SYMPOSIUM ON MALIGNANCY.

V. HYPOTHYROIDISM FOLLOWING COMBINED THERAPY IN CARCINOMA OF THE LARYNGOPHARYNX.*†‡

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ABSTRACT.

There is an increasing trend to combine high dosage pre-operative radiation with radical surgery for carcinoma of the laryngopharynx. This could be a hazard to thyroid function, especially when surgery includes a partial thyroidectomy. We initiated a study in 1969 to determine the effect on thyroid function produced by external radiation of the neck followed by radical surgery of the laryngopharynx. A group of 24 patients previously treated with external radiation and/or surgery for carcinoma of the laryngopharynx, and without recurrence, were studied with laboratory determinations of PBI and total serum thyroxine (T_4).

Out of 12 patients treated with 3,800 to 5,500 tissue rads of pre-operative Cobalt 60 to the neck, laryngectomy and hemithyroidectomy, eight or 66 percent were found to be hypothyroid at varying time periods (two to 74 months) after treatment. A PBI determination was done on five of these patients and ranged from 0.8 to 3.2 mcg percent (n = 4.0 to 8.0). A total serum thyroxine was done for all eight patients. Those performed by the column method ranged from 0.8 to 2.5 mcg percent thyroxine iodine (n = 2.9 to 6.4) and those performed by the Murphy-Pattee method ranged from 1.3 to 4.9 mcg percent thyroxine (n = 5.0 to 13.7).

Two of the other 12 patients were found to be hypothyroid. One patient received 7,000 tissue rads of Cobalt 60 and no surgery. One year following therapy his thyroid studies were normal, but two years after therapy his studies were within the hypothyroid range. The other patient found to be hypothyroid had a laryngectomy and hemithyroidectomy with no pre-op-

*Presented as part of a Symposium at the Meeting of the Middle Section, American Laryngological, Rhinological and Otological Society, Inc., Omaha, Nebr., January 23, 1972.

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‡This work supported by the National Institute of Neurological Diseases and Stroke, Grants NS 05349 and NS 04615.

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Editor's Note: This Manuscript received in THE LARYNGOSCOPE Office and accepted for Publication January 28, 1972.

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erative Cobalt 60. The operative report indicated that both the superior and inferior thyroid vessels to the remaining lobe were ligated.

CONCLUSIONS.

We propose the following: first, external radiation to the neck produces a reduction in thyroid function in all patients; second, present day high dosage external radiation to the neck can itself produce hypothyroidism in patients with "susceptible" thyroid glands. The reason for this susceptibility is not entirely clear at this time. Third, when external radiation of the neck is combined with laryngectomy and hemithyroidectomy, a significant incidence of hypothyroidism is created. We believe the hypothyroidism in such patients is a result of pre-operative radiation reducing the thyroid reserve and subsequent surgery removing a significant amount of an already compromised thyroid.

RECOMMENDATIONS.

The pre-treatment level of thyroid function should be established in all patients who are to be treated for carcinoma of the laryngopharynx. There should be a clinical evaluation of the patient and laboratory determination of the PBI and especially total serum T_4 by the column method, or Murphy-Pattee method if iodine contamination is a possibility. These studies should be repeated frequently during the first year following treatment to identify those patients who develop hypothyroidism quickly and every six to 12 months thereafter to detect hypothyroidism occurring after a gradual decline in thyroid function.

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INTRODUCTION.

There is an increasing trend to combine high dosage pre-operative radiation with radical surgery for carcinoma of the laryngopharynx. This could be a hazard to thyroid function, especially when surgery includes a partial thyroidectomy. At this institution, 4,000 tissue rads of Cobalt 60 to the neck, followed by a widefield laryngectomy, ipsilateral hemithyroidectomy and radical neck dissection, is a common method of treatment for carcinoma of the laryngopharynx. A review of the literature did not reveal any report concerning the effects of combined therapy on thyroid function; therefore, we initiated a study in 1969 to determine its effect by obtaining thyroid function tests in patients previously treated for carcinoma of the laryngopharynx.

In 1964, Koulumies, *et al.*,[1] found no cases of hypothyroidism in 118 patients previously treated with approximately 5,000 rads for carcinoma of the larynx. Serial tests performed in 34 of these patients showed a de-

crease of the PBI in one-half of those tested. In 1965, Markson and Flatman[2] reviewed the literature; they found only one case, and reported another five cases of hypothyroidism after external radiation of the neck for carcinoma not involving the thyroid gland. Einhorn and Wikholm,[3] published a report in 1967 concerning 41 patients treated with external radiation for carcinoma of the larynx or hypopharynx. Three of these patients were found to be hypothyroid. All of the other 38 patients had a significant decrease in response to thyrotropin (TSH) stimulation as measured by I^{131} uptake. The authors concluded that the thyroid reserve was diminished in these 38 patients, and hypothyroidism would not be uncommon in their future years.

In August, 1971, Lavelle,[4] published a report about thyroid function in 42 patients treated with combined therapy for carcinoma of the larynx between 1964 and 1969. All patients were treated with pre-operative external radiation and total laryngectomy, which in most patients included a hemithyroidectomy. After three patients were found hypothyroid following treatment, all patients were given thyroid hormone postoperatively as prophylaxsis against later development of hypothyroidism. This prophylactic thyroid administration was discontinued in the last 18 months of the study, and instead, the patients were followed for clinical and laboratory evidence of hypothyroidism. In 21 of the 42 patients, the PBI was determined while the patients were receiving L-thyroxine. The report did not state how many of these 21 patients were taking L-thyroxine as prophylaxsis and how many had actually been found to be hypothyroid. The 21 patients who had never taken thyroid hormone prior to their PBI determinations constitute the group of patients that give some indication of the effect of combined treatment on thyroid function. All of these 21 patients were treated with an unstated amount of pre-operative radiation and total laryngectomy. This was combined with a hemithyroidectomy in 12 of the 21 patients. The post-treatment PBI averaged 3.8 mcg percent in the 12 patients whose treatment included hemithyroidectomy and 5.8 mcg percent in the nine patients who did not have any thyroid gland resected.

METHOD.

Group Selection.

During the 20 months from October, 1969, to May, 1971, patients previously treated for carcinoma of the laryngopharynx, and seen in regular follow-up visits, were studied in regard to thyroid function. All such patients seen by the authors were not studied, but no attempt was made at selection of patients. From those studied, a group of 24 patients was selected for this report. They all met the following qualifications: *1.* the patient must have been treated with external radiation, surgery or both for squamous cell carcinoma of the laryngopharynx; *2.* enlarged cervical lymph nodes prior to treatment were allowed, but there could not have

TABLE I.

Summary of Thyroid Function in Patients Treated for Carcinoma of the Laryngopharynx.

Method of Treatment	Number of Patients	Number of Patients Found	
		Hypothyroid	Euthyroid
Cobalt 60	2	1	1
Laryngectomy	2	0	2
Laryngectomy and Hemithyroidectomy	4	1	3
Cobalt 60 and Laryngectomy	4	0	4
Cobalt 60, Laryngectomy and Hemithyroidectomy	12	8	4
Total	24	10	14

been; *a.* direct extension by the primary lesion into the neck; *b.* clinical or microscopic involvement of the thyroid gland; *c.* distant metastases; *3.* any history of a thyroid disorder prior to treatment disqualified the patient; *4.* only those who remained free of tumor and were alive at the end of this study were included; and *5.* any patient who had a recurrence after his primary therapy, although secondarily treated and free of tumor, was excluded.

Thyroid Function Evaluation.

Serum protein-bound iodine (PBI) consists primarily of thyroxine (T_4 — 90 percent) and triiodothyronine (T_3 — 5 percent). These are reversibly bound to serum proteins, primarily the thyroid binding globulin. About 0.1 percent of T_4 and 1.5 percent of T_3 are unbound and are sometimes referred to as "free hormone"; whereas, free T_4 alone is commonly referred to as "free thyroxine." A measurement of the PBI, total serum T_4 or T_3 are only indirect measurements of the metabolically active free T_4 and T_3.

The serum PBI correlates with the thyrometabolic status in most patients but is much less sensitive and is much more affected by outside influences (iodine containing drugs and X-ray contrast material, pregnancy, oral contraceptives, estrogens, androgens, diphenylhydantoin, sodium salicylates, etc.) than the total or free thyroxine. The best laboratory tests to obtain when iodine contamination is not a problem, are the total and free thyroxine determined by the column technique. If there is iodine contamination, the total and free thyroxine should be obtained by the Murphy-Pattee method which is not affected by contaminating organic or inorganic iodine resulting from prior drug use or an X-ray contrast study.

FINDINGS.

Table I is a composite listing of all patients studied and our evaluation of their thyrometabolic status. All patients said to be hypothyroid: *1.* had

TABLE II.

Thyroid Function Tests in Patients Found Hypothyroid After Treatment for Carcinoma of the Laryngopharynx.

Age When Treated	Rads Cobalt 60 to Neck	Months Between Rx and Studies	PBI	Total Serum T_4 by Column Method	Total Serum T_4 by Murphy-Pattee Method
Cobalt					
63 (H. K.)	7,000	13	3.3	Free T_4 = 1.2	
Laryngectomy and Hemithyroidectomy					
75 (O. A.)		64	3.2		3.0
Cobalt, Laryngectomy and Hemithyroidectomy					
56 (L. A.)	4,000	17		1.4	
46 (H. M.)	4,800	74	2.5		3.1
48 (E. R.)	4,000	7			3.0
71 (J. R.)	5,500	72	3.2		1.3
50 (W. O.)	4,000	20	4.4		4.4
62 (W. A.)	4,000	3	1.5	0.8	
46 (T. P.)	4,000	30	3.2	2.5	3.1
62 (J. M.)	3,800	33	*7.4	1.8	Free T_4 = 0.6
Normal Values					
PBI (mcg percent of Protein Bound Iodine)					4.0 to 8.0
Total Serum T_4 Column Method (mcg percent thyroxine iodine)					2.9 to 6.4
Murphy-Pattee Method (mcg percent thyroxine)					5.0 to 13.7
Serum Free T_4 (Milli mcg percent thyroxine)					1.4 to 2.6

*Patient takes SSKI and other iodine containing expectorants.

TABLE III.

Thyroid Function Test in Patients Found Euthyroid After Treatment for Carcinoma of the Laryngopharynx.

Age When Treated	Rads Cobalt 60 to Neck	Months Between Rx and Studies	PBI	Total Serum T_4 by Column Method	Total Serum T_4 by Murphy-Pattee Method
Cobalt					
34 (W. W.)	6,500	33			6.5
Laryngectomy					
46 (E. O.)		5	4.4	3.3	
43 (H. O.)		48	6.7		
Laryngectomy and Hemithyroidectomy					
56 (G. V.)		6	5.5	3.9	
61 (J. G.)		11	6.5	4.2	
58 (D. F.)		5		3.9	
Cobalt and Laryngectomy					
76 (A. D.)	5,000	54	6.7		11.1
51 (V. E.)	5,000	46	3.8		6.6
60 (F. K.)	5,000	70	5.1		8.0
51 (J. S.)	6,000	42	5.7		8.9
Cobalt, Laryngectomy and Hemithyroidectomy					
52 (R. A.)	4,000	24	4.8		7.4
62 (B. J.)	4,000	11	6.0		9.6
59 (W. M.)	4,000	25	3.7	3.5	
72 (C. C.)	4,000	42	4.1	4.5	(Free T_4 = 1.7)

PBI and serum T_4 values within the hypothyroid range; and *2.* demonstrated one or more of the clinical effects of hypothyroidism (increased fatigue, weight gain, constipation, mental dullness or depression). Results of the thyroid tests performed in this study are listed in Table II for those patients felt to be hypothyroid and in Table III for those found euthyroid.

Two patients were treated with Cobalt 60 and no surgery. One of these, (H. K.), was found to be euthyroid 11 months after treatment, but later developed hypothyroidism.

CASE REPORT.

Case 1. H. K. was 63 years old when he was found to have carcinoma of the hypopharynx. He received 7,000 rads of Cobalt 60 to the neck from November, 1968, to January, 1969. In December, 1969, 11 months after treatment, his PBI was 5.2 mcg percent, and a 24-hour I^{131} uptake was 9.8 percent (n = 5 to 35 percent). In December, 1970, nearly two years after treatment, his PBI had fallen to 3.3 mcg percent, and his 24-hour I^{131} uptake had decreased to 4.1 percent. A serum-free thyroxine was 1.2 milli mcg percent (n = 1.4 to 2.6 milli mcg percent). H. K. was then seen by the endocrinology service, who confirmed that he was hypothyroid. They obtained his serum TSH level which was 200 units/ml (normal in the lab which performed the test is less than 14 units/ml). This is a very high concentration of TSH and denotes hypothyroidism.

COMMENT.

This case represents sequential evidence of declining thyroid function after high dosage external radiation of the neck with no surgery.

Neither of the two patients treated with a laryngectomy became hypothyroid. We did not obtain a total serum T_4 on one of these patients, (H. O.), but he had a normal PBI and was classified as euthyroid.

One of the four patients having a laryngectomy and hemithyroidectomy was found to be hypothyroid. Microscopic study showed the resected thyroid tissue to be normal. The operative report was unusual, however, because it described ligation of the right inferior thyroid artery in addition to a left hemithyroidectomy. Although not described, the right superior thyroid artery was probably ligated as part of the laryngectomy; therefore, the major blood supply to the remaining lobe seems to have been removed.

Four patients received pre-operative Cobalt 60, ranging from 5,000 to 6,000 rads, followed by a laryngectomy without any resection of the thyroid. None of these patients was found to be hypothyroid.

In contrast to the other patients studied, those treated with pre-operative Cobalt 60, laryngectomy and hemithyroidectomy were found to have a high incidence of hypothyroidism. Out of 12 patients, eight or 66 percent were found to be hypothyroid. One of these eight patients, (W. O.), had thyroid studies which were borderline hypothyroid, but the laboratory determinations in the remaining patients were clearly within the hypothyroid

range. The patients found hypothyroid ranged in age from 46 to 71 years old at the time their treatment began. They received from 3,800 to 5,000 tissue rads of Cobalt 60 to the neck followed by a widefield laryngectomy, hemithyroidectomy and usually *en bloc* radical neck dissection. The laboratory studies were obtained at varying lengths of time, two to 74 months, after the initiation of treatment. One of the eight patients found to be hypothyroid, (T. P.), demonstrates the decline in thyroid function after combined therapy including hemithyroidectomy.

CASE REPORT.

Case 2. T. P. was 46 years old when found to have carcinoma of the larynx. He received 4,000 tissue rads of Cobalt 60 over four weeks followed by a laryngectomy, hemithyroidectomy and radical neck dissection in November, 1968. Five months later, April, 1969, he had a normal PBI of 4.6 mcg percent; however, nearly two and one-half years following treatment, May, 1971, his PBI had fallen to 3.2 mcg percent. Further testing showed his total serum T_4 to be 2.5 mcg percent thyroxine iodine by the column technique and 3.1 mcg percent thyroxine by the Murphy-Pattee method; therefore, his PBI and total serum T_4 were both within the hypothyroid range.

COMMENT.

This case seems to document a decrease in circulating thyroid hormone following combined therapy.

The pathologist's microscopic description of resected thyroid tissue was available in seven of the 12 patients treated with combined therapy including hemithyroidectomy. Three of the seven were euthyroid and four were hypothyroid. All reports described normal thyroid except in one patient, (L. A.), who was found to be hypothyroid. His resected thyroid tissue was described as showing various sizes of follicles containing colloid with a moderate increase in fibrous tissue and scattered round cell infiltrate, characteristic of a benign adenomatous goiter.

DISCUSSION.

In the few published reports[1,2,3] about thyroid function after external radiation of the neck, it is uncommon to find accounts of hypothyroidism; however, two of these same studies[1,3] have shown that the reduction of thyroid function is very common. In those reports finding hypothyroidism to be unusual, the dosages of radiation used have been considerably less than the present day full-course regimens. Koulumies, *et al.*,[1] reported no evidence of hypothyroidism in 118 patients previously treated with external radiation for carcinoma of the larynx; however, the dosages used were approximately 5,000 tissue rads, which is considerably less than the present day full-course treatment of 7,000 or more tissue rads. The report by Koulumies, *et al.*,[1] was based on a follow-up period of two to 11 months which is not long enough to detect the late development of hypothyroidism. Our patient, (H. K.), in Case 1, shows that thyroid function can gradually decrease enough after external radiation to produce hypothyroidism, and

also demonstrates a need for longer surveillance. H. K. received 7,000 tissue rads of Cobalt 60 to the neck and 11 months later, which was Koulumies' maximum observation time, he was euthyroid by PBI and borderline euthyroid by I^{131} uptake; however, two years after treatment his PBI, I^{131} uptake and serum free thyroxine were within the hypothyroid range.

Of the four patients treated by a laryngectomy and hemithyroidectomy, without pre-operative radiation, we found one to be hypothyroid. It was this patient who probably had ligation of both the superior and inferior thyroid arteries to the remaining lobe. It would be unusual to ligate both the superior and inferior thyroid arteries to the remaining lobe during a laryngectomy and hemithyroidectomy; however, the superior thyroid artery to the remaining lobe is ligated routinely. A patient left with one thyroid lobe having either or both of its major arteries ligated, would seem to be more prone to develop hypothyroidism, especially when there has been previous radiation of the neck.

Although our study is not based on a large series of patients and we do not have any pre-treatment laboratory values of thyroid function; we feel it is very significant that eight out of 12 patients treated with pre-operative Cobalt 60, laryngectomy and hemithyroidectomy were found to be hypothyroid. We believe the hypothyroidism is caused by the treatment, and our reasoning is as follows.

The pre-operative Cobalt reduces the thyroid function by its direct effect on the thyroid gland. Surgery then removes one-half or more of an already compromised thyroid and may reduce the blood supply to the remaining lobe. The remaining thyroid tissue does not possess enough reserve to increase its function and maintain adequate production of thyroid hormone with the result being hypothyroidism.

CONCLUSIONS.

We propose the following: first, all patients have a decrease in thyroid function as a result of external radiation of the neck; second, present day high dosage external radiation can and does produce hypothyroidism in those patients with "susceptible" thyroid glands. The reason for this susceptibility is not entirely clear at this time. The decline in thyroid function can occur rapidly in some patients, but probably is gradual in most; and third, when external radiation of the neck is combined with laryngectomy and hemithyroidectomy, a high incidence of hypothyroidism is produced.

We think the pre-treatment level of thyroid function should be established in all patients who are to undergo radiation and/or surgery for carcinoma of the laryngopharynx. Pre-treatment levels of PBI and total serum T_4 by column should be obtained. If there is any possibility of iodine contamination, a total serum T_4 by the Murphy-Pattee method should be

substituted for the total serum T_4 by column. These studies should be repeated one month after the completion of radiation treatments or just prior to, and one month after, the planned post-radiation surgery. Following surgery the pathologist should be asked to examine specifically any resected thyroid tissue for evidence of adenoma or inflammation which may indicate that those patients are more susceptible to the development of hypothyroidism. The PBI and total serum T_4 should be repeated every three months during the first year following treatment to identify those patients who will develop hypothyroidism quickly, and every six to 12 months thereafter to detect hypothyroidism occurring after a slow decline in thyroid function.

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(End of Symposium.)

THE 13th CONGRESS OF THE PAN-PACIFIC SURGICAL ASSOCIATION.

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