

## SOME CLINICAL CONSIDERATIONS OF BASAL METABOLISM

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By metabolism, we mean the sum total of chemical change occurring in the organism. This includes not only processes of oxidation and reduction, but also synthesis and degradation of a large number of chemical compounds. Our total knowledge of the finer metabolic changes is meager and even the knowledge of the metabolism of hormones which have been known in relatively pure or crystalline forms for some time is not understood in any degree of completeness. Of the many measures of metabolism, the basal metabolic rate has become one of the most common and for that reason is of great practical significance. This consideration of the basal metabolic rate is for the main purpose of emphasizing the simple fact that it is a symptom and is of significance only in consideration of the total clinical picture. The metabolic rate is as much a symptom as the pulse rate or body temperature and not more specific.

### HYPERTHYROIDISM

The typical case of hyperthyroidism is always associated with hypermetabolism. In Grave's disease, remissions may occur, however, and at such times the basal metabolic rate may fall to normal. It is for this reason that one other factor is more important in the diagnosis of hyperthyroidism than an elevated basal metabolic rate, namely, a good history. In some of these cases, the presence of goiter, the facial expression so typical of the disease, some tachycardia, tremor or skin changes usually lead to the diagnosis. Iodine remissions may bring about the same changes. In some instances, it is necessary to observe the patient repeatedly. Cases of hyperthyroidism with the basal metabolic rate below the normal have been reported by Duncan Graham and Roger Morris<sup>1</sup>. Such patients have shown the usual improvement after thyroidectomy. Fortunately for us as clinicians, the opposite condition is more frequently true, however; i. e., in chronic low grade hyperthyroidism and in atypical hyperthyroidism, such as auricular fibrillation or cardiac failure of thyroid origin, the basal metabolic rate is usually high.

There are a few conditions which may closely simulate clinical hyperthyroidism and may be associated with elevated metabolic rates. The most outstanding of these is neurocirculatory asthenia. This condition occurs chiefly in young people and is not infrequently accompanied by a goiter. The basal metabolic rate is not consistently high, however, and although it frequently varies from plus 14 to plus 22 per cent, normal levels may be found subsequently. High readings in such cases

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are probably not due to gross errors in technic but are to be related to the very unstable state of the sympathetic nervous system. The patient is frequently of the neurasthenic type although the condition is seen in otherwise strong, athletic individuals. The pulse is extremely variable, sinus arrhythmia is present, sighing is common, the hands are cold and moist, and a glove type of cyanosis, purple discoloration, or mottling may be seen. The pulse can frequently be slowed markedly by acute flexure of the trunk (Erben's phenomenon) or by pressure over the eyes or the carotid sinus. Flushing and blushing are common and excessive perspiration is present in the hands, feet, and axillae.

Hypermetabolism occurs in cases of cardiac decompensation but the condition in such instances is not usually basal because of dyspnea. There are, however, instances of arterial hypertension in which, as far as can be determined, basal conditions are obtained and yet the metabolic rate is high. These are usually cases of malignant hypertension with retinal edema or exudation about the vessels and perhaps retinal hemorrhage. Thyroidectomy in such cases may not lower the basal metabolic rate below normal. It is well to remember that a diastolic blood pressure of over 100 mm. of mercury is rare in hyperthyroidism.

Certain diseases of the blood, especially leukemia, may be associated with a high basal metabolic rate.

### HYPOTHYROIDISM

If the thyroid gland is completely removed, the basal metabolic rate falls to minus 40 or minus 45 per cent and the clinical evidences of myxedema become apparent. Under other circumstances, however, the basal metabolic rate may fall to lower levels with none of the common clinical signs of thyroid failure.

The question as to how much the thyroid gland is implicated in the production of low basal metabolic rates without myxedema is not clearly settled. Certain facts appear to indicate that it may be little if at all involved. True myxedema can be controlled well with relatively small doses of thyroid, whereas patients with non-myxedematous hypometabolism may tolerate large doses with little change in the basal metabolic rate and relatively no change in symptoms. The blood cholesterol is usually not elevated in these cases as it is in myxedema. The clinical features differ also.

In true hypothyroidism arising from partial or complete destruction of the thyroid gland from disease, removal, or both, when the basal metabolic rate falls below minus 20, the characteristic nonpitting edema usually appears. In addition, there is a characteristic group of symptoms. Since there are many cases in which the basal metabolic rate is low in the absence of these symptoms and in order to decide whether or not

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the case is one of hypothyroidism, it is necessary to be thoroughly acquainted with these symptoms and signs. The relative frequency with which they occur was judged from a study of 194 cases of hypothyroidism reviewed recently

The chief complaints were numerous and varied, as many as 25 symptoms being listed. The commoner ones, in order of their frequency, are:

<i>Complaint</i>	<i>Per cent</i>
Lack of endurance .....	93
Lack of energy .....	89
Tendency to nervousness .....	79
Drowsiness .....	78
Diminished memory .....	68
Numbness and tingling of the hands and feet .....	67
Stiffness of the joints .....	48

Constipation occurred in practically 50 per cent of the cases and, with this, abdominal pain may be a presenting symptom. Mild abnormalities of menstruation were common and were listed in 30 per cent of the women affected before the age of 40. Very minor changes which ordinarily would not be considered entirely abnormal were also listed. Diminution in sexual potency was not uncommon.

The signs which are so characteristic are not always very obvious. The patient's own observations frequently must be carefully considered and elicited by leading questions. Even in many of the mild cases, some edema is present. It was found in 67 per cent of our cases, occurring in the lower lids, the feet, and hands more frequently than elsewhere. Of the 194 patients, 48 per cent were underweight and 18 per cent overweight. The pulse rate was below 60 at rest in only 15 per cent of the cases. Red cell counts of below four million were present in 18 per cent. When anemia occurs, it is frequently accompanied by achlorhydria and this, together with the paresthesia of the extremities, may simulate pernicious anemia, especially since macrocytosis may occur. Achlorhydria was present in 22 per cent of the cases. The anemia of hypothyroidism responds better to iron plus thyroid therapy than to thyroid alone. The heart may be enlarged in all diameters as seen by roentgenograms. Electrocardiographic changes are common, the principal changes being flattening and inversion of the T-waves, occasionally prolongation of the PR interval, or QRS complexes. Mild albuminuria may occur and in outspoken myxedema the condition is often mistaken for nephritis.

In definite uncomplicated myxedema, the blood cholesterol is invariably elevated above 220 mg. per 100 cc. In such cases, thyroid medication gives almost complete relief of the symptoms.

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In infants and children, the presence of hypothyroidism is not uncommon. Here the basal metabolic rate is not a very useful diagnostic measure and it is valuable to bear in mind that childhood hypothyroidism does not produce the clinical appearance of cretinism. In the milder cases, however, dentition may be retarded. In many instances, the mentality is affected but little and school work may be good. The growth rate tends to be diminished and a very useful sign is the slowness of the appearance of centers of ossification and delayed epiphyseal union. The blood cholesterol is usually high.

There is a clinical group of cases of subnormal mentality in children who come for examination in order that hypothyroidism may be excluded. Sometimes, there are distinct evidences of birth injury, but this may not be apparent. Large body size and obesity are common and, in children over ten years of age, low basal metabolic rates may be found. In these cases, if the bone age is normal, dentition good, and the blood cholesterol within normal range, thyroid medication is of little or of no value.

There is a much larger group of adults who have hypometabolism with little or no edema. Here, the cases range all the way from those patients with typical, mild symptoms and signs of hypothyroidism to individuals of the neurasthenic type who complain of little but fatigue. In many such cases, a definite diagnosis of hypothyroidism may remain questionable. In the majority of cases, improvement on thyroid therapy parallels in a general way the clinical evidence of hypothyroidism and not the level of the basal metabolic rate.

Exophthalmos, such as is seen in thyroid disease, is not infrequently associated with depressed basal metabolic rates. The fact that exophthalmos can appear or increase while the basal metabolic rate is rising and in the presence of hyperthyroidism, and the fact that it can appear or increase while the metabolic rate is normal or low indicates that the rate of metabolism in itself is not directly connected with the degree of exophthalmos. In patients with progressive exophthalmos, there is frequently a marked edema of the lids whether or not the basal metabolic rate is low. This may also affect the conjunctiva and there is congestion of the conjunctival vessels. In extreme cases, there may be ulceration of the cornea, extreme engorgement of the orbit, and enucleation may be necessary. It is remarkable that, in the presence of progressive exophthalmos postoperatively where the basal metabolic rate is minus 20 to minus 25 per cent, signs and symptoms of hypothyroidism may be entirely lacking. It is probably wise in such instances to give enough thyroid to maintain a relatively normal basal metabolic rate. Whether excess of thyrotropic hormone is intimately connected with the production of such exophthalmos is not known.

Pituitary abnormalities may cause marked changes in metabolism. In acromegaly, goiter is present in about 75 per cent of the cases and hyperthyroidism in some degree occurs in the active phase of the disease in the majority of these. Occasionally, very severe hyperthyroidism with basal metabolic rates increased to 100 or more may be seen. In the later stages of the disease, the metabolic rate falls below zero but the typical evidences of hypothyroidism do not occur. Thyroid medication is of limited value.

In the chromophobe adenomata of the pituitary, low basal metabolic rates are the rule. Frequently, they fall to minus 30 per cent, again without the typical evidences of hypothyroidism. The same may be true in craniopharyngiomas.

The symptom complex usually designated Fröhlich's syndrome is of frequent occurrence in boys and girls at about the age of puberty. In these cases, depressed basal metabolic rate is common. It is not infrequent to find rates ranging about minus 25 per cent. In the typical case, the child is obviously obese and the skin is of fine texture. The obesity is chiefly about the breasts, abdomen, and hips. The genitalia are retarded in development. Dentition is usually excellent and the bone age and blood cholesterol are normal. In the majority of such cases, the advent of puberty is followed by a return to normal conditions but this does not necessarily occur. Thyroid in small doses can be used to considerable advantage in conjunction with limitation of diet. The genitalia are frequently judged to be underdeveloped, due to the large accumulation of fat at the pubis, but simple reduction in weight is often all that is necessary to bring about what appears to be normal genital development. The diet itself does not need to be greatly restricted in most instances, and good results are consistent when the diet is reduced to one calculated to contain 20 per cent more than the basal caloric requirement for the ideal weight of the child. When the development of the genitalia tends to remain retarded, the persistent use of pregnancy prolan in doses of about 200 units three times a week will be followed by gratifying results in most instances if the treatment is continued for three or four months or more.

In pituitary cachexia, the basal metabolic rate falls to levels lower than those seen in myxedema. The patients have a characteristic pallor but the skin appears to be waxy and transparent. It may be slightly dry but no edema appears. There is a tendency to alopecia but it affects body hair much more than the hair of the scalp. Impotency in males and amenorrhea in females is an almost constant finding. Extreme emaciation usually leads to death but patients with severe cachexia following pituitary surgery may live for many years. Treatment of the condition is extremely difficult. Clinical results do not indicate that

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suitable pituitary extracts are available in sufficient strengths. Until they are obtainable, normal nutrition is the chief therapeutic measure. Sporadic cases have been reported as cured following the use of antuitrin or antuitrin-S but the fact that improvement remained after treatment was stopped throws some doubt on the validity of the diagnosis.

Gonadal disease may have a bearing on the basal metabolic rate. In 11 male castrates, the average basal metabolic rate was minus 12 per cent. Gain in weight is consistent with the low metabolic rate. In eight female castrates, the average basal metabolic rate was minus 16 per cent. The low basal metabolism is not uncommon and signs of mild hypothyroidism are seen frequently at the female climacteric. When the metabolic rate is low and the symptoms are those of hypothyroidism, this can be treated as a separate entity entirely apart from whatever other endocrine disorders are present except for one fact, i. e., the sympathetic nervous system is excessively irritable and stimulated at this time and since thyroid produces further stimulation it must be used with considerable caution if the patient is to be kept comfortable. The use of ovarian hormone in the female or the continued use of large doses of testis hormone in the male will not raise the basal metabolic rate to a degree of clinical importance.

Thyroid deficiency, on the other hand, may be the cause of excessively low testicular function. We have seen cases of impotency in the male in relatively thin individuals who had basal metabolic rates of minus 25 or minus 30 per cent and showed unusually low readings for assays for testis hormone in the urine. In one individual, a physician of 45 years, the amount of testis hormone in the urine was between zero and five international units per day, whereas the normal range usually lies well above 20. His basal metabolic rate was minus 27 per cent and there were some symptoms of hypothyroidism. Injection of testosterone sufficient to bring the testis hormone content of the urine to within normal ranges caused disappearance of impotence, and sexual vigor improved to about 75 per cent of normal. The basal metabolic rate, however, did not rise. Subsequently, when this treatment was stopped and symptoms were still present, it was found that a greater amount of symptomatic improvement could be obtained by the use of thyroid alone. In addition, after thyroid had been used for a month, the amount of testis hormone in the urine was within normal range, reaching 44 units in a 24 hour specimen of urine. This, of course, could not be ascribed to the effect of the testis hormone previously injected. When sterility is associated with hypometabolism, a cure may follow the use of thyroid.

When disorders of menstruation accompany distinct clinical evidences of hypothyroidism and a low basal metabolic rate, clinical improvement, in the majority of cases, follows the administration of thyroid

without other treatment. It is more remarkable that, in many women with menstrual disorders in the absence of other signs of hypothyroidism, the administration of thyroid alone may be followed by clinical improvement.

In Addison's disease, the low basal metabolic rate can probably not be explained on a satisfactory thyroid basis and may be related directly to nutrition. It is possible that a lack of adrenal cortical hormone may play a rôle but there is no definite evidence to indicate that such is the case.

Low basal metabolic rates are common in cases of atrophic arthritis. It is interesting, however, that on taking an unselected group of 31 cases of atrophic arthritis in which determinations of the basal metabolic rate had been made, the average rate in the whole group was only minus five per cent. Although such arthritis can in no way be ascribed to thyroid failure, small doses of thyroid may be a useful adjunct in the treatment when the metabolism is low.

In true lipid nephrosis, the basal metabolic rate is usually distinctly depressed, rates of minus 25 to minus 35 per cent being common. The mechanism of this depression is not known. It has been suggested that large amounts of thyroid hormone may be lost with the proteins in the urine. In such cases, the basal metabolic rate may be excessively difficult to raise by the use of thyroid and questionable clinical improvement results. In some cases, diuresis increases following thyroid administration.

Hypersecretory rhinitis will sometimes improve remarkably following thyroid administration.

Nutrition has a very marked influence on the basal metabolic rate. In extreme obesity, however, it is very unusual to find excessively low basal metabolic rates. Von Grafe believed in the Theory of "Luxus Konsumption," that is, that the metabolic rate could be increased in proportion to the amount of food taken and that in a normal individual this explained the fact that obesity did not occur while following a diet which was not carefully controlled. He recognized, however, that if this theory were accepted, such a control of metabolism must at times break down because otherwise there would be no cases of obesity. It appears to have been definitely proved that, when nutrition is normal, the basal metabolic rate tends to remain normal but if the food intake is high, the basal metabolic rate is not stimulated beyond normal range, the excess of food being stored. In undernutrition, however, the basal metabolic rate falls and we, as clinicians, frequently unwittingly change it by diets or do not meet a given basal metabolic rate with sufficient nutrition.

In cases of fever, the patient may be kept on a low or average intake while the basal metabolic rate may be remarkably increased because

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of the fever. On the other hand, considerable depression of the basal metabolic rate may be produced by causing undernutrition due to such diets as are frequently prescribed in hypertension or obesity.

It is important to remember that simple fasting alone may lower the basal metabolic rate to minus 30 per cent or below. Benedict's<sup>2</sup> famous experiments in fasting showed that his patient, Levanzin, had a basal metabolic rate of minus 31 per cent at the end of three weeks' fast. Benedict has also shown that groups of students who are maintaining stationary weights at a caloric intake of about 3000 calories per day could also maintain stationary weights on an intake of 1900 calories per day. Such a weight balance was made possible because the basal metabolic rate fell following the use of lower caloric intakes for a period. Clinically, such a mechanism explains the fact that certain individuals lose weight rapidly when a limited caloric intake is begun but stop losing weight after a few weeks even though the same diet is maintained, the metabolic rate having fallen meanwhile to a point which balances the low intake. In such cases as this, it is frequently imperative to maintain a normal basal metabolic rate by the use of thyroid if it is desirable to continue the reduction in weight at the original rate and by means of the same diet. Where reduction of very large amounts of weight is required, it is also necessary to bear in mind that the basal caloric requirement for a very stout individual is much more than that for the same individual after the weight has been reduced, due to change in total bulk of the individual and granting that the metabolic rate is still normal.

Anorexia nervosa is a term applied to a group of symptoms resulting from psychic disturbances and leading to starvation. The clinical characteristics are sufficiently constant to warrant its acceptance as a disease entity. In such individuals, the psychic disturbance is followed by an extreme loss of appetite, marked decrease in food intake, inanition, and basal metabolic rates frequently as low as minus 40 per cent. A basal metabolic rate of minus 76 per cent was found by Wittkower<sup>3</sup> in such a case. The clinical features of hypothyroidism are not present, although the individuals may be intolerant to cold. The condition usually occurs in women between the ages of 18 and 35 years. Amenorrhea is present in almost all cases. Symptoms of functional disturbance of the gastro-intestinal tract are very common. Secondary anemia of consequence is usually not present although it may be overshadowed by hemoconcentration. These cases are frequently mistaken for Simmonds' disease which, it appears to me, has become an unduly popular diagnosis in the past few years. Since the differentiation between anorexia nervosa and true Simmonds' disease is very difficult, it may easily be that some of the cases reported as Simmonds' disease are really primary psychic disorders.



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In anorexia nervosa, spontaneous improvement and recovery may occur and the menses return. I have recently observed a case in which a girl of 18 complained of extreme loss of appetite, amenorrhea, and loss in weight. The only distinctly physical abnormalities, apart from her weight, were indicated by the glucose tolerance test which showed potential diabetes mellitus, and the basal metabolic rates were minus 42 and minus 40 per cent. Her height was sixty-four and one-half inches and her weight varied at about 90 to 95 pounds. Between 1932 and 1934, various forms of treatment were tried, including attempts to have her use a high caloric diet, insulin, large amounts of salt and water, antuitrin, antuitrin-S, prephysin, pituitrin, enforced rest, large doses of vitamins, and a thorough trial on adrenal cortical extract (eschatin). When the treatment was finally stopped in February, 1935, her weight was 95 pounds and she felt no better. When she was seen in May, 1937, at the age of 21 years, her weight was 159 pounds and she appeared energetic and in excellent health. The breasts had developed normally; the nipples, however, were quite small, and the hips were unduly large. The uterus was somewhat underdeveloped and there was still amenorrhea.

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