Henry Ford Hospital Medical Journal

Volume 6 | Number 3 Article 4

9-1958

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A PREVIOUSLY UNREPORTED EFFECT OF THE PROLONGED ADMINISTRATION OF DESICCATED THYROID

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The effect of prolonged thyroid administration in the euthyroid patient has received a minor degree of attention in the medical literature. Available reports have emphasized the apparent complete recovery of the thyroid gland after abrupt or gradual discontinuance of exogenous thyroid medication administered over varying periods of time.[1-4] Recovery usually occurred within three months after cessation of thyroid feeding, based on both clinical and laboratory evidence. Since the administration of exogenous thyroid hormone suppresses thyrotropic hormone of the anterior pituitary and leads to involution of the thyroid gland, the question may be raised that if a total replacement dose of thyroid were taken over a long period of time, might not irreversible atrophy of the gland eventually take place. We have recently had occasion to observe three patients who had been on thyroid hormone in doses of 120 to 180 milligrams for 15 to 25 years and whose thyroids were refractory to the administration of exogenous TSH at the time they were seen in the clinic. All had been placed on thyroid originally for reasons that seemed unrelated to thyroid hypofunction, and they seemed in no way to differ from the large group of patients whose thyroid therapy is initiated for reasons that are best described charitably as "empirical". One of these cases had been studied in sufficient detail so that certain speculative observations can be made.

CASE REPORT: M. A., a 32-year-old white housewife, was first seen at Henry Ford Hospital in 1942 with the chief complaint of cough. The only symptom possibly relating to disorder of thyroid function was that of fatigue. Physical examination was entirely normal. The blood pressure was 110/70, pulse rate 80. The skin was warm and smooth. The reflexes were recorded as normal. Two years later, she was seen by her family physician for fatigue and nervousness over a family situation. A B.M.R. was performed which, to the patient's recollection, was —30. She was placed on desiccated thyroid up to 180 milligrams daily with no appreciable change in her symptoms. She was again seen at Henry Ford Hospital in the Gynecology Division in 1951, at which time she was taking 90 milligrams of USP thyroid. Her B.M.R. was —17 and a year later, having increased the thyroid dose to 120 milligrams, it was —6. In 1958 her B.M.R. was —14 while she continued on 120 milligrams of thyroid. She was subsequently seen in the Endocrine Clinic where a review of her history revealed that in the previous year she had stopped thyroid for two weeks with no obvious ill effect. The thyroid medication was terminated and six weeks later she noted some cold intolerance, increasing fatigue and had gained ten pounds in weight. The only objective change on physical examination was some slowing of the recovery phase of the deep tendon reflexes. No further medication was given for the next six weeks and on her return she had developed a full-blown picture of myxedema with infraorbital swelling, dryness and thickening of the skin, slowness of speech, constipation, and

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marked slowing of the recovery phase of the deep tendon reflexes. Her B.M.R. was —33. The protein-bound iodine was 1.2 micrograms per cent. The radioactive iodine uptake in three hours was four per cent. In order to ascertain whether the thyroid was capable of being stimulated, five units of TSH were administered daily for three days, at the end of which time the three-hour I-131 uptake was still four per cent. Thyroid was again prescribed. Her most recent B.M.R. was —11 after two months maintenance therapy of 180 milligrams daily.

DISCUSSION: Previous reports on the effects of exogenous thyroid ingestion in euthyroid subjects have emphasized the complete recovery of the thyroid gland after the cessation of treatment. This has been observed in patients receiving physiologic or greater amounts for prolonged periods of time. These reports have stressed the absence of clinical signs of myxedema, even in those patients whose indices of thyroid function did not return to normal or pre-treatment levels for considerable periods of time. The patient of this report presented classical features of myxedema three months after stopping thyroid therapy. The B.M.R. of —33, the P.B.I. of 1.2 micrograms, and the three-hour I-131 uptake of four per cent, all support this diagnosis. The failure of the thyroid gland to respond to three days of TSH administration confirms the presence of primary thyroid failure. Stanley and Astwood[5] have demonstrated that human subjects do not accumulate an appreciable amount of thyroidal radioactive iodine while under the influence of exogenous thyroid hormone, but such glands can be stimulated to normal activity within eight hours following a single small dose of thyrotropic hormone.

We are unable to state with certainty that this patient (or the other two patients referred to in the introduction) did not have hypothyroidism at the time thyroid was first prescribed. Neither can we prove that if they were indeed euthyroid initially, the reason for subsequent hypothyroidism was causally related to the prolonged dormant state of the gland. In our experience, the majority of patients previously given thyroid because of low basal metabolic rates have no true thyroid deficiency. They have not been found hypothyroid by any other parameters of thyroid function, and the responses of the B.M.R. to desiccated thyroid have been highly variable. We consider the patient of the present report to fall into this classification for the following reasons: 1) two years before thyroid therapy, she had no symptoms or findings suggestive of hypothyroidism, and she developed none prior to therapy; 2) the administration of 180 milligrams of desiccated thyroid produced no improvement in the symptoms of alleged thyroid dysfunction; 3) subsequent cessation of thyroid therapy led to frank clinical myxedema, easily recognized by the patient as an entirely new set of symptoms.

These cases were originally studied to see if the long-term administration of thyroid hormone might permanently suppress pituitary thyrotropin with resulting myxedema. Whether or not this happened or spontaneous selective (TSH) failure of anterior pituitary function occurred, we cannot state. If either one, the thyroid gland in addition became unresponsive to exogenous TSH. Other authors have mentioned the importance of withholding thyroid for periods up to six months before assessing the thyroid function after prolonged use of the hormone. We considered this unnecessary because the gland had been found unresponsive to thyroid stimulating hormone.

It is our interpretation that this case represents induced myxedema from prolonged

thyroid feeding in an initially euthyroid individual. This type of therapy will cause suppression of endogenous TSH, leading to involution of the thyroid gland. It may produce eventual irreversible atrophy with inability to respond to thyrotropic hormone, comparable to the state of primary myxedema. This observation is not consistent with previous reports in the literature. In 1941 Farquharson and Squires were the first to call attention to the inhibition of thyroid secretion following continued ingestion of thyroid substances.[1] They gave thyroid to several euthyroid patients with obesity, neuroses, or minor chronic disorders. The period of therapy varied from several months to more than two years. All patients were given at least 120 milligrams of thyroid daily, and for some the dose was 300 milligrams. The treatment was stopped abruptly. The B.M.R. fell rapidly to below pre-treatment levels, and some patients complained of mild fatigue, weakness, and cold intolerance. Over a period of several weeks, however, the B.M.R. gradually returned toward pre-treatment levels. By three months, all had stabilized at the initial level and symptoms previously mentioned had disappeared.

Johnston et al. in 1951 reported further observations with similar clinical conditions.[2] Measurements of the B.M.R., protein-bound iodine and I-131 uptake were made at intervals before, during and after treatment with exogenous thyroid. The dosage ranged from 120 to 600 milligrams of thyroid daily. The period of observation extended from one to three years. Thyroid ingestion was stopped abruptly. The B.M.R. and P.B.I. fell rapidly below pre-treatment levels for one to three weeks, followed by gradual rise to normal levels in two to three months. In the few patients having I-131 studies, the initially suppressed uptakes returned to normal range within four weeks after termination of thyroid feeding. Subjective symptoms of hypothyroidism occurred in some patients, but all symptoms cleared in a short period of time. No mention was made of clinical evidence to suggest myxedema.

In 1951, Greer reported the effect of exogenous thyroid administration on the production of endogenous thyroid hormone by euthyroid subjects.[3] He used the 24-hour I-131 uptake to assess thyroid function. Physiologic amounts of thyroid were given, usually 120 to 180 milligrams daily, for short periods of time. Four of the patients had been taking 180 milligrams daily for several years. Twenty-four hour I-131 uptakes were determined previous to, during and subsequent to ingestion of desiccated thyroid. He found that marked suppression of I-131 uptake could be produced in one week with daily administration of 60 to 180 milligrams of desiccated thyroid in 93 per cent of his 47 patients. One patient required 540 milligrams for several weeks to reduce the I-131 uptake to hypothyroid levels. Abrupt withdrawal of the hormone resulted in a gradual return of the 24-hour I-131 uptake to pre-treatment levels within two weeks. An occasional patient required a longer period to revert to the pre-treatment range. In the four patients on 180 milligrams or more for several years, I-131 uptakes returned to euthyroid range as promptly as those on short-term therapy. No patient developed symptoms or signs of myxedema after stopping treatment. Greer concluded that no permanent injury to the thyroid gland resulted from prolonged exogenous thyroid ingestion in euthyroid subjects.

In 1954, Bartels and Higgins reported four cases in which prolonged thyroid administration was stopped abruptly.[4] All subjects were considered euthyroid when

therapy was instituted, as judged from the patient's history. One patient had taken 240 milligrams of desiccated thyroid daily for eight months. Cessation of treatment caused symptoms suggestive of hypothyroidism, but no clinical evidence supported this. After five months she was euthyroid clinically, and the B.M.R. and serum cholesterol were in the normal range. A second patient had been on 60 mg. of thyroid plus Lugol's solution for 18 months. When these were stopped some symptoms of hypothyroidism resulted but again no clinical evidence supported it. Within four months these symptoms had disappeared and she was considered euthyroid.

SUMMARY: A case is presented of primary myxedema occurring after cessation of prolonged thyroid therapy in what is presumed to have been an initially euthyroid individual. It is felt that long continued use of exogenous thyroid led to permanent atrophy of the thyroid gland. Since the possibility exists that continued use of desiccated thyroid can lead to irreversible damage to this gland, it is suggested that its prolonged use be restricted to those cases in which clinical and laboratory findings indicate a real need for replacement therapy.

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