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PATHOLOGIC EFFECTS OF DIFFERENT DOSES OF RADIOSTRONTIUM IN MICE

Changes in the haematopoietic system

by

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The early and late effects of ^{90}Sr on the haematopoietic system have often been investigated (2, 3, 7, 8, 9, 10, 12, 15, 19, 21) but they are in many respects poorly understood since the time-dependent distribution in the tissues and the biologic behaviour of ^{90}Sr are very complex. Most of the tissues are initially subjected to short irradiation, before the radiostrontium is almost completely confined to the skeleton. The marrow will be particularly exposed but the irradiation dose will differ considerably depending on size and shape of the bone and the rate of redistribution of the ^{90}Sr in the different parts of the skeleton. The extraskeletal parts of the haematopoietic system may on the other hand to some extent be directly, but more and more indirectly, influenced by the successively decreasing regeneration capability of the bone marrow after protracted irradiation.

Some of these aspects have earlier been investigated and reported on (16, 17). The present paper deals with the quantitative and qualitative as well as the time-dependent effects of various doses of ^{90}Sr on the haematopoietic system.

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Table 1

Experimental conditions and ^{90}Sr doses employed

Dose of ^{90}Sr in μCi/g body weight	Total number of mice investigated	Number of mice killed in groups of five at given intervals	Last day for sacrifice	Number of mice that died naturally
Sacrificed mice				
1.6	120*	65	300	50
0.8	121	75	360	46
0.4	122	95	480	27
0.2	122**	103***	540	17
Control	95	94****	570	1
Mice used for cell distribution analysis				
0.8	20	20	60	0
0.4	60	50	300	0
0.2	20	20	60	0
Control	50	50	300	0

Of these animals five* and two** were lost during the experiment; only three*** and four**** animals, respectively, were sacrificed in the last test group.

The extent to which different doses of ^{90}Sr affect the functional relations between the thymus, spleen and bone marrow will also be considered.

Material and Methods. Four groups of CBA male mice, 75 days old, were treated intraperitoneally with different doses of $^{90}Sr(NO_3)_2$. A group of 95 untreated animals were used as controls. Five mice from each group were selected at random and sacrificed at intervals of 7, 14, 21 and 30 days after injection of ^{90}Sr and then at monthly intervals until all the surviving mice in each series had been used up.

The quantitative relation between cells in the bone marrow, spleen and thymus was studied by distribution analysis. One hundred mice were separated into three groups and then injected with 0.2, 0.4 and 0.8 μCi/g body weight respectively. Fifty mice were used as untreated controls. Five mice from each of these groups were killed after 7, 14 and 21 days and after 2 months. In addition, five mice from the control groups and from the 0.4 μCi group were investigated at 3, 4, 5, 7, 9 and 10 months. Experimental conditions and the doses of ^{90}Sr employed are recorded in Table 1.

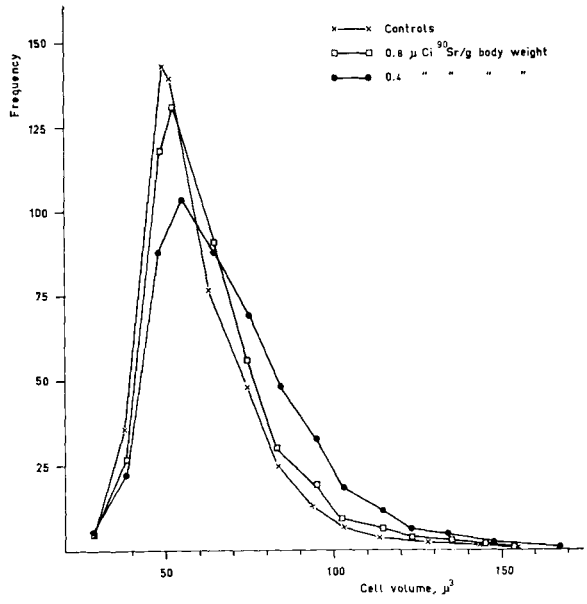

Fig. 1. Cell volume diagram (Coulter counter) of peripheral blood with macrocytosis 21 days after injection of ^{90}Sr.

The mice before sacrifice were anaesthetized and blood samples were obtained with a Pasteur pipette from the medial venous plexus of the eye. Total counts of leukocytes and thrombocytes were made. The haemoglobin values were expressed in gram per 100 ml blood. Blood smears for the differential counts were dried in air, stained with May-Grünewald-Giemsa, and 200 cells were counted in each smear.

For the histologic investigation, the femora, tibiae and humeri as well as the pelvic bones, the spine, thymus, spleen, mesenteric lymph nodes, liver, kidneys and the brain were fixed in Stieve's fluid. These tissues were prepared according to conventional histologic methods and stained by the van Gieson method, haematoxylin and eosin, Lillie's azure-eosinate and PAS according to Hotchkiss.

The bone marrow in the distal, proximal and diaphysial parts of each pair of the long bones and in the cervical, thoracic, lumbar and sacral spines, as well as in the regions of the tuber sacrale, tuber ischii, ilia, acetabula and basis cranii were analysed with respect to their degree of cellularity. The cellularity of the marrow was classified according to an arbitrary scale from 0 (aplastic marrow) to 5 (normal marrow). The cellularity for a group of five mice was expressed as the mean obtained from 155 measurements.

The analysis of the cell volume distribution was made in combination with the investigation of the histologic features in order to demonstrate as objectively

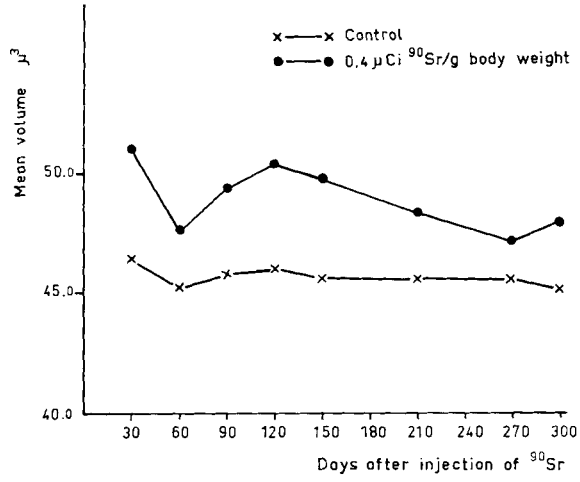

Fig. 2. Mean volume of erythrocytes in peripheral blood in relation to time after injection of ^{90}Sr. Persistent macrocytosis.

as possible the ^{90}Sr-induced quantitative variations in the different cell populations. Parts of the thymus and spleen were suspended in homogenization tubes containing a relatively particle-free balanced salt solution. After cutting both ends of the femur, the marrow was forced out by compressed air and handled in the same way as the thymus and spleen. All the organ suspensions were adjusted to contain between 10^4 and 3×10^4 cells per milliliter. The peripheral blood was also investigated in suspensions of 1 : 2 000.

The cell volume distribution was studied with an electronic counter (Coulter-Counter Model B) equipped with an 'automatic particle size distribution analyser' (Coulter Plotter Model J). The principle and operation of this instrument have been described by BRECHER et coll. (1962). The instrument was calibrated with rat erythrocytes and essentially monosized 'Ragweed Pollen' for the absolute cell volume determination.

The cells investigated were divided into 'small cells' of size 40 to 100 μ^3, 'moderate-sized cells' 100 to 200 μ^3, and 'large cells' 200 to 500 μ^3. The limits for the three groups of cells were approximate but chosen as far as possible to represent the main bulk of morphologically defined cell entities; they seem to agree fairly well with the results obtained by HAOT et coll. (1967). The reason for setting the upper limit for the 'small cells' at 100 μ^3 was that the main part of these cells consists of erythrocytes with a mean volume of between 40 and 50 μ^3 (range 20 to 140 μ^3). The influence of leukocytes on the volume distribution of the peripheral blood could be designated as insignificant. The 'moderate-sized cells' were chosen within limits mainly representing the lymphoid cell elements. Their mean volume was between 120 and 140 with a range of 100

to 200 μ^3. The 'large cells' were mostly various types of blasts (usually over 200 μ^3).

Results

Peripheral blood. A significant and persistent leukopenia developed in all the dose groups at 7 days. Expressed as the mean for the whole experimental period the following dose-related levels of leukocytes were observed:

1 687.7 ± 153.2 (range 1 072—2 970) in the 1.6 μCi group
3 063.7 ± 181.4 (range 2 112—4 548) in the 0.8 μCi group
4 223.5 ± 213.3 (range 2 980—5 972) in the 0.4 μCi group
4 837.9 ± 238.2 (range 2 820—6 948) in the 0.2 μCi group
8 383.3 ± 247.8 (range 6 836—10 378) in the control group

A shift in the differential counts also occurred. The mean percentage distribution of granulocytes in the ^{90}Sr-treated groups was over 30 % (range 25.6—38.4 in the 1.6 μCi group, 29.0—62.8 in the 0.8 μCi group, 23.6—43.8 in the 0.4 μCi group and 25.6—36.0 in the 0.2 μCi group). The control value was 19.9 % (range 15.6—29.2). A corresponding and persistent lymphopenia was observed.

The haemoglobin values in all the dose groups reached a minimum within 14 days. A slight recovery then occurred but normal values were never regained in anyone of the groups. The mean values (g/100 ml blood) for the whole experimental period were as follows:

11.2 ± 1.95 (range 9.9—12.5) in the 1.6 μCi group
11.7 ± 1.52 (range 10.4—12.4) in the 0.8 μCi group
12.1 ± 1.70 (range 10.7—13.4) in the 0.4 μCi group
12.5 ± 1.02 (range 11.4—13.2) in the 0.2 μCi group
13.3 ± 2.14 (range 11.6—15.6) in the control group

Marked macrocytosis (Fig. 1) accompanied by an increase of polychromatic erythrocytes were present in the peripheral blood in all the dose groups investigated (0.2, 0.4, 0.8 μCi ^{90}Sr/g body weight) as early as at 7 days. The macrocytosis persisted when investigated for a period of up to 300 days after the injection of 0.4 μCi ^{90}Sr/g body weight (Fig. 2).

The thrombocyte counts reached their minimum values at 14 days in all the dose groups but thereafter a rapid increase to normal or even higher values occurred. The following mean values were obtained:

532 000 ± 51 900 (range 247 800—771 000) in the 1.6 μCi group
536 000 ± 50 500 (range 225 600—854 800) in the 0.8 μCi group
549 500 ± 39 400 (range 196 000—984 000) in the 0.4 μCi group
596 100 ± 40 800 (range 259 600—885 000) in the 0.2 μCi group
534 000 ± 19 000 (range 384 400—720 750) in the control group

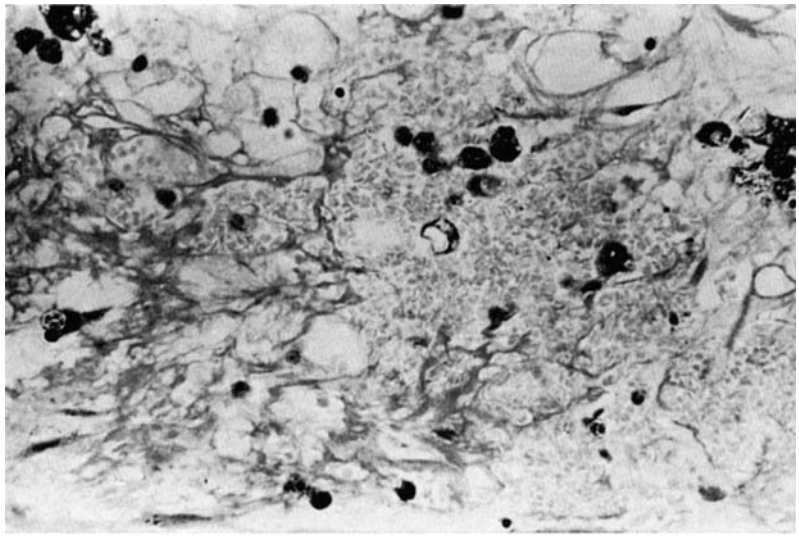

Fig. 3. Haemosiderin-loaded macrophages, in aplastic and necrotic bone marrow of femur, 300 days after injection of 1.6 μCi ^{90}Sr/g body weight. van Gieson × 500.

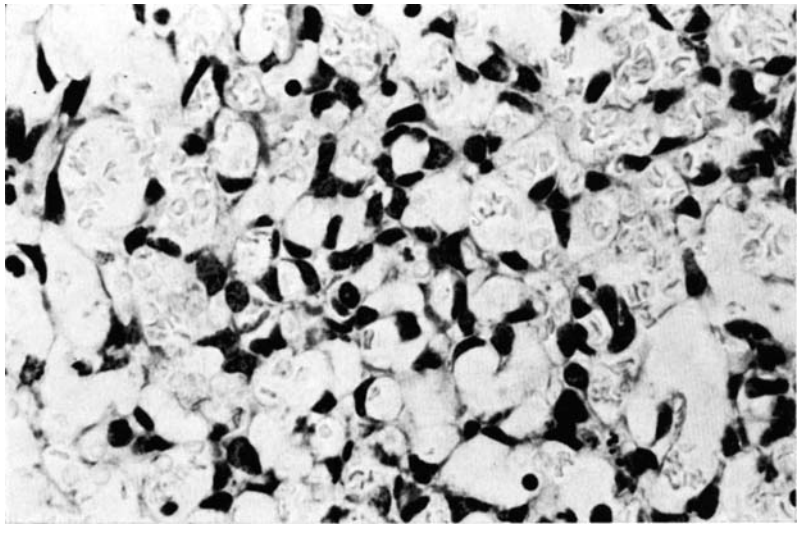

Fig. 4. Proliferation of reticular cells in aplastic bone marrow, of diaphysis of femur, 300 days after injection of 0.8 μCi ^{90}Sr/g body weight.

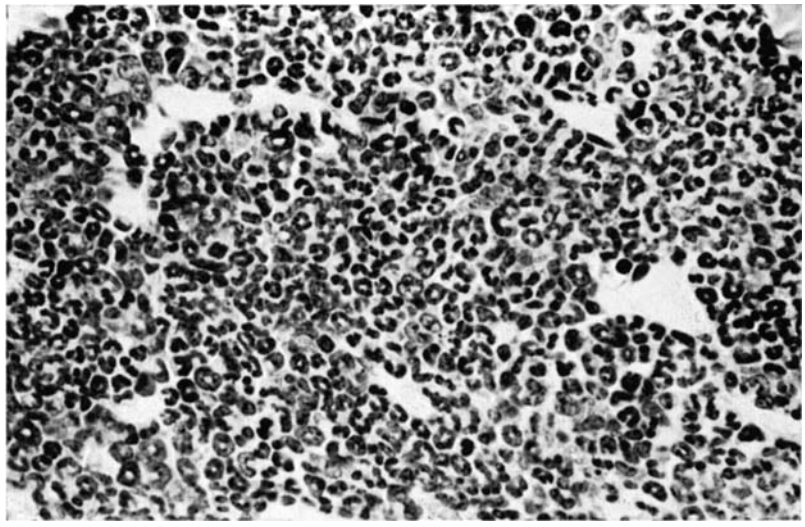

Fig. 5. Bone marrow of femur. Granulocyte proliferation 150 days after injection of 0.2 μCi ^{90}Sr/g body weight. van Gieson × 500.

Bone marrow. The histologic changes differed quantitatively but were principally of the same type in all the dose groups. Dilatation and hyperaemia of the medullary sinusoids accentuated with increasing dose. Increased amounts of fatty tissue appeared, more abundant and earlier in the two higher dose groups than in the others. Appreciable amounts of fat appeared in the 1.6 μCi group as early as at 7 days.

Destruction of the sinusoids with formation of localized 'blood lakes' was more extensive in the lower than in the higher dose groups. This was the case particularly at 270 days in the 0.4 μCi group. Thromboses in different stages of organisation were also a common feature long after the injection of ^{90}Sr, particularly in the 0.2 μCi group at 390 days but also in the 0.4 μCi group. They appeared most frequently in the diaphysial part of the marrow of the long bones.

Marrow necrosis was present, above all in the femur, in all the dose groups, but earlier (Fig. 3) in the 1.6 μCi group (210 days) and the 0.8 μCi group (360 days) than in the others. In many aplastic or markedly hypoplastic marrows, only reticular cells remained, or were increased, or were in a state of proliferation (Fig. 4). This occurred particularly in mice given 0.4 μCi/g body weight. These cells have in earlier work (SUNDELIN & NILSSON 1968) been shown to start the development of predominantly fibroblastic osteosarcomas.

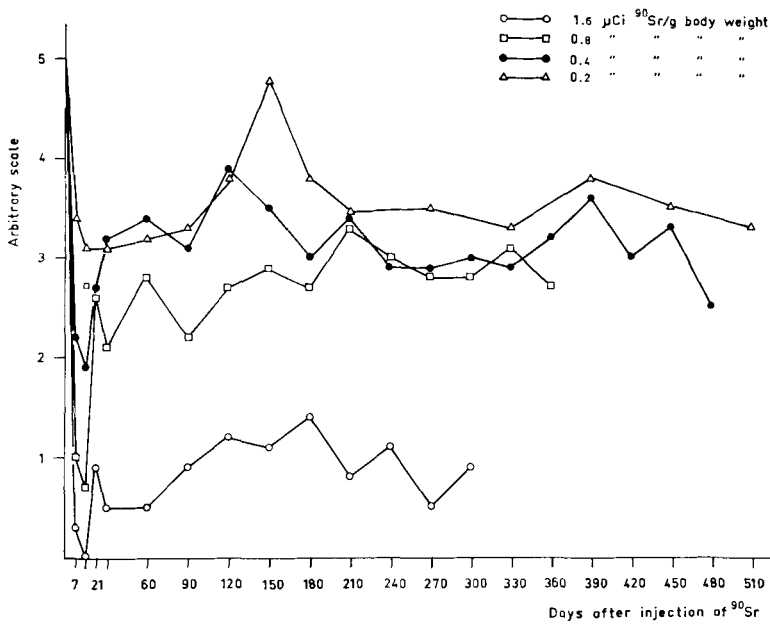

Fig. 6. Bone marrow cellularity in relation to dose and time after injection of ^{90}Sr according to an arbitrary scale. 0 equals aplasia, 1—4 varying degrees of hypoplasia, and 5 normal marrow cellularity; each point on the diagram represents the mean marrow cellularity from 155 estimations.

Five mice were investigated, in each of which the marrow cellularity was estimated in the distal, diaphyseal and proximal parts of the femora, tibiae and humeri respectively; in each of the two pelvic bones at the tuber ischii, tuber sacrale, the ilium and the acetabular region; in the spine in one marrow cavity in each of the cervical, thoracic, lumbar, and sacral vertebrae; and in the head the base of the cranium.

The 1.6 μCi group was the only one in which early fibrosis (before 30 days) was detected. This fibrotic tissue in one instance contained large cells with cytoplasmatic non-metachromatic diastase-resistent PAS + granules. Almost total destruction of all types of marrow cells occurred in the 1.6 μCi group during the initial phase. Small islands of erythroblastic elements containing immature polychromatic erythrocytes could be detected at about 14 days. Prominent anisochromia, macrocytosis and poikiliocytosis were characteristic of these cells, many of which were migrating through the capillary walls into the circulation. A shift in the relative proportions between the granulocytic and erythrocytic series was detected 21 days after ^{90}Sr administration and from that time onwards a predominance of the granulocytic series took place.

In the other groups, the erythrocytic series showed a tendency to predominate

Table 2

Distribution of mice (per cent) in relation to ^{90}Sr dose and bone marrow cellularity

Dose group μCi/g	Bone marrow cellularity					
	Aplastic 0.0—0.5	Markedly hypoplastic 0.6—2.5	Moderately hypoplastic 2.6—3.5	Slightly hypoplastic 3.6—4.5	Normal 4.6—5.0	Hyperplastic >5
1.6 n: 65	32.3	67.7	0.0	0.0	0.0	0.0
0.8 n: 75	0.0	45.4	52.0	0.0	2.7	0.0
0.4 n: 95	0.0	19.0	68.4	8.4	3.2	1.1
0.2 n: 103	0.0	0.0	60.0	32.9	5.7	1.4

in regeneration during a short period (before 30 days). The granulocytic series started to dominate at 90 days in the 0.8 μCi group and after about 120 to 150 days in the others. This granulocytosis was temporary in the 0.2 μCi group and ended after about 360 days.

Marked hyperplasia, particularly in the bone marrow but also in the spleen, of hardly any other cells than those representing the granulocytic series, occurred in several instances, especially in the lower dose groups (Fig. 5).

Megakaryocytes were more abundant than normally in the 0.4 and 0.2 μCi groups, and this particularly between 330 and 390 days. In the 1.6 μCi group, megakaryocytes re-appeared after the initial period but never attained their normal number.

An abundance of mastocytes were seen in some instances in the 0.8 and 0.4 μCi series in the bone marrows and in most lymphoid tissues, including the thymus.

Quantitative analysis. The effect of the various doses of ^{90}Sr on the bone marrow cellularity among the sacrificed mice is recorded in Fig. 6. The minimum values were observed in all series at 14 days, the cellular depletion increasing with increasing dose. The marrow depletion within each group was initially of about the same magnitude in the various marrow cavities investigated but the start and degree of marrow regeneration differed greatly in the various parts.

The percentage distribution of sacrificed mice in relation to dose and their mean bone marrow cellularity is shown in Table 2. Six out of fifty mice in the

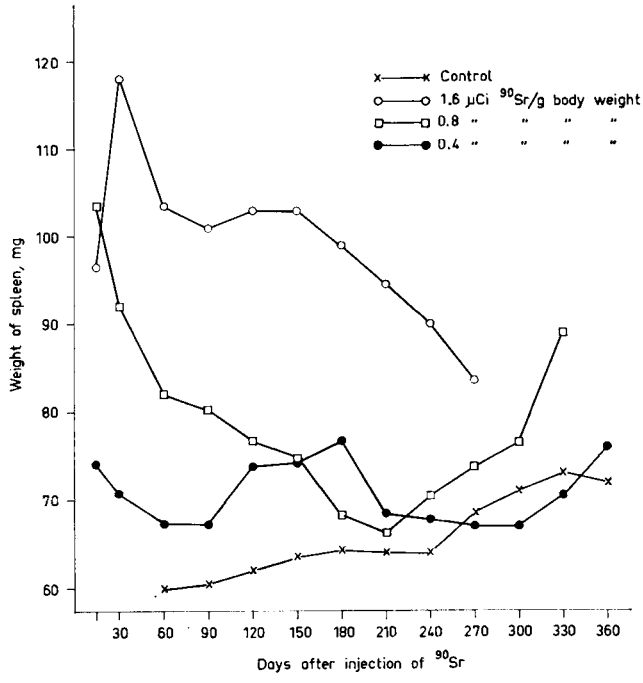

Fig. 7. Weight of spleen in relation to dose and time after injection of ^{90}Sr.

1.6 μCi group died naturally of acute and four of chronic aplastic anaemia. Chronic aplastic anaemia occurred in the 0.8 μCi group in one out of forty-six and in the 0.2 μCi group in one out of seventeen mice.

The Coulter analysis revealed a prominent and persistent increase of 'small cells', mostly representing the engorgement of the sinusoidal space by erythrocytic elements. The degree of hyperaemia seemed to be initially related to dose, i.e. the degree of hyperaemia increased with increasing dose. Moderate-sized cells, representing lymphoid elements, were considerably reduced and never regained normal values, nor did the large cells representing blasts.

Marrow regeneration. Topographically the start and intensity of regeneration varied and proceeded according to the bone in which the marrow was located. The marrow of the femurs in the 1.6 μCi group presented little evidence of regeneration apart from scattered small foci of dividing cells and was practically aplastic until the death of the animals. On the other hand, considerable regeneration took place focally in the marrows of the tuber sacralae, tuber

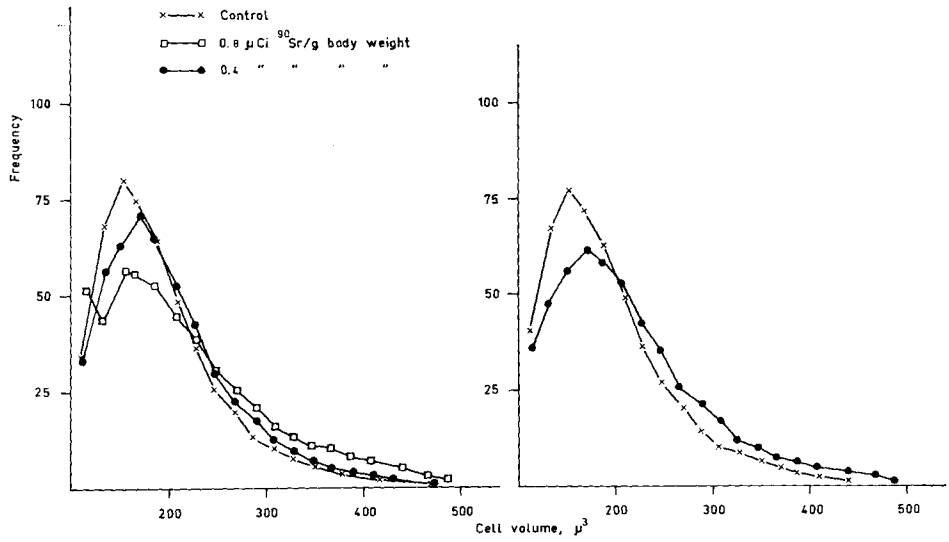

Fig. 8. Cell volume diagram (Coulter counter) for spleen 21 days (left) and ten months (right) after injection of ^{90}Sr. Dose-related and persistent lymphocyte depletion.

ischii, the thoracic vertebrae as well as in the sternal marrow, and reached its peak at about 180 days after the injection of the ^{90}Sr. Cells of the granulocytic series predominated in these islands of regeneration.

Also in the other groups the marrow of the femur was more damaged than other parts. The most active marrows were present at the same sites as in the 1.6 μCi group but the regenerative capacity was greater and related to dose, reaching its peak in the 0.8 μCi group at 210 days, as compared to between 120 and 150 days in the other groups. The decreased marrow activity in the femurs was however compensated for predominantly in the thoracic vertebrae and sternal marrow.

Spleen. Changes in the weight of the spleen are illustrated in Fig. 7. In spite of a heavy loss of lymphatic tissue in the higher dose groups and a moderate loss in the two lower dose groups (Fig. 8), a most significant increase in weight persisted over a long period; this was caused by hyperaemia and a heavy erythro-, megakaryocyto- and granulocytopoiesis (Fig. 9). The degree of lymphoid depletion depended upon the dose.

Histologically the findings largely agreed with those described in an earlier paper (16). It should however be noted that in the 1.6 μCi group the increased extramedullary blood formation, which was initially dominated by the erythroid

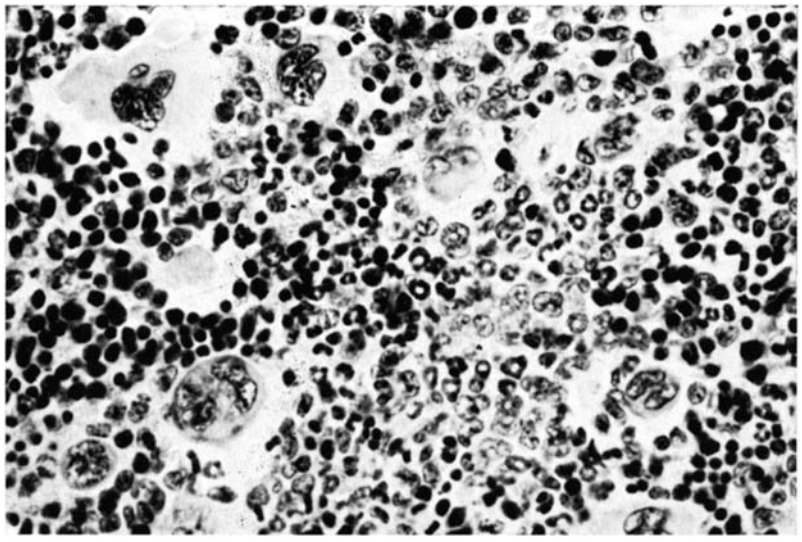

Fig. 9. Appearance of cells of spleen two months after injection of 1.6 μCi ^{90}Sr/g body weight. Extra medullary haematopoiesis of all types of cells. H—E × 500.

series, was successively and after about 200 days completely replaced by the granulocytic cell series.

Extramedullary haematopoiesis in the 0.8 μCi group was marked but in contrast to the 1.6 μCi group erythroid elements were usually more abundant in the process of regeneration than the granulocytic series of cells.

Megakaryocytopoiesis was much more prominent in the two lower dose groups than in the two others.

Thymus. Changes in the weight of the thymus in the control groups and in the different ^{90}Sr series are illustrated in Fig. 10. The loss of weight and enhanced rate of involution are dose-dependent and, as shown by the cell volume distribution analysis, predominantly caused by a depletion of lymphoid cells (Fig. 11). This lymphoid depletion was not detectable histologically.

Discussion

A general depletion of all haematopoietic tissues occurred in all the dose groups but only in the 1.6 μCi group was a high frequency of aplasia recorded among the sacrificed animals (see Table 2). In this group the mice also died naturally from acute aplastic anaemia.

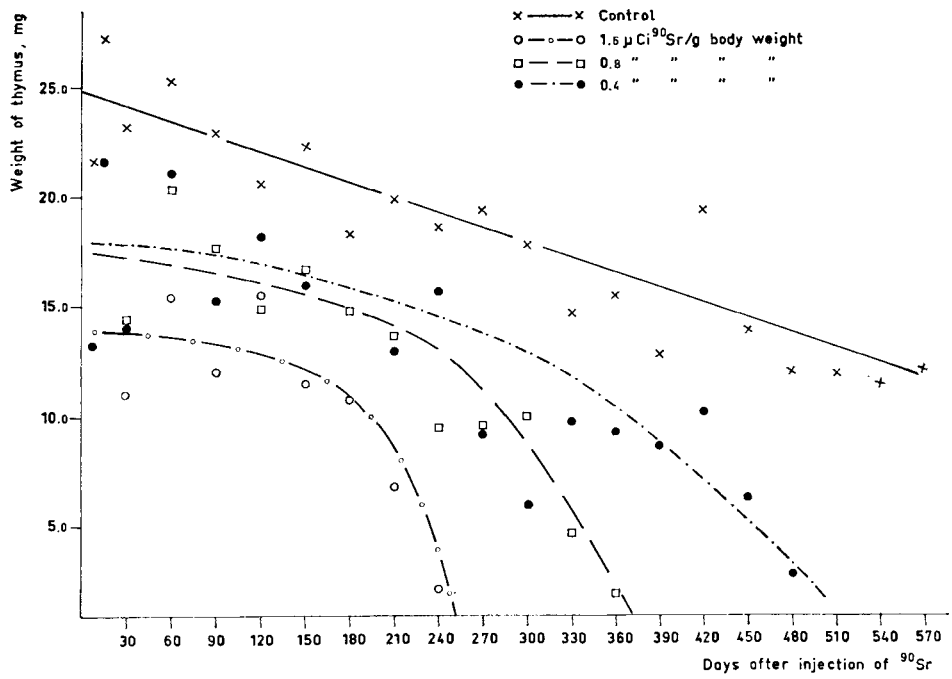

Fig. 10. Weight of thymus in relation to dose and time after injection of ^{90}Sr.

The weight of the thymus diminished increasingly with enhanced dose and the weight of the spleen increased progressively. It is obvious from the cell volume distribution diagram that the diminished weight of the thymus is caused by a constant depletion of lymphocytes, predominantly in the cortical zone. Persistent lymphoid depletion occurred also in the spleen but the increased weight was brought about by hyperaemia and an extramedullary diffuse haematopoiesis, the intensity of which mainly mirrored the degree of damage to the bone marrow, in which practically all cell types were depressed, and the degree of this depletion was largely related to dose.

The destruction of the sinusoids in the bone marrow may have been directly related to the effect of irradiation since it was most widespread at the highest dose level. Vascular disorders may have been indirectly involved, as was indicated by the more frequent occurrence of 'blood lakes' and necrosis in conjunction with thrombosis in the lower dose groups. It should be noted in this connection that thrombocytosis predominated, particularly in the lower dose groups.

In the regeneration of bone marrow a general pattern could be distinguished

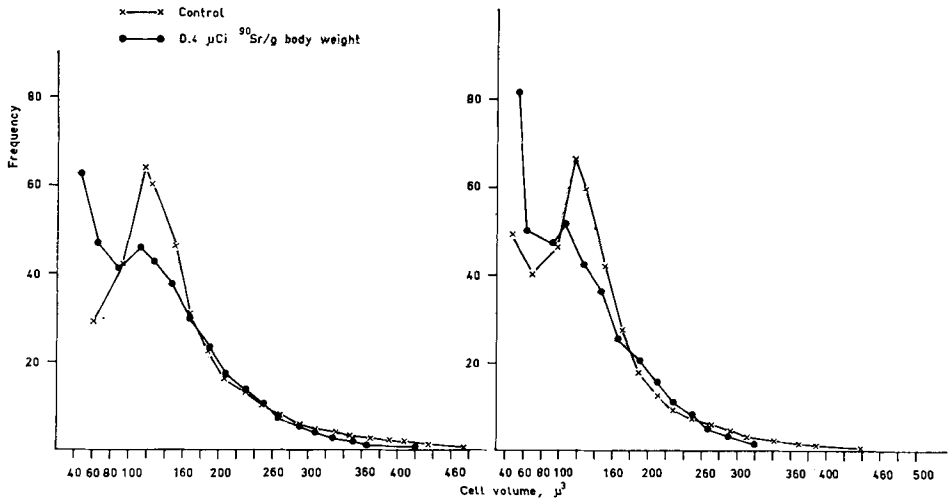

Fig. 11. Cell volume diagram (Coulter counter) for thymus one month (left) and ten months (right) after injection of ^{90}Sr. Persistent lymphocyte depletion.

irrespective of the dose. Topographically this regeneration was mainly determined by the redistribution and amount of ^{90}Sr released, and by the size and shape of the bone. The most active locations were the thoracic vertebrae, the sternum and certain sites in the pelvic bones. The evidence of regeneration was insignificant in the 1.6 μCi group, with the exception of sites in which cells of the granulocytic series generally predominated. In the other dose groups the regeneration with decreasing dose was more diffusely distributed. A persistent predominance of the granulocytic over the erythroid series in the marrow also occurred but started somewhat later with decreasing dose. This granulocytosis was intense but temporary in the 0.2 μCi series and decreased or disappeared after about 360 days.

The bone marrow seemed to play a comparatively small role in the thrombocytopoiesis. Even though most of the marrow was destroyed in the highest dose group, no peripheral thrombocytopenia developed, since sufficient compensatory megakaryocytopoiesis took place in the spleen.

A generally diminishing erythropoiesis in the marrow occurred with increasing dose. This was however principally taken over by the spleen but was largely of insufficient magnitude, as apparent from an increased macrocytosis and a diminished haemoglobin content. At the highest dose level and with progressing time this capacity of the spleen gradually decreased in favour of a more accentuated granulocytopoiesis. None of the destructive effects observed

in lymphocytopoiesis could be fully compensated for, and there was as a consequence a discernible shift in the relative proportions of granulocytes and lymphocytes in the peripheral blood.

The dose-related, persistent and absolute decrease in granulocytes in the peripheral blood principally mirrors the diminished granulocytopoietic capacity, particularly of the bone marrow. It is however noteworthy that especially in the two lowest dose groups the granulocytosis, accompanied by a proliferation of myeloid elements, was sometimes of such extent and intensity that it might be identical with the leukaemoid reaction observed in rats by BOEGLER & KRIEGEL (1968), and the so-called myeloproliferative disorders in beagles (GOLDMAN et coll. 1969), characterized by a terminal anaemia and a spectrum of disorders varying from myeloid metaplasia to granulocytic leukaemia. One of the causes of this reaction may be related to the fact that the granulocytic cell series is more radiation-resistent than the erythroid and lymphoid series (1. 3).

As regards the mutual relationship between thymus, bone marrow and spleen it is obvious that the involution of the thymus is accelerated and accentuated by an increasing dose, which may be explained on the basis of a dose-related scarcity of bone marrow stem cells capable of repopulating the thymus. A generally enhanced consumption of thymus lymphocytes with or without destruction by the continuous irradiation from the bones surrounding the thymus may also be factors to consider. The spleen seems at least in the higher dose groups to serve as a reserve to compensate for the diminished bone marrow function. This interrelationship seems to be of some importance for a better understanding of differences in the leukaemogenesis between ^{90}Sr and fractionated external irradiation. Most cases of leukaemia induced by the latter method are of thymic origin (cf. JÄRPLID 1968) in contrast to those induced by ^{90}Sr (8, 13, 18). With fractionated irradiation the entire haematopoietic system is repeatedly and uniformly damaged, and stem cells capable of repopulating the thymus may be acutely lacking (cf. JÄRPLID). The bone marrow is continuously irradiated with ^{90}Sr but the degree of damage and regeneration varies considerably in different parts of the marrow, while other parts of the haematopoietic system initially are not damaged to the same extent as by external irradiation.

SUMMARY

The quantitative and qualitative effects of various doses of ^{90}Sr on the haematopoietic system in four groups of CBA male mice and in controls are described.

ZUSAMMENFASSUNG

Der quantitative und qualitative Effekt von verschiedenen Dosen von ^{90}Sr an vier Gruppen von männlichen CBA Mäusen und an Kontrolltieren werden beschrieben.

RÉSUMÉ

L'auteur décrit les effets quantitatifs et qualitatifs de diverses doses de ^{90}Sr sur le système hématopoïétique dans quatre groupes de souris CBA mâles ainsi que sur des témoins.

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