THE THYROID GLAND IN HYPOGLYCEMIA*

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In the maintenance of body economy it is apparently necessary that the level of sugar in the blood should not be allowed to fall too low. When this does occur, either spontaneously or following the injection of insulin, certain clinical symptoms develop that have been explained as being due to a sudden excessive secretion of adrenalin. Our clinical experience in patients with spontaneous hypoglycemia has tended to confirm this observation on numerous occasions. Apparently, the action of adrenalin under such conditions is to mobilize sugar from the liver, so that the hypoglycemia can be relieved, and in so doing to produce other adrenalin effects in the body with ensuing clinical symptoms. That the adrenal medulla is not the only structure capable of producing an increased glycogenolysis is well known and will be discussed in detail subsequently. Certainly the thyroid gland has such a function and because of the fact that increased activity of the thyroid is generally associated with an increase in glycogenolysis, it has occurred to us that there may also be times in which it may be necessary for the body to utilize the secretion of the thyroid gland in hypoglycemia to maintain homeostasis. With this conception in mind the following case reports are presented.

Case Reports

Case 1.—A. G., white, male, age 36, was admitted to the St. Louis City Hospital November 6, 1933, with the complaints of nervousness, tachycardia, dizziness and attacks of staggering while walking. His family and previous personal history were quite irrelevant other than that in 1917, following an attack of mumps, the right testicle underwent atrophy, and that he had contracted both gonorrhea and syphilis in 1920. Treatment for the latter was undoubtedly inadequate. He had been only an occasional user of alcohol, but is a heavy cigarette smoker and his consumption of coffee has been rather excessive.

Shortly after the World War the patient began to notice an increase in nervousness. This at first was extremely vague and the patient was unable to describe it accurately. It consisted for the most part in occasional dizzy spells and a sense of palpitation, none of which were severe enough to produce any incapacity. About four years before his admission into the hospital vague digestive disturbances began to appear, evidenced chiefly by constipation, distention and belching after meals. Shortly after this he began to have spells of smothering in which it was difficult to get his breath. This was followed by a marked increase in the frequency and degree of the attacks of dizziness. At times while walking, the patient would have such an attack during which he would stagger in a drunken fashion, not losing consciousness, but at the same time being com-

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щело дисориентирован. Парадизция стала заметной. В этот период времени не было истории гибели или резкой боли, а также не было заметно каких-либо аномалий в отношении равновесия.

**Physical Examination.**—Он казался особенно беспокойным. Зрачки были нормальными и реагировали на два вида света и аккомодацию. Было заметно небольшое эксфалмиоз, связанное с ложной мишенью. Тонкость языка была атрактическая. Ректальный динамик был нормальным. Все рефлексы были излишне усилены и положительная Бабинский была заметна на правой стороне. Рефлекс Гардона и Оппenheim, хотя и были отрицательными. Слабый тремор был заметен, когда пальцы были вытянуты. Парикмахерский волос был обилиным и густым.

**Laboratory Data.**—Спинной мозг был полностью нормальным. Он содержалше шесть клеток, и коллоидное золото было отрицательно. Кровь и спинномозговая жидкость были нормальными. Уретропатография была отрицательной; содержание непротеинового нитрида было 37 мг процента, гемоглобин 85 процента, и кровь и белая кровь были нормальными. Рентгенологические исследования свода черепа показали наличие нормального сеффа и отсутствие каких-либо признаков внутричерепного кровотечения. Эти результаты, соответственно, показывали нормальные данные.

Базальный обмен на двух определениях был +42 и +37 соответственно.

Иммануелм следующего после своего первого базального определения, он внезапно стал дисориентированным и вошел в атаку, в которой он был автоматически совершал движения примерно за три минуты. В отличие от его нормального состояния. Было проведено определение сахара крови на этот период (14 часов голодания) и оно показало низкую величину. Сахарный тест после еды следующего за инъекцией глюкозы был низким. Сахарный толерантный тест был проведен следующего за инъекцией глюкозы 1 граммон в пересчете на килограмм веса, его результаты представлены в табл. I.

**Table I**

<table>
<thead>
<tr>
<th>Fasting</th>
<th>30 Minutes</th>
<th>One Hour</th>
<th>Two Hours</th>
<th>Three Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>72</td>
<td>117</td>
<td>96</td>
<td>72</td>
<td>62 (11/17/33)</td>
</tr>
<tr>
<td>66</td>
<td>133</td>
<td>100</td>
<td>71</td>
<td>47 (11/20/33)</td>
</tr>
</tbody>
</table>

Несколько сахарных тонагенов находились в диапазоне от 60 до 80 мг процента. Все эти определения были сделаны согласно Фолин-Уо-методу; истинная концентрация сахара была бы примерно на 20 мг процента ниже.

Несколько более дисориентированным пациентом, было принято решение о его хирургическом лечении. Рациональное для этого решение будет рассмотрено в обсуждении случая.

**Operation.**—November 11, 1933. Через левую прямую разрез была проинсирована гастроциклеская связка. Без каких-либо признаков, особенно на правой стороне, была удовлетворительная. После размежевания передней границы, желудок был вправлен и поверхность передней поверхности вновь была обнаружена, как нормально. Было проведено исследование аденальных желез, которое не обнаружило признаков увеличения. Это исследование, особенно на правой стороне, было неудовлетворительным. Было решено произвести подкожную резекцию поджелудочной железы в порядке удаления части изолирующего ткани, которая являлась железа, секретирующая инсулин. Было выполнено удаление в области таза и основания тела. Струйка поджелудочной железы была сшита, а тяжесть смылась. Абдоминальная рана была закрыта в два слоя. Послесurgicalный период был необычным. Следующий за несколькими днями и после удаления, оставался нетелесно. Иммануелм был дезориентированным, и его гетерохрония характеризовалась периодом после облучения и его удаления. Это также результат имеющихся данных о коже.

**Pathologic Examination.**—**Gross:** Поджелудочная железа не обнаружила признаков опухоли и ткани были нормальными. **Microscopic** examination подтверждало, что, размеры в незначительной степени, ваккуолизация, гиалинизация и синусоиды. Было обнаружено большое количество крови в пропорции альфа-клеток (Доктор Джеймс О'Лэри).

**Postoperative Course.**—Сахар в крови был повышен, со временем, постепенно, стал нормальным. Через два-три недели стало ясно, что....
thyroid gland was decreasing in size and the eye signs were beginning to recede. A basal metabolism determination at the time of the patient's discharge from the hospital on December 29, 1933, showed it to be zero. An examination to determine his sugar tolerance on January 10, 1934, gave the result as shown in Table II.

**Table II**

**SUGAR TOLERANCE DETERMINATION TWO MONTHS POSTOPERATIVE**

<table>
<thead>
<tr>
<th></th>
<th>Fasting</th>
<th>30 Minutes</th>
<th>One Hour</th>
<th>Two Hours</th>
<th>Three Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>80</td>
<td>190</td>
<td>235</td>
<td>173</td>
<td>80</td>
</tr>
</tbody>
</table>

The patient stated that most of the symptoms (including the manifestations of goiter) of which he complained had completely disappeared. No iodine medication of any kind was given either before or after operation. Since his operation about two and one-half years ago, the patient has been on relief and extremely difficult to follow. He was seen about two months ago, at which time he stated that there had been no return of his attacks, which we feel was explicable on the basis of his hypoglycemia. His thyroid was not enlarged. What his basal metabolic rate is and what his sugar tolerance curve is, however, we are unable to report upon.

![Chart 1](image)

**Chart 1.—** (Case 1.) Showing graphically the sugar tolerance curves taken before partial resection of the pancreas and eight weeks after the operation.

For the privilege of presenting the second case we are indebted to Dr. S. H. Gray of the St. Louis Jewish Hospital. This case will be reported by him subsequently with others in greater detail, but because it presents morphologic evidence of the concept which we are suggesting, we are including it in our presentation.

**Case 2.—** An infant, born of an apparently normal mother, died about two hours after birth; it was comatose at birth and remained so until death. Upon autopsy the pancreas showed an extreme degree of hypertrophy and hyperplasia of the islet tissue (Fig. 1 A). The adrenal medulla as well as part of the cortex on both sides was completely destroyed by an old hemorrhage. (Fig. 1 B). The thyroid gland, instead of showing the usual picture of fetal thyroid, resembled that seen in Graves' disease to a marked extent (Fig. 1 C and D). Unfortunately, the hypophysis was lost. A notation made at autopsy, however, states that it was definitely enlarged.

The presence of compensatory hyperactivity of the thyroid is likewise suggested in a case recently under the care of Dr. L. F. Aitken²⁶ and which
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is being reported by him elsewhere. This patient, a married woman of 44, developed symptoms of amnesia, automatism, confusion and unconsciousness occurring before breakfast. Several months later she was said to have had a characteristic clinical picture of Graves' disease, the basal metabolic rate being plus 80 per cent. With the appearance of the hyperthyroidism the symptoms referable to hypoglycemia became less. A subtotal thyroidectomy was performed, following which the hypoglycemic symptoms increased in severity. After the removal of a Beta cell adenoma of the pancreas and the return to

apparently normal carbohydrate metabolism, which was several years after the thyroidectomy, the patient developed evidence of hypothyroidism, and now requires one and one-half to two grains of desiccated thyroid per day.

For a number of years it has been suspected by many observers that the primary cause of toxic goiter is probably not to be found in the thyroid itself. It has been felt that the anatomic and physiologic changes brought about by the overfunction of this gland are the result of an unknown stimulus coming from some other part of the body. Indeed, such changes have already been produced experimentally by a varied group of substances. Perhaps the

Fig. 1.—(Case 2.) Photomicrograph of the pancreas showing hypertrophy and hyperplasia of the islet tissue. (B) Photomicrograph of the adrenal gland showing the medulla completely destroyed by an old hemorrhage that is encroaching on the cortical layer. Both adrenals showed the same change. (C) Photomicrograph of the thyroid gland showing the general architecture. The loss of colloid, hyperplasia and plication of the epithelium may be seen (low power). (D) A higher power photomicrograph of the section shown in C. Morphologic evidence of increased thyroid activity is apparent.
most striking is that which follows the injection of extracts from the anterior lobe of the pituitary gland.\textsuperscript{1} We have observed such changes following certain types of infections\textsuperscript{2} and toxemias and after the administration of some of the methylated purines.\textsuperscript{3} Because of the dominant rôle that the thyroid plays in the fundamental activities of the body, it has appeared extremely important to us that this fact should not be lost sight of in studying the pathologic entity of toxic goiter. While the interrelationship of all the so called glands of internal secretion in their influence upon the metabolic processes of the body is becoming more and more apparent, especially is this true in carbohydrate metabolism and, although we feel that at the present time this effect is still poorly understood, it occurred to us that it would be of value to review some of the work on the action of the thyroid gland relative to sugar metabolism. The two cases that we have reported seem to us to illustrate a phase in the activity of the thyroid that we have never previously encountered clinically.

As early as 1867 Dumontpallier\textsuperscript{4} called attention to the association of exophthalmic goiter with diabetes mellitus, and at that time expressed the opinion that this was not an accidental finding, but that a certain relationship may exist between the two. Since that time the association of these two diseases has been adequately confirmed by a number of authors, and various statistics as to its frequency have been quoted. These reports have differed markedly, and at times have appeared inconstant because of the failure to differentiate between true diabetes mellitus and the glycosuria that is seen so often in toxic thyroid disease. Recently, however, in a series of 25 cases of exophthalmic goiter, Anderson\textsuperscript{5} has made a very comprehensive study of the subject. By the use of a special technic he was able "to demonstrate the presence of spontaneous glycosuria in every one (100 per cent)" of the 25 cases. All of these patients were on an "ordinary" diet. Likewise, in all of these patients he was able to show that after the ingestion of 70 grams of glucose, blood sugar determinations at ten minute intervals showed a higher and more protracted curve than that seen in normal individuals. In other reports glycosuria is not quite so frequent. John\textsuperscript{6} found fasting glycosuria in only 19 per cent of the cases of hyperthyroidism. Joslin and Lahey\textsuperscript{7} found the incidence somewhat greater. This subject was reviewed by Fitz\textsuperscript{8} in 1921 and more recently by Andersen\textsuperscript{9} in a detailed monograph. The incidence of hyperglycemia in hyperthyroidism, while generally showing a definite increase, likewise shows a marked variation. A number of reports on this aspect of the subject have been tabulated by John.\textsuperscript{10}

Further evidence of this apparent lowering of carbohydrate tolerance by excessive thyroid function can be seen in the tendency of true diabetics to become worse following the development of toxic goiter. The reverse is true following thyroidectomy in these patients. While recognizing the difficulty in accurately estimating the amount of carbohydrate tolerance gained in diabetics with toxic thyroid disease after thyroidectomy, Joslin estimates it as "not far from 30 grams."\textsuperscript{10} This type of improvement has been recognized and
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reported on by a number of other investigators including Fitz,8 Wilder11 and John. Similarly there is a tendency toward a lowered blood sugar in hypothyroidism, although in many instances clinical reports have been controversial, probably due to the interrelationship of other endocrine glands. Led by the observation that some diabetics seem to be improved following the development of myxedema, Wilder, Foster and Pemberton18 have described a case of severe diabetes without evidence of hyperthyroidism upon whom a total thyroidectomy was performed with the production of hypothyroidism and a definite increase in sugar tolerance. This increase in tolerance seemed to parallel the decrease in metabolic rate. However, because of the unpleasant symptoms resulting from the myxedema, Wilder and his associates hesitated to recommend the procedure as a routine treatment. Shortly after their report a similar case was recorded by Rudy, Blumgart and Berlin,14 in which a marked improvement in carbohydrate tolerance was noted following the total ablation of a normal thyroid gland in a severe diabetic. They were able to control the unpleasant symptoms of myxedema by small doses of thyroid extract, and are of the opinion that the procedure can be recommended in “the rare case with very severe diabetes which cannot be controlled adequately by the application of all known therapeutic measures.”

From a study of the above clinical reports and others of the same type, it seems justifiable to conclude that in patients with hyperfunction and hypofunction of the thyroid gland there is clinical evidence of alteration of the tolerance to glucose in the body.

Experimentally, the evidence is even more conclusive. As early as 1904 Lorand15 reported that ten days after thyroidectomy in dogs made diabetic by previous pancreatectomy there was a disappearance of the glycosuria. This experiment was repeated by Eppinger, Falta and Rudinger16 and subsequently by W. G. MacCallum17 with results of a similar nature but not so striking. They were able to obtain a diminution of the glycosuria, but not a complete disappearance. More recently, however, Yriat27 has failed to confirm such findings. In an effort to explain this phenomenon the first important contribution was that by Cramer and Krause18 who, in 1913, showed that the feeding of thyroid substance to cats and rats resulted in a diminution in the amount of glycogen in the liver. This finding has been confirmed by others on numerous occasions. Lichtman19 has used it as a basis of explaining the occasional clinical evidence of hepatic disease in severe cases of hyperthyroidism. By the use of a functional test based on the ability of the liver to oxidize cinchophen he was able to show a disturbance in function in 16 of 20 cases of uncomplicated hyperthyroidism. “There was no apparent relationship between the degree of functional impairment of the liver and the basal metabolic rate, the known duration of the disease or the percentage of weight lost. . . . The constancy of depletion of glycogen in the liver cells in animals that have been fed thyroid substance, and probably in clinical thyrotoxicosis suggests that the disturbance in oxidation of cinchophen is related to the capacity of the cells to store and mobilize glycogen.” Youmans
and Warfield,20 using the phenoltetrachlorphthalein test, found an impairment of hepatic function in 50 per cent of their cases and concluded that “it is probable therefore that a change in thyroid activity in thyrotoxicosis may result in a glycogen free or poor liver, more susceptible to damage by some toxic agent present in this disease or more susceptible to injury by the disturbed thyroid function itself.” In an extensive study of the morphologic changes in the liver in Graves’ disease, Weller21 was able to show definite damage in 54 per cent of a group of selected cases, while in a matched control series the frequency was only 2 per cent. A similar study by Beaver and Pemberton22 describes three predominant types of hepatic lesions in exophthalmic goiter: (1) acute degenerative lesions; (2) simple atrophy; and (3) subacute toxic atrophy and toxic cirrhosis.

Burn and Marks,23 in 1925, while studying the relation of the thyroid gland to the action of insulin, noted that “the presence of large amounts of thyroid hormone in the circulation enables the organism to prevent the occurrence of severe hypoglycemia in spite of the injection of relatively large doses of insulin.” This observation was found to be true until the liver had been depleted completely of available glycogen and was thought to be explained by the action of the thyroid in stimulating glycogenesis. Recently, Goldblatt24 has observed that in many instances when an apparent sensitivity to insulin has existed, the underlying factor has been an inability on the part of the organism to mobilize sugar readily from the liver to replenish the falling level in the blood stream. Such an explanation would suffice in the insulin sensitivity seen following removal of the adrenals. In the recent work of Cope and Marks,25 a similar explanation of the insulin sensitivity following hypophysectomy may be given. These workers have developed the conception that the effect of adrenalin on glycogenolysis depends upon the presence of the anterior lobe of the hypophysis. Through hormonal secretion this structure apparently possesses the ability to mobilize liver glycogen, and is stimulated to do so by the presence of adrenalin. Without the presence of the anterior lobe of the hypophysis, adrenalin loses its ability to free the liver of sugar, and the reaction to a small dose of insulin becomes much more marked.

The presence of an increased sensitivity to insulin in myxedema and in the thyroidectomized animal has been known to exist for a long time. Goldblatt has shown that the response to adrenalin in the thyroidectomized animal is both slower in onset and less in degree in so far as the blood sugar determinations are concerned. He is of the opinion that lack of thyroid secretion produces a “failure to initiate adequate glycogenolysis at the hypoglycemic blood sugar levels” and that this is due to “the sluggishness of response of the sympathetic mechanism responsible for glycogenolysis in the liver.”

From the above studies, therefore, it seems apparent that the thyroid secretion is capable of elevating the level of sugar in the blood with the potential production of glycosuria. It depletes the liver of glycogen and tends to make the body more resistant to the action of insulin. While these effects

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may be due partly to the increase in the utilization of glucose caused by an increase in the amount of oxidation in the body, they probably are best explained by the marked effect of the thyroid secretion in producing more rapid glycogenolysis. Such an action as has been shown on repeated occasions occurs quite dramatically when the adrenal-sympathetic mechanism is stimulated. With the presence of a similar function in the thyroid gland we are apparently dealing with a balanced physiologic synergy in which three different structures act toward the same end, enhancing the action of each other. They all tend to elevate the blood sugar level. Such a statement, however, should not be construed to mean that these structures do not likewise exert an action independent of each other.

Discussion.—While differing in degree, it is apparent that the thyroid, as well as the adrenal-sympathetic system, acts in effecting the mobilization of glycogen from the liver. It is only by the utilization of such a complex mechanism that the organism is able to preserve the blood sugar at the constant level obviously necessary in the economy of the body. During phases of acute hypoglycemia, occurring spontaneously or induced by insulin, the most important factor in restoring the sugar to the normal level in all probability is the adrenal gland. Certainly there is considerable experimental and clinical evidence in support of this. However, it seems reasonable to believe that if for some reason this mechanism were altered so that the adrenal action was insufficient, the thyroid gland might compensate by increasing its functional activity. The two cases described above suggest that this is true. If the evidence of increased thyroid activity noted in the first case were of a compensatory nature, we cannot help but feel that thyroidectomy would only tend to aggravate the symptoms of hypoglycemia. It is for this reason that pancreatic resection was advised. It is only fair to state that in our opinion such a situation is rare. Certainly, in our experience, this is the first patient that we have encountered with a blood sugar consistently low and severe enough to produce symptoms associated with a toxic goiter. However, we do wish to emphasize one thing. The presence of a goiter and signs of hyperthyroidism are not necessarily indications for thyroidectomy until detailed study offers evidence that this is the best treatment. Until this is done the clinician can hope to contribute but little to the solution of the problem of Graves’ disease.

Conclusions

(1) Evidence of the effect of the thyroid gland on carbohydrate metabolism is briefly reviewed.

(2) The action of the thyroid secretion in mobilization of sugar from the liver is considered in detail.

(3) Evidence is brought forward to show that because of this action the thyroid gland may undergo compensatory hyperactivity in occasional hypoglycemic states in an effort to elevate the level of sugar in the blood.

(4) Two cases are presented, one of which shows clinical evidence and
the other morphologic evidence of such compensatory hyperactivity of the thyroid. In the first case the presence of the classical features of Graves' disease was noted.

(5) In one of these cases an apparent toxic goiter disappeared following the relief of the hypoglycemia after partial resection of the pancreas.

REFERENCES