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HYPERTHYROIDISM, TWO CASES DEMONSTRATING ITS INCEPTION DURING CORTISONE AND THYROID THERAPY

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In the past few years, considerable attention has been directed to adrenal-thyroid-pituitary relationships. The development of radioactive iodine tracer techniques for study of thyroid function, and the availability of cortisone and purified thyroid-stimulating hormone have made possible new approaches to the intricate interplay of these several endocrine systems. As a result, thyroid hormone and, to a lesser extent, cortisone have been shown to inhibit the function of the thyroid gland. Periodically, interesting cases come under study which may fail to support the new concepts derived from planned experimentation. The two cases which are reported here suggest that concepts of pituitary-thyroid and adrenal-thyroid relationships are not to be oversimplified, particularly in disease.

CASE REPORTS

Case No. 429413, Mrs. A. S. is a 47-year-old white woman who was first treated in the Henry Ford Hospital in 1944. At that time she was a patient of the Gastroenterology Division with a diagnosis of functional bowel distress. She was then taking 60 mg. of thyroid daily which had been prescribed elsewhere for complaints of fatigue, menstrual irregularity, and dizzy spells. She stated that she "felt awful" if thyroid were omitted.

The patient continued her treatment elsewhere. The amount of thyroid was gradually increased to a maximum of 240 mg. daily, which dose the patient began in the fall of 1952. She felt well, but during the following winter noted a much greater tolerance for cold weather and a gradually increasing appetite. On April 11, 1953 the patient was attending Good Friday services when she was suddenly seized with a terrifying episode of paroxysmal tachycardia. She consulted a cardiologist who, after controlling the attack, advised a program of 6-propylthiouracil and iodine therapy. There was noticeable improvement within a week. The patient regained eight pounds of weight she had lost, but she continued to be extremely nervous and apprehensive. She discontinued her medications and came to the Endocrinology Division in May, 1953.

At no time did the patient notice unusual weakness. Nervousness, palpitations, and excessive sweating were her chief complaints. She was of normal weight and there was no sign of muscle wasting. The skin was soft, warm and moist. The blood pressure was 150/75 and the pulse varied from 132 to 160 per minute. There was no exophthalmos, but stare and lid-lag were present. The thyroid gland, diffusely enlarged to twice normal size, was firm and symmetrical. The heart was not enlarged. Besides the sinus tachycardia, an apical systolic murmur

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and a prominent third heart sound were noted. The lungs were clear and there was a trace of ankle edema. The BMR was +39 on May 14, 1953.

It was felt unlikely that the hyperthyroidism was a response to exogenous thyroid, since it had persisted a full month after discontinuing the hormone. Accordingly, the patient was given Tapazole in divided doses, totalling 25 mg. daily. Rapid clinical improvement followed and the dose was reduced to 15 mg. daily on July 20. By September, however, there was clinical evidence that the patient had relapsed, and the BMR was +35. This confirmed the fact that the patient had indeed developed hyperthyroidism with diffuse goiter while receiving 240 mg. of desiccated thyroid daily. The dosage of Tapazole was increased and the patient continues to respond satisfactorily to this treatment.

Case No. 446109, Miss M. M. is a 24-year-old white telephone operator who has had progressive rheumatoid arthritis since the age of fourteen. She was originally studied in the Henry Ford Hospital in 1944, at which time there was no palpable abnormality of the thyroid gland and the BMR was +12. The remainder of the findings were compatible with the diagnosis of active rheumatoid arthritis.

Despite varying therapies, there was a steadily progressive increase in joint involvement and disability. In December 1951, the patient was given cortisone therapy for about one month with considerable symptomatic improvement. This was resumed in the spring of 1952 and continued for an eight-month period when it was interrupted for a trial of Butazolidin therapy. Cortisone was once more resumed in January 1953, and the patient continued to take 62.5 mg. daily in divided doses until her re-admission to the hospital in October of that year. The cortisone treatment was supplemented with aspirin and oral potassium chloride.

In late summer 1953, the patient experienced an acute exacerbation of her arthritis during a period of extremely hot weather. The joint distress was accompanied by a persistent tachycardia, anorexia, weight loss of twenty-five pounds, sweating, and diarrhea three or four times daily. A BMR in June 1953, prior to this flare-up, was reported to be normal.

When admitted to the hospital, she showed considerable progression of her arthritis. There was evidence of weight loss, but specific muscle wasting could not be evaluated. The skin was warm and moist but the hair was not of unusual texture. There was a slight widening of the palpebral fissures, but no lid-lag or exophthalmos. The right lobe and isthmus of the thyroid gland were very firm and diffusely enlarged to two or three times normal size. The left lobe appeared not to be involved. The gland was easily movable and was not tender. There was a definite but irregular tremor of the hands and a persistent tachycardia, with a pulse of 140. The blood pressure was 130/50. There was no cardiac enlargement, and a grade III apical systolic murmur was present.

The hemoglobin was down to 8.5 gm. per 100 c.c. of blood. There were 9700 white blood cells per cu. ML. with 27 per cent lymphocytes. The direct eosinophil count was 173. Serum electrolytes were normal. The cholesterol was 148 mg. per cent. Cephalin-cholesterol and thymol flocculations were four-plus with

twelve units of thymol turbidity. The bromsulphalein test was negative in sixty minutes and the sedimentation rate was 41 mm. The BMR was +55. Radioactive iodine uptake was 80 per cent in twenty-four hours, and the contact counts were uniformly elevated over the entire thyroid gland.

The patient was placed on Tapazole therapy, twenty-five milligrams in divided doses daily, while she continued to take the same dose of cortisone and aspirin. By December 21, 1953, she felt much improved. She no longer had palpitations or excessive sweating, and the diarrhea had subsided. She had gained six pounds and the joint distress was much improved. The pulse rate was down to sixty-four, and the blood pressure was 122/64. The thyroid gland seemed to be somewhat smaller than it had been on her admission to the hospital. The patient has continued to improve, and has now gained fifteen pounds since the beginning of Tapazole therapy. She has no symptoms of hyperthyroidism.

DISCUSSION:

The etiology of hyperthyroidism with diffuse goiter is unknown. The observation that hypopituitarism produces hypothyroidism, and that pituitary thyroid-stimulating hormone (TSH) is capable of increasing thyroid size and rate of thyroid hormone secretion has led, naturally, to the assumption that diffuse goiter with hyperthyroidism is really a form of hyperpituitarism with increased TSH elaboration. The occasional association of the disease with acromegaly is some support for this idea. In Graves' disease, the presence of exophthalmos, which is believed by many to be caused by a pituitary principle, also suggests that pituitary hyperfunction is the cause of the hyperthyroidism. However, attempts to demonstrate abnormal amounts of assayable TSH in serum of patients with hyperthyroidism have not yielded uniform results (1). This does not indicate, necessarily, an absence of pituitary hyperfunction, since the hyperplastic thyroid could utilize the circulating TSH so completely that the demonstration of increased hormone titers in the blood would be impossible.

Exogenous thyroid hormone is a potent inhibitor of thyroid function. Greer (2) has shown that 180 mg. of desiccated thyroid by mouth will reduce the radioactive iodine uptake of the normal thyroid to myxedematous levels within one week. That this effect is due to TSH inhibition is confirmed in the demonstration by Perlmutter (3) that the inhibited gland will respond to even small amounts of TSH. If diffuse goiter with hyperthyroidism is due to excessive TSH elaboration, the normal pituitary-thyroid relationship obviously must be disrupted. Otherwise, the increased amounts of thyroxin would rapidly inhibit the pituitary hyperfunction and cure the disease.

Werner (4) has demonstrated that in untreated Graves' disease, the administration of desiccated thyroid does not significantly reduce the elevated I-131 uptake by the gland. Furthermore, administering TSH to these patients produced a further increase in the serum hormonal iodine. After remission was produced by radioactive iodine, the glands responded almost normally to these hormones; that is, thyroid administration reduced the I-131 uptake, and TSH injection markedly increased the serum protein-bound iodine. The above author

feels that if Graves' disease were due to primary TSH excess, thyroid ingestion would reduce the I-131 uptake of the untreated gland, but the gland would not react to additional amounts of TSH. Since these results were not obtained, he concluded that the pituitary is not primarily involved in Graves' disease. However, these observations are also compatible with the thesis that the hyperactive pituitary gland is the cause of the disordered thyroid function, but that the pituitary has achieved an autonomy of function, free of the normal checks and balances. It can be further postulated that the hyperplastic thyroid gland is not operating at its maximal capacity to respond to TSH, and increases its hormone output still more when an additional stimulus is applied. The apparent recovery of pituitary responsiveness to the inhibiting influence of thyroxin after I-131 therapy of Graves' disease is difficult to explain, however, unless I-131 has a direct pituitary effect. Whatever the explanation of his findings, inspection of Werner's data indicates that the differences between treated and untreated hyperthyroid patients are only those of degree.

Several studies have shown that cortisone is also an inhibitor of the function of the normal thyroid gland, but a less effective one than is thyroxin. Prolonged administration of the hormone has lowered the serum protein-bound iodine and decreased the I-131 uptake by the thyroid gland of normal individuals (5, 6). It has been suggested that the reduced I-131 uptake after cortisone therapy might be secondary to an increased renal clearance of plasma iodide, making the administered isotope unavailable to the gland, rather than being a result of primary impairment of thyroid function. However, simultaneous determinations of renal and thyroidal clearances of plasma I-131 by Berson and Yalow (7) have shown that both effects occur independently. The cortisone-inhibited thyroid gland will increase its I-131 uptake in response to TSH administration (8) just as the thyroxin-inhibited gland will do. It is assumed, therefore, that the mechanism by which cortisone reduces thyroid function involves the pituitary, with an inhibition of TSH secretion.

In view of these observations, it would appear unlikely for diffuse goiter with hyperthyroidism to appear in patients receiving thyroid or cortisone in therapeutic doses. However, the two cases reported demonstrate this occurrence. The first case developed hyperthyroidism while taking a dose of desiccated thyroid sufficient to inhibit the function of a normal gland completely. That this could cocur is evidence that the hyperfunctioning gland has escaped from its normal controls. Whether this disease represents a primary autonomous overfunctioning of the thyroid or is a disorder of the hypothalamus and pituitary which renders them unresponsive to circulating thyroid hormone remains unknown. Nevertheless, the case demonstrates that the use of desiccated thyroid did not prevent the development of the disease. It is suggested that the use of desiccated thyroid as a pituitary inhibitor in cases of hyperthyroidism with "pituitarigenic" exophthalmos would not be likely to succeed.

The second patient developed hyperthyroidism after taking cortisone for about eighteen months. The goiter was somewhat unusual in that the left lobe did not appear to be enlarged, although the radioactive iodine tracer indicated that the

entire gland was hyperfunctioning. This case demonstrates that cortisone is not a sufficiently potent inhibitor of thyroid function to prevent the development of marked hyperthyroidism. It is likely that the effects of both cortisone and thyroxin in the hyperthyroid patient are different from those observed in normal patients, owing to alterations in pituitary-thyroid-adrenal relationships inherent in the disease state. Since these hormones seem to affect thyroid function by inhibiting TSH elaboration, they would be expected to exert a greater influence in hyperthyroidism secondary to pituitary activity than in a primary thyroid disease such as hyperfunctioning adenoma. The unquestioned beneficial effects of adrenal steroids which we have observed in several patients in thyroid crisis are probably not due to a reduction of thyroid function, but reflect improved resources for the patient to meet the severe stress.

SUMMARY

Two cases of hyperthyroidism with diffuse goiter are reported. One patient developed her disease while taking 240 mg. of desiccated thyroid daily; and the other, a patient with rheumatoid arthritis, became hyperthyroid while receiving 62.5 mg. of cortisone daily. Since both cortisone and thyroxin have been shown to inhibit TSH elaboration and thyroid function in normal subjects, such cases would appear to be unexpected. Their occurrence implies a derangement of pituitary-thyroid-adrenal relationships in hyperthyroidism which cannot be elucidated by the study of normal subjects alone.

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