurements were therefore more exact and reliable than those from the measurements of the femurs.

The radiation doses per injected Bq in the time interval t_1–t_2 were calculated by the formula:

$$1.38 \cdot 10^{-5} \cdot \bar{E}_\beta \cdot \lambda \cdot Q(1) \cdot \int_{t_1}^{t_2} f(t)\,dt \quad Gy$$

where $\bar{E}_\beta$ is the mean beta-energy (in MeV) and λ the fraction of the beta-energy absorbed in the bone. Q(1) is the fraction of the injected amount of ^{90}Sr and ^{90}Y respectively per g of bone (wet weight) one day after the injection and $Q(1) \cdot f(t)$ the corresponding concentration of the activity at time t.

The upper integration limit, t_2, cannot be adequately determined since the time of tumor induction is unknown. The doses up to the time of tumor appearance were cer-



Retention of ^{90}Sr and ^{90}Y in humeri. Values from a) expt. A and from b) expt. B. Concentration of $_{90}Sr$ in $_{90}Sr$ treated mice (×—×) and in $^{90}Sr+^{131}I$ treated mice (●—●).

tainly higher than those necessary for the actual induction of a tumor and much of the late exposure would thus be 'wasted'.

PARMELY et coll. (15) have calculated and measured the fraction λ, of absorbed β-energy from ^{90}Sr and ^{90}Y in various animal bones. In the mouse femur they found $\lambda=0.78$ for ^{90}Sr and $\lambda=0.30$ for ^{90}Y. The radiation doses to the femurs as estimated by the formula above, is thus only a mean gross-dose to the bones. We have not been able to estimate the doses to the proliferating osteoblasts, i.e. to the peri- and endo-osteal parts of the bones. We have, however, assumed that the estimated doses are proportional to those to the bone surfaces and hence made comparisons between the results possible.

As can be seen in the Figure, the functions f(t) for ^{90}Sr and for ^{90}Y at $t\geq 27$ days are close to logarithmic curves, i.e. $f(t)=t^{-0.207}$ in expt. A and $f(t)=t^{-0.214}$ in expt. B. However, during the first 27 days after the injections the ^{90}Y doses deviate from the logarithmic course. The expression $Q(1)\cdot f(t)$ for ^{90}Y during this period has therefore been approximated by its arithmetic means:

$$Q(1)\cdot\int_1^{27} f(t)\,dt \approx \frac{Q(1)+Q(5)}{2}\cdot 4+\frac{Q(5)+Q(27)}{2}\cdot 22$$

The small dose contribution from the first day of exposure is neglected.

From this calculation and the values in Table 2, we obtained Table 3.

Results

Uptake and retention of ^{90}Sr. The uptake and retention values of ^{90}Sr and ^{90}Y in the femurs, the parietal bones, and in the humeri were essentially equal. In the thoracic vertebrae the uptake of ^{90}Sr was around 60 per cent and the ^{90}Y uptake about 50 per cent lower than those in the other bones. The similarity of the uptake and retention of ^{90}Sr–^{90}Y in the various bones in the mouse-body made it possible to restrict the measurement in expt. B and the comparisons between the groups in expt. A and expt. B to measurements of the activities in the humeri. The choice of humeri as objects for the measurements was mainly due

Table 2

Beta doses to the femur

Period of time, days	Group A-2			Group A-3		
	^{90}Sr (Gy)	^{90}Y (Gy)	Total (Gy)	^{90}Sr (Gy)	^{90}Y (Gy)	Total (Gy)
1–27	4.2	9.5	13.7	4.2	5.9	10.1
1–213*	23.1	43.2	66.3	–	–	
1–371*	–	–		36.0	62.8	98.8
1–413**	39.2	72.2	111.4	–	–	
1–452**	–	–		42.1	73.8	115.9
1–467	43.2	79.4	122.6	43.3	75.8	119.1
	Group B-2			Group B-3		
1–27	3.6	7.9	11.4	3.6	6.5	10.4
1–280*	–	–		24.4	43.7	68.1
1–288*	24.9	46.0	70.9	–	–	
1–360**	–	–		29.8	53.3	83.1
1–439**	34.9	63.8	98.7	34.9	62.4	97.3

* Time of appearance of the first tumour (9).
** Mean incidence time for tumours (9).
The last surviving mouse in group A-3 died on day 467 and that in group B-3 on day 440.

Table 3

Weights of humeri and thyroid glands. Concentrations of ^{90}Sr and ^{90}Y in humeri of mice receiving either ^{90}Sr only or in combination with ^{131}I

Days after treatment	Group	Treatment	Humerus weight (mg)	Concentration percentage of injected amount per gram wet-weight		Thyroid weight (mg)
				^{90}Sr	^{90}Y	
1	A-2	^{90}Sr	30.0±1.4	32.8±1.1	37.9±1.0	2.7±0.2
1	A-3	^{90}Sr+^{131}I	28.9±1.4	33.1±2.2	27.8±1.4	2.3±0.1
1	B-2	^{90}Sr	31.9±1.0	28.3±1.3	33.9±1.3	2.9±0.2
1	B-3	^{90}Sr+^{131}I	30.7±0.7	31.0±1.1	22.9±3.4	3.1±0.1
5	A-2	^{90}Sr	32.6±1.4	25.2±1.1	30.8±1.7	2.4±0.3
5	A-3	^{90}Sr+^{131}I	32.5±1.3	21.2±1.9	14.0±2.0	2.4±0.1
5	B-2	^{90}Sr	33.6±1.0	20.5±0.9	25.2±1.1	2.9±0.1
5	B-3	^{90}Sr+^{131}I	34.7±0.6	20.3±1.5	19.9±1.6	2.4±0.3
27	A-2	^{90}Sr	30.4±1.6	17.9±0.6	17.3±1.0	2.8±0.2
27	A-3	^{90}Sr+^{131}I	32.5±0.6	17.7±0.7	16.2±1.0	0.5±0.3
27	B-1	–	35.2±0.8	–	–	2.6±0.2
27	B-2	^{90}Sr	34.1±0.6	14.2±0.5	14.2±0.5	3.1±0.1
27	B-3	^{90}Sr+^{131}I	33.9±0.6	13.4±0.7	13.4±0.7	1.0±0.4
180	A-1	^{90}Sr	33.2±1.0	10.8±0.4	10.8±0.4	3.8±0.3
180	A-2	^{90}Sr+^{131}I	32.4±1.0	11.1±0.4	11.1±0.4	–*
180	B-1	–	26.8±0.8	–	–	4.8±0.2
180	B-2	^{90}Sr	31.1±0.6	10.1±0.3	10.1±0.3	5.0±0.4
180	B-3	^{90}Sr+^{131}I	32.0±1.1	9.5±0.4	9.5±0.4	–*

* In expt. A only fragments of the thyroid tissues remain and in expt. B no traces of functional thyroid glands could be seen.

to technical reasons; the humerus is big enough to give reliable number of counts at measurements in the liquid scintillation counter, but small enough to give a minimal quenching. The results are given in Table 2 and the Figure.

The uptake and retention of ^{90}Sr was independent of whether the animals were ^{131}I-treated or not. As has earlier been found in female C57 Bl/S mice (22), the uptake of ^{90}Y was a little higher than that of ^{90}Sr and this difference was still more pronounced after 5 days. Equilibrium, however, was reached on the 27th day after the injection. In ^{131}I-treated animals, the uptakes were the

reverse of those found in animals injected with ^{90}Sr only (Figure).

Doses to the thyroid gland and the femur. The mean doses to the thyroid glands were calculated on the basis of measurements of the uptake and retention of ^{131}I. In expt. A the mean dose to the central parts of the thyroidal lobes was 1 100 Gy and that to the peripheries of the lobes was about 450 Gy. The corresponding figures in expt. B were 1 700 Gy and 700 Gy, respectively. In expt. B no remnants of thyroid tissue could be found at 180 days post-injection (21).

The mean gross-doses from ^{90}Sr and ^{90}Y deposited in the femurs are calculated for various times. The ideal exposure time for such calculations should be the time interval from the day of nuclide administration to the first cellular change that eventually leads to an observable, macroscopic tumor. Such an event can, however, not be discerned so the dose values given in Table 3 have been calculated up to the point of time when the first tumor appeared in each group of the mice as well as to the mean time of incidence of femoral tumors (9). Since both of these time points are later than that of the event of tumor-initiation, a part of the radiation must be considered 'wasted'.

Discussion

No changes could be found in uptake and retention of ^{90}Sr in the humerus resulting from the high ^{131}I doses to the thyroid gland. The ^{90}Y-uptakes were, however, depressed after the thyroidal irradiation, but the differences in these ^{90}Y uptakes did not result in any appreciable change in the total radiation dose to the bones (Table 3). The uptake of ^{90}Sr in the male mice was slightly lower than that earlier found in female C 57 Bl mice (22), but the retention values were similar. The ^{90}Y-uptake in both male and female mice was somewhat higher than the ^{90}Sr-uptake, but the contrary was true after a massive thyroidal irradiation.

Destruction of the thyroid gland implies destruction of the C-cells (7) but it is not actually known to what extent this leads to an essential depression of the calcitonin production in the mouse, since polypeptides, immunologically similar to CT can be produced in other organs as well (3), and immunoreactive CT has been shown to persist after total thyroidectomy in man (17).

Neither the turnover of ^{90}Sr in the bones, nor any changes in the bone weights could verify a depression of the CT production in amounts that could affect its antagonistic capacity vis-à-vis PTH with regard to the bone metabolism. Instead, there was a reduction in the ^{90}Y-uptake similar to that found by STEVENSON (19) after parathyroidectomy in rats. Could it be that the thyroid irradiation also resulted in a reduced production of PTH despite the fact that the parathyroid tissue was not, or only moderately damaged, as judged by the histologic evidence? We have not yet examined the effect of heavy irradiations of the thyroid gland on the production of PTH.

Since ^{90}Y is incorporated primarily at sites of resorption (5), and the number of resorption sites is dramatically increased in animals treated with moderate, pharmacologic amounts of thyroxine (11), losses in production of thyroid hormones in the irradiated thyroids cannot be disregarded as one of several possible causes of the depression of the ^{90}Y-uptake. The difficulty in such explanations is, however, that thyroidal irradiation should have affected the ^{90}Sr-uptake as well. If a CT-depression would have exerted an effect as suggested in the introductory remarks, the effect should primarily have acted on the retention of the two nuclides rather than on their uptakes. Thus, we have not been able to find any simple mechanisms by which a thyroidal destruction can depress the ^{90}Y-uptake without affecting the uptake of ^{90}Sr.

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