The Effects of Irradiation on the Thyroid Gland with Particular Reference to the Induction of Thyroid Neoplasms: a Review

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CONTENTS

Introduction 1099
Radiation-induced Degenerative Lesions in the Thyroid Gland 1099
Radiation-induced Thyroid Neoplasms in the Rat 1100
Radiation-induced Thyroid Neoplasms in Other Animals 1101
Thyroid Nodules in Children Following Therapy with I^{131} 1102
Relation of Irradiation of the Head and Neck Area in Children to Development of Thyroid Carcinomas 1102
Relation of External Irradiation of Head and Neck Areas in Adults to Development of Thyroid Carcinomas 1104
Résumé 1104
References 1105

INTRODUCTION

Early investigations, both experimental and clinical, created the impression that the thyroid gland is relatively resistant to injury by ionizing radiation (86, 87). The results of the many studies carried out during the past decade, however, not only have reversed this view, but have, in fact, emphasized that destructive lesions of the gland can be readily produced in man and several species of animals by various forms of irradiation. Thus, injury in the human thyroid gland was observed after its irradiation for thyrotoxicosis, thyroid carcinoma, and cardiac disease. The most recent developments in this field indicate: (a) that benign and malignant neoplasms can be made to appear in rat thyroid glands by exposing them to I^{131} or x-rays (54, 56, 69); and (b) that benign nodules and at least one malignant nodule have been found in the thyroid glands of patients long after I^{131} treatment for thyrotoxicosis (75, 76). The administration of even minute doses of I^{131}—1 μc., for example—has now been shown to have a carcinogenic effect on the thyroid gland of the Long-Evans rat (34), and it is equally significant that thyroid carcinomas have been observed in patients who, during infancy or childhood, were exposed to low dosages of x-radiation to the thyroid area (21). These observations in both animals and man can leave little doubt that irradiation is an important factor in carcinogenesis of the gland.

In this review we have dealt primarily with three aspects: (a) Histogenesis of the destructive lesions induced in the thyroid gland by various types of internal and external irradiation is discussed. (b) The secondary thyroid epithelial proliferative processes that presumably result from thyrotropic hormone stimulation of portions of the gland still capable of responding to growth stimuli after radiation injury are described. These proliferative lesions are generally focal and may lead to development of benign nodules or adenomas and, possibly, of carcinomas. The decided similarity in the patterns of obvious injury and proliferative reactions (benign and malignant neoplasms) induced by irradiation in the glands of animals and man is emphasized. (c) The induction of thyroid carcinomas by low doses of irradiation which apparently do not cause other changes in the gland—at least that can be demonstrated microscopically—is described.

RADIATION-INDUCED DEGENERATIVE LESIONS IN THE THYROID GLAND

Destructive lesions in the thyroid gland resulting from irradiation with I^{131} have been studied extensively in fish (49), mice (35, 36, 81), rats (24, 25, 29, 33, 54, 56, 61, 69), rabbits (39), dogs (32, 39, 43, 57), sheep (9, 63), and cows (28). The effects of external irradiation on the dog thyroid, produced by x-rays, have also been described (82). Thyroid injury induced by alpha radiation from astatine has been reported for rats and monkeys (40–42). In the human being the effects of I^{131} irradiation in normal thyroid glands of patients treated for cardiac disease have been described by Freedberg et al. (26). Andrews et al. (2) also reported pathologic lesions in normal human glands that were irradiated with I^{131}. Various effects of radiation from radioactive iodine on human hyperplastic glands have been presented by Dailey et al. (14), Chapman and Maloof (10), and Dobyns et al. (16). A comparison of radiation effects induced by I^{131}, x-rays, radon, and neutrons on normal and hyperplastic human thyroid glands has been made by Lindsay et al. (53). Although no systematic studies of the effects of irradiation on malignant neoplastic thyroid tissue have appeared, Lindsay et al.
compared biopsies of cervical lymph nodes containing malignant thyroid tissue, before and after irradiation with I\textsuperscript{131}.\textsuperscript{1}

Thyroid tissue in animals and human beings is severely injured by the administration of high doses of I\textsuperscript{131}. Ultra-microscopic studies of rat thyroids irradiated with radiiodine indicate that the earliest changes are alterations in the endoplasmic reticulum, involving formation of spherical vesicles. The mitochondria swell and form spherical vesicles, and membrane-like structures appear in the cytoplasm (64). The earliest changes in the thyroid epithelial cells observed by light microscopy are similar to those shown to occur in other tissues that were irradiated—namely, cytoplasmic swelling, vacuolization, nuclear pyknosis, and fragmentation (33, 53). These degenerative alterations were found in all types of thyroid epithelial cells (normal, hyperplastic, and malignant) and are characteristic of irradiation changes generally observed in epithelial cells (37, 53). The disintegration of these epithelial cells leads to disruption of follicles, accompanied by an acute inflammation characterized by a fibrinous and neutrophilic leukocytic infiltration and edema. Endothelial swelling and necrotizing vasculitis with thrombosis may persist for considerable periods. Vascular, fibrous thickening occurs, but this is not a prominent feature of the late irradiation changes observed in the thyroid gland.

Eventually the lobular structure of the gland disappears, cells and follicles being no longer visible. Stromal condensation is associated with the appearance of mucoid ground substance, and chronic inflammatory cells eventually replace neutrophilic leukocytes. Six to 8 months after the irradiation, the thyroid gland is fibrotic. The few distorted epithelial cells that remain frequently display nuclear hyperchromatism and pleomorphism consistent with Askanazy changes (nuclear pleomorphism and hyperchromatism, oxyphilia). Dobyns and Didtschenko (15) have demonstrated a significant increase in deoxyribonucleic acid in the abnormal epithelial nuclei of irradiated rat thyroid glands. Since the cells that contain these nuclei are usually devoid of mitoses, nuclear chromatin presumably accumulates without cellular division. Maloof et al. (61) have shown that these nuclear changes in the irradiated rat thyroid may be prevented by administration of thyroid hormone.

Early regenerative phenomena have been found in human thyroid glands that were treated with large doses of radiiodine (14) and in thyroid glands of sheep that were fed small doses of radiiodide daily (63). These consisted of intrafollicular proliferation of syncytial groups of epithelial cells that extended into follicular spaces, a reaction closely resembling that observed in earlier stages of subacute thyroiditis.

In the human being the lesions found in the thyroid gland long after administration of large doses of I\textsuperscript{131} show chronic inflammation, interlobular and perifollicular fibrosis, follicular atrophy, and frequent Askanazy changes in the remaining epithelial cells (53). These lesions cannot always be ascribed to irradiation, for they have also been observed singly or in combination in a variety of thyroid diseases of nonirradiated patients. The use of a test, retest method demonstrated objectively that acute necrosis, pronounced follicular atrophy, and extensive perifollicular fibrosis could be reliably identified as having resulted from irradiation with high doses of I\textsuperscript{131} (65).

The degree of injury produced by ionizing radiation probably depends upon the type and structure of the thyroid gland irradiated, the amount and distribution of radiation delivered to and absorbed by the gland, and the duration of the reaction induced by the radiation. Probably other factors also influence the effects of irradiation on the thyroid gland. In the human being the effects on thyroid tissue of particle radiation and of gamma or roentgen rays appear to be qualitatively similar (53). Lippincott et al. compared the effects of astatine and I\textsuperscript{131} on rat thyroid glands and concluded that the degree of injury was not related to the type of radiation, but rather was correlated, both qualitatively and quantitatively, with the equivalent energy released from the two isotopes (58).

Studies at the University of California Hospitals (14) showed that most hyperthyroid patients treated with I\textsuperscript{131} became euthyroid. Since only nine of 24 irradiated glands showed histologic lesions regarded as having been caused directly by I\textsuperscript{131}, decreased hormone production apparently resulted from cellular injury not demonstrable by ordinary histological methods. Seven of the 24 glands showed predominantly the pattern of involuting hyperplasia, suggesting not only that cellular injury was accompanied by decreased thyroid hormone production but also that the injury may have prevented further stimulation of thyroid epithelial cells by thyrotropic hormone (14). Ten of 24 patients with diffuse toxic goiter, who had been treated with I\textsuperscript{131}, presented the typical pattern of chronic thyroiditis of the Hashimoto type. The frequency of this chronic inflammatory reaction was significantly greater in hyperplastic glands irradiated with I\textsuperscript{131} than in diffuse toxic goiters not treated by irradiation (14). In the light of the studies by Doniach and Roitt (19), irradiation of the hyperplastic thyroid gland may increase the loss of thyroglobulin from follicles and thus accentuate the development of an autoimmune reaction in the gland (6).

RADIATION-INDUCED THYROID NEOPLASMS IN THE RAT

The relation between thyroid irradiation and the subsequent development of thyroid neoplasms in the rat has been studied extensively. Goldberg and Chaikoff were the first to demonstrate malignant thyroid neoplasms developing about 2 years after a single injection of I\textsuperscript{131} (30, 31). Doniach (17, 18) induced benign and malignant neoplasms in rat thyroid glands, mainly by combining methylthiouracil feeding and thyroid irradiation with either I\textsuperscript{131} or x-rays. Although one malignant tumor was found in a rat in which only external x-radiation was applied to the thyroid gland, none was found in rats treated only with I\textsuperscript{131} (17, 18). Lindsay et al. (54) and Potter et al. (69) reported the highest incidence of thyroid neoplasms in Long-Evans rats that received low doses of I\textsuperscript{131}—either a single dose of 25 microcuries or four separate doses of 10 µc—at weekly intervals. The failure of Frantz et al.
jected to subtotal thyroidectomy and, in addition, injected
dience was significantly higher in rats that had been sub-
stromas was found in both lobes, the irradiated and the
of J131 either destroy them or prevent their development
ment of benign and malignant thyroid neoplasms (54).
Frantz et al. (25) found four carcinomas, papillary and
and follicular, in thyroid glands of Long-Evans rats that had
bent in rats that had been x-irradiated. Lindsay et al. (36)
den nodules or adenomas in 30 of 74 rats, and papillary
m loosen in nine of 74 rats in which the
thyroid glands had been subjected to external x-radiation.
Naturally occurring thyroid carcinomas frequently
ng in Long-Evans rats (54–56, 69) have been designated
odular or alveolar carcinomas (54), microadenomas (18),
odos (3), or solid carcinomas (25). The high doses of
either destroy them or prevent their development
A sequence of changes from focal regenerative hyper-
plasia to benign nodule formation has been clearly
-demonstrated in the rat thyroid gland treated with low doses of
131I (25–40 µc.) or x-rays (500–2000 r) (54–56, 69). The
benign neoplasms probably arose from focal areas that were
still able to respond to prolonged thyrotropic hor-
stimulation by epithelial proliferation—despite the
jury by irradiation. Both the benign adenomas and
the papillary and follicular carcinomas observed in these
studies closely resembled those in animals that had re-
ceived goitrogens or that had been subjected to chronic
iodine deficiency (5, 66). In rats in which the glands were
x-irradiated but in which one lobe was shielded, identical
focal hyperplasia resulting in development of benign
adenomas was found in both lobes, the irradiated and the
shielded (56). This indicates that at least the focal hyper-
plasia and benign nodule formation are probably thyro-
tropic hormone effects. Carcinomas were found only in
the nonshielded lobes, but it could not be decided whether
carcinogenesis was the result of continued thyrotropic
hormone stimulation of benign nodules or adenomas, or
whether x-radiation per se had induced the malignant
process (56).
A report that thyroid neoplasms that appear in partially
thyroidectomized rats are identical with those found after
irradiation (20) led us to compare the pathogenesis of
thyroid neoplasms induced by (a) subtotal thyroidectomy,
(b) irradiation with 131I, and (c) a combination of these
procedures (34). Single and multiple adenomas were
found in the thyroid remnants of the rats that had been
subjected to subtotal thyroidectomy only, but their inci-
dence was significantly higher in rats that had been sub-
jected to subtotal thyroidectomy and, in addition, injected
with 1 µc. of 131I. The development of these adenomas
could be largely prevented in both rats that were sub-
totally thyroidectomized only, and in those also given
injections of 1 µc. of 131I, by feeding them desiccated
thyroid powder. Two papillary carcinomas were ob-
served in thyroid glandular remnants of 68 rats subjected
to subtotal thyroidectomy alone. One papillary carci-
oma was found among 61 rats that were subtotally
thyroidectomized and also received 1 µc. of 131I. The
feeding of the desiccated thyroid powder did not prevent
development of this neoplasm.

Of considerable interest was the finding of one papillary
and one follicular carcinoma among 94 rats that had been
given injections of a single µc. of 131I. One of these animals
had been fed the desiccated thyroid-containing diet.
Thus, in this recent study, the appearance of two papillary
carcinomas in the residual thyroid tissue following sub-
total thyroidectomy alone suggests that stimulation of
the thyroid gland by thyrotropic hormone can result in
the development not only of benign neoplasms but of
malignant papillary carcinomas as well. On the other
hand, the finding of one papillary and one follicular carci-
noma in intact thyroid glands of rats that had received
only 1 µc. of 131I suggests that these malignant neoplasms
had been induced by thyroid irradiation. It is of interest
that rats treated with a single, very small dose of 131I (1
µc.) did not develop benign thyroid neoplasms and failed
to show evidence of thyrotrophic effects in their thyroid
glands (Askanazy cells) and of increased thyrotropic ac-
tivity in their pituitary glands. It was concluded from
this study that thyrotropic hormone stimulation must be a
promoting factor in development of both benign and
malignant thyroid neoplasms in the rat, and may also
initiate the development of thyroid malignant neoplasms
(34, 38). It also seems clear that the administration of 1
µc. of 131I alone may initiate the development of malignant
thyroid neoplasms. In this case, the promoting factor
might be normal thyroid growth, as suggested by Doniach
(18). The possibility, however, of other initiating and
promoting factors must be considered because of the
consistently high incidence, in Long-Evans rats, of naturally
occurring, low-grade, malignant, thyroid neoplasms. It
should be emphasized that the latter neoplasms differ
distinctly from those induced by subtotal thyroidectomy
or by irradiation. It is important to note that we have
never observed papillary or follicular carcinomas in Long-
Evans control rats (34, 54–56, 69).

Although the follicular and papillary carcinomas in-
duced in the rat by irradiation closely resembled those
observed in the human being, several neoplasms in the rat
clearly had arisen in pre-existing, benign nodules. Al-
though follicular carcinomas in human beings may origin-
ate in adenomas, papillary carcinomas are not usually
derived from pre-existing benign nodules (51). In human
beings, thyroid carcinomas appear more frequently in
females than in males (51), but in rats the administration
of low doses of radioiodine results in a higher frequency of
malignant thyroid neoplasms in males than in females
(55).

RADIATION-INDUCED THYROID NEOPLASMS
IN OTHER ANIMALS

Reports that neoplasms also develop in thyroid glands of
mice, sheep, and dogs given injections of 131I have
appeared. Speert et al. (81) studied the thyroid glands of
mice born to mothers given injections of 131I during preg-
nancy. The offspring showed thyroid changes consisting
of early fibrosis, later compensatory hyperplasia with adenoma formation, and eventually colloid goiters.

Bustad et al. (9) encountered thyroid adenomas and a fibrosarcoma in five sheep that were exposed to 5 μc. of \(^{131}I\) per day for their lifetime. In a later study, Marks and Bustad (62) found thyroid adenomas in eleven sheep, 4–8 years old, that had been fed daily quantities of \(^{131}I\) ranging from 1.5 to 135 μc. The exposure was either continuous from conception or was initiated at 15 months of age. Thyroid adenomas in control animals were limited to those 10 years of age or older. The patterns of these adenomas in irradiated sheep thyroids were macro- or microfollicular, trabecular or papillary. Several showed invasive perforation of their capsules, and two showed intravascular invasion. One thyroid neoplasm was a poorly differentiated follicular carcinoma that had metastasized widely to the liver, cervical lymph nodes and other sites.

Andersen (1) described thyroid adenomas in five of eight dogs (beagles) after administration of 0.3–0.6 mc. of \(^{131}I\)/kg as a single dose.

**THYROID NODULES IN CHILDREN FOLLOWING THERAPY WITH \(^{131}I\)**

Thyroid nodules have been found in human beings several years after they were treated with \(^{131}I\) for hyperthyroidism (75, 76). At the University of California Hospitals, such nodules were discovered in eight of 256 patients with Graves' disease, 5–14 years after the beginning of \(^{131}I\) therapy. Six patients were less than 18 years of age at the time of the \(^{131}I\) administrations, and two were between 25 and 30 years. Apparently, the younger the patient, the greater the chance of development of thyroid nodules following \(^{131}I\) therapy for thyrotoxicosis. At the time the nodules appeared, none of the patients was hypothyroid, and none had been treated with thyroid hormone.

Histologic examination of the glands of these eight patients revealed typical irradiation effects in their thyroid parenchyma. The lesions consisted of follicular atrophy, perifollicular fibrosis and mild chronic inflammatory infiltration. As a rule the remaining thyroid epithelial cells in the irradiated thyroid lobules displayed severe Askanazy changes. Pronounced activity of a number of intracellular enzymes was demonstrated in these Askanazy cells by histochemical methods (52, 75, 76). The nodules present seemed to have originated mainly in focal hyperplastic and regenerating segments of the lobules. The nodules varied from microstructures to grossly visible and palpable nodules measuring up to 2 cm. or more in diameter. The majority of the nodules had macrofollicular or microfollicular patterns, but some were trabecular. Others showed papillary hyperplasia. One nodule showed extension of neoplastic epithelium beyond the capsule, a process regarded as evidence of an early, low-grade carcinoma (75). In another patient, the neoplastic tissue extended into the capsule of the nodule (76). In six of the eight glands the pattern of Hashimoto's thyroiditis was also present, and in one gland, which showed the most pronounced thyroiditis, a similar inflammatory reaction involved the nodules as well as the parenchyma. Similar nodules with trabecular and follicular patterns have been observed in nonirradiated thyroid glands after surgical thyroidectomy. Askanazy changes both in epithelial cells of the nodules and in the parenchyma of these glands were as pronounced as those seen in irradiated glands. These findings indicate that the Askanazy changes are only indirectly due to irradiation and presumably represent an effect of prolonged stimulation by thyrotropic hormone. Nodules did not occur in patients who developed hypothyroidism following \(^{131}I\) therapy for thyrotoxicosis, a finding which suggests that, in these individuals, the administered radiation had so injured the gland that it was rendered incapable of regeneration and nodule formation (76). The glands in these patients resembled those of rats that had received higher doses (400 μc.) of \(^{131}I\) (54).

Although some epithelium remained and, as a rule, displayed distinct Askanazy changes, it showed little or no evidence of regenerative activity.

It has been recommended that young patients not be treated with \(^{131}I\) for thyrotoxicosis because of the possible development of thyroid neoplasms. If such treatment should be necessary, doses large enough to destroy all thyroid tissue completely should be administered so that regeneration and nodule formation will be prevented (76).

**RELATION OF IRRADIATION OF THE HEAD AND NECK AREA IN CHILDREN TO DEVELOPMENT OF THYROID CARCINOMAS**

The possibility of a relation between irradiation of the thymus gland in infancy and the subsequent development of thyroid carcinoma was first pointed out by Duffy and Fitzgerald (21). Ten of their 28 patients who developed thyroid carcinomas before 18 years of age had had their chests irradiated during infancy for thymic enlargement. Clark (11) later reported that in all fifteen children he treated for thyroid carcinoma, x-rays had been applied to their head and neck or upper thorax during their first 6 years. The interval between irradiation and the diagnosis of thyroid carcinoma ranged from 3 to 10 (average, 7) years.

Among 1400 of 1722 children whose thymus glands had been treated with x-rays between 1925 and 1951, Simpson et al. (79) found seven cases of leukemia and six of thyroid carcinoma. This incidence of neoplastic disease was much higher than that among either the children's untreated siblings or the general population. Simpson and Hemplemann (78) later investigated these same 1722 children who had received roentgen-ray irradiation in the thoracic area during infancy. Of these, 1502 were traced for subsequent study. Nineteen had developed thyroid carcinomas, and six were found with thyroid adenomas. These investigators concluded that their study provided strong circumstantial evidence for the view that therapeutic irradiation is an etiologic factor in thyroid cancer in children and adolescents. They indicated that the x-ray dosages employed were generally smaller than those usually considered harmful.

Fetterman (22) reported on ten children with thyroid carcinoma; eight had received irradiation to the neck 3–12 years previously. Three of eight patients under 14 years

\[ S. \text{ Lindsay, unpublished data.} \]
of age, with thyroid carcinoma, were reported by Buckwalter (8) to have received radiation for thymic enlargement. Ten of fifteen childhood thyroid cancer cases were shown by Majarakis et al. (60) to have a history of irradiation to the head or neck administered between 2 months and 6 years of age. The doses of irradiation varied between 200 and 625 r. Of the fifteen patients, five were over 15 years of age at the time of diagnosis, and none had been irradiated. All under 15 years of age at the time of diagnosis had been irradiated.

In a study of 100 cases of thyroid carcinoma, Kilpatrick et al. (48) found that three of eight patients who had developed thyroid carcinomas before 35 years of age presented a history of irradiation of the neck during childhood.

In their study of eleven cases of thyroid carcinomas in patients under the age of 21, Petit et al. (67) found that none had received irradiation of the head and neck areas between 1 and 8 years of age; the carcinomas were discovered 4–14 years later. Wilson and Asper (89) described thyroid carcinomas in seven patients, including two children, all of whom had had preceding irradiation of the neck. Rooney and Powell (72) found that seven of ten patients under the age of 17 years, with thyroid carcinoma, had received previous irradiation of the neck. Latourette and Hodges (50) reported that in 1867 of 1958 patients irradiated in the thymic region, malignant lymphomas developed in two and a thyroid carcinoma in one. These investigators suggested that the increased incidence of neoplasia resulted from the irradiation.

Wilson et al. (90) note that of 37 patients under the age of 25, with thyroid carcinoma, sixteen, or 43 per cent, had been previously irradiated. In the patients under 17 years of age, 72 per cent had had their head, neck, or upper chest irradiated, whereas only 3 per cent of the patients over 17 years of age received such irradiation. These findings led Wilson et al. (90) to conclude that the incidence of preceding irradiation was significantly higher in children with thyroid carcinomas than in the general hospital population and that x-rays can be a causative factor in the development of thyroid carcinomas in young persons.

A group of 2300 children whose thymus glands had been irradiated between the years 1925 and 1951 was studied by Simpson (77). Ten thyroid carcinomas and nine thyroid adenomas were detected in those who had received more than 200 r. The smallest ports employed measured 6 X 8 cm. No thyroid neoplasms were encountered in the untreated siblings. The younger children who developed thyroid tumors were all boys, whereas the older ones were mostly girls. Conti et al. (12) studied 1564 children, 95 per cent with normal-sized thymus glands and 5 per cent with enlarged thymus glands. Between 1938 and 1946 the former received 75–100 r of x-rays as a prophylactic radiation procedure, and the latter were given 200–450 r. The ports measured 4 X 4 cm. Conti et al. (12) found that, whereas the incidence of malignant neoplasms was not significantly lower than in the group of untreated siblings, the incidence of thyroid carcinoma was significantly below that in children treated through larger ports.

Howard (46) reports on three children with thyroid carcinomas, all of whom had had their necks irradiated during the first year of their lives. Saenger et al. (74) studied the medical histories of 1644 patients out of 2230 in whom the head and neck areas had been irradiated during infancy and childhood, and compared them with those of 3777 untreated siblings. Although eleven cases of thyroid carcinomas were found in the irradiated group and one in sibling controls, and although thyroid cancer appeared to increase significantly following irradiation (as compared with the general population), these authors concluded that irradiation was not the sole factor responsible for the increased tumor incidence, but rather a contributing one. Winship and Rosvoll (91, 92) showed that, in 562 patients in whom thyroid carcinoma had appeared before the age of 15, 79 per cent of those from whom histories were obtained received irradiation during infancy or childhood. Malignant neoplasms appeared about 9 years after irradiation.

Eight of Cahan's and Venet's 25 patients who developed thyroid carcinomas after irradiation for benign neck conditions had been treated after the age of 18. The cancers developed more than 6 years after the irradiation.

Beach and Dolphin (4) summarized the findings of Simpson et al. (79), Simpson (77), and Latourette and Hodges (50). Twenty-three malignant and sixteen non-malignant thyroid neoplasms were encountered among 4673 irradiated children. Those with thyroid carcinoma had received between 90 and 1270 rads absorbed in the gland, whereas those with benign thyroid nodules had received between 70 and 630 rads. The mean latent period after irradiation was 11 years, but the actual period might have been as long as 25 years. No significant differences in latent period distribution were observed: (a) between cases in upper and lower dose ranges, (b) between cases treated before 1 year of age and those treated after 1 year; and (c) between sexes. On the basis of the dose-response (a linear relation was assumed) Beach and Dolphin (4) indicated an incidence of about 1.7 per cent per 500 rads.

Among 458 patients whose necks had been irradiated for benign conditions (mainly enlarged thymus glands, toxic goiter, and tuberculous adenitis), Hanford et al. (44) reported that the actual number of thyroid cancers far exceeded the expected number. A significant increase in the incidence of thyroid carcinoma was found only in the group suffering from tuberculous adenitis. These cancers occurred 10–27 years after irradiation. The radiation doses were between 500 and 1500 r.

Among 216 patients affected by thyroid carcinoma, Rose et al. (73) reported that 70 gave a history of prior irradiation to the head and neck. Two children under 10 years of age, thirteen of seventeen under 15 years of age, and twenty of 23 under 20 years of age at the time of diagnosis gave such a radiation history. The latent interval between irradiation and apparent onset of thyroid carcinoma averaged 12 years. These authors suggested caution in the use of irradiation in the management of benign conditions of the head and neck of infants and children.
A recent report of Toyooka and co-workers (83, 84) and Pifer et al. (68) deals with the incidence of tumors among 2809 children who had been treated with x-rays for thymic enlargement during infancy. Benign and malignant thyroid neoplasms comprised about half (43 per cent) of all tumors found. These workers encountered nine thyroid carcinomas and 21 adenomas, six of the latter being regarded as possibly malignant. The incidence of thyroid tumors was considerably higher in patients who received half the radiation anteriorly and half posteriorly than in those who received the entire dose anteriorly.

Thyroid carcinoma may also follow irradiation for malignant disease of the head and neck area. Raventos and Duszynski (71) described two instances of thyroid carcinoma that appeared 7 and 11 years after irradiation for medulloblastoma.

Despite the considerable body of evidence cited above, favoring the view of a relation between irradiation of the head and neck during infancy and childhood and subsequent development of thyroid carcinoma, Uhmann (85) denies such a relation and cites a number of reports of thyroid carcinoma in which previous irradiation was not mentioned. One of these reports was from the University of California Hospitals (13), where the majority of patients had been studied before the initial report of Duffy and Fitzgerald (21). Since 1950, however, a significant number of patients at the University of California Hospitals, under the age of 21 and found to have thyroid carcinomas, particularly of the papillary type, had histories of previous irradiation of their head and neck areas (51). Uhmann (85) cites a number of instances in which thyroid carcinomas were already present in children referred to him for irradiation of adenoid tissue, and expresses the belief that thyroid carcinomas found after irradiation probably had been present at the time of irradiation therapy. Uhmann (85) also states that the amount of irradiation applied for the treatment of thymic enlargement is generally less than that received during chest fluoroscopy and that the thyroid gland receives only scattered radiation. Recently, Garland (27) studied 1780 patients who had received thymic irradiation, and he also denies an etiologic connection between irradiation of the neck area and development of thyroid carcinoma.

RELATION OF EXTERNAL IRRADIATION OF HEAD AND NECK AREAS IN ADULTS TO DEVELOPMENT OF THYROID CARCINOMA

Thyroid cancer following external irradiation of the head or neck has been observed on a few occasions in adults. As early as 1949, Quimby and Werner (70) were concerned with the question of the late development of thyroid neoplasia from irradiation. In surveys made by radiologists and thyroid specialists they found ten cases in which carcinomas in the thyroid gland had developed after irradiation with x-rays for hyperthyroidism; but in only three did they concede the possibility that irradiation might have been responsible for development of the thyroid carcinomas. Later, Jelliffe and Jones (47) reviewed eleven cases of thyroid carcinoma that appeared at intervals ranging from 8 to 41 years after application of external x-irradiation to the neck. In eight patients x-radiation had been administered for thyrotoxicosis, in one for "thyroid swelling," in another for tuberculous cervical lymphadenitis, and in one for a keloid. Of 293 patients with thyroid carcinoma reported from the University of California Hospitals, two had been previously treated with x-rays during adult life for diffuse toxic goiter (51). Willis (88) discussed three patients treated with irradiation for thyrotoxicosis who, after a significant latent period, developed thyroid carcinoma. Since all three patients were females and since the carcinomas were similar to those occurring in nonirradiated thyroid glands, Willis was reluctant to ascribe their development to irradiation.

That thyroid irradiation in the adult can cause carcinoma still lacks proof, but the implications that such is the case are nevertheless suggestive. The probability seems greater in children because mitotic growth of the child's thyroid gland may be a promoting factor in the development of thyroid carcinoma, whereas mitotic activity does not occur in the normal, adult thyroid gland (18). The occurrence of occult sclerosing carcinomas, in some instances of multicentric origin, in nonirradiated hyperplastic glands of patients with thyrotoxicosis may cast some doubt upon the relation of irradiation for Graves' disease to the subsequent development of thyroid carcinoma. Such small sclerosing carcinomas might conceivably grow slowly for many years before becoming evident clinically.

Recently, Socolow et al. (80) presented data suggesting a significant correlation between irradiation exposure during the atomic bombing in Japan and the development of thyroid carcinoma. Of their nineteen patients, eight were under the age of 21 at the time of the exposure. Hollingsworth et al. (45) found twelve patients with thyroid carcinoma in the Hiroshima Adult Health Study Group. These constituted 7 per cent of the total number of patients with thyroid disorders. The frequency of thyroid nodules was greater among those more closely exposed to the radiation than among the less closely exposed. Despite the greater number of thyroid malignancies among the most heavily exposed, the differences between groups with different amounts of exposure were not statistically significant. These investigators suggest caution in interpretation of the data in their report.

RÉSUMÉ

The mode of development of benign and malignant neoplasms in thyroid glands of rats given injections of I\(^{131}\) (10–40 μc.) (54, 55, 69) and in glands that had been x-irradiated (500–2000 r) (56) resembles that of adenomas and possibly of a low-grade follicular carcinoma in human thyroid glands that were irradiated with I\(^{131}\) (75, 76). For example, the parenchyma of rat thyroid glands irradiated with I\(^{131}\) or x-rays closely resembles that of human thyroid glands irradiated in a similar fashion. In both cases evidence of irradiation injury, Askanazy changes in epithelial cells, chronic thyroiditis, and the development of neoplasms have been observed. In the human being an amount of irradiation comparable with that which regularly induces thyroid carcinomas in rats is generally de-
livered by $^{131}I$ or x-radiation in treatment for diffuse toxic goiter.

In contrast, the development of malignant thyroid neoplasms in the rat 2 years after administration of only 1 μc. of $^{131}I$ appears comparable with the situation in children in whom malignant neoplasms were found some 7—10 years after irradiation of their thymus glands, cervical lymph nodes, or nasopharyngeal lymphoid tissues. No evidence of radiation injury or Askanazy changes in the thyroid glands of children developing thyroid carcinoma following thymic irradiation, although these malignant neoplasms have probably been initiated by such radiation therapy. These findings suggest that, both in rats that received small doses of $^{131}I$ (1 μc.) (34) and in infants and children who received low levels of irradiation in the thyroid area, a direct, nonlethal mutant effect on thyroid epithelial cells, caused by radiation, may be responsible for initiation and development of malignant thyroid neoplasms. The finding of chromosome aberration after irradiation of other tissues by either x-rays (7) or $^{7}Li$ (59) indicates that such cellular mutations are possible.

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