Alterations in Serum Thyrotropin (TSH) and Thyroid Function Following Radiotherapy in Patients with Malignant Lymphoma[1]

ELI GLATSTEIN, STUART McHARDY-YOUNG,[2] NEIL BRAST, JAMES R. ELTRINGHAM,[3] AND JOSEPH P. KRISS

Departments of Radiology and Medicine, Stanford University School of Medicine, Stanford, California 94305

ABSTRACT. Seventy-seven of 174 patients (44%) with lymphomas who had lymphangiography and who received high-dose bilateral neck irradiation developed elevated serum TSH concentrations. Many of the elevations were recorded during the first post-treatment year. Elevated serum TSH values were observed with a higher frequency in treated patients under 20 yr of age. In untreated (X-irradiation) Hodgkin's disease, serum TSH levels were normal. Similarly, normal values were seen in patients whose field of irradiation did not include the neck. Nineteen patients developed radiation-induced pericarditis; 16 of the 19 had elevated serum TSH levels and 9 were clinically hypothyroid. Twenty-five patients (11%) developed clinical hypothyroidism and/or showed evidence of thyroid hypofunction by laboratory test other than serum TSH. The post-treatment incidence of abnormally high serum TSH levels was lower in a group of patients with tumors involving the neck region who received irradiation without prior lymphangiography, suggesting that an expanded extrathyroidal iodide pool may increase the susceptibility to hypothyroidism in the irradiated subject. The present data suggest that the concept of relative radioresistance of normal thyroid tissue should be revised. It is recommended that all patients undergoing high-dose bilateral neck irradiation for treatment of neoplasm be evaluated at least quarterly thereafter for laboratory and clinical evidence of hypothyroidism. Determination of immunoassayable serum TSH appears to be a sensitive means of detecting impaired thyroid function in such patients. The finding of an elevated serum TSH level is by itself probably sufficient evidence to indicate that thyroid dysfunction is present; prompt and adequate replacement thyroid therapy not only may give the patient great symptomatic relief, but may also resolve a question of recurrence or extension of the neoplastic process and/or forestall the development or lessen the severity of post-radiation pericarditis with effusion. (*J Clin Endocr* **32**: 833, 1971)

ALTHOUGH hypothyroidism has been recognized as a relatively frequent complication of ^{131}I-iodide therapy for Graves' disease (3–5), the normal thyroid gland has been considered to be resistant to external irradiation (6). There have been but few reports of hypothyroidism occurring after X-irradiation to the neck in the treatment of a variety of neoplasms (7–9). In a preliminary report from this institution, Rogoway *et al.* described the development of myxedema following lymphangiography and neck irradiation in five of 124 patients with malignant lymphomas (10). The diagnosis of myxedema was based primarily on clinical evidence because of the difficulty in assessing thyroid function from determinations of serum protein-bound iodine and thyroidal radioactive iodine uptake following the administration of iodine-containing contrast agent for the lymphangiographic procedure.

More recently, the development of several new laboratory procedures has provided better means of evaluating thyroid gland function following lymphangiography. These include determinations on serum of the resin uptake of labeled triiodothyronine (T_3) (11), thyroxine (T_4) (12), free thyroxine (free T_4) (13) and immuno-

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Please address reprint requests to Dr. Joseph P. Kriss, Department of Radiology, Stanford University School of Medicine,

[1] Portions of this work have been presented in preliminary form (1, 2).

[2] *Present address:* Department of Medicine, Guy's Hospital Medical School, London, England.

[3] Advanced Clinical Fellow, American Cancer Society.

TABLE 1. Analysis of Group II patient population who had completed treatment for lymphoma

Diagnosis	No. patients	No. males	No. females	Age (yr) (mean & range)
Hodgkin's disease	162	87	75	26 (5–64)
Non-Hodgkin's lymphoma	63	33	30	44 (9–68)
Totals	225*	120	105	

* Excludes 4 patients studied while on maintenance thyroid hormone for a diagnosis of radiation-induced hypothyroidism.

assayable serum thyrotropin (TSH) (14, 15). Since serum TSH values rise relatively soon after withdrawal of thyroid hormone in the hypothyroid patient, or fall soon after replacement therapy is started in such subjects (14, 15), this test would seem to be particularly useful in assessing mild or developing hypothyroidism. Accordingly, we decided to study the effect of external neck irradiation on serum TSH values in patients being treated for neoplasms and to correlate the results with other laboratory tests of thyroid function and the clinical incidence of hypothyroidism. The results indicate that irradiation of the neck in the dose range sufficient to produce lymphoid tumor destruction is followed by evidence of thyroid hypofunction in a relatively large percentage of patients. The findings thus indicate that the thyroid gland is not as radioresistant as was hitherto assumed.

Subjects and Methods

Serial serum samples were obtained from the following groups of patients:

Group I. Forty-eight consecutive patients with a diagnosis of Hodgkin's disease studied prior to lymphangiography and radiotherapy (pretreatment control group).

Group II. Two hundred twenty-nine patients with malignant lymphoma who had undergone lower extremity lymphangiography and subsequent megavoltage radiotherapy. Included in this group are 20 patients similarly investigated and treated, but who did not receive radiation therapy to the neck. An analysis of the patient population in this group according to age, sex and diagnosis is presented in Table 1.

Group III. Nine patients who received large field neck irradiation by lateral fields for advanced carcinoma of the head and neck, in whom no attempt was made to shield the thyroid gland.

Most of the patients in Groups I and II were part of a randomized clinical trial comparing local and extended field radiation therapy in the treatment of Hodgkin's disease and other lymphomas (16). Most patients received between 4000 and 4500 rads at the midplane level of the neck; however, in a few cases 1500 rads were delivered.

Two methods were used to measure TSH levels: (a) a double antibody technique and (b) a solid-phase system utilizing the wells of plastic microtiter plates.[4] For each method, iodine labeling of purified human thyrotropin was carried out by the method of Hunter and Greenwood (17) using 1 mCi of ^{125}I-iodine and 2.5 μg of human TSH. Human thyrotropin research standard A, kindly supplied by Dr. R. Bangham, Division of Biological Standards, National Institute for Medical Research, Mill Hill, London, was used as the standard.

The double antibody technique described by Odell *et al.* (18) was used with slight modifications. All tubes contained the same total quantity of serum, rabbit serum for standards, and human serum plus rabbit serum to standard volume for unknowns. The labeled TSH was added to the incubation mixture after 24 hr. The microtiter cup method was adapted from the double antibody method following investigation into the feasibility of solid-phase systems for measurement of human TSH (19). Disposable microtiter plates (Cooke Eng. Co., San Mateo, Cal.) containing 96 small cups, each holding about 0.28 ml, were used as reaction chambers for antibody binding. Antibody coating of the cup was achieved by allowing 0.28 ml of a 1/10,000 solution of anti-TSH in 0.05M carbonate-bicarbonate buffer, pH 9.6, to stand in the well of the cup for 1–2 hr at room temperature; the antiserum could be reused 4–5 times. The cups were then rinsed in 2.5% bovine serum albumin in phosphate-buffered sa-

[4] The microtiter plate method was adapted from an insulin immunoassay procedure employed in the laboratory of Dr. Robert W. Bates, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, and communicated to one of us (N.B.).

line (PBS) for 5 min and washed 3 times with 0.15M NaCl. The plates were allowed to dry at room temperature and could be used immediately or stored at 4 C for later use. To each well was added: TSH standards in rabbit serum[5] (total volume 0.1 ml) or 0.1 ml of the serum to be tested; 10 IU of human chorionic gonadotrophin in 0.15 ml PBS containing 2% normal rabbit serum, pH 7.8. The total incubation volume for each well was 0.28 ml. Incubation at room temperatures was continued for 16–24 hr, when 0.02 ml of labeled TSH containing 35,000–50,000 cpm (at a spectrometer window setting of 10–60 kv), and approximately 0.2–0.5 μU TSH was added to each cup. Twenty-four hr later the incubation mixtures were aspirated and the emptied cups were washed 3 times in cool tap water. The cups were sealed, separated, and individually counted in a well-type scintillation counter.

Calculation. Handling of the data via a computer program followed the procedure outlined by Rodbard *et al.* (20), the percentage of labeled hormone bound in the absence of unlabeled hormone (B/T) being arbitrarily defined as the 100% point and all other bound over total (B/T) ratios expressed in relation to this and designated B/T*. Linearization of the dose response curve was achieved by logit transformation of B/T* and log transformation of TSH dose.

Normal values. The mean serum TSH of normal individuals (44 subjects) using the double antibody method was 6.9 ± 2.1 SD μU/ml, and using the microtiter cup method (28 subjects) was 6.2 ± 4.3 SD μU/ml. For the purposes of this study, the upper limit of normal was considered to be 15 μU/ml for both methods. Only 1 of the normal subjects had a serum level exceeding that limit.

In all patients found to have elevated TSH levels, additional thyroid function studies were carried out in the clinical laboratories of Stanford University Hospital. These included measurement of the serum of resin uptake of labeled triiodothyronine (11) (normal range 26–39%), butanol-extractable iodine (21) (3.6–6.5 μg/ml), total thyroxine (12) (2.9–6.4 μg/100 ml), free thyroxine (13) (1.0–2.1 ng/100 ml as thyroxine), and cholesterol (160–280 mg/100 ml). Measurement of the speed of the Achilles reflex (photomotography) was also performed (normal range 250–350 msec). Because thyroidal radioiodine uptake studies were so low in our patients who had lymphangiography, we did not perform these, nor did we do TSH stimulation tests to study thyroid reserve.

[5] In recent experiments performed after the completion of this work, greater precision of the assay has been achieved by using serum from patients with hypopituitarism rather than rabbit serum.

Results

Group I. *Hodgkin's patients studied prior to lymphangiography and therapy.* These patients were studied in order to compare the pretreatment range of serum TSH values for the type of patient studied with that of the normal range and to exclude the possibility of a previously unrecognized association between lymphoma and hypothyroidism. Forty-seven of the 48 patients had normal serum TSH levels and normal additional thyroid function tests. One patient with an elevated TSH level had been previously diagnosed as suffering from hypothyroidism approximately one year prior to the diagnosis of lymphoma. For this reason, she has been excluded from a statistical analysis of this group. The mean TSH level for the group was 6.9 μU/ml ± 5.9 (2 SD), a value which does not differ significantly from that of normal subjects.

Group II. *Post-radiation therapy for lymphoma.* We have analyzed the relationship between sex, age, histological diagnosis, length of post-radiation interval, radiation dose and treatment field on the frequency with which elevations in serum TSH, clinical hypothyroidism and certain other clinical phenomena occurred. Of the 162 patients in this group with the diagnosis of Hodgkin's disease (Table 1), 72 (44%) showed an elevated serum TSH value (mean = 75 μU/ml ± 9.6 SE) some time after the completion of therapy, while, of the 63 patients with non-Hodgkin's lymphoma, 11 (17%) had an elevated value (mean = 70 μU/ml ± 27 SE). Although this difference in frequency between the Hodgkin's and non-Hodgkin's groups would appear to be significant, it is likely that factors other than diagnosis *per se* contribute to the observed difference. The non-Hodgkin's patients tended to be older,

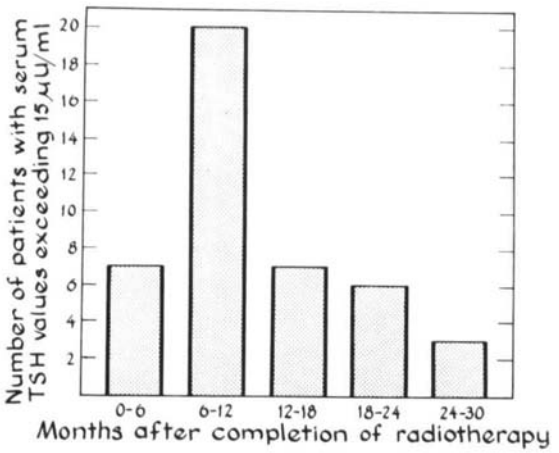

FIG. 1. Interval post irradiation at which first serum TSH elevation was observed in Group II patients who were initially tested during the first post-treatment year.

and a greater proportion of that group received relatively low-dose radiation therapy. In addition, the better prognosis associated with Hodgkin's disease when compared to the non-Hodgkin's lymphomas (16) has selected a higher proportion of long-term survivors in the Hodgkin's group for study during this retrospective analysis.

Age appears to be a factor influencing the incidence of post-treatment serum TSH elevations. Of 60 Group II patients who were under 20 years of age, 29 (48%) had elevated TSH values (mean = 113 μU/ml ± 13 SE), compared with 54 of 165 (33%) (mean = 60 μU/ml ± 8.0 SE) who were over that age. This difference was statistically significant, $p < .05$.

Sex did not appear to be a significant determinant in the incidence with which elevated serum TSH values were observed. However, it should be noted that 20 of the females were taking oral estrogens either for contraception or to relieve the menopausal symptoms induced by radiation therapy to the pelvis. Sixteen of these 20 had elevated TSH values. In seven of the 16, a normal TSH value was obtained shortly after the completion of therapy, but the TSH level subsequently became elevated following the initiation of oral estrogen therapy. Doses employed usually were in the physiologic range, *e.g.*, 0.625–1.25 mg Premarin daily when used to control menopausal symptoms.

TABLE 2. Serum TSH levels in relation to the dose and extent of the radiation field in Group II patients

Radiation dosage and field	Serum TSH		
	No. normal (≤15 μU/ml)	No. elevated (>15 μU/ml)	Total no.
4000–4500 rads			
(a) to whole neck	97*	77†	174
(b) to one side only	19	3	22
1500 rads			
(a) to whole neck	4	2‡	6
(b) to one side only	3	0	3
No radiation to neck	19	1‡	20
Total	142	83	225

* Excluded 4 patients with normal TSH values while on thyroid replacement for a diagnosis of radiation-induced hypothyroidism.

† Hypothyroidism was confirmed by other laboratory test in 21 patients of this group.

‡ Patients in whom hypothyroidism was diagnosed prior to the diagnosis of lymphoma.

In 124 of the Group II patients, the initial TSH determination was obtained within the first year following completion of radiotherapy. Forty-three of these 124 patients (35%) have developed elevated TSH levels, and in 27 of the 43 (63%) the first noted elevation occurred within the first 12 months (Fig. 1). Of the 83 individuals who ultimately developed an abnormal TSH level, 53 (64%) did so within 24 months. In 30 other patients with elevated serum TSH levels, the first serum TSH test was not obtained until more than three years after the completion of radiation therapy.

The influence of the dose of radiation and of treatment field on serum TSH levels in Group II patients is detailed in Table 2. The data suggest that the frequency of elevation in serum TSH levels may be radiation-dose dependent and also show that bilaterality of neck field is an im-

TABLE 3. Thyroid function in patients who became hypothyroid after radiotherapy including the neck for Hodgkin's disease and malignant lymphoma

Pt.	Sex	Age at diagnosis of hypothyroidism (yr)	Interval $\bar{p}$ start of treatment (mos)	Serum TSH (μU/ml)	Serum BEI (μg/100 ml)	% Serum resin-T_3 uptake	Serum total T_4 (μg/100 ml)	Serum free T_4 (ng/100 ml)	Serum cholesterol (mg/100 ml)	PMG* (msec)	Therapeutic response thyroid	History of radiation-induced pericarditis
1	F	30	15	Not done	4.4	23	—	—	—	—	+	+
2	F	50	23	120	1.4	—	—	—	490	600	+	0
3	F	17	7	20	3.6	9	—	—	250	480	+	0
4	M	36	20	115	2.2	25	—	—	350	400	+	+
5	F	14	11	300	3.8	23	—	—	560	—	+	+
6	F	25	20	18		24†	3.9	1.3	—	—	+	+
7	M	22	36	133		25	0.8	—	345	400	+	0
8	F	36	36	34		23	2.0	—	—	500	+	0
9	M	28	14	Not done		25	—	—	335	480	+	0
10	F	25	23	33		24†	0.4	—	—	500	+	0
11	F	44	9	Not done	—	27	—	—	300	520	+	0
12	F	27	42	70	—	20†	—	—	—	—	+	+
13	M	21	32	83	—	28	3.7	1.1	150	—	Not given	0
14	F	20	11	94	—	—	1.6	—	—	—	+	+
15	M	38	60	65	—	30	2.6	—	275	380	+	0
16	F	20	23	37	—	34†	3.0	—	—	—	Not given	0
17	M	27	49	201	—	—	2.4	—	—	—	+	0
18	F	37	14	122	—	20†	0.8	—	—	450	+	0
19	M	21	13	19	—	—	2.4	—	—	—	+	+
20	F	53	19	110	—	19	0.5	—	250	580	+	+
21	F	37	23	Not done	—	—	0.7	0.3	—	—	+	0
22	M	16	36	93	—	23	1.8	—	285	500	Not given	+
23	F	18	11	200	—	24	2.5	—	175	360	+	0
24	F	56	19	45	—	—	1.6	—	—	—	Not given	0
25	M	25	43	145	—	—	2.5	—	—	—	Not given	0

* Photomotogram.

† On estrogen therapy.

portant determinant. Of the 20 patients whose radiation therapy did not include the neck, only one patient had an elevated TSH level and she was known to have hypothyroidism prior to the onset of lymphoma.

Because one of us noted an apparent correlation between the occurrence of hypothyroidism and the syndrome of radiation-induced pericarditis (22) as described by Cohn *et al.* (23), an analysis was made of serum TSH values in the patients with that syndrome. The results confirmed the impression that elevated serum TSH values and hypothyroidism are frequently present in the individual who develops a post-radiation pericarditis. Of 19 such patients who were studied, 16 (84%) had elevated serum TSH values. The additional thyroid function tests confirmed the diagnosis of hypothyroidism in nine of the 16 patients (56%).

In Table 3, results of thyroid function tests are shown for 25 patients in whom a diagnosis of hypothyroidism appears to be valid on clinical grounds, or on the basis of laboratory evidence other than serum TSH levels. All but two of the patients had Hodgkin's disease and 16 of the 25 were females. Four of these patients were studied prior to the availability of the TSH radioimmunoassay. The TSH values were elevated in each of the other 21 patients, with values ranging from 18 to 300 μU/ml. One or more other laboratory values in the hypothyroid range were observed in all patients. Five asymptomatic patients with low total serum T_4 have not received replacement thyroid therapy. In the remainder, replacement thyroid therapy has relieved the patient's symptoms. Unilateral goiter (associated with bilateral ophthalmopathy and transient thyrotoxicosis) developed on the unirradiated side of the neck in one patient who received unilateral neck irradiation. In the entire population

TABLE 4. Serum TSH levels in selected patients with advanced head and neck epidermoid cancer whose entire thyroid gland was included in the radiation field

Patient	Sex	Age (yr)	Location of primary carcinoma	Neck radiation dose (rads)	Serum TSH (μU/ml)	Post-treatment interval (mos.)
1	M	72	Pharynx	6000	3.4	25
2	M	63	Tonsil	6000R 6600L	10.3	30
3	M	65	Pyriform sinus	6000R 6600L	12.0	78
4	F	67	Tongue	6600R 6000L	12.5	84
5	M	72	Larynx	6000	5.0	15
6	F	54	False cord	6200	6.0	34
7	M	65	Nasopharynx	6600	19.6	20
8	M	65	Pyriform sinus	6000	6.0	6
9	F	65	Tongue	6000	18.8	60

of Group II patients, there was one in whom a thyroid nodule was noted on follow-up examination; excisional biopsy of the nodule revealed nodular hyperplasia.

Post-mortem findings. Post-mortem examination has been made in nine patients in Group II. Four of these patients had elevated TSH values during life and one was diagnosed as hypothyroid by other laboratory tests. The thyroid gland weights ranged from 4 to 17 g. The pattern on thyroid microscopy was similar in all cases regardless of the observed serum TSH level. Histologically, the thyroid of the clinically hypothyroid patient could not be distinguished from that of the others. There were focal areas of atrophy and moderate-to-severe fibrosis. Interspersed throughout were focal areas of relatively normal-appearing thyroid in which the follicles were somewhat distended and the epithelium flattened. Electron microscopy was not performed.

Group III. *Patients with advanced head and neck cancer.* In order to evaluate the effect of high-dose irradiation on thyroid function independent of the possible effect of lymphangiography (iodine loading), a group of patients with advanced head and neck cancers who had not undergone lymphangiography was also studied. These patients had all received high doses of radiation (minimum 6000 rads) (Table 4). These patients were selected because their entire thyroid gland was incidentally included in the treatment field. All received large lateral fields of irradiation to encompass their lesions, either the primary tumor, or bulky cervical adenopathy. Unfortunately, the number of patients available for this group was small. Only two of nine patients had slightly elevated TSH values; additional thyroid function tests were entirely normal in both these patients.

Discussion

The results of these studies indicate that external irradiation of the thyroid gland within the therapeutic dose range used for malignant disease will, in many cases, significantly impair its functional capacity. The previous impression that such treatment has little effect on the normal thyroid gland thus requires modification. Factors affecting the incidence of hypothyroidism are dose, extent of radiation field and the time interval following

treatment. An additional factor of probable, possibly crucial, importance is iodide loading (lymphangiography). Indeed, our studies indicate that nearly half of all patients with Hodgkin's disease who received bilateral neck irradiation following diagnostic lymphangiography showed evidence of hypothyroidism when serum TSH tests were employed. In patients with untreated Hodgkin's disease serum TSH values were normal.

Irradiation, however delivered, progressively impairs the capacity of thyroid cells to divide and to respond to a goitrogenic stimulus (24, 25). The exact incidence of hypothyroidism following external irradiation of the neck, with or without iodide loading, is unknown. Prior to this study, there has been no large survey of patients at risk. Forty-one cases studied following irradiation of the neck revealed only three cases of hypothyroidism, but evidence of a reduced thyroid reserve, as measured by TSH stimulation, was demonstrated in other patients similarly treated (5). One additional case was reported six years after irradiation of the neck, and in another study, four cases developed myxedema 4 to 36 months after irradiation (6, 26). In neither of the latter studies was the total number of cases studied following irradiation stated. Although a possibility exists that radiation-induced thyroid disease may involve an auto-immune mechanism (8, 27), the pathological changes seen in the thyroid are more consistent with the changes seen in other tissues following irradiation. Mildly elevated levels of antimicrosomal and antithyroglobulin antibodies (28) have been found in some of the treated patients studied in this series, but not in as high concentrations as in autoimmune thyroiditis or Graves' disease (Mori, T., and J. P. Kriss, unpublished observations).

Routine thyroid function tests on irradiated patients may fail to indicate evidence of thyroid damage (5, 29), and some more sensitive assessment of the functional capacity of the thyroid gland is required to demonstrate the presence of dysfunction. Thyroidal radioiodine uptake studies following TSH stimulation have been used to evaluate thyroid functional capacity (30). However, iodine studies are often invalidated by iodine loading incident to such diagnostic procedures as intravenous pyelography, inferior venocavography and lymphangiography. Most radiopaque dyes are water soluble and are rapidly excreted. In contrast, Ethiodol used in lymphangiography is fat soluble and is excreted more slowly. Koehler *et al.*, using ^{131}I-Ethiodol, analyzed the total body distribution of this agent following lymphangiography in dogs (31). Seventeen days following the lymphangiogram, 20% of the labeled Ethiodol was present in lymph nodes and 10% was present in the lungs. If the retained Ethiodol is gradually broken down over a prolonged period of time, and if the normal volume of Ethiodol for lymphangiography is approximately 15 ml for an adult (475 mg of iodine/ml), then over 2 g of iodine would be expected to be present in the body and available for gradual breakdown. This amount of iodine available is presumably sufficient to induce goiter and/or hypothyroidism, as has been shown to occur with other iodinated contrast agents (32, 33). It is perhaps surprising that no cases of hypothyroidism following lymphangiography alone have been reported to date. Our patients in Group II who underwent lymphangiography but did not receive any irradiation to the neck constitute such an "at risk" group; all but one of these patients had normal TSH levels and no clinical evidence of hypothyroidism or goiter (minimum follow-up period 15 months). The incidence of iodide-induced goiter and hypothyroidism is low and factors predisposing to this condition remain uncertain, but probably include damage to the thyroid parenchyma (33). Iodides administered to euthyroid patients who had received ^{131}I-iodide therapy for diffuse toxic goiter are capable of inducing

myxedema in these patients (34); none of these patients developed a goiter in spite of the increased serum TSH levels recorded. Similarly, in our series only one patient who was myxedematous had a goiter. This infrequent association of goiter with hypothyroidism may well be related to the previous external neck irradiation. Thus, hypothyroidism following external irradiation of the thyroid gland after iodide loading may involve mechanisms similar to those involved in iodide-induced hypothyroidism in Graves' disease patients previously treated with radioiodine. The fact that neck irradiation without iodide loading (our Group III patients) was not followed by hypothyroidism suggests again that iodide loading is an important cofactor contributing to radiation-induced thyroid disease.

Our results indicate that many clinically euthyroid patients who have received radiation therapy to the neck are in a state of compensated thyroid dysfunction in which the thyroid activity is marginally adequate under continuous stimulation by the elevated serum TSH level. Some of these patients may become frankly hypothyroid over a period of months. Others may remain clinically euthyroid for relatively long periods during which the serum TSH is persistently elevated. Less frequently, serum TSH levels are only transiently elevated and return to normal spontaneously. The precise cause for spontaneous recovery remains in doubt, but rapid resolution of hypothyroid states has been seen following withdrawal of iodides (34), and it is possible that in some cases the excretion of the iodide load may allow a return to normal thyroid function. Further studies are required to evaluate the significance of high levels of serum TSH seen in females soon after commencing estrogen therapy. In at least several instances this phenomenon occurred following use of physiologic doses of estrogen. Alterations in serum TSH levels following estrogen therapy, without alteration in serum thyroxine concentration, have been noted (35), although previous studies had not shown such changes (36).

Because some of our patients were first studied well after the completion of radiotherapy, our results tend to indicate that hypothyroidism develops later after radiation treatment than probably actually occurs. Elevation of serum TSH levels was, however, noted in 22% of patients tested within 12 months after treatment, and 20% of the hypothyroid patients were diagnosed within 12 months. Late development of hypothyroidism during subsequent years undoubtedly occurs, however. The final incidence of hypothyroidism will be known only after prolonged study of the survivors. An additional consideration is the risk of neoplastic change in the unshielded irradiated thyroid gland (37). We have on record one patient who, nine years after radiation therapy, including 3000 rads to the neck, developed a mixed papillary and follicular carcinoma of the thyroid. There was, however, no documented clinical evidence of thyroid deficiency; TSH levels were never determined.

The diagnosis of hypothyroidism has traditionally been a clinical one, frequently confirmed by laboratory tests. It is possible that the symptoms of hypothyroidism in the irradiated patient may be overlooked by the physician who attributes the symptoms of fatigue, weakness and loss of energy to sequelae of radiation therapy or to progression of the initial disease. Attention should be directed to the symptoms of muscle cramps and weakness in leg and foot muscles, which were frequent complaints in our hypothyroid group. The importance of diagnosing hypothyroidism in these patients is that simple, effective and inexpensive treatment is available in the form of thyroid hormone supplement. Whether the frequent association of radiation-induced hypothyroidism and pericarditis in the same patient represents an increased sensitivity to thyroid dysfunction of the irradiated heart, or whether the

association represents a coincidence of separate organs whose individual radiation tolerance has been exceeded simultaneously is not yet clear.

In view of the significant incidence of hypothyroidism and elevated TSH levels in patients undergoing neck irradiation, we recommend the periodic clinical and laboratory assessment of thyroid function in all patients receiving high-dose neck irradiation, particularly those also studied by lymphangiography. Such assessments should probably be made at least quarterly during the first three years after treatment. The serum TSH test is recommended as a sensitive indicator of impaired thyroid function. Serious consideration should be given to the advisability of treating with thyroid hormone all those patients with elevated serum TSH values in order to reduce the morbidity of hypothyroidism, alter the course, frequency, or severity of radiation-induced pericarditis, and potentially reduce the risk of thyroid carcinoma.

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