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POTENTIATING AND INHIBITING EFFECTS OF STEROID HORMONES ON THE INCIDENCE OF ^{90}Sr INDUCED OSTEOSARCOMA

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Abstract

Eight hundred and twenty male CBA-mice, 75±3 days of age were divided into four main series. Three of these; A, B and C were further divided into three subgroups. To these ^{90}Sr was given at three different dose levels alone (A) or in combination with either oestrogen (B) or prednisolone (C). In one series (D) all animals were given only oestrogen. The development of intramedullary oestrogen induced bone formation and the early events of bone tumour induction are reported. The ^{90}Sr activities were selected in such a way that the lowest one would be below, the intermediate beyond and the highest well above the limit of bone tumour induction. Comparing the ^{90}Sr injected animals with those given also oestrogen revealed that oestrogen had no promoting effect at the lowest and intermediate dose levels but increased the tumour incidence with a factor 4 at the highest dose level whereas prednisolone had an inhibitory effect. From the results obtained it was proposed that oestrogen may act only as a preparatory promoter and not assist in the initiating events. As has been reported elsewhere, the frequency of osteoblastic and osteoclastic osteosarcomas was higher in animals given oestrogen and ^{90}Sr than ^{90}Sr only. Mice given only oestrogen did not develop bone tumours.

Key words: Bones, neoplasms; mice, ^{90}Sr, oestrogen, prednisolone, cancerogenic effects, interactions.

Most, if not all, types of cancer apparently result from multi-stage or multi-event mechanisms. This includes initiating events that confer neoplastic potential upon cells, and local or remote promotional events that act to stimulate the potentiated cells to proliferate as neoplastic entities (3). In normal and healthy animals ^{90}Sr is a potent cancerogen which may both initiate and promote events ultimately leading to cancer. Biological and physiological parameters which are affected by various diseases, age, sex, immunological and hormonal dysfunctions could, however, be suspected to exert a considerable effect as potentiators or inhibitors (6, 7, 10, 11).

In this context the tumour potentiating and inhibiting effects of oestrogenic and glucocorticosteroid hormones on the cancerogenicity of ^{90}Sr have been studied. The specific aim of the present study was to determine whether oestrogen acts merely as a preparative promoter in the pathogenesis of ^{90}Sr-induced bone tumours, or if it could also potentiate or assist the initiating effect proper of ^{90}Sr.

In order to study this question ^{90}Sr was distributed with and without oestrogen in three different activities, selected in such a way that the lowest one would be well below, the intermediate just beyond and the highest well above the limit for bone tumour induction. The number of tumours per mouse was used as an index of the cancerogenicity. The stimulatory effect of oestrogen on the osteosarcoma incidence was also compared with the inhibitory effect of long-acting glucocorticosteroids.

Material and Methods

The experiment was commenced when mice derived from brother–sister matings within the CBA strain reached 75±3 days of age. A total of 820 male mice were divided into 4 main series (A, B, C and D) (Table 1). Each of the series A, B and C were further divided into 3 subgroups (1, 2, and 3) containing 100, 100 and 50 mice respectively. Carrier-free ^{90}Sr $(NO_3)_2$ in equilibrium with ^{90}Y was administered intraperitoneally to each of the subgroups at 3 different activity levels (0.925; 1.850 and 7.400 kBq/g bw). One of the main series (A) was given ^{90}Sr only, one (B) in addition polyestradiolphosphate (Estradurin, Leo) subcutaneously (0.5, 0.25 and 0.25 mg respectively to each animal) on 3 consecutive occasions 7 days before, 21 and 51 days after the injection of ^{90}Sr (day 0) respectively. Series C was, in addition to ^{90}Sr, injected with 1 mg

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Table 1

Male CBA mice treated with ^{90}Sr $(NO_3)_2$, Estradurin, Depomedrone** hormones. ^{90}Sr was given at different dose levels and was administered intraperitoneally at 75±3 days of age (= day 0). The hormones were given repeatedly by subcutaneous injections*

Series	Sub-group	No. of mice	^{90}Sr KBq/g Day 0	Estradurin (mg/mouse)			Depomedrone (1.0 mg/mouse)									
				Day−7	21	51	Day−7	7	21	35	49	63	77	91	105	119
A	A:1	100	0.925	−	−	−	−	−	−	−	−	−	−	−	−	−
	A:2	100	1.850	−	−	−	−	−	−	−	−	−	−	−	−	−
	A:3	50	7.400	−	−	−	−	−	−	−	−	−	−	−	−	−
B	B:1	100	0.925	0.5	0.25	0.25	−	−	−	−	−	−	−	−	−	−
	B:2	100	1.850	0.5	0.25	0.25	−	−	−	−	−	−	−	−	−	−
	B:3	50	7.400	0.5	0.25	0.25	−	−	−	−	−	−	−	−	−	−
C	C:1	100	0.925	−	−	−	+	+	+	+	+	+	+	+	+	+
	C:2	100	1.850	−	−	−	+	+	+	+	+	+	+	+	+	+
	C:3	50	7.400	−	−	−	+	+	+	+	+	+	+	+	+	+
D		70	−	1.0	0.5	0.25										

* Long-acting polyestradiolphosphate.
** Long-acting methylprednisolone.

methylprednisolone (Depomedrone, Upjohn) subcutaneously every second week on 10 consecutive occasions. In a fourth series (D) each of 70 animals was given only Estradurin (1, 0.5 and 0.25 mg) as described in series B.

All calculations as regards survival and induction times began at day 0, i.e. when the mice were 75 days of age.

All mice were kept in conventional animal rooms under uniform conditions and inspected twice daily. They were grouped at random and maintained in cages with 10 animals in each. A commercial pelleted diet (Standard Feed for Rats and Mice, Astra-Ewos) and water were supplied ad libitum.

Moribund animals were killed by cervical dislocation. Dorsoventral roentgenograms were made and the films were used as guides for locating skeletal lesions. All macroscopic tumours and roentgenologically suspected bone tumours as well as both femora, tibiae, humeri, parts of the vertebral spine (thoracic and lumbar vertebrae) and sternum were fixed in Stieve's fluid. Hard tissues were decalcified in 20% formic acid. Conventional histologic methods were used. Routine Ehrlich's haematoxylin–eosin and van Gieson's stains were employed.

Results

Early lesions. Very prominent endosteal and intramedullary formation of bone was found in the distal femoral metaphyses and proximally in the tibiae and humeri around 50–60 days after the start of the experiment in series B and D, when the first mice were autopsied. In the opposite ends of the long bones and in the mid-diaphyses apposition was rather scanty. Formation of 'oestrogenic' bone was also observed in other parts of the skeleton but to a lesser extent. The newly formed bone was composed of irregular, fairly thick trabeculae circumscribing spaces filled with bone marrow. Generally at this time the number and activity of the osteoblasts was low considering the abundance of new bone, but was still much more pronounced than in the corresponding non-oestrogen treated groups. Osteoclasts were not detected. Osteocyte lacunae and osteocytes were larger than in the preformed compact bone. No differences related to the given ^{90}Sr activity were discernible, except for the bone marrows which in the highest dose (B:3) group were severely depleted and mainly consisted of dilated sinusoids. In the lowest dose series only a narrow zone close to the epiphyseal plate was slightly depleted.

In all animals dying between 110–120 days an increasingly compact bone almost filled the marrow cavity of the long bones in both the B and D groups. No obvious differences were found between different ^{90}Sr activities. In the diaphyses, endosteal apposition of a cone-like and irregularly formed bone composed of twisted, whorl-like fibres, projected from all directions into the marrow cavity. In these ingrowths were found numerous defective osteones, lacking a central channel of Haver. Osteocyte lacunae were fairly large and had partly lost their regular normal distribution. The osteoclasts were few and the number of osteoblasts varied between different areas. In the highest dose group (B:3) there was a minor infiltration of fat and slight hypoplasia in the marrow close to the epiphyseal plate, while in the lowest one (B:1) only an insignificant depletion was discernible.

After 150–160 days there seemed to be some decrease of the compactness of the bone particularly in the mid-diaphysis and in some cases also nearest to the epiphyseal plate. The bone marrow was still hypoplastic. The reduction of the 'oestrogenic' bone was even more obvious after about 210 days, especially in the diaphysis of some bones. Distally, large marrow-filled spaces were now separated by narrow trabeculae. A slight increase in numbers of scattered osteoclasts were detected compared to earlier

Table 2

Classification of skeletal lesions and tumours

Groups	Dysplastic repair	Osteoma	Chondro-sarcoma	Osteo-blastic	Osteosarcomas		Fibroblastic teleangiect.	Mixed	Osteo-clastic
					Eburnating	Fibroblastic			
A:1	4	1	–	–	–	–	–	–	–
B:1	9	–	–	–	–	–	–	–	–
C:1*	4	–	–	–	–	–	–	–	–
A:2	1	–	–	1	–	1	4	–	–
B:2	3	1	–	3	1	1	2	–	–
C:2	1	–	1	2	–	1	–	–	–
A:3	2	1	–	1	–	1	9	–	–
B:3	19	1	–	25	4	7	–	7	4
C:3	1	–	–	–	–	–	–	1	–

* One angiosarcoma was found in the bone marrow cavity of a lumbar vertebra.

observations, indicating a beginning bone destruction. At some sites it was now possible to identify 3 clearly separated layers of bone: outer new-formed bone emanating from the periosteum; an intermediate remnant consisting of preformed bone, and an endosteal zone of 'oestrogenic' bone which was partly undergoing remodelling and destruction. The destructive events were most prominent in the highest ^{90}Sr dose group. In the D group the compactness of the bone was not visibly affected which is in congruence with earlier observations (11).

In mice given only ^{90}Sr (A) the changes in the skeleton were completely different from those found when ^{90}Sr was given in combination with oestrogen. Practically no lesions except for a slight bone-marrow depletion were found within the 2 lowest dose intervals (A:1, A:2). At the high-dose level (A:3), however, a very pronounced cellular depletion of the bone marrow in the diaphyseal parts of the long bones was observed. Sometimes this hypoplasia was later accompanied by a varying destruction of the sinusoides, which could result in the formation of blood lakes and sometimes thrombosis. No conspicuous depletion of osteoblasts was discernible.

In the groups treated with ^{90}Sr and glucocorticosteroids (C) the lesions were not appreciably different from those found when ^{90}Sr was given alone (A).

Dystrophic and dysplastic changes. As indicated earlier the apposition of 'oestrogenic' bone seemed to have reached a maximum around day 150 in the highest dose group (B:3). From that time on there was a clear predomination, particularly in the high-dose group, of dystrophic and dysplastic lesions evidenced by a progressively decreasing amount of 'oestrogenic' bone and an increasing proliferation of osteoblastlike, fusiform or reticular cells along the endosteal linings or within bone porosities (B:3).

Thus, by about 320–350 days almost 50% of the 'oestrogenic' bone had disappeared, mainly because of a general thinning of the trabeculae but partly also because of numerous intratrabecular porosities. At many sites clusters of osteoclasts were forming so-called 'cutting cones' in both 'oestrogenic' and preformed bone. The resulting cavities could be either completely reactionless or contain a varying amount of defective repair tissue which in some places demonstrated a tendency to transform into osteoblast-like cells. In other bones numerous large osteoblasts covered the bone surfaces. Around day 400 these features were even more conspicuous. In other areas of the same bone the trabeculae were coarser and partly composed of devitalized bone. In such areas osteoclasts were frequently found along the bone surfaces as well as fusiform and osteoblast-like cells. This cellular response still had much of the characteristics of repair tissue, but did, however, at some sites show a varying degree of dysplasia and cellular atypia.

In the 2 lowest dose groups (B:1, B:2) dystrophic and dysplastic lesions were fewer (Table 2), usually less advanced and appeared much later than in the highest dose group.

When ^{90}Sr was administered alone (A) dysplastic and presarcomatous lesions were few and generally appeared later than in the counterparts treated with oestrogen plus ^{90}Sr (B). The changes were generally confined to the diaphyseal parts of the long bones.

Dysplastic lesions were remarkably scanty in the groups treated with ^{90}Sr combined with glucocorticosteroids (C).

Tumour induction. No malignant bone tumours were found in any of the groups at the lowest dose level (Table 3). In the intermediate dose series a few malignant bone tumours were found, but without any preponderance for any of the groups. In the highest dose group the tumour frequency of the oestrogen-treated animals (B:3) was about a factor 4 greater than that of the animals given only ^{90}Sr (A:3), in spite of the fact that the survival time of A:3 was 17% longer than for B:3. In A:3, on the other hand, the tumour incidence was approximately 10 times greater than in C:3, given ^{90}Sr + glucocorticosteroids, despite the fact that the latter group survived about 16% longer than

Table 3

Mean survival time, tumour incidence and mean time of tumour appearance (mean "induction" time) for male CBA mice given three different doses of ^{90}Sr alone (A:1, A:2, B:3) or Depomodrone (C:1, C:2, C:3). Group D was given Estradurin only. The approximate mean irradiation dose to the whole skeleton at mean survival time is included

Groups	No. of mice	Mean survival Days ± SE	No. of mice with malignant tumours	Total no. of malignant tumours	Mean 'induction' time Days ± SE	No. of tumours/ mouse	Approx. dose whole skeleton Gy
A:1	100	640±1	0	–	–	–	4.5
A:2	100	627±16	4	6	528±36.3	0.06	9
A:3	50	458±26	11	11	612±32.5	0.22	31
B:1	100	446±25	0	–	–	–	4
B:2	100	500±18	5	7	647±18.8	0.07	8
B:3	50	380±30	22	47	486±18.4	0.94	28.5
C:1	100	715±12	1	1	686	0.01	4.5
C:2	100	723±15	4	4	691	0.04	
C:3	50	531±28	1	1	574	0.02	32.5
D	70	502±21	0	–	–	–	

the ^{90}Sr-treated one (B:3). In the main series D no bone tumours were found.

Tumour classification. In animals treated with oestrogen at the highest ^{90}Sr level (B:3) the spectrum of subtypes of osteosarcomas was broader than when ^{90}Sr (A:3) was given alone (Table 2). Furthermore there was a considerable predomination of osteoblastic and eburnating osteosarcomas (62%) as compared to the ^{90}Sr-group (A:3) where fibroblastic and particularly fibroblastic osteosarcomas with telangiectactic pattern were predominant (91%). Even though the numbers are small the same was evident for the intermediary dose series (B:2, A:2). In the ^{90}Sr + oestrogen group (B:2) 57% were strongly bone forming, compared to only 17% in the ^{90}Sr group (A:2). Mixed and osteoclastic osteosarcomas were also found mostly after treatment with oestrogen (B:3). The chondrosarcoma in group C:2 was of a low grade of malignancy and seemed to be derived from the epiphyseal plate. In group C:1 no bone tumours were found but one angiosarcoma.

Animal survival. It was evident that increasing ^{90}Sr activities (A:1–3) decreased the survival time (Table 3) and furthermore that oestrogenic hormones in combination with ^{90}Sr significantly shortened the life span for the 2 lowest dose groups (A:1 vs B:1 $t=6.996$; $p<0.001$; A:2 vs B:2 $t=5.273$; $p<0.001$). In the highest dose group there was also a reduced life span, however not significant. Comparison of the ^{90}Sr groups (A) with those given both ^{90}Sr and glucocorticosteroids (C) revealed generally prolonged survival times for the latter which for the 2 lower dose groups were significant at the 99.9% level.

Discussion

This investigation confirms previous observations (7, 11) that oestrogenic hormones, in combination with ^{90}Sr in activities sufficiently high to induce cancer initiating events, highly significantly increases the osteosarcoma yield. The results of this investigation also clearly demonstrate that oestrogenic hormones, when combined with ^{90}Sr below or just above the critical limit of tumour induction, are unable to enhance the incidence of osteosarcomas.

Interaction between ^{90}Sr-dose and oestrogen as evidenced by histology. The reason why the impetus of oestrogen is dependent on the dose of ^{90}Sr may have a very complex background, but may partly be explained after histological evaluation. This seems to indicate an interplay of both quantitative and qualitative events related to differences in the altered histological structure and irradiation environment between ^{90}Sr and ^{90}Sr + oestrogen treated animals. The bones of the latter are thus characterized by an increased number of osteoprogenitor cells and osteoblasts as well as a pronounced apposition of a compact 'oestrogenic' bone which is in a complete contrast to mice treated with ^{90}Sr only or particularly ^{90}Sr + glucocorticosteroids. A comparison between the oestrogen groups themselves also reveals that the incidence of dystrophic lesions was related to the dose of ^{90}Sr. Therefore, provided that the ^{90}Sr dose is sufficient, the 'oestrogenic' bone on its mere quantity may contribute to the large number of multicentric regressive events which is evidenced in this investigation. Qualitatively these events also seem to play a crucial role as a stimulus for transient hyperplasia and reparative cell proliferation since at such sites it is obvious that the proliferating tissue in a number of cases does develop into a morphologically abnormal and functionally defective tissue, successively expressing more and more dysplasia, dysdifferentiation and finally malignant features. Berenblum (1) postulates that the function of an initiator is to convert normal cells into latent tumour cells, which then persist until exposed to a promoter. It is now quite clear that any procedure that causes transient hyperplasia, such as healing of dystrophic lesions, can act as a promoter. It is likewise obvious that only a few such lesions do progress into tumours. Provided that the initiating events expressed by ^{90}Sr are strong enough this experiment, however, seems to show

that oestrogen by its stimulatory effect upon bone cells and dysplastic lesions may increase the tumour progression in contrast to glucocorticosteroids, which highly significantly suppress such events.

Does oestrogen act as a true or preparative promoter? An important question is whether or not oestrogenic hormones act as true promoters, i.e. take part in the completion of the cancerogenic process instigated by the initiating potential of ^{90}Sr, or if they do act merely as 'pseudo-promoting' factors (2) exerting only preparative or permissive influences. According to Warwick (15) the theoretical basis for preparative action on the responding tissue rests on the fact that the intensity of cancerogenic action differs somewhat according to the functional state of the cell with respect to proliferation versus differentiation. In practical terms (2), preparative action rendering tissues more responsive to cancerogenic agents is most pronounced with hormonal influences on hormone sensitive tissues or in other tissues following reparative hyperplasia resulting from non-specific injury. One of the difficulties in determining the role of hormones as 'sensitizers' of tissues for cancerogenic action is to distinguish such a preparative action from actual participation in the cancerogenic process. In this experiment oestrogen alone did not induce oestosarcomas but did so to a significant level in combination with ^{90}Sr which, as earlier postulated, seems to indicate that oestrogen may act as a cocancerogen. The fact that an enhancing effect of the tumour incidence was seen only when the highest ^{90}Sr (B: 3) dose was employed seems on the other hand to indicate that oestrogen did not interact or assist in the initiating mechanism proper, since in that case the tumour incidence should have increased as well at the lower combination levels despite B: 1 survives shorter than A: 1. This is based on the fact that oestrogen in combination with higher doses of ^{90}Sr generally gives a tumour yield 2 to 4 times greater than ^{90}Sr alone despite a significantly reduced survival time (7, 11). The lacking histologic evidence of imminent tumour development strengthens this viewpoint. It is therefore considered that oestrogen promotes the tumour incidence merely as a preparative factor. One theoretical basis for this opinion is the fact that oestrogen increases the actual number of cells at risk and/or consequently force an enhanced number of cells to undergo sensitive stages of their cell cycles, thereby indirectly reinforcing the action of ^{90}Sr. Finally, oestrogenic stimulation on the growth of dysplastic repair tissues, carrying malignant potentialities, must be considered.

Immunologic aspects. Since both oestrogenic (4) and corticosteroid hormones (5, 13) have lymphocytolytic properties and since ^{90}Sr induced osteosarcomas have been shown to have antigenic properties (9) also immunological factors have to be considered as a cause of the changed tumour frequency. However, the antigenicity of these tumours is rather weak and it could therefore be anticipated that the immunological factors may play only a minor role. This is indicated by the fact that osteoblastic osteosarcomas, which seem to be the most antigenic type of ^{90}Sr-induced bone tumours, are most numerous in combination with oestrogenic hormones. The corticosteroid hormones, in spite of their strong lymphocytolytic effect, significantly reduced the tumour frequency. This also seems to indicate that the immune response may play an insignificant role as compared to the depressive effect of glucocorticosteroids on the bone cells. In this context it should be kept in mind that corticosteroids to a very low degree deplete the cells of the thymic dependent areas of lymphoid tissues (5).

Is the skeletal accumulation of ^{90}Sr influenced by oestrogen or glucocorticosteroids? Another possible reason for the increased or decreased tumour incidence in the oestrogen and corticosteroid series may be related to an enhanced or diminished accumulation of ^{90}Sr in the bone tissue. As regards this question it has been reported by Rönnbäck & Nilsson (12) that the retention of ^{90}Sr in oestradiol treated mice is not higher than in mice given ^{90}Sr alone.

Nilsson & Broomé-Karlsson (7) have also shown that Depomedrone treatment only slightly influences the accumulation of ^{90}Sr as compared to non-Depomedrone treated animals. The accumulated skeletal burden of ^{90}Sr therefore seems to be approximately the same in the different groups and series in these experiments. On these grounds, but with reservation for the influence of the increased bone volume in the oestrogen treated mice, the approximate irradiation dose delivered to the whole skeleton has been calculated at the mean survival time (Table 3).

Impact of oestrogen on osteosarcoma subtypes. The fact that the tumour spectrum differed between the mice given combined treatment and ^{90}Sr alone has been observed earlier (11). Generally there is a prominent overrepresentation of predominantly bone-forming and osteoclastic osteosarcomas when oestrogen is supplied. New data indicates that ^{90}Sr-induced bone tumours in female mice regularly show the same shift of the tumour panorama as do oestrogen treated males. The reason why oestrogen may interfere in the histology of the bone tumours is not known but may be related to several mechanisms. According to Simmons, (14) osteogenic stem cells are localized in the bone marrow cavity in mice and will after stimulation differentiate into osteoblasts. Their osteogenic potential will, however, be evidenced mainly at sites where the cells are adjacent to bone surfaces. This might —because of the abundancy of 'oestrogenic' bone—be one possibility for the preponderance of the bone forming tumours. The increased frequency of osteoclastic osteosarcomas also seems to be related to the formation of 'oestrogenic' bone and the stimulus it may exert on osteoclastic activity in the process of bone destruction and remodelling.

Concluding remarks. In conclusion it is likely that a

stimulatory event, such as oestrogen, provided that the ^{90}Sr dose is sufficient as an initiator, acts as a preparatory factor which in this investigation is mainly responsible for the 4-fold increased tumour incidence to that obtained when ^{90}Sr is given alone. The drastically reduced tumour incidence brought about by the inhibition of cell replication by glucocorticosteroids furthermore supports this hypothesis as do the enormous cellular activity and bone apposition after treatment with oestrogen only.

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