

FROM INSTITUTO DE PATOLOGIA, FACULTAD DE CIENCIAS VETERINARIAS, UNIV. DE LA PLATA, 1900 LA PLATA, ARGENTINA, UNIT OF RADIOLOGICAL ONCOLOGY, UNIVERSITY OF STOCKHOLM, S-172 46 SUNDBYBERG AND THE NATIONAL VETERINARY INSTITUTE, S-750 07 UPPSALA, SWEDEN.

EFFECT OF HIGH ^{131}I DOSES TO THE THYROID GLAND ON TUMORIGENICITY OF ^{90}Sr AND ^{90}Y IN MICE

E. J. GIMENO, G. WALINDER, R. E. FEINSTEIN and C. REHBINDER

Abstract

The incidence of tumors was studied in mice injected with ^{90}Sr only or with ^{90}Sr in combination with high amounts of ^{131}I . The high ^{131}I -dose to the thyroid gland was necrotizing to the glandular tissue and the main aim of the investigation was the possible effects of the thyroïdal destruction on the formation of bone tumors. After correction for competing mortality, no significant difference in the frequency of bone tumors could be found between ^{90}Sr -treated and (^{90}Sr + ^{131}I)-treated mice. The incidence rate of bone tumors, however, was higher in mice with radiogenically destroyed glands than in those with intact glands. The limitations of using the concept of 'actuarial tumor incidence' in correction for competing mortality in animal experiments are discussed. Large numbers of lymphatic tumors were found in all animal groups. The frequencies of such tumors were independent of the radiation doses but their incidence rates were shortened in a dose dependent manner. Other, directly or indirectly radiation induced tumors were observed.

Key words: Radiobiology; mice, high ^{131}I doses, ^{90}Sr - ^{90}Y tumorigenicity.

Persons exposed to recent radioactive fallout from detonation of a nuclear weapon or nuclear reactor accidents may incorporate amounts of ^{90}Sr corresponding to those producing bone tumors in animals. The levels of ^{131}I simultaneously incorporated in such cases may then be as high as to destroy the thyroid tissue completely.

Several hormones may affect the biologic behaviour and tumorigenic capability of the bone-seeking radionuclide ^{90}Sr and its daughter nuclide ^{90}Y (17-21).

Calcium (and bone) metabolism is regulated by different hormones, e.g. parathyroid hormone (PTH), calcitonin (CT), thyroxine (T_4). The influence of Ca-regulating hormones on the tumorigenic effects of internally deposited ^{90}Sr and ^{90}Y is not yet elucidated.

The present studies are primarily aimed at the possible

influence of high ^{131}I -doses to the thyroid gland on the development of osteosarcomas by concurrently administered ^{90}Sr - ^{90}Y . Other ^{90}Sr -induced tumors are also discussed.

A comparative study in which two groups of mice were injected either with a ^{90}Sr -tumorigenic amount alone or in combination with a thyroïdectomizing amount of ^{131}I did not reveal changes in the skeletal concentration of ^{90}Sr due to the thyroïdal destruction (26), however, the ^{131}I -injected group showed a slightly reduced ^{90}Y concentration in the skeleton during the first weeks after the nuclide injection. This small dose reduction could, however, not be expected to have an observable effect on the formation of bone tumors. Nevertheless, we considered it interesting to see whether the loss of thyroïd hormones and calcitonin due to the thyroïdal destruction would have any effects on the sites and frequencies of ^{90}Sr induced osteosarcomas.

These investigations were divided into two parts called expt. A and expt. B. Since the ^{131}I -amounts injected in expt. A, 1.1 MBq, did not cause total thyroïd destruction as intended, a second experiment was performed, expt. B, injecting 2.2 MBq of ^{131}I . The interval of time between commencements of both experiment was one year.

Material and Methods

The experimental animals were male C57 Bl/S mice, 6 to 8 weeks old at the beginning of the experiments. The animals were conventionally bred and kept at the animal colony of the Unit of Radiological Oncology, University of Stockholm. They were maintained on an iodine-defi-

Accepted for publication 17 December 1985.

cient diet (Astra-Ewos) for 14 days prior to intraperitoneal injections of the nuclides. The iodine-deficient diet was replaced by a normal, standard one (Astra-Ewos) the day following that of treatment. The mice were kept under controlled temperature, humidity and light conditions throughout the study. Water was supplied ad libitum. The radionuclides used were from Amersham International (England).

At the start of the experiments each one of the groups in expt. A, A-2, A-3, and A-4, consisted of 50 mice (Table 1). The number of mice in the control group, A-1, was 41. The corresponding number in expt. B were 35 in B-1 and 20 in each of the groups B-2 and B-3. The number of mice as given in Table 1 refers to those surviving more than 100 days after nuclide injections.

All mice found dead or killed, by means of cervical dislocation when reaching a moribund state, were examined by dorsoventral radiography in order to locate tumors of the hard tissues. Routine histological studies were performed on the spleen, liver, lungs, kidneys, heart, testicles, adrenals, thyroid, parathyroid, lymph nodes, and salivary glands. All macroscopic hard and soft tissue lesions, tumors and roentgenologically suggested bone tumors were fixed in Stieve's fluid. The heads were divided longitudinally along the midline, and were fixed together with the brain left in situ whenever lesions were found or suspected. Hard tissues were decalcified in 20% formic acid. The histological sections were stained with haematoxylin and eosin, or by the van Gieson method.

Statistical methods. The mortality rate caused by bone tumors has been examined for differences in cumulative tumor rates by means of a logrank test (1). The numbers of tumor bearing mice in A-2 and B-2 were compared with the expected numbers of mice with tumors in the two groups under the acceptance of the null-hypothesis, i.e. the tumor frequencies in A-2 and B-2 were considered identical with those in A-3 and B-3 respectively. From this comparison a Z-value was derived and tested against the standard normal distribution (e.g. if $Z < 1.96$ equality of the tumor rates in the two groups was rejected with a two-side error probability of equality less than 0.05),

$$Z_i = \frac{\sum |n_{ii} - \bar{n}_{ii}| - 0.5}{\sqrt{\sum \sigma_i^2}}$$

where n_{ii} is the number of merely ^{90}Sr -treated, tumor bearing mice observed on day t_i and \bar{n}_{ii} is the expected number of such mice. If N_{ii} is the corresponding number of surviving mice on the same day and if index 2 denotes the corresponding values for the group of comparison, we should obtain:

$$\bar{n}_{ii} = \frac{N_{ii}(n_{ii} + n_{2i})}{N_{ii} + N_{2i}}$$

For $\sum |n_{ii} - \bar{n}_{ii}| \leq 0.5$, Z_i is given the value zero. For

Table 1

Experimental design

Experiment group	No. of mice	Treatment	
		^{90}Sr kBq/mouse	^{131}I MBq/mouse
A-1	41	—	—
A-2	47	370	—
A-3	49	370	1.1
A-4	48	740	1.1
B-1	33	—	—
B-2	19	370	—
B-3	18	370	2.2

* The groups in expt. A consisted originally of 50 mice each, and in expt. B of 35, 20, and 20 mice respectively. The lower numbers in the table are due to deaths at the very beginning of the experiments.

$\sum (n_{ii} - \bar{n}_{ii}) < 0$, Z_i is negative and for positive differences, Z_i is positive. The term 0.5 is a continuity correction. The estimated variance (of a hypergeometric distribution) is:

$$\sigma_i^2 = \frac{N_{1i} \cdot N_{2i} (n_{1i} + n_{2i}) (N_{1i} + N_{2i} - n_{1i} - n_{2i})}{(N_{1i} + N_{2i})^2 \cdot (N_{1i} + N_{2i} - 1)}$$

The number of mice with tumors has been corrected for competing mortality by a quantity (actuarial incidence) which can be obtained in terms of the Kaplan-Meier product limit estimate (9, 11):

$$\hat{I}(t) = 1 - \prod_i \left(1 - \frac{n_i}{N_i} \right); \quad (t_i \leq t)$$

The standard error of $\hat{I}(t)$ is:

$$SE(\hat{I}) = (1 - \hat{I}(t)) \cdot \sqrt{\sum_i \frac{n_i}{N_i^2}}; \quad (t_i \leq t)$$

$I(t)$ is the probability (corrected for competing mortality) of an animal at risk up to the time t to have incurred a tumor. The validity of these quantities is discussed in the paragraph 'Statistical considerations'.

The 'mean time-at-tumor', $\langle \hat{t} \rangle$, is the mean time (corrected for competing mortality) that has elapsed from the radionuclide exposure to the point of time at which tumor-bearing mice are observed (7)

$$\langle \hat{t} \rangle = \sum_{i=1}^m \frac{(I_i - I_{i-1}) \cdot t_i}{I_m}; \quad (I_0 = 0)$$

$$SE(\langle \hat{t} \rangle) = \sqrt{\frac{1}{m-1} \left[\sum_{i=1}^m \frac{(I_i - I_{i-1}) \cdot t_i^2}{I_m} - (\langle \hat{t} \rangle)^2 \right]}$$

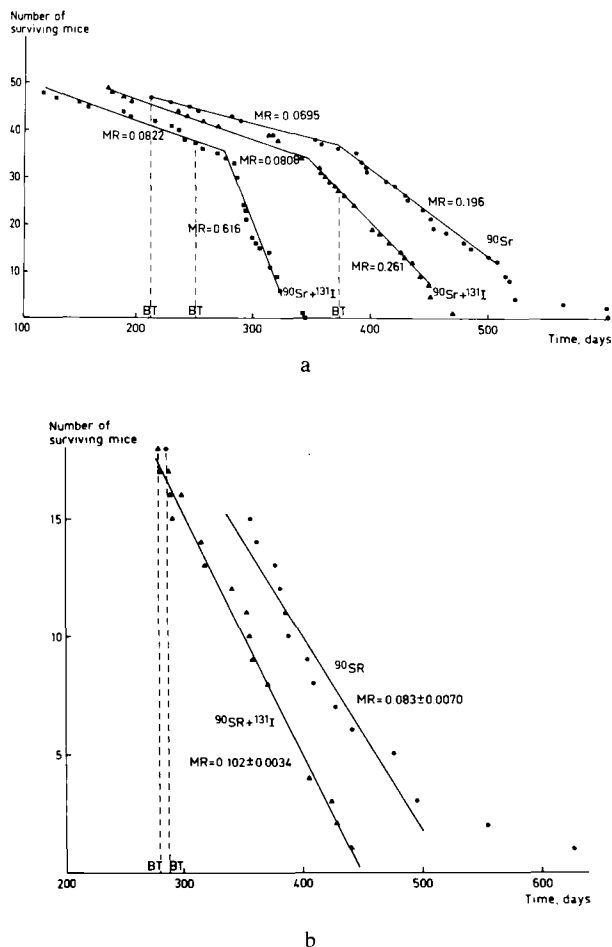


Fig. 1. a) Experiment A. Mortality rate (MR) in mice treated with 370 kBq ^{90}Sr (A-2 ●) 370 kBq ^{90}Sr + 1.1 MBq ^{131}I (A-3 ▲) and 740 kBq ^{90}Sr + 1.1 MBq ^{131}I (A-4 ■). The time for the detection of the first tumor in the skeleton is denoted by BT. b) Experiment B. Mortality rate (MR) in mice treated with 370 kBq ^{90}Sr (B-2 ●) and with 370 kBq ^{90}Sr + 2.2 MBq ^{131}I (B-3 ▲). The time for the detection of the first tumor in the skeleton is denoted by BT.

Results

Rates of mortality and induction of bone tumors. The mortality rate (MR) is defined as the slope of the curves in Fig. 1 and its values have been determined by the least square method. The survival curves were clearly biphasic in expt. A which was not the case in expt. B. Mean survival times, mortality rates, non-adjusted number of tumors, and number of animals with tumors are given in Table 2.

The bone tumors found in the present work were predominantly of osteoblastic type, and the histological characteristics were generally similar to those previously reported in the literature (4, 13). The crude number of tumors (i.e. number not adjusted for competing mortality) as well as the crude number of mice with tumors in A-2 were higher than those in A-3 and A-4, and the mean

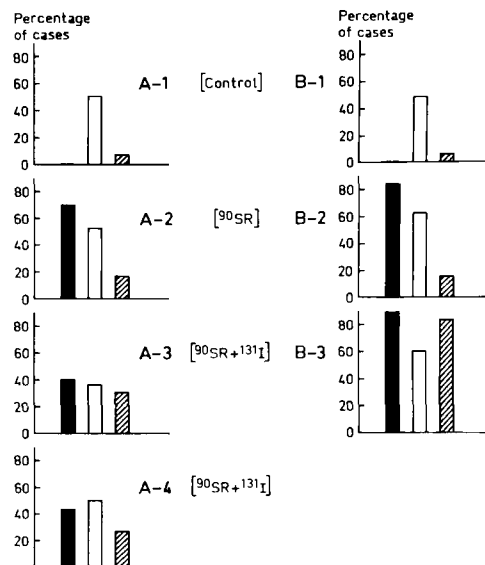


Fig. 2. Frequency of osteosarcomas (■), lymphoreticular tumors (□) and other types of tumors (▨). Percentage of mice affected by each type of tumor in the different groups.

survival times for mice with bone tumors were higher in A-2 and A-3 than that in A-4.

The crude number of tumors and number of mice with tumors did not significantly differ between the two irradiated groups in expt. B (B-2 and B-3).

The relative frequencies of osteosarcoma, lymphoreticular tumors, and other tumor types found, are presented in Fig. 2.

Anatomical location of bone tumors. Femora were the commonest location for osteosarcoma in mice injected with 370 kBq of ^{90}Sr . However, after 740 kBq ^{90}Sr the vertebrae and the bones of the skull were the predominant sites. As suggested by Table 3, there is a tendency to higher frequencies of head tumors and to lower frequencies of pelvic tumors in groups A-2 and B-2 as compared to the corresponding frequencies in A-3 and B-3 respectively.

Lymphoreticular tumors (LR-tumors). LR-tumors were most commonly located in the spleen, lymph nodes and bone marrow, but metastatic infiltrations were also seen in other organs, e.g. liver, lungs, kidneys, skeletal muscles, meninges, salivary glands and heart.

The incidence of LR-tumors was high both in controls and in treated groups (Table 4). The crude frequencies of LR-tumors did not exhibit any dependence on the amounts of administered ^{90}Sr but the mean incidence time for such tumors decreased at increasing ^{90}Sr -doses (Table 4).

Pituitary tumors. A high incidence of pituitary tumors was found. They appeared mostly in the groups that received ^{131}I . One single case was found in a mouse treated with ^{90}Sr only (Table 5). The first pituitary tumor from

Table 2*Mean survival times, mortality rates, and crude mean bone tumor incidence rates*

Expt. group	Mean survival time, days (SD)	Mortality rates, day ⁻¹		Mice with tumors	Tumors	Mean number of tumors per tumor-bearing mouse
		Phase 1	Phase 2			
A-1	649 (140)					
A-2	422 (94)	0.0695	0.196	33	57	1.73
A-3	359 (82)	0.0808	0.261	20	28	1.40
A-4	274 (53)	0.0822	0.616	21	35	1.67
B-1	700 (198)					
B-2	405 (94)	0.083	0.083	16	31	1.63
B-3	353 (50)	0.102	0.102	16	28	1.56

Table 3*Location of osteosarcomas*

Location	Group									
	A-2		A-3		A-4		B-2		B-3	
	No.	%	No.	%	No.	%	No.	%	No.	%
Femur	18	31.6	8	28.6	4	11.4	7	22.6	7	25.0
Tibia	12	21.0	4	14.3	1	2.9	2	6.5	5	17.9
Humerus	5	8.8	3	10.7	5	14.3	5	16.1	3	10.7
Vertebral column	7	12.3	4	14.3	11	31.4	5	16.1	5	17.9
Pelvic bones	2	3.5	3	10.7	0	0	2	6.5	4	14.3
Head	9	15.8	1	3.6	12	34.3	8	25.8	2	7.1
More than one bone	4	7.0	5	17.8	2	5.7	2	6.5	2	7.1

Table 4*Incidence and mean incidence times of lymphoreticular tumors*

Group	Affected mice		Mean incidence time (days ±SE)
	No.	%	
A-1	21	51.2	666±19
A-2	25	53.2	426±20
A-3	18	36.7	323±24
A-4	24	50.0	259±13
B-1	16	48.5	638±47
B-2	12	63.1	390±21
B-3	11	61.1	354±13

Table 5*Incidence of pituitary tumors*

Group	No. of pituitary glands available for histologic study	Pituitary glands presenting tumor	
		No.	%
A-1	8	—	—
A-2	15	1	6.7
A-3	17	13	76.5
A-4	23	5	21.7*
B-1	21	—	—
B-2	17	—	—
B-3	16	15	93.7

* Number of tumors significantly lower than that of A-3 ($p < 0.001$).

the (⁹⁰Sr + ¹³¹I)-series was seen 290 days after the radio-nuclide treatment and the single one from the ⁹⁰Sr groups after 498 days.

Other neoplasias. Thirty-three mice bearing 36 neoplasms other than osteosarcoma, LR-tumors and pituitary tumors were found. The majority of these tumors appeared in groups treated with both ⁹⁰Sr and ¹³¹I (52.8 per

cent), while 27.8 per cent were detected in the ⁹⁰Sr groups, and 19.4 per cent in the controls. The different types of tumors found are presented in Table 6.

The commonest neoplasia among these other types of tumors was squamous cell carcinoma, 61 per cent of them being found in group A-4 and the remaining 39 per cent among other ⁹⁰Sr groups. All the tumors of this type

Table 6

Neoplasias other than osteosarcomas, LR-tumors and pituitary tumors that were found affecting 33 mice

Type of tumor	Group							Total
	A-1	A-2	A-3	A-4	B-1	B-2	B-3	
Squamous cell carcinoma	—	3	—	11	—	1	3	18
Carcinoma of the lung	1	1	2	—	—	1	—	5
Thymoma	—	—	—	1	1	—	—	2
Thyroid adenoma	—	2	—	—	—	1	—	3
Thyroid carcinoma	—	1	—	—	—	—	—	1
Salivary gland adenoma	1	—	—	—	—	—	—	1
Hepatocellular adenoma	—	—	—	—	—	—	1	1
Bile duct carcinoma	—	—	—	—	1	—	—	1
Ganglioneuroblastoma	1	—	—	—	—	—	—	1
Malignant melanoma	1	—	—	—	—	—	—	1
Anaplastic sarcoma	1	—	—	1	—	—	—	2
Total No. of other tumors	5	7	2	13	2	3	4	36
Total No. of mice bearing other types of tumors	3	7	2	12	2	3	4	33

Table 7

Test values from the intergroup comparisons of the actuarial incidence of bone tumors (\hat{I}), mean times to tumor incidence ($\langle \hat{t} \rangle$), and cumulative bone tumor rates (Z)

Group	Treatment	\hat{I} (SE) for mice with tumors	\hat{I} (SE) for tumors	$\langle \hat{t} \rangle$ (SE)	Z
A-2	⁹⁰ Sr	0.738 (0.069)	0.943 (0.021)	452 (17)	
A-3	⁹⁰ Sr+ ¹³¹ I	0.554 (0.095)	0.696 (0.078)**	419 (9)	-2.41*
B-2	⁹⁰ Sr	0.433 (0.118)	0.642 (0.099)	426 (22)	
B-3	⁹⁰ Sr+ ¹³¹ I	0.464 (0.116)	0.609 (0.103)	352 (13)**	-2.55*

* $p < 0.02$, ** $p < 0.01$.

affected the nasal mucosa and the oral mucosa covering the hard palate and areas of the mandible and the upper jaw in close contact with the teeth. One thyroid carcinoma was detected in a ⁹⁰Sr-treated mouse of about 600 days of age. The tumor, small in size, was composed of large oval cells proliferating from the thyroid follicles in an infiltrative way without any follicular or papillary arrangement.

Other histologic findings. Apart from the tumors already described different non-neoplastic changes were found, such as aplasia of the bone marrow, extra-medullary haemopoiesis (spleen and liver), degenerative processes in various locations, and necrotizing and fibrosing lesions in the thyroid gland of mice treated with ¹³¹I. The thyroids of ¹³¹I-treated mice displayed histologic characteristics similar to those seen in other experiments (3, 24).

Intergroup comparison. From Table 2 it is evident that the control groups hold exclusive positions as to the mean survival times and to the absence of bone tumors. It is also clear that the tumors in group A-4 appeared earlier

than in the other groups of irradiated animals, although the crude number of tumors is not deviating from that in A-3.

However, the question whether the incidence rates and risks of tumors differ between the groups A-2 and A-3 or between B-2 and B-3 cannot be directly answered on basis of the crude values given in Table 2. It is thus necessary to correct for competing mortality and to take into consideration that the tumors appeared at different times in these groups.

The actuarial bone tumor incidence, (\hat{I}), the adjusted mean time elapsed from the start of exposure to tumor incidence, ($\langle \hat{t} \rangle$), and the test values for intergroup comparisons of the cumulative bone tumor incidence (Z), are given in Table 7 for the groups A-2, A-3 and B-2, B-3. The actuarial tumor incidence has been calculated up to the level of 10 surviving mice and the intergroup comparison from the first appearing tumor to the last surviving mouse in any of the groups under comparison.

There was a tendency of lower actuarial incidence rates with regard to the bone tumors in mice with ^{131}I -destroyed thyroid glands as compared to those with intact glands but, as pointed out in the Discussion, this tendency may be accidental.

The logrank test of the cumulative incidence of bone tumors indicates a significantly slower bone tumor incidence rate in mice with intact thyroid glands than in those with destroyed glands. However, the mean times to tumor incidence in the groups A-2 and A-3 do not differ significantly.

Discussion

The observation that the femur was the most frequent location for osteosarcomas agrees with VYE et coll. (23) who also pointed out the importance of the geometry of individual bones in relation to the absorbed radiation dose and the further development of tumors. NILSSON (13, 15) reported long bones to be preferentially affected in CBA mice that had received doses similar to those in A-2 and B-2, and showed a shift from long bones to vertebrae and flat bones when the dose of ^{90}Sr was increased. The finding by FINKEL et coll. (4) that more bone tumors were located in the vertebral column than in the long bones in similarly treated CF_1 and CBA mice differed, accordingly from those by Vye, Nilsson and by us. The reason for this difference is not known.

The finding of large numbers of LR-tumors in all experimental groups was not unexpected since C57Bl mice are reported to have a high incidence of spontaneous LR-tumors (10). It has been proposed that all strains of laboratory mice carry leukemogenic viruses and that the induction of leukemia varies with an as yet undefined threshold of susceptibility (8). The incidence of LR-tumors among our groups was variable and a correlation between the type of treatment and incidence could not be established (Table 4). LR-tumors evidently occurred later in the controls than in the treated groups. Thus, as interpreted from the present evidence, radiation does not increase the crude number of LR-tumors in C57Bl/S mice, but shortens the exposure-incidence time, apparently in a dose-dependent manner (Table 4).

Pituitary tumors are readily induced by a combination of hormonal derangement and ionizing radiation, or other carcinogenic agents (6). Pituitary tumors of the TSH-type (angular type) develop when the response of the thyroid to TSH is deficient or fails to occur, as in cases when the thyroid tissue is destroyed by high doses of radioiodine (5, 2, 25). The radiation dose from ^{90}Sr deposited in bones, adjacent to the pituitary gland has been shown capable of inducing pituitary tumors in rat fetuses (22), but it is doubtful whether this is the case in the adult mouse. NILSSON et coll. (17) have shown in adult CBA mice that the induction of pituitary tumors caused by oestrogen administration is synergistically enhanced by injections of ^{90}Sr prior to oestrogen injections.

The capacity of ^{90}Sr to induce carcinomas in epithelial tissues adjacent to bones is a wellknown phenomenon (14, 16). In the present investigation squamous cell carcinomas were detected in the ^{90}Sr -treated groups, being more common when high ^{90}Sr amounts were used.

The thyroid carcinoma detected in one mouse treated with ^{90}Sr seems to be an uncommon type of tumor in C57Bl mice. With the exception of the CBA/S mouse (25) tumors of the thyroid gland in mice are rare (10, 12).

Statistical considerations. In animal experiments, various procedures have been suggested to correct for competing risks, i.e. intercurrent mortality not related to the damage under study.

In the present investigation we have used a frequently recommended quantity called actuarial tumor incidence or incidence of tumors corrected for competing risks, that can be derived in terms of the Kaplan-Meier product limit estimate (9).

The formula for the actuarial tumor incidence rate, $\hat{I}(t)$, contains the expression $\prod(1 - n_i/N_i)$, where n_i is the number of tumorbearing animals observed on day t_i and N_i the corresponding number of survivals. This implies that in experiments where the tumor frequency is high, the terminal member of the product would be given an unreasonable weight. If the last surviving animal has a tumor, the actuarial incidence would be 1 and its standard deviation 0. The calculations have thus to be interrupted at a predetermined stage of the experiment. Several possibilities for such an interruption may be chosen. We decided to stop the calculations at a point of time when ten mice were still alive. Other decisions regarding when to stop the calculations may give somewhat different results, which demonstrate the vagueness of the concept of actuarial tumor incidence in cases where the number of tumors is not negligible in comparison with the number of surviving animals.

The results given in Table 7 refer to the number of mice with tumors. Several of the mice had, however, multiple tumors. Multiple tumors are seldom considered in conventional analysis because of the possible correlation between the formation of tumors in one and the same animal, which may make the standard deviations less conservative. On the other hand, the mean number of tumors per animal may be very elucidative of the 'strength' of a carcinogenic agent in cases where the tumors are not interrelated. In the present experiments, the distribution of the numbers of bone tumors per mouse was very close to a Poisson distribution and the ratio between observed and expected tumors did not exhibit any positive trend. The actuarial bone tumor incidences based on the total number of observed tumors have therefore been included in Table 7. However, the above mentioned vagueness of the concept of actuarial incidences when used in experiments like the present one, makes it impossible to draw any conclusions from the tendency of the figures in Table 7 to a depression in actuarial incidences of bone tumors in

mice with ^{131}I -destroyed thyroid glands as compared to the corresponding numbers as found in mice with intact glands.

The logrank test is not equally sensitive to high tumor-survival ratios as is the actuarial incidence, so the conclusion that the destruction of the thyroid glands did give rise to an earlier tumor incidence seems to be valid in spite of the non-significant reduction of the mean tumor incidence time in experiment A. This 'accelerated' incidence in animals with destroyed thyroid glands is obviously not a result of the changed radiation doses to the bones but probably a consequence of losses of thyroidal hormones. The mechanism for such a hormonal effect on the incidence rate of bone tumors is, however, unknown.

In conclusion: the somewhat lower ^{90}Sr -doses to the skeleton in combination with the reduced production of thyroid hormones and calcitonin in mice exposed to ^{131}I -doses high enough to necrotize the thyroid glands, did not result in significantly fewer bone tumors than in mice solely injected with ^{90}Sr . Although the contrary was not true either, the logrank test indicated that the tumors appeared earlier in mice exposed to both ^{90}Sr and ^{131}I than in those only exposed to ^{90}Sr . The high crude occurrence of tumors in the group A-2 can thus essentially be ascribed to the long survival of the animals in this group. No less than 27 out of the 57 tumors in A-2 appeared after the day at which the last mouse in A-3 died.

ACKNOWLEDGEMENT

This work was carried out as part of the program of the European Late Effects Project Group (EULEP).

Request for reprints: Professor Gunnar Walinder, Sveriges lantbruksuniversitet, Box 7031, S-750 07 Uppsala, Sweden.

REFERENCES

1. COX D. R.: Regression models and life tables. *J.R. Stat. Soc.* 34 (1972), 361.
2. EDELMANN A. and GORBMAN A.: Endocrine factors influencing the development of hypophyseal tumors. *Proc. Amer. Ass. Cancer Res.* 2 (1955), 13.
3. FEINSTEIN R. E., GIMENO E. J., EL-SALHY, M., WILANDER E. and WALINDER G.: Evidence of C-cell destruction in the thyroid gland of mice exposed to high ^{131}I doses. *Acta Radiol. Oncology* 25 (1986), 199.
4. FINKEL M. P., BERGSTRAND P. J. and BISKIS B. O.: The latent period, incidence, and growth of ^{90}Sr -induced osteosarcomas in CF_1 and CBA mice. *Radiology* 77 (1961), 269.
5. FURTH J.: Experimental pituitary tumors. *Recent Prog. Horm. Res.* 11 (1955) 221.
6. — NAKANE P. and PASTEELS J. J.: Tumors of the pituitary gland. *In: Pathology of tumors of laboratory animals. Vol 1. Tumors of the rat, part 2, p. 201.* Edited by V. S. Turusov. Int. Agency for Res. on Cancer, Lyon 1966.
7. HOEL D. G. and WALBURG H. E. JR: Statistical analysis of survival experiments. *J. Natl. Cancer Inst.* 49 (1972), 361.
8. KAJIMA M. and POLLARD M.: Wide distribution of leukaemia virus in strains of laboratory mice. *Nature* 218 (1968), 188.
9. KAPLAN E. L. and MEIER P.: Non-parametric estimation from incomplete observations. *J. Amer. Stat. Assoc.* 53 (1958), 457.
10. KASUGA T., SADO T., NODA Y., TERASIMA T. and KITAGAWA T.: Radiation-induced tumors in C57 B1f/6 J. Nrs (SPF) and C 2Hf/He Ms Nrs (SPF) strain male mice. *Proc. Symp. Late Biol. Eff. of Ionizing Radiation. Vol. 2, p. 29.* IAEA, Vienna 1978.
11. KELLERER A. M. and CHMELEVSKY D.: Analysis of tumor rates and incidences. A survey of concepts and methods. *Proc. European Seminar on Neutron Carcinogenesis.* Edited by J. J. Broerse and G. B. Gerber. EUR 8084 EN. Luxembourg 1982, p. 209.
12. MEISSNER W. A. and WARREN S.: Tumors of the thyroid gland. *Atlas of tumor pathology, Second series, Fasc. 4.* Armed Forces Inst. Pathol., Washington 1968.
13. NILSSON A.: Histogenesis of ^{90}Sr -induced osteosarcomas. *Acta Vet. Scand.* 3 (1962), 185.
14. — Pathologic effects of different doses of ^{90}Sr in mice. Development of carcinomas in the mucous membranes of the head. *Acta Radiol. Ther. Phys. Biol.* 7 (1968), 27.
15. — Pathologic effects of different doses of radiostrotrium in mice. Dose effect relationship in ^{90}Sr -induced tumors. *Acta Radiol. Ther. Phys. Biol.* 9 (1970), 155.
16. — Radiostrotrium-induced carcinomas of the external ear. *Acta Radiol. Ther. Phys. Biol.* 10 (1971), 321.
17. — BIERKE P., HARALDSSON I. and BROOMÉ-KARLSSON A.: Induction of pituitary tumours by combination of oestrogenic hormones and ^{90}Sr . *Acta Radiol. Oncology* 19 (1980), 373.
18. — and BROOMÉ-KARLSSON A.: Influence of steroid hormones on the carcinogenicity of ^{90}Sr . *Acta Radiol. Ther. Phys. Biol.* 15 (1976), 417.
19. — NELSON A., RÖNNBÄCK C., SJÖDÉN A.-M., WALINDER G. and HERTZBERG O.: Influence of gestation and lactation on radiostrotrium-induced malignancies in mice. II. Retention of radiostrotrium and relation between tumor incidence and excretion rate. *Acta Radiol. Ther. Phys. Biol.* 6 (1967), 129.
20. — and RÖNNBÄCK C.: Influence of oestrogenic hormones on carcinogenesis and toxicity of radiostrotrium. *Acta Radiol. Ther. Phys. Biol.* 12 (1973), 209.
21. RÖNNBÄCK C. and NILSSON A.: The influence of oestrogen on the excretion of radiostrotrium in mice. *Acta Radiol. Ther. Phys. Biol.* 14 (1975), 485.
22. SCHMAHL W. and KOLLMER W. E.: Radiation-induced meningeal and pituitary tumors in the rat after prenatal application of Sr-90. *J. Cancer Res. Clin. Oncol.* 100 (1981) 13.
23. VYE M., ZANDER-PRINCIPATI G. E. and KUSMA J. E.: The distribution of carcinogenic doses of ^{89}Sr in the skeleton of rats and mice. *Lab. Invest.* 10 (1961), 514.
24. WALINDER G.: Quantitative effects of ^{131}I on different components in foetal and goitrogen challenged mouse thyroids. *Acta Radiol. Ther. Phys. Biol.* 11 (1972), 1.
25. — Late effects of irradiation on the thyroid gland in mice. I. Irradiation of adult mice. *Acta Radiol. Ther. Phys. Biol.* 11 (1972) 433.
26. — FEINSTEIN R. E. and GIMENO E. J.: Effect of high ^{131}I doses on the bone uptake and retention of ^{90}Sr and ^{90}Y . *Acta Radiol. Oncology* 25 (1986), 255.