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NUTRITIONAL FACTORS IN GRAVES' DISEASE *

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THAT marked grades of malnutrition may result from thyrotoxicosis has been long known. In 1893 it was that Friedrich Müller [1] noted the paradox of weight loss in the face of increased food intake and concluded therefrom that there must be in this disease an increased rate of katabolism.

Whether or not weight loss or general wasting will occur in Graves' disease depends on whether the appetite increase causes sufficient increase in the ingestion of total calories to offset the increased combustion. Compensatory hyperorexia we may call it. The bank balance, in other words, is determined by the relation of amounts deposited to those withdrawn. In Graves' disease we not infrequently encounter weight losses of as much as 50 pounds or more.

Not only, however, may thyrotoxicosis cause malnutrition, but lately it has come to our attention that malnutrition may cause, or precipitate, thyrotoxicosis.

A few years ago one of us (S. H.) was impressed with the number of patients with toxic goiter who gave histories of having started their thyrotoxic symptoms at the conclusion of a reduction program for obesity. An overweight person would go on a low calory diet and after having lost the desired amount of weight would increase the diet, but find that weight loss continued, perhaps at an accelerated rate. Along with this, nervousness, tremor and other symptoms of thyrotoxicosis would make their appearance. In some of these cases thyroid had been used to augment weight reduction, but in others, mere calory restriction.

Interest having been aroused in this sequence of events, we began to be on the lookout for such cases. They have turned out to be numerous. The total to date is 35. In 14 of these the prethyrotoxic weight loss was occa-

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sioned by reduction cures and in the remainder it was due to a variety of conditions such as restriction of diet in the treatment of ulcer, ulcerative colitis, diabetes and other diseases leading to malnutrition.

It seems to us that this series is too large not to be of significance. Episodes which activate thyrotoxicosis have long been recognized. Psychic traumata, prolonged infections, accidents or physiologic strains, such as puberty, pregnancy or the menopause, fall in this category. Now it seems that acute malnutrition can be added. How it operates, we are not prepared to say, but it is not known how any of the others operate for that matter. It may be associated with changes in blood chemistry or with vitamin or protein deficiency.

In approaching the problem of the inroads which nutritional factors may play in the production of the clinical picture in Graves' disease it will be convenient to distinguish between what we may term general malnutrition due to total negative calory balance and more specific types of malnutrition, or deficiency due to absolute or relative shortage of specific dietary elements. Of general malnutrition, save insofar as it constitutes an indication for treatment, I need say nothing further, it being thoroughly familiar. Certain specific or special types of malnutrition, on the other hand, I believe can be discussed with some profit.

In this group of special forms of malnutrition let us consider first the *musculature*. Myasthenia is a common symptom in toxic goiter. Plummer,[2] Lahey [3] and others have devised diagnostic tests to bring this symptom or sign into evidence. Actual muscle atrophy occurs less commonly, but in certain cases is very striking. Some years ago we [4] reported a case in which there was a picture closely resembling progressive muscular atrophy in an advanced stage. The patient was also found to be suffering from toxic goiter. Cure of the latter by surgery was followed by recovery of the muscles. This is the most marked example of muscle atrophy we have seen in toxic goiter, but very often we encounter lesser grades with atrophy of the temporal, interossei or shoulder girdle muscles. Such atrophy is usually present in a patient who has been severely thyrotoxic over a long period of time and is therefore of prognostic significance. The exophthalmos, in certain types at least, may be a local expression of general muscle weakness. The degenerative changes in the striated recti muscles of the eye and the normal appearance of the smooth muscle of the eye, described by Askanazy,[5] suggest a muscle imbalance which may explain exophthalmos. On the chemical side there is a disturbance in creatinine metabolism with creatinuria and, as shown by Shorr and Richardson [6] a decreased creatine tolerance test.

The skeleton in certain cases shows marked decalcification. This is properly to be classed under specific forms of inanition. Aub and his coworkers [7] in 1929 showed that the thyroid hormone causes a marked increase in the rate of withdrawal of calcium and phosphorus from the skeleton, without, however, in contrast to the parathyroid hormone, any sig-

nificant change in the blood levels of these elements. It is indeed in thyrotoxic persons that the highest levels of calcium and phosphorus excretion are to be found. This high excretion is a specific effect of the hyperthyroidism, not merely a feature of elevated general metabolism, for Aub et al.

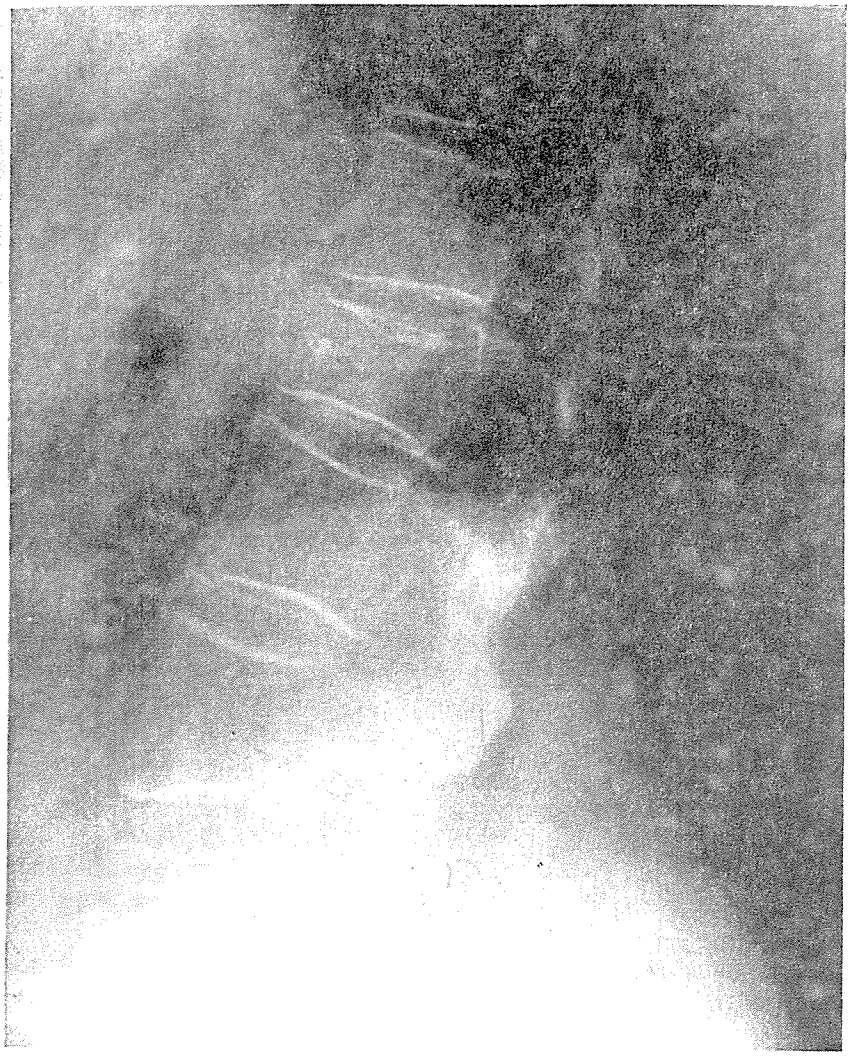

FIG. 1. Osteoporosis with compression fracture of a lumbar vertebra following thyrotoxicosis.

found in cases of fever and leukemia with marked elevation in general metabolism, normal elimination of calcium.

The rate of decalcification of the skeleton in thyrotoxicosis will depend not alone on the rate of calcium loss, but upon the intake. Although the

increase in calcium excretion is great, it usually takes a long time for osteoporosis to become apparent. Patients with acute forms of toxic goiter usually get treated successfully before any marked grade of osteoporosis has been produced. The increased appetite probably causes an increased ingestion of calcium and offsets to some extent the process of bone wasting.

In a few cases of long-standing thyrotoxicosis, however, we have observed very marked osteoporosis, both in the spine and in long bones. In some of these cases symptoms have resulted, taking the form of deep aching pain in the extremities or back, and in one remarkable case there was a pathologic fracture of the body of a vertebra. This patient had been treated by us [8] in 1919 for mild Graves' disease, then of three years' duration, by means of roentgen-ray therapy. She had improved somewhat, but, since she had not recovered completely, a subtotal thyroidectomy was done in March 1922. After that she was fairly well until August 1931, when while driving her car she was seized with sudden knife-like pain in the region of her lumbar spine. This persisted intensely and continuously for one and a half hours, then upon motion for three to four weeks, and finally as tenderness in the lumbar region until December 1, 1931, when she returned to the hospital for study. Roentgen-ray examination showed marked decalcification of the entire spine and pelvis and a compression fracture of the first lumbar vertebra. The body was half its natural thickness and was irregular and mushroomed.

The patient was put on a high calcium diet with 5 drachms of calcium glycerophosphate and 30 drops of viosterol per day, under which regime her symptoms were quickly relieved. We have followed her since and although by roentgen-ray there is no great evidence of recalcification, the symptomatic result has been excellent.

Another striking example (a private patient of J. L.) is that of a woman of 58, who became bedridden as a result of long-standing thyrotoxicosis and cardiac failure. She showed a marked degree of osteoporosis. As a result of her semi-sitting position, she developed a dorsal kyphos and flaring of the lower ribs. The latter were exquisitely tender to pressure.

With removal of the thyroid, she has gradually assumed her normal activities and her heart is well compensated. Her kyphos has straightened considerably, the flaring of the rib margins is less and tenderness has disappeared. She is on an adequate diet with emphasis on milk, vegetables, cheese and meat.

In cases of long-standing thyrotoxicosis then, or even past thyrotoxicosis, in which pains in the spine or extremities are complained of, the possibility of osteoporosis should be given consideration and, if found, suitable treatment by a recalcifying regime instituted.

A shortage of iron is suggested in an impressive number of patients with thyrotoxicosis by the presence of nail changes of the sort characteristic of hypochromic anemia—that is to say spoon-shaped, brittle, lustreless and

longitudinally ridged—together with smooth tongues and gastric achlorhydria. Even when these signs are well marked, one usually finds but a slight degree of anemia. One patient recently, however, a woman of 58, presented symptoms of thyrotoxicosis, minimal eye signs and goiter, basal metabolic rate at the level of about plus 40 and along with all this, smooth tongue, spoon fingernails, achlorhydria, red count of 3.6 million and hemoglobin of 45 per cent. She was placed on both iodine and iron. She made a characteristic and good response symptomatically and metabolically to iodine, her basal metabolic rate falling to standard in nine days. She was continued on iodine for a year at the end of which time her basal metabolic rate was normal and she was symptom-free. The anemia also, in less than a month, rose to a red cell level of 6 million and hemoglobin of 75 per cent. Iron was then omitted. We presume that iron was responsible for the result. At the end of a year her blood picture showed a red cell count of 4.8 million and hemoglobin of 85 per cent.

Of late we have been interested in the question of avitaminosis in thyrotoxicosis. In the case of vitamin B_1, at least, Cowgill and his co-workers [9] and others have shown that the need for vitamin increases in parallel fashion to the metabolic rate. Thus a person who had been receiving an adequate amount of vitamin B_1 during health might develop a deficiency on the same vitamin intake if he became thyrotoxic.

In view of these facts, two of us (S. H. and J. L.) administered vitamin B_1 in the form of Harris Yeast Powder to a small series of thyrotoxic patients and found that although it caused no change in basal metabolic rate, there was, coincident with its administration, a marked improvement in appetite and consequent gain in weight. Since that time we have employed treatment with yeast routinely in the preparation of thyrotoxic patients for operation. Although it is too early to draw a conclusion based on statistics of the effect of this maneuver on operative mortality, it is becoming increasingly clear that it is of value in improving general nutrition through the increase it causes in appetite. Its use is chiefly indicated in those patients whose appetite increase has been inadequate.

Shortage of vitamin B_1 may also play a more specific rôle in thyrotoxicosis. Weiss [10] has shown that in alcoholics with cardiac insufficiency avitaminosis B_1 may play a rôle. It is quite possible, as he suggested to us, that it may also play a rôle in the cardiac insufficiency of thyrotoxicosis. Certainly one is more apt to see cardiac insufficiency in the malnourished than in the well nourished thyrotoxic patient. We recalled four recent striking examples as soon as Weiss mentioned the matter to us. One of these also had a moderate hypochromic anemia. Since iodine produces benefit in nearly any thyrotoxic patient, and since it is our practice not to withhold iodine in the thyrotoxic patient with cardiac insufficiency, we cannot say with certainty how much, if any, benefit to the heart vitamin B_1 administration has conferred per se. It will only be after large numbers have been treated that a dependable conclusion can be drawn.

Evidence of shortage of other vitamins has not been impressive. Scurvy we have not seen, but in one recent case in which thyrotoxicosis followed a grossly inadequate diet, night blindness became a striking symptom. It cleared up directly when an adequate diet was received. It may be interpreted as evidence of a shortage of vitamin A.

The chief point which we wish to make about all these matters, is that there is much more to the preparation of the thyrotoxic patient for operation than mere iodinization. The preparation, which we believe should be under the direction of the physician, but observed also by the surgeon, should include a positive attempt to improve general nutrition and relieve any specific deficiencies insofar as this is possible. Sometimes it will be the part of wisdom to defer operation, even though a good iodine response has been obtained, in order to meet more adequately a nutritional indication. The following case is a good example.

A 43 year old widowed supervisor of nurses, who had acute rheumatic fever at the age of 28, followed by mitral stenosis, entered the medical ward February 16, 1936, with a story that for two years or more she had been running herself ragged, eating very little, taking a great excess of tea and coffee, sleeping badly, having marked anorexia and losing in 18 months some 25 pounds. She had been a thin, frail woman to start with and after the loss mentioned was markedly malnourished.

For two months prior to entry in addition there had been marked nervous irritability. At the time of entry she showed marked hyperirritability, slight bilateral exophthalmos, marked tremor, warm moist skin, tachycardia of 140, slight diffuse enlargement of the thyroid and a basal metabolic level of plus 30. Her heart showed the murmur characteristic of mitral stenosis, with normal rhythm. She weighed 106 pounds. Her tongue was sore and atrophic, but there was no anemia. Her red count was 5.0 million and her hemoglobin 90 per cent.

At this time one of us (J. H. M.) made a note to the effect that she undoubtedly had exophthalmic goiter and that this appeared to have followed the development of a state of malnutrition, also that although her thyrotoxicosis was mild she was a poor risk for surgery on at least three counts: (1) because she had the complication of chronic rheumatic heart disease; (2) a very unstable psyche; and (3) a very severe grade of malnutrition.

She was given iodine and made a good response as far as symptoms went and her basal metabolic rate dropped to a normal level. Instead of operating at this point, however, it was felt wiser to send her home on iodine and high calory, high vitamin diet. She was given vitamin B in the form of Harris Yeast Tablets.

On March 19, 1936, she reëntered, having gained seven pounds and become less nervous. A subtotal thyroidectomy was done on March 27, which she went through uneventfully and on April 4 her basal metabolic rate was minus 1.

She did well for about eight months, but then developed a mild recurrence of thyrotoxicosis which threw her heart into fibrillation. Iodine controlled the thyrotoxicosis adequately, but the fibrillation continued. In January of 1937 she went through a sharp attack of bronchopneumonia without thyrotoxic exacerbation or gross cardiac decompensation. Although it cannot be proved, our guess is that her course through thyroidectomy would have been far less smooth if she had been operated upon immediately after the establishment of iodinization.

In conclusion, we should like to warn physicians and patients against too vigorous reduction cures for obesity; thyrotoxicosis may be induced thereby; and in the preparation of the thyrotoxic patient for operation we should like to urge that the possibility of nutritional disturbances be considered and, if found, that an attempt be made to correct them.

The manifestations of nutritional disturbance, which may be found in thyrotoxic patients, include, as well as general inanition, changes in musculature, skeleton, hematopoietic system and very likely in the heart and psyche. While these findings may be merely incidental and their causal relationship to thyrotoxicosis ascertainable only by an extensive statistical study, we feel that they are of sufficient frequency to warrant consideration in the complete management of patients ill with Graves' disease.

The methods of correcting these defects include not only a high calory diet for relieving general malnutrition, but one high in vitamins and minerals as well. Vitamin B_1 may be of special significance as having appetite increasing proclivities, and also perhaps some special beneficial action upon cardiac function. We are now using Harris Yeast Tablets for this purpose. Pure vitamin B_1 preparations can be used when the indication seems urgent.

For the high calory intake the chief dependence should be placed upon carbohydrate. Excessive protein is undesirable because through its specific dynamic action protein raises metabolism. Carbohydrate, on the other hand, in large amounts is insurance against depletion of the glycogen stores of the liver and thus safeguards that organ. With regard to fat, there is no special indication that we know of. Fat may be given to whatever extent the patient's appetite demands.

We feel that there is good reason for regarding the malnourished thyrotoxic patients and the psychotic as well as those with cardiac insufficiency as poor operative risks. It is wise to get their weight curves at least started upward before permitting operation. This sometimes will require several weeks of pre-operative medical treatment. There is a tendency to rush thyrotoxic patients too fast to the surgeon. It is the physician's responsibility to see that this be not done. It is also his responsibility to avoid unnecessary delay in the securing of relief of thyrotoxicosis by operative intervention. Although it is desirable that he have certain definite routine procedures—the use of iodine, for example—it is also desirable that he study

each case as an individual problem and plan his actual therapeutic program to meet individual indications.

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