FROM THE DIVISION OF RADIOBIOLOGY, THE RESEARCH INSTITUTE OF NATIONAL DEFENCE, 172 04 SUNDBYBERG, SWEDEN.

LATE EFFECTS OF IRRADIATION ON THE THYROID GLAND IN MICE

III. Comparison between irradiation of foetuses and adults

GUNNAR WALINDER and ANNE-MARIE SJÖDÉN

Late effects of ^{131}I and roentgen irradiation on the thyroid gland of the CBA mouse have been previously investigated after exposing adult animals (WALINDER 1972 b) and foetuses (WALINDER & SJÖDÉN 1972) to various radiation doses. It was not possible, however, to make any direct comparisons between the results of the two experiments since they were carried out at different times and because a substantial number of the animals that were irradiated at the foetal stage died before the age of 2 years.

These complications were avoided in the present investigation by studying mice that were born at the same time. Some of the animals were irradiated at the foetal stage and others when they had reached the age of 3 months. Furthermore, the animals were killed already at one year of age, i.e. at a time before which very few mice had died.

Material and Methods

Males and females of the CBA mouse strain were used. The animals were born within the course of one week. The foetuses were exposed to radiation by intra-

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Table

Thyroid and pituitary weights and number of thyroid neoplasms in mice exposed to ^{131}I, roentgen rays, or a combination of the two types of radiation. P denotes the significance of the deviations from the glandular weights in non-irradiated mice. The roentgen dose given in the table is the mean dose to the central parts of the pregnant mothers.

^{131}I dose to central thyroid lobe, rad	Roentgen dose, rad	No. of mice	Sex	Thyroid weight, mg (±SE)	p	Pituitary weight, mg (±SE)	p	No. of adenomas	No. of carcinomas
Mice irradiated in utero									
—	—	53	M	13.8±0.2		1.94±0.04		0	0
—	—	62	F	12.3±0.2		2.14±0.05		0	0
2400	—	14	M	13.0±0.6	—	2.09±0.09	—	0	0
2400	—	5	F	11.9±1.3	—	2.26±0.09	—	0	0
4700	—	53	M	11.2±0.2	< 0.001	2.13±0.03	< 0.001	0	0
4700	—	48	F	9.3±0.2	< 0.001	2.24±0.05	—	0	0
7800	—	58	M	7.8±0.2	< 0.001	2.21±0.04	< 0.001	3	2
7800	—	51	F	6.9±0.2	< 0.001	2.47±0.05	< 0.001	0	2
—	180	47	M	14.2±0.3	—	1.85±0.05	—	0	0
—	180	35	F	11.7±0.2	—	2.05±0.05	—	0	0
2400	180	5	M	11.7±0.6	< 0.01	1.66±0.09	< 0.05	0	0
2400	180	4	F	10.6±1.2	< 0.05	1.93±0.26	—	0	0
4700	180	45	M	9.1±0.3	< 0.001	1.99±0.04	—	0	0
4700	180	29	F	8.4±0.2	< 0.001	2.03±0.05	—	2	0
Mice irradiated as adults									
8500	—	45	M	9.0±0.2	< 0.001	2.02±0.04	—	0	0
9500	—	46	F	6.7±0.2	< 0.001	2.11±0.04	—	0	0

venous injections of ^{131}I solutions into the mothers or whole body roentgen irradiation on the 18th day of gestation, i.e. usually 2 days before the birth of the animals. The adult mice were irradiated by intraperitoneal injections of ^{131}I on their 96th day of life. The mice irradiated as foetuses were killed at 323 to 348 days of age and those irradiated as adults at 374 to 376 days of age.

The housing and management of the mice were the same as described earlier. The doses from ^{131}I to the thyroid glands were determined according to WALINDER (1971 and 1972 a). The whole body irradiations of the pregnant mothers with roentgen rays were carried out with the animals placed in a slowly rotating

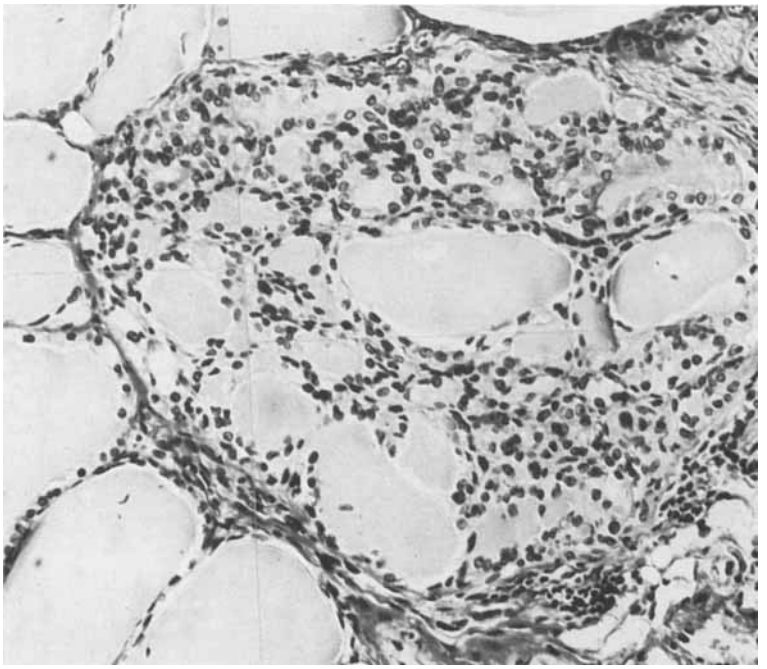
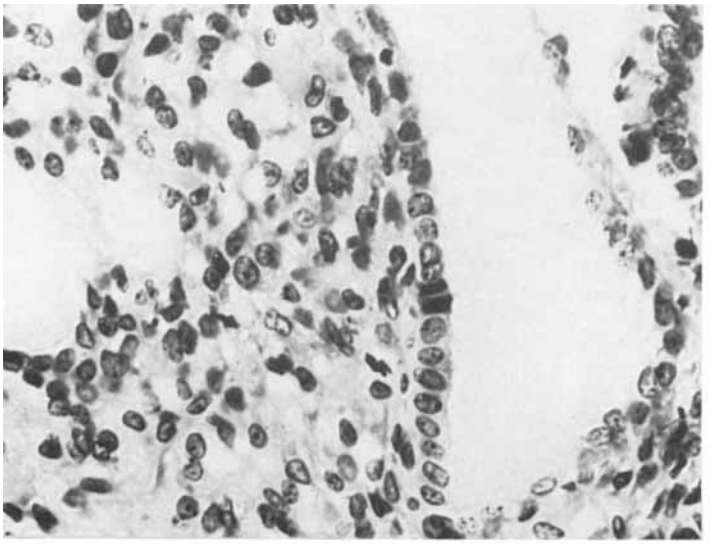


Fig. 1. The most common type of benign tumour observed in the irradiated thyroid gland; mixed micro- and macro-follicular adenoma. (van Gieson × 300).

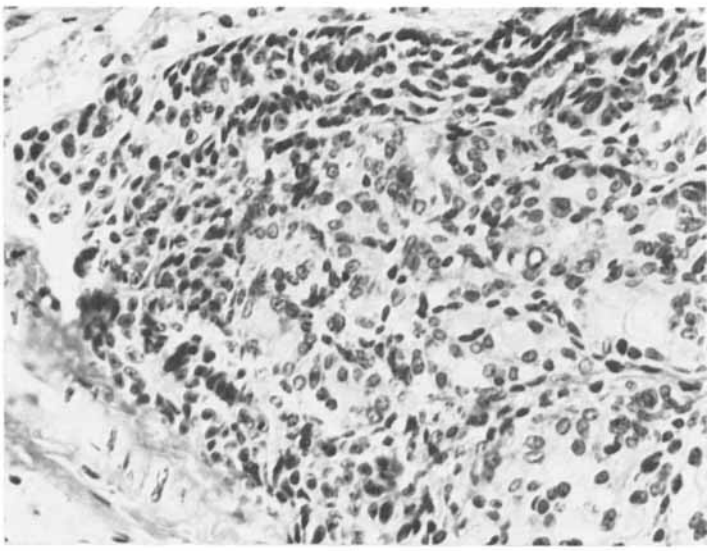
plexiglass wheel at a distance of 45 cm from the anode of the roentgen tube. The average dose rate to the 'midline' of the pregnant mice was 68 rad/min. The roentgen dose distribution within the animals was not uniform according to the definition of ICRU (1963) because of suboptimal backscatter conditions. The entrance dose rate was 75 rad/min and the exit dose rate was 58 rad/min, i.e. the ratio between maximum and minimum doses was 1.3. The exposure time was 2.65 minutes giving a total dose to the central parts of the pregnant mothers of 180 rad. The roentgen radiation data were identical with those described in paper II.

The techniques used for sectioning, fixation, and staining of the thyroid and pituitary tissues have been described earlier in paper I.

The criteria applied for distinguishing adenomatous goitre nodules from true adenomas and the classification of benign and malignant neoplasias were identical with the corresponding definitions in the two previous papers.



a



b

Fig. 2. Follicular carcinoma. a) Two follicle cells showing advanced atypical nuclei with concentration of chromatin. Some mitotic figures can be seen. b) Neoplastic tissue from the same tumour invading (from the right) a parathyroid gland. (van Gieson × 300).

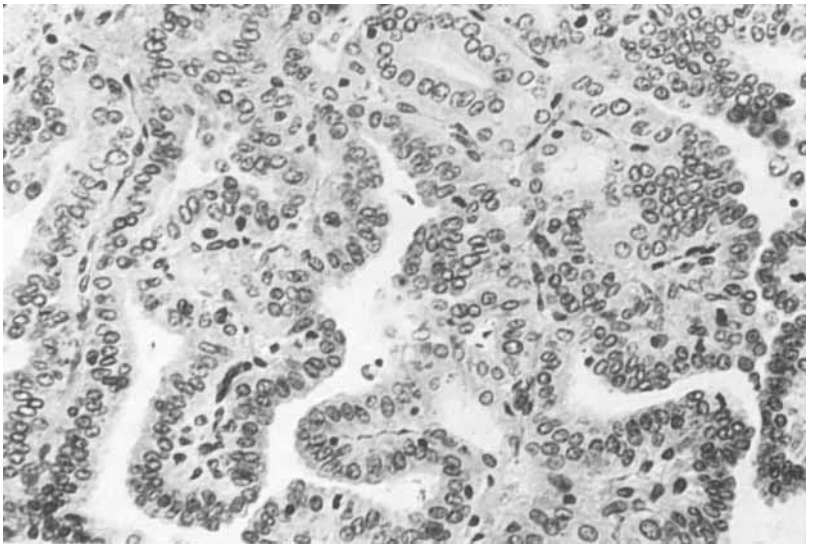


Fig. 3. Papillary carcinoma. Characteristic features of this type of tumour: Papillae with prominent connective tissue stalks, pale nuclei, irregular aggregation of cells, and often (as in this case) abundant mitotic figures. (van Gieson × 300).

Results

With the exception of some losses during the suckling period there were few premature deaths among the animals in this investigation (3 females exposed to 7 800 rad, 2 males exposed to roentgen rays, and 1 male and 1 female exposed to ^{131}I as adults). No significant difference in the size of the litters between irradiated and non-irradiated foetuses was detected.

The different ^{131}I doses had no effect on the body weights. The roentgen irradiation decreased the mean body weight by 8 %.

The effect of irradiation on the weights of the thyroid and pituitary glands, as well as the number of tumours in the thyroids, are shown in the Table. There was a significant inhibition of the age dependent thyroid growth in the about 1-year-old mice that had been irradiated as foetuses with a mean ^{131}I dose of 4 700 rad to the central parts of the thyroid glands and in those that had received 180 rad roentgen radiation in combination with a ^{131}I dose exceeding 2 400 rad in the central lobes.

The weights of the pituitary glands increased with increasing doses to the thyroid in animals that had been exposed in utero solely to ^{131}I. This was not the case in roentgen irradiated mice nor in animals that had been irradiated at 96 days of age. No hypophyseal adenomas were observed.

Three benign and four malignant tumours were found in the thyroid glands of mice that had been exposed as foetuses to 7 800 rad from ^{131}I and 2 thyroid adenomas were found among the animals that had received 180 rad roentgen radiation in combination with 4 700 rad from ^{131}I in utero. No thyroid tumours could be seen in any of the other animal groups. In spite of the high radiation doses to the thyroids in the mice irradiated at 96 days of age no tumours could be found in their glands.

Discussion

The relationship between radiation doses to the thyroid and the degree of growth inhibition of the gland was similar to that observed in the previous investigation (paper II). The positive correlation between radiation doses to the thyroids and the pituitary weights observed in the ^{131}I irradiated animals could not be seen in mice exposed to a combination of ^{131}I and whole body irradiation with roentgen rays. Despite the substantial shrinkage of the thyroid tissue in the latter cases, the roentgen irradiated pituitary glands could obviously not respond to this growth challenge, as was the case with the non-irradiated hypophyses. This appears to indicate an even higher radiosensitivity of the hypophyseal epithelium than that of the thyroidal cells. This difference might, however, be an apparent one since changes in the number of cells in the pituitary are immediately reflected in a corresponding change in the weight of the gland, which is usually not the case in the thyroid.

There were seven thyroid tumours in 109 mice exposed on the 18th day of gestation to 7 800 rad from ^{131}I to the central parts of the glandular lobes. No tumours were found in animals irradiated as adults. If we assume that a) the high doses to the adult animals had not seriously affected the neoplastic development of the initial radiation damage and b) the occurrence of tumours is binomially distributed, we find, by applying the 'null hypothesis', that the mouse foetus is more susceptible to radiation induced thyroid neoplasia than the adult animal ($p = 0.013$). Since the thyroid glands in animals that had been irradiated as adults were not smaller (and consistently not more atrophic) than those irradiated with 7 800 rad from ^{131}I when in utero, the point (a) above does not contradict the conclusion that the foetal thyroid gland is more radiosensitive than that of the adult mouse.

In the earlier investigation the irradiated mouse foetuses were examined when they had reached the age of 2 years. The tumour frequency in the thyroid glands was then very high in mice that had been exposed to 4 700—4 900 rad in the central parts of the lobes (31 % in males and 25 % in females). These figures were approximately equal to those found in mice that had been exposed to 6 800

—7 300 rad. The present investigation indicates that although the eventual tumour frequency in the thyroids might be similar in the two groups of mice, the tumours will appear earlier in those mice that had received the higher doses. The high fequency of thyroid tumours in the irradiated 2-year-old mice is probably to a great extent a consequence of the marked thyroidal growth in CBA mice between their first and second year of life (WALINDER et coll. 1971).

The number of benign thyroid tumours is similar to that of malignant ones (2.8 % and 3.7 % respectively) in the 1-year-old mice exposed to 7 800 rad, whereas the percentage of benign tumours found in the previous investigation of 2-year-old mice exposed to 6 800 to 7 300 rad was 22 against 6 % for the malignant neoplasms. These figures indicate that the thyroid carcinomas in most instances did not develop in previously benign tumours.

Acknowledgement

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SUMMARY

The thyroid glands of mice born within the course of one week were irradiated a) at the foetal stage, by intravenous injections of ^{131}I solutions to the mothers on the 18th day of gestation, by whole body roentgen exposure, or by a combination of the two forms of radiation, or b) as adults, by intraperitoneal injections of ^{131}I. In 109 1-year-old mice exposed in utero to 7 800 rad from ^{131}I (to the central parts of the glandular lobes), three benign and four malignant thyroid tumours were observed. No thyroid tumours could be found in 91 1-year-old animals exposed to 8 500 to 9 500 rad from ^{131}I at 3 months of age.

ZUSAMMENFASSUNG

Die Thyreoidea von Mäusen, die innerhalb einer Woche geboren waren, wurden a) während des Foetalstadiums durch intravenöse Injektion von ^{131}I Lösungen in das Muttertier am 18. Gestationstag, durch Gesamtkörperbestrahlung oder durch eine Kombination dieser beiden Bestrahlungsformen, oder b) im Erwachsenenstadium durch intraperitoneale Injektion von ^{131}I bestrahlt. Bei 109 1-Jahr alten Mäusen, die in utero mit 7 800 rad von ^{131}I (die zentralen Teile des Thyreoidealappen) bestrahlt worden waren, fanden sich drei benigne und vier maligne Thyreoideatumoren. Bei 91 1-Jahr alten Tieren, die im Alter von 3 Monaten mit 8 500—9 500 rad von ^{131}I bestrahlt worden waren, konnten keine Tumoren gefunden werden.

RÉSUMÉ

La glande thyroïde de souris nées en une semaine a été irradiée a) au stade fœtal par injection intraveineuse de solution de ^{131}I aux mères au 18e jour de la gestation, par irradiation roentgen totale du corps, ou par une combinaison de ces deux formes de radiations, ou

b) quand elles étaient adultes par injections intrapéritonéales de ^{131}I. Sur les 109 souris âgées d'un an exposées in utero à 7 800 rad de ^{131}I (dose dans les parties centrales des lobes glandulaires) les auteurs ont observé trois tumeurs bénignes et quatre tumeurs malignes de la thyroïde. Ils n'ont pas trouvé de tumeur thyroïdienne sur les 91 animaux âgées d'un an exposés à 8 500—9 500 rad de ^{131}I à l'âge de trois mois.

REFERENCES

ICRU Report No. 10e: Radiobiological dosimetry. NBS Handbook 88. National Bureau of Standards, Washington D. C. 1963.

WALINDER G.: Determination of the ^{131}I dose to the mouse thyroid. Acta radiol. Ther. Phys. Biol. 10 (1971), 558.

— (a) Beta doses in wet tissue. FOA Reports, Vol. 6, No. 7 (1972).

— (b) Late effects of irradiation on the thyroid gland in mice. I. Irradiation of adult mice. Acta radiol. Ther. Phys. Biol. 11 (1972), 433.

— and SJÖDÉN A.-M.: Late effects of irradiation on the thyroid gland in mice. II. Irradiation of mouse foetuses. Acta radiol. Ther. Phys. Biol. 11 (1972), 577.

— — and JONSSON C.-J.: Aging processes in the thyroid gland of the CBA mouse. FOA Reports, Vol. 5, No. 7 (1971).