LONG-TERM EFFECTS OF EXTERNAL RADIATION ON THE PITUITARY AND THYROID GLANDS

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Chronic damage following external irradiation of the normal pituitary and thyroid glands, delivered incidentally during radiotherapy of neoplasms of the head and neck may be more common than has been appreciated in the past. A case of a child who developed pituitary dwarfism 5½ years after radiation therapy had been delivered for an embryonal rhabdomyosarcoma of the nasopharynx is described. A review of similar cases from the literature is presented. Likewise, external irradiation of the normal thyroid gland produces a spectrum of radiation-induced syndromes. Clinical damage to the pituitary and thyroid glands is usually manifested months to years after treatment and is preceded by a long subclinical phase. A careful exclusion of these glands from radiation treatment fields is recommended whenever possible. An early detection of endocrine function abnormalities in patients receiving radiation to these glands is desirable, since appropriate treatment may prevent the late deleterious effects of external irradiation of the pituitary and thyroid glands.

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THE DETECTION OF CHRONIC RADIATION DAMAGE in tissues depends on the rate of mitotic divisions occurring in the irradiated tissues, on the extent of damage to supporting vascular tissues, and on the duration of the observation period. Within the range of doses conventionally employed in external radiation therapy, cell killing is usually a postmitotic event. Despite the fact that damage occurs immediately following radiation, the cell continues to function until a subsequent mitotic division, when the killing effect of radiation is expressed and the cell dies. The endocrine tissues are classified as examples of "slow renewal" tissues, in which mitosis is normally an infrequent event. This may account for the fact that the hormone-producing tissues, with the exception of the ovary, are considered radiation resistant and manifest minimal or no acute damage following therapeutic dose levels.

The prognosis of many neoplastic diseases has greatly improved in the last two decades due to the introduction of aggressive radiotherapeutic and chemotherapeutic treatment programs. Thus, the chances of observing long-term radiation effects on "slow renewal" tissues have already increased and will increase in the future.

The purpose of this presentation is to review the long-term effects of radiation on the normal pituitary and thyroid glands, which have frequently been included in the treatment field for malignant diseases not involving the glandular tissue itself. These examples may serve as models for the long-term events that may follow irradiation of other endocrine tissues.

THE PITUITARY GLAND

Although significant morphological changes have not been detected in the irradiated pituitary gland at dose levels employed in conventional radiotherapy, it is possible to destroy the normal pituitary by using extremely high radiation doses and special techniques. Radiation hypophysectomy can be performed by various methods such as by intrapituitary implantation of radioactive sources,[16,47,57,66] or by external irradiation with high-energy proton

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or alpha particles,[32,33,39,60] high-energy electrons,[46] or x-rays produced by a multiple source ^{60}Co stereotaxic irradiation unit.[2] The dosimetry of these techniques is extremely complex, and the estimated radiation doses employed range between 17,000 and 300,000 rads. Obviously, these doses exceed by far the radiation employed in conventional radiotherapy.

Lower doses of radiation have been delivered by conventional methods to the normal nonadenomatous pituitary for various disease states (Table 1), including amenorrhea and other menstrual irregularities,[30,35] essential hypertension,[4,50] malignant exophthalmos,[3,27] and metastatic breast and prostatic carcinoma.[13,31,45,53] In addition, some pituitary functions have been tested following radiotherapy of nasopharyngeal tumors.[9] Functional and histologic examinations performed in some of these studies have suggested that the human pituitary is resistant to radiation doses up to 10,000 rads. However, this is not conclusive for several reasons. Firstly, in some cases there were decreases in the levels of human gonadotrophins and of the ^{131}I uptake by the thyroid.[31,53] Secondly, the number of pituitary function tests performed was small, and many of the more recent tests of pituitary function were not performed. Most notable is the lack of measurement of blood levels of pituitary hormones, and in particular, gonadotrophins, TSH, and growth hormone. Thirdly, it should be noted that the studies mentioned involved adults exclusively. Following radiation dose levels comparable to those employed in conventional radiotherapy, animal experiments have demonstrated degenerative changes of the pituitary in young or immature animals (rats, rabbits, cats, or dogs). Adult animals

TABLE 1. Diseases Treated by Pituitary Irradiation

Author and reference	Disease	No. of irradiated patients	Estimated pituitary dose (rads)	Period followup	Endocrine functions tested	Histologic examination of pituitary
Kotz et al.[35]	Menstrual irregularities	243	400–500	6 mo–9 yr	N.D.	N.D.
Kaplan[30]	Amenorrhea	296	150–225	?	N.D.	N.D.
Pendergrass et al.[50]	Essential hypertension	142	1000–2000	3–56 mo	ADH decreased (?)	N.D.
Best et al.[4]	Essential hypertension	25	1100	2–24 mo	ADH decreased (?)	1 pt normal
Hermann[27]	Malignant exophthalmos	12	3000–5000	1–4 yr	N.D.	N.D.
Beierwaltes[3]	Malignant exophthalmos	28	700–1500	4 mo–4 yr	N.D.	N.D.
Murphy et al.[45]	Prostatic ca	30	750–4860	$\geq$ 4 yr	N.D.	N.D.
Douglas[13]	Metastatic breast ca	37	3000	?	N.D.	N.D.
Kelly[31]	Metastatic breast ca	1	8150	2 mo	Urinary gonadotrophins & 17 KS normal	N.D.
	Metastatic breast ca	1	10500	2 mo	Urinary gonadotrophins decreased; 17 KS normal	at 4.5 mo normal
	Metastatic melanoma	1	8500	2 mo	Urinary gonadotrophins decreased; 17 KS normal	at 3 mo normal
Plunkett[53]	Metastatic ca of breast or prostate	30	4000–6000	$\geq$ 1 yr	8/12 24-hr ^{131}I uptake decreased 4/10 urinary gonadotrophins decreased 1/10 urinary 17 KS decreased	5 pts (1 mo–5 yr) normal
De-Schryver et al.[9]	Ca of nasopharynx	29	1700–6800	5–30 yr	PBI, TSH, ^{131}I uptake 17 KS normal	N.D.

have shown little or no discernible effect following such pituitary irradiation.[54,58]

Furthermore, there have been a few reports of hypopituitarism occurring after irradiation for neoplasia of the head and neck. Table 2 presents a summary of all cases known to date. In each case an uninvolved pituitary gland was included in the radiation field. Case 7 has never been described before, and will be presented briefly.

D.T. (SUH #00 38 30), a 4-year-old boy, initially noted symptoms of nasal congestion in September, 1959. A thumbnail size tumor was noted at the right nostril, with a projection seen in the nasopharynx. This was partially resected and was initially thought to be benign. Two months later, however, the tumor was seen to have recurred to its original size. In December, 1959, the ethmoid sinuses, middle turbinate, and a portion of the sphenoid on the right side were resected and electrocoagulated. On histologic examination, the mass was interpreted as an embryonal rhabdomyosarcoma, presumably originating in the nasopharynx.

He was initially seen in the Division of Radiation Therapy, Stanford University Medical Center, in January, 1960. At that time, there was no suggestion of an endocrine abnormality and no obvious evidence of tumor on physical examination. Roentgenograms of the skull showed no bony destruction. His treatment was initiated with two lateral opposing fields and a single anterior field. The dose was weighted in favor of the anterior field two-to-one. The child received a tumor dose of 7500 rads delivered in 32 fractions over 48 days (Fig. 1) with the 4.8-MeV Stanford Medical Linear Accelerator.[18] The pituitary was included in the treatment field. Treatment was surprisingly well tolerated; only a mild mucositis and skin reaction were seen. Approximately 10 months later, the child developed a palpable right neck node outside the radiation field. This was biopsied and shown to contain metastatic embryonal rhabdomyosarcoma. A right radical neck dissection was performed; of 22 nodes available for examination, 2 contained tumor. No thyroid tissue was removed. To date, 14 years later, there has been no further evidence of disease.

TABLE 2. Hypopituitarism Following Incidental Pituitary Irradiation Delivered for Tumors of the Head and Neck

Author and References	Sex	Age	Primary disease	Estimated pituitary dose	Interval of radiation to hypopituitarism	Pituitary function tests
Bradley[6]	M	45 yr	Ca of nasopharynx	6000 rads	8 yr	PBI decreased; urinary gonadotrophins decreased; urinary 17-OHCS decreased; response to metyrapone ±
Larkins and Martin[38]	M	39 yr	Ca of l. maxillary sinus	6500 rads	7 yr	PBI decreased; TSH decreased, rise following TRH injection; urinary gonadotrophins decreased; growth hormone decreased, no response to insulin; plasma cortisol decreased, no response to insulin, rise following vasopressin injection
Tan and Kunaratnam[59]	F	12 yr	Ca of nasopharynx	9000 rads	11 yr	Growth retardation, amenorrhea. BMR decreased; PBI normal; urinary 17 KS & 17 OHCS decreased
Grumbach et al.[24]	M	8 mo	Retinoblastoma	4000 rads	7 yr	Growth hormone decreased; other pituitary functions normal
	M	6 yr	Midbrain tumor	5060 rads	7½ yr	Growth hormone decreased; other pituitary functions normal
	M	4 yr	Medulloblastoma	4500 rads	6 yr	Growth hormone decreased; other pituitary functions normal
Fuks et al. (present case)	M	4½ yr	Embryonal rhabdomyosarcoma of nasopharynx	7500 rads	5½ yr	Growth hormone decreased, no response to insulin and arginine stimulation; other pituitary functions normal

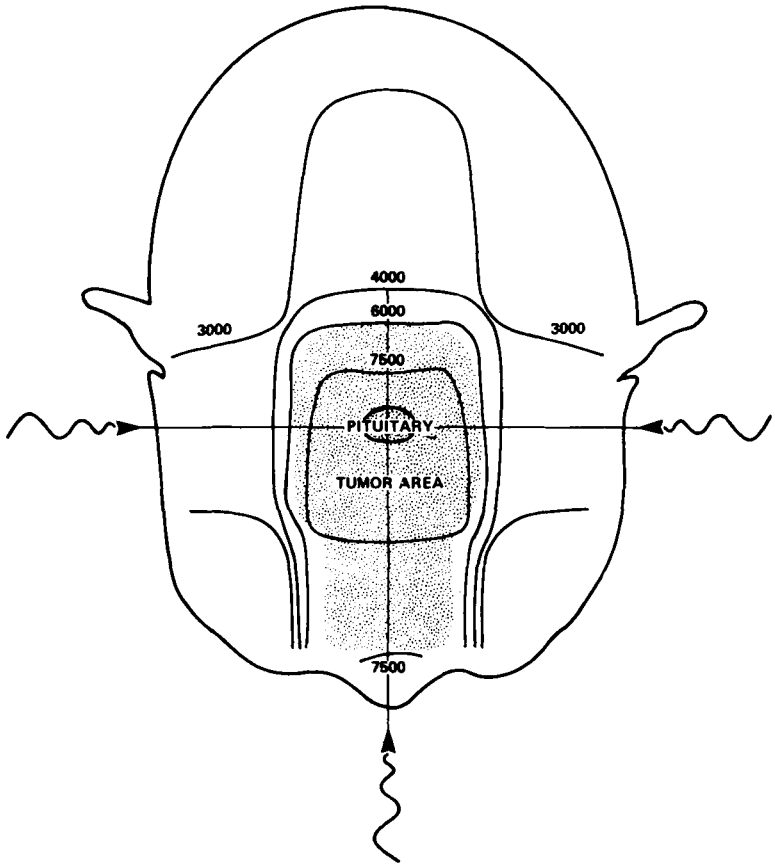

FIG. 1. Isodose distribution curves of radiation doses delivered to the tumor and to the pituitary gland.

Approximately 5½ years after his treatment, he was noted to be small for his age. Examination of his growth curve revealed a marked decrease in growth rate (Fig. 2). Whereas originally his height and weight were within one standard deviation of the mean for children of his age, following treatment a growth retardation ensued, and both his height and weight fell more than one standard deviation below the mean. An endocrine evaluation at the time included a radiographic examination of the skull, hemogram, serum electrolytes, urine osmolarity, water loading test, insulin tolerance test for glucose, serum thyroxine, ^{131}I uptake and scan, urinary levels of 17-ketosteroids and 17-hydroxycorticosteroids and their responses to ACTH and metyrapone, all of which were within normal limits. TSH and growth hormone levels could not be studied at that time.

Approximately 8 years after his radiation therapy, he underwent another endocrine evaluation. The general physical examination was unremarkable except for small stature, a saddle-nose deformity from his radiation therapy, and evidence of the right radical neck dissection. His chronological age was 12½ years, and his bone age was 9 years. There was no sign of sexual maturation. A hemogram and serum electrolytes were entirely normal. A serum thyroxine was normal at 5.5 μg/100 ml; a serum-free thyroxine was normal at 1.9 μg/100 ml; a serum cholesterol was 146 mg/100 ml; a TSH level was not obtained. Twenty-four-hour urinary 17-ketosteroids and 17-hydroxycorticosteroids were normal. The values for growth hormone assayed by radioimmunoassay as well as the response to stimulation by insulin and arginine infusions were well below the normal range for children of his age. The initial value of fasting growth hormone was 1 ng/ml. Following an insulin tolerance test with 0.1 μg/ml insulin, the highest growth hormone level was observed 60 minutes later, 2.4 ng/ml. The highest growth hormone level following intravenous infusion with arginine was observed at 45 minutes, 2.6 ng/ml. The initial low values of growth hormone and the failure to observe a significant elevation of growth hormone titers following stimulation established a diagnosis of growth hormone deficiency. This deficiency appeared to reflect an isolated pituitary deficiency, since all other direct and indirect tests of pituitary function were normal.

Since growth hormone was not available, the patient was not treated specifically for his deficiency. Although a diagnosis of hypothyroidism was not established by any chemical test, he was empirically

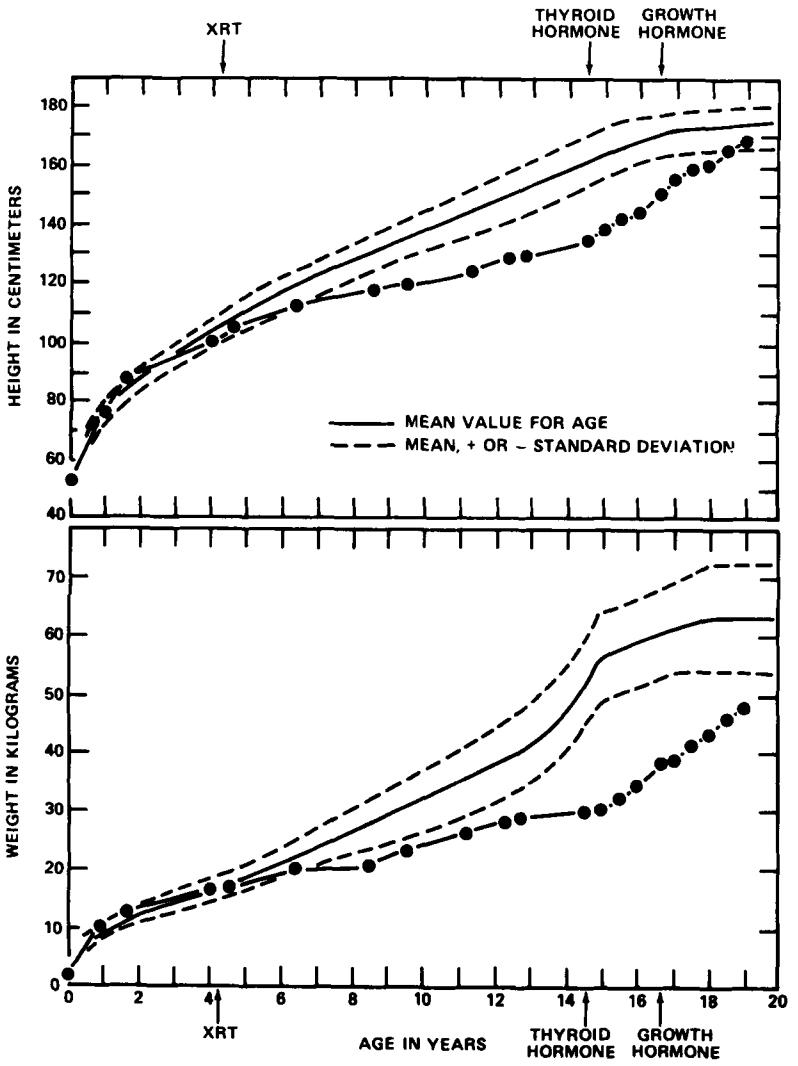

FIG. 2. Height and weight curves of the treated patient, compared with the mean ± one standard deviation of height and weight for 6000 normal boys as studied by Pryor.[55]

started on thyroid hormone, ultimately up to doses of 65 mg three times a day, which moderately accelerated his growth (Fig. 2). Approximately 3 years after he had been begun on thyroid hormone, human growth hormone became available for injection. He was started on 5 mg three times a week, with striking improvement in his size and weight, as seen in Fig. 2. Currently, his chronological age is 18 years and 9 months, and his bone age averages 16 years and 9 months. His recent height and weight are again within one standard deviation of the mean for youngsters of his age, and general sexual development seem adequate for his age.

The characteristic feature common to all the cases described in Table 2 is the long time interval between irradiation and the diagnosis of hypopituitarism. Five of the patients were children during irradiation; of these, four had established growth hormone deficiency and the fifth had marked growth retardation. One of the two adult patients also had growth hormone deficiency; in the seventh patient, GH levels are unknown. Somatophoric cells which produce GH may be the most radiosensitive cells within the pituitary, and growth hormone may be the first pituitary hormone to decline following radiation. It will be of interest to observe whether the production of other hormones also becomes compromised in the future.

The pathogenesis of radiation hypopituitarism in these cases is unknown; hypothalamic damage has been suggested as a possible explanation,[38] but the evidence for such a mechanism is inconclusive. An alternative explanation may be radiation-induced cell kill-

ing. Since the pituitary is considered a slow renewal system, the expression of the damage may occur many years after radiation has been delivered.

The true incidence of hypopituitarism after radiotherapy of the head and neck is also unknown. It may be more common than has been suspected in the past, especially in children. With the greater sophistication of current tests of pituitary function, evidence of this complication should be sought more diligently, and early replacement treatment should be instituted whenever necessary.

THE THYROID GLAND

Early experimental and clinical studies suggested that the thyroid gland was relatively resistant to external irradiation.[61] However, ablation of normal thyroid tissue has been produced after uptake of ^{131}I at estimated dose levels ranging from 30,000 to 39,000 rads.[22] Histologic evidence for radiation damage has been produced in normal thyroids irradiated externally with doses ranging from 225 r to 4300 r;[40] furthermore, several clinical studies have demonstrated thyroid gland dysfunction in patients treated previously with external radiotherapy to the neck for malignancies not involving the thyroid gland itself (Table 3). Some of the earlier studies lack many of the more sophisticated thyroid function tests currently available. In others, the post-treatment period of assessment for hypothyroidism was too short to allow meaningful conclusions. In general, however, it seems that external irradiation of the normal thyroid may cause dysfunction of the gland within months to years following treatment. The study with the longest followup of patients was that presented by Einhorn.[14] In 41 patients followed for more than 10 years after treatment for carcinoma of the larynx and hypopharynx, the incidence of established hypothroidism was 7.3%. However, the 24-hour ^{131}I uptake following TSH stimulation was decreased in all 41 patients, indicating thyroid dysfunction in all treated patients. The incidence of hypothyroidism seems to increase in patients who have a hemithyroidectomy following radiation.[44] The inci-

TABLE 3. Published Series of Radiation-Induced Thyroid Dysfunction Following External Radiation to the Neck

Author and reference	Disease	Estimated thyroid dose (rads)	Period followup	Incidence of thyroid dysfunction	Thyroid functions tested
Felix et al.[15]	Ca of larynx	11500 r in air	6 yr	1	BMR, ^{131}I uptake, cholesterol
Koulumies et al.[36]	Ca of larynx	5000	1–14 mo	0/118 (0%)	PBI, ^{131}I uptake
Greig et al.[23]	Ca of larynx	3700–6500	1.5–6 yr	0/20 (0%)	PBI, ^{131}I uptake, 48-hr $PB^{131}I$
Markson & Flatman[42]	Ca of hypopharynx, breast; lymphoma	2900–4850	4 mo–3 yr	5	BMR, cholesterol, ^{131}I uptake
Einhorm & Wikholm[14]	Ca of larynx and hypopharynx	5700–6000	18 yr	3/41 (7.3%)	PBI, ^{131}I uptake ± TSH stimulation*
Bosch et al.[5]	Ca of head & neck	2900–6600	1–3 mo	0/27 (0%)	PBI, ^{131}I uptake & conversion
Glatstein et al.[19]	Hodgkin's disease & lymphoma (post-LAG)†	4000–4500	1–5 yr	77/174 (44%)	TSH only
				25/174 (14%]	TSH, T_4, T_3, BEI, cholesterol
	Ca of head & neck (no LAG)	6000–6600	1–6.5 yr	2/9 (22%)	TSH
Prager et al.[55]	Hodgkin's disease (post-LAG)	3900–4600	6–12 mo	5/23 (22%)	T_4, ^{131}I uptake ± TSH stimulation
Murken & Duval[44]	Ca of larynogopharynx	3800–5500‡	2–74 mo	8/12 (66%)	T_4, PBI
		3800–7000§	2–74 mo	1/6 (16%)	T_4, PBI
Brase & Sippel[7]	Ca of larynx	5500–7000	$\geq$ 5 yr	10/72 (14%)	PBI, T_3, T_4, ^{131}I uptake

* ^{131}I uptake following TSH stimulation—decreased in all 41 patients.

† In another 48 patients, TSH before LAG and irradiation was within normal limits in 47. LAG = lymphangiogram

‡ Radiation followed by laryngectomy and hemithyroidectomy.

§ No hemithyroidectomy.

dence of thyroid dysfunction also seems to increase in patients with an iodide load.

Glatstein et al.[19] have observed a high incidence of thyroid dysfunction in a group of patients treated with radiotherapy for Hodgkin's disease and malignant lymphoma. The incidence of impaired thyroid dysfunction in a small group of patients with carcinoma of the head and neck, who received higher doses of neck irradiation, appeared significantly lower. We have recently extended these observations to a larger series of patients (363) in the same three clinical categories. The thyroid function tests performed included measurements of plasma levels of total thyroxine (T_4) and thyroid stimulating hormone (TSH) as described previously.[19] All patients had been treated with radiation therapy for Hodgkin's disease (usually 4000–5000 rads), non-Hodgkin's lymphoma, or carcinoma of the head and neck (5000–7000 rads). All but 14 of the patients with Hodgkin's disease or other lymphomas had received radiation to the neck which encompassed the thyroid gland. The interval between irradiation and thyroid function screening tests ranged from 6 months to 14 years. All patients with Hodgkin's disease and other lymphomas had a lower-limb lymphogram prior to treatment, whereas none of the patients with carcinoma of the head and neck had lymphograms. Some patients were also treated with chemotherapy following radiation.

The results of this study (Table 4) indicate that the incidence of thyroidal dysfunction in patients with Hodgkin's disease and other lymphomas is significantly increased compared to that in patients with carcinoma of the head and neck, despite the fact that the former group received less irradiation to the neck. This is true both for the incidence of "compensated hypothroidism" (normal level of T_4 and increased levels of TSH) and for the incidence of overt hypothroidism (decreased level of T_4 and elevated TSH ($p < 0.05$).

This apparent paradox may be related to the lymphogram performed prior to irradiation in the lymphoma patients. The lymphographic contrast medium, which contains a fat-soluble organic iodide, is slowly but constantly released from lymph node deposits into the lymph and travels through the thoracic duct into the blood stream, thus producing a prolonged iodide load. This process has previously been demonstrated in dogs undergoing lymphography using ^{131}I-Ethiodol.[34] It has been estimated that the amount of iodide deposited in the body following a lymphogram may be sufficient to induce goiter and/or hypothyroidism.[19] It is therefore not surprising that we also have observed mild thyroid dysfunction in 2 of 14 lymphoma patients who had a lymphogram but had not received neck irradiation. The mechanism of induction of hypothyroidism by iodide is unknown; factors predisposing to this condition remain uncertain but probably include damage to the thyroid parenchyma.[65] Since damage is known to be induced by thyroid irradiation, a large iodide load may be an important cofactor contributing to radiation-induced thyroid disease. That such an iodide load is not essential for the causation of thyroid dysfunction can be deduced from its significant incidence (38%) in patients with carcinoma of the head and neck who did not receive a lymphogram.

The high incidence of radiation-induced thyroid disease is not generally appreciated. Indeed, the observed incidence may continue to increase, since serial examinations have shown the late development of radiation in-

TABLE 4. Incidence of Thyroidal Dysfunction Following Neck Irradiation

Disease	Pre-radiation lymphography	Radiation dose to the neck (rads)	Euthyroid (normal T_4 and TSH)	Compensated hypothyroid (TSH increased T_4 normal)	Hypothyroid (TSH increased T_4 decreased)	Total thyroidal dysfunction
Hodgkin's disease (235)	+	4000–5000	85/235 (36%)	103/235 (44%)	47/235 (20%)	150/235 (64%)
Non-Hodgkin's lymphoma (62)	+	4000–4500	26/62 (42%)	27/62 (43%)	9/62 (15%)	36/62 (58%)
Hodgkin's and non-Hodgkin's lymphoma (14)	+	-	12/14 (86%)	1/14 (7%)	1/14 (7%)	2/14 (14%)
Carcinoma of head & neck (52)	−	5000–6500	32/52 (62%)	13/52 (25%)	7/52 (13%)	20/52 (38%)

jury in some patients. The final incidence of hypothyroidism will be known only after prolonged and systematic study of survivors. Based on these observations, periodic clinical and laboratory assessment of thyroid function in patients receiving high-dose neck irradiation is clearly indicated. Not only do patients with proven hypothyroidism need appropriate replacement therapy, but consideration should be given to the administration of thyroid hormone to those patients with elevated serum TSH levels to reduce the incidence and severity of true hypothyroidism, and possibly to reduce the potential risk of thyroid carcinoma.

The association of thyroidal radiation and the subsequent development of thyroid carcinoma has been extensively reviewed by numerous investigators.[8,10,21,25,26,28,29,41,52,63,64] This complication of thyroidal irradiation is considered much more common when the thyroid is irradiated in infancy and early childhood than in adults. The risk of cancer appearing in adolescence or young adulthood (from birth to 25–30 years) after irradiation in childhood is in the order of 1.6–9.3 cases per year per million children exposed per rem as calculated by the N.A.S.-N.R.C. Advisory Committee on the "Biological Effects of Ionizing Irradiation."[1] The data suggest that cancer induction may decline as the irradiated population enters the third decade, implying a decrease in risk at later ages.

Relevant to the issue of radiation-induced thyroid carcinoma, Modan et al. have followed 10,902 children who have been irradiated for ringworm of the scalp.[43] The estimated dose delivered to the thyroid by scattered irradiation was 6.5 rads. Twelve patients developed thyroid carcinoma during a followup period of 23 years; this represents a 5-fold increase in the incidence of thyroid cancer over that of sibling controls. The calculated absolute risk of thyroid cancer following 6.5 rads was 6.1 cases per 10^6 man-rad-year,[17] which is in agreement with the values of risk presented previously.[1] The importance of this study is that it indicates that there may be no "safe" dose of thyroidal irradiation in childhood. Indeed, there has been a report of carcinoma of the thyroid occurring in a 20-year-old woman who had undergone diagnostic radioactive iodine procedures at 4 and 12 years of age.[51]

There are few data available on the development of thyroid carcinoma in adults who had previously received neck irradiation. Documented cases have been reported[21,28,49] 20 or more years following irradiation. The prolonged elevation of plasma TSH levels following thyroidal irradiation may represent a potential carcinogenic risk in some patients. It is unknown whether such a state is related to the induction of thyroid cancer in man. However, thyroid tumors can be produced experimentally in rats and mice by various methods which cause an increase in TSH stimulation for prolonged periods.[11,41] We have on record one patient who, 9 years after radiation therapy for Hodgkin's disease, including 3300 rads to the neck, developed a mixed papillary and follicular carcinoma of the thyroid. Unfortunately, no thyroid function tests were performed prior to her thyroidectomy. The average period of followup in our patients is still short; if more radiation-induced cancers are detected, the "prophylactic" administration of thyroid hormone to patients with elevated serum TSH levels may be indicated.

Finally, an interesting complication of thyroid irradiation has recently been described by Wasnich et al.[62] These investigators observed seven patients who developed Graves' ophthalmopathy, with or without overt hyperthyroidism, within a period of 18 to 84 months following x-irradiation to the neck for nonthyroidal neoplasms. The mechanism of this complication is unclear. It is known, however, that at the time of ophthalmopathy, each patient showed elevated serum levels of long-acting thyroid stimulating factor (LATS), antithyroglobulin, and antimicrosomal antibodies; these abnormalities presumably were the consequence of thyroid irradiation. That the thyroid gland and the orbit share common lymphatic pathways has been well demonstrated.[37] A possible explanation for this uncommon complication of thyroidal irradiation is the induction of vascular and lymphatic damage from radiation with the simultaneous access of thyroidal antigen, antibody, or lymphocytes to the orbit via such common lymphatic channels. Such an autoimmune hypothesis is obviously speculative but highly intriguing.

In view of the significant incidence of radiation-induced thyroid disease, careful exclusion of the thyroid from radiation fields should be attempted whenever possible. In some instances, especially in adults with Hodgkin's disease receiving prophylactic irradiation to the neck, an accurate outline of the thyroid gland using a radionuclide scan may be neces-

sary to provide adequate shielding of the thyroid. In patients receiving high-dose irradiation to the neck, periodic clinical and laboratory assessment of the thyroid function is necessary. Early detection and early treatment will reduce the morbidity of radiation-induced thyroid disease.

CONCLUSION

External irradiation of the normal pituitary and thyroid glands delivered incidentally during radiotherapy of neoplasms of the head and neck may produce a wide spectrum of radiation-induced syndromes. Clinical damage is usually manifested months to years after treatment, and is usually preceded by a long subclinical phase. Careful exclusion of the pituitary and the thyroid from radiation treatment fields is recommended whenever possible. Periodic assessment of relevant endocrine functions in patients receiving radiation to these glands is indicated, especially in childhood. Early detection of such abnormalities and appropriate treatment may prevent the late deleterious effects of external irradiation of the pituitary and thyroid glands.

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