

HYPERTHYROIDISM SHOWING CARBOHYDRATE METABOLISM DISTURBANCES

TEN YEARS' STUDY AND FOLLOW UP OF CASES

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For several decades writers in this country and abroad have reported the coincident finding of glycosuria in some cases of hyperthyroidism. Joslin and Lahey,¹ in their recent study of 500 cases of disease of the thyroid, reported the occurrence of glycosuria in 38.6 per cent of 228 cases of primary hyperthyroidism and in 27.7 per cent of 83 cases of adenomatous goiter with secondary hyperthyroidism, as compared with only 14.8 per cent in 189 cases of nontoxic goiter and 13.6 per cent of patients without diabetes or any disease of the thyroid gland. In a series of 100 dextrose tolerance tests which I² did in 82 cases of hyperthyroidism and 10 cases of colloid goiter, there was a fasting glycosuria in 19 per cent. In table I are given the reports of various authors as to the incidence of glycosuria in cases of hyperthyroidism.

TABLE I
Glycosuria in Hyperthyroidism

<i>Author</i>	<i>Number of Cases</i>	<i>Percentage of Cases Showing Glycosuria</i>
Marsh.....		2.0
Joslin and Lahey:		
Primary hyperthyroidism.....	228	38.6
Secondary hyperthyroidism.....	83	27.7
Nontoxic goiter.....	189	14.8
Schulze.....	16	25.0
John: present publication.....	100	19.0
Bryan:		
Toxic adenoma.....	244	3.2
Nontoxic adenoma.....	982	1.0
Exophthalmic goiter.....	361	1.1

When chemical analyses of the blood began to be generally used, hyperglycemia, either with or without glycosuria, was demonstrated in sporadic cases of hyperthyroidism. A review of the literature showing the incidence of hyperglycemia in hyperthyroidism (table 2) shows a great discrepancy in the findings of different investigators.

TABLE 2
Incidence of Hyperglycemia in Hyperthyroidism

<i>Author</i>	<i>Number of Cases</i>	<i>Percentage of Cases Showing Hyper- glycemia</i>
Fitz.....	1,800*	0.5
Wilder.....	2,340*	0.6
Von Noorden and Isaac.....	1,000	0.6
Wilder.....	1,131†	2.0
Sattler.....		3.0
Lund and Richardson.....	29	3.4
John: present publication.....	9,000	6.88
John: 1928.....	3,335	8.5
Mojarova.....	84	25.3
Flesch.....		60.7
Geyelin.....	27	90.0
Total.....	18,746	
*Exophthalmic goiter.		
†Toxic adenoma.		

Experimental studies on animals made to determine the relation of the thyroid gland to the blood sugar content showed that extirpation of the thyroid gland leads to a lower blood sugar level, while, on the other hand, the injection of thyroxin, the feeding of hashed thyroid gland to animals or the injection of thyroid extract produces hyperglycemia. In other words, various workers tried to duplicate the clinical finding of hyperglycemia in the syndrome of hyperthyroidism. Many observations regarding the thyroid-blood-sugar relation in human beings are recorded.

The incidence of hyperthyroidism among cases of diabetes is comparatively low, as can be gleaned from table 3, the average being 1.68 per cent. A diabetic patient is, of course, subject to the same ailments as is a nondiabetic person. The incidence of diabetes among cases of hyperthyroidism, on the other hand, is a fairly consistent figure, as can be gleaned from table 4, and is nearly twice as high as the general incidence of diabetes.

The present study comprises clinical and laboratory observations made over a period of ten years, including an intensive study made during the period from January 1, 1925, to October 1, 1931. During this time, about 9,000 cases of thyroid disease have been seen in the Cleveland Clinic, most of which were cases of hyperthyroidism (exophthalmic goiter, adenoma with hyperthyroidism). Of this group, 620 cases, or 6.88 per cent, showed some degree of nonphysiologic hyperglycemia (fasting or two and one-half hours or more postprandial) either with or without glycosuria. During

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TABLE 3
Incidence of Hyperthyroidism in Diabetes

<i>Author</i>	<i>Number of Cases of Diabetes</i>	<i>Number of Cases with Hyperthyroidism</i>	<i>Percentage</i>
Greeley.....	614	6	0.97
Joslin and Lahey.....	4,917	..	
Primary hyperthyroidism.....		43	0.87
Toxic adenoma.....		28	0.57
Simple goiter.....		4	0.08
Wilder.....	1,249	..	
Primary hyperthyroidism.....		14	1.10
Toxic adenoma.....		22	1.80
Rabinowitch.....	3,000	24	0.80
Von Noorden.....	1,000	30	3.00
Murphy-Moxon.....	827	8	0.96
Average.....			1.68

TABLE 4
Incidence of Diabetes in Hyperthyroidism

<i>Author</i>	<i>Thyroid Disease</i>	<i>Diabetes</i>	<i>Percentage</i>
Joslin and Lahey: total hyperthyroidism.	5,908	75	1.26
Primary hyperthyroidism.....	1,751	43	2.5
Secondary hyperthyroidism.....		28	4.3
Sattler.....	1,866	56	3.0
O'Day.....		4	
Fitz.....	1,800	9	0.5
John: all thyroid diseases.....	9,000	207	2.3
Average.....			2.31

these years, it has been the practice of my associates and myself to make a routine blood sugar estimation in every new case, as this gave much information about many unsuspected cases of diabetes which would not have been picked up otherwise. Most of the cases, which showed some degree of nonphysiologic hyperglycemia, were then followed up and studied further for a period up to ten years. These data I am offering here.

When the 620 cases showing nonphysiologic hyperglycemia were followed up further, it was found that in some cases the hyperglycemia was present in only the primary examination and that in some others the hyperglycemia disappeared without any medication. Consequently, these cases are not included in my consideration. In some other cases the patients have not been observed for a long enough period to be included in this series. In some cases inadequate data were available, and for that reason they are not

included. Intensive observations over a period of from one to ten years were made on 166 cases which alone are included in this special study. All of these showed a definite disturbance of carbohydrate metabolism. The number of years the patients in this series have been under observation is shown in table 5.

TABLE 5
*Length of Observation on 166 Cases of Hyperthyroidism and Diabetes
Over a Period of Years (John)*

Years of observation	1	2	3	4	5	6	7	8	9	10
Number of cases	82	32	19	11	8	4	1	—	1	8

By a very conservative estimate, however, I should say that about 200 cases showed what might be called definite hyperglycemia like that of diabetes. In some of these cases the hyperglycemia was purely functional in type and therefore disappeared in a few weeks or months after thyroidectomy on dietary treatment alone or combined with insulin, but — as further experience taught me — the hyperglycemia would not have disappeared in all cases without such treatment. In the total of 620 cases of hyperthyroidism in which hyperglycemia was present, it remained in 30 per cent and disappeared in 70 per cent. This makes the incidence of diabetes in this series of cases of thyroid disease 2.1 per cent, a figure that is close to the average incidence of diabetes in cases of hyperthyroidism as reported in the literature (2.3 per cent). Thus, of this series approximately 200 patients remained diabetic and had to be treated as such, and 35.7 per cent of them are still taking insulin in order to control the diabetic state.

This summarizes briefly the problem and is an answer to those who try to offer an academic discussion of this subject, which, interesting as it may be from the standpoint of the laboratory, cannot be fully adopted by a clinician who has to treat these patients, many of them for the rest of their lives.

This point is well illustrated by the report of Sattler,³ who in 1909 collected 56 reported cases in which diabetes was associated with hyperthyroidism. Thirty-seven of these cases had been followed for a sufficient length of time to afford positive information. Of these 37 cases, in 24 (64.8 per cent) there was a fatal termination within comparatively short periods of time, and in 7 cases the patients died in coma.

The incidence of diabetes in this special series of 166 cases and its distribution, according to sex and decades, are given in table 6. The highest incidence is in females, as one would expect, since the highest incidence of hyperthyroidism occurs in females. As for the age distribution of the associated occurrence of diabetes and hyper-

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TABLE 6

*Incidence of Diabetes and Hyperthyroidism and Its Distribution
According to Sex and Decades (166 Cases; John)*

Age decade	II	III	IV	V	VI	VII	Percent- age
Male	..	1	9	11	8	5	20
Female	I	4	13	37	53	23	80
Total	1	5	22	48	61	28	
Percentage	0.6	3.0	13.2	28.9	36.7	16.8	

Joslin and Lahey: Male, 19 and female 81 per cent.

thyroidism, I have tried to discover how it compares with the age incidence of diabetes without hyperthyroidism, and I have found that the two curves run quite parallel, as shown in chart 1. This suggests that hyperthyroidism does not play any important etiologic role so far as the age incidence is concerned. Table 7 shows clearly the priority in appearance of hyperthyroidism, which occurred in 85.5 per cent in primary hyperthyroidism and in 51.9

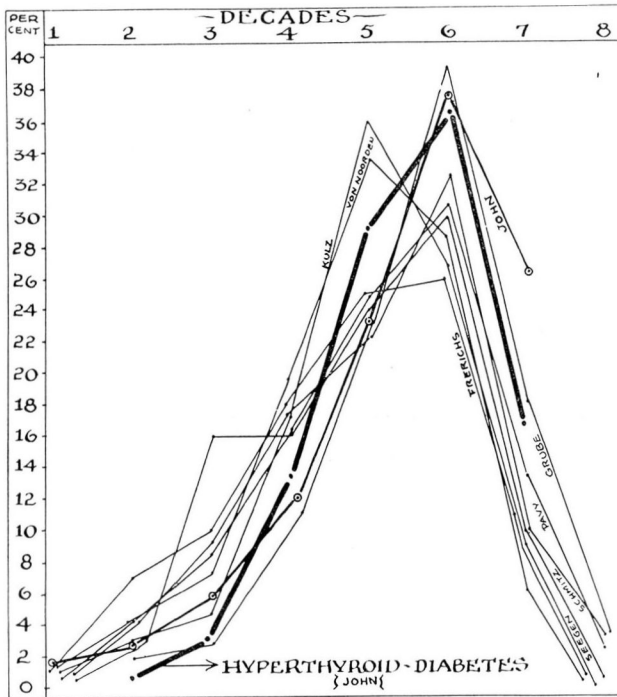


Chart I.—The incidence of diabetes in various decades according to eight authors.

TABLE 7
Priority in Appearance of Hyperthyroidism or Diabetes in 152 Patients, According to Joslin

Condition	Number of Cases	Hyperthyroidism Precedes Diabetes	
		Number of Cases	Per- centage
Primary hyperthyroidism:			
Fitz, primary and secondary not differentiated.....	22	21	95.5
Wilder.....	12	9	75.0
Joslin-Lahey.....	28	23	82.1
Total.....	62	53	85.5
Secondary hyperthyroidism:			
Toxic adenoma			
Wilder.....	19	9	47.4
Joslin-Lahey.....	8	5	62.5
Total.....	27	14	51.9
Sattler.....	56	37	66.0

TABLE 8
Analysis of 166 Cases of Hyperthyroidism and Diabetes (John)

	Percentage
Male.....	20.0
Female.....	80.0
Diabetes severe in.....	31.0
Diabetes mild in.....	69.0
Hyperthyroidism severe in.....	35.0
Hyperthyroidism mild in.....	65.0
After thyroidectomy:	
Diabetes improved in.....	55.0
Of these still taking insulin.....	23.5
Diabetes more severe in.....	30.0
Of these still taking insulin.....	46.0
Diabetes stationary in.....	15.0
Of these still taking insulin.....	62.0
All patients still taking insulin.....	35.7

per cent in toxic adenomas, an observation that may have an important etiologic significance.

In table 8 I offer an analysis of the 166 cases in this series in order to show the progress of the patients. After thyroidectomy 55 per cent of the patients improved as far as their diabetic status

was concerned; in 15 per cent the diabetic condition remained stationary, and in 30 per cent the patients either required more insulin or, if not taking insulin, it is but a question of time until insulin will have to be administered. As stated, 35.7 per cent of the entire group are still taking insulin.

It is obvious that glycosuria in itself does not tell a great deal regarding the status of the carbohydrate metabolism unless one knows also the blood sugar response to the ingestion of carbohydrates and the level of the renal permeability to sugar. In a series of 100 dextrose tolerance tests which I did some years ago² in 82 cases of hyperthyroidism and 10 cases of colloid goiter, 66 per cent of the curves indicated an impaired tolerance. In a larger series of 239 cases of hyperthyroidism which I published in 1930,⁴ 63.5 per cent showed an impaired tolerance. Such an incidence is high and ranks as high as obesity (65.6 per cent). The renal threshold, on the other hand, estimated in 180 cases of hyperthyroidism, was low; thresholds for sugar below 180 occurred in 81.1 per cent of the cases. The average renal threshold was 147. The excretion of sugar by a patient with a low renal threshold is usually of little or no significance. The measure of sugar excretion by the application of Allen's paradoxical law,* however, does throw some definite light on the differentiation of glycosuria in this group of cases and is of distinct value, as Rabinowitch has shown. However, I should offer a caution as to any hurried diagnosis until such a case has been followed up over a sufficiently long period for one to make sure of his premises, as no single laboratory functional test should ever be considered as final.

HEPATIC LESIONS ASSOCIATED WITH HYPERTHYROIDISM

The liver in a case of hyperthyroidism is supposed to be glycogen-poor; it either does not bind dextrose or else lets it go too readily, or there is such an enormous demand for the dextrose in the body that it is rapidly used up and has no chance of being stored in the liver. In an editorial in the *Annals of Internal Medicine*,⁵ regarding the hepatic lesions associated with exophthalmic goiter, the author brings out the following points: "Patients dying in exophthalmic goiter show some degree of simple or pigmented atrophy, but the most marked change was the very frequent occurrence of marked diffused fatty degenerative infiltration bearing all the earmarks of a severe toxic process (like the classic phosphorus liver). The heart and the kidneys presented a marked fatty degenerative infiltration." The author explained these changes as being

*The more the carbohydrate taken by a diabetic patient, the less is utilized.

the result of acute disturbances in the oxygenation of the body resulting from or dependent on the syndrome of exophthalmic goiter. "The livers further show at times a peculiar form of chronic parenchymatous hepatitis in the form of lymphocyte infiltration, bile duct proliferation and increase in stroma of the islands of Glisson." To study these changes, Weller⁶ studied 44 autopsies on patients who had shown no condition other than hyperthyroidism; his report is shown in table 9, which was presented before the Association of American Physicians in 1930.

TABLE 9
Weller's Data

	<i>Hyper- thyroidism</i>	<i>Controls</i>
Number of cases showing no hepatitis.....	6	30
Number of cases showing slight or moderate hepatitis.....	16	13
Number of cases showing well marked hepatitis.....	22	1

Weller summarized his findings as follows:

A well marked chronic parenchymatous hepatitis was found at autopsy in 22 of 44 selected cases of Graves' disease, while but one case of the same degree of hepatic lesions was found in a control series of the same number of autopsies. In the Graves' disease group, only six showed no evidence of hepatitis while in the control series 30 out of the total of 44 cases showed no hepatitis. The coincidence of hepatitis with exophthalmic goiter is therefore significant and is in accord with clinical observations of the occurrence of functional disturbance of the liver in cases of Graves' disease.

Simonds and Brandes⁷ rendered dogs thyrotoxic by heavy thyroid feeding (for from thirty-two to one hundred days). The livers of these dogs were practically devoid of glycogen.

Asher⁸ found that in animals made absolutely free from carbohydrate by thyroid feeding and phlorhizin, the addition of fat to the food increased the output of sugar. From this he decided that the hyperthyrotic liver possesses the ability to form glycogen but cannot fix it so that after its formation it gives it up.

Charvát and Gjurič,⁹ who studied the problem of carbohydrate metabolism in hyperthyroidism, came to the conclusion that the liver in cases of exophthalmic goiter is the cause of hyperglycemia because it does not bind its glycogen in a stable manner, its glycogen is labile and the tissues burn dextrose well; furthermore, in order to use up as much of the circulating dextrose as possible, the renal threshold in hyperthyroidism is raised.

These authors offered as an explanation that in exophthalmic goiter a condition of liver shock is present in which the glycogen-

poor liver binds glycogen very loosely and lets go of it easily, whereas the tissues in patients with hyperthyroidism need sugar badly as a ready and excellent supply of energy; moreover, sugar does not burden the organism with any specific dynamic action as do fats and proteins. As the liver through the lability of its dextrose causes a marked hyperglycemia, the renal threshold is easily crossed and theoretically glycosuria should result in all cases. This, however, is not the case, as Charvát and Gjurič have shown, for the threshold rises in order to enable the tissues to use up a greater portion of the dextrose.

In view of their experiments the authors studied the arterial and the venous blood sugar for a period of several hours after the injection of physiologic solution of sodium chloride in normal persons and in patients with diabetes and again in cases of hyperthyroidism. In normal persons they found that without the injection of saline the arterial and the venous sugar fluctuates but inappreciably. After the injection of saline into normal persons, the discrepancy between arterial and venous blood is also slight (chart 2). They said that such an injection is not sufficient to mobilize the sugar, either in the tissues or in the liver.

On the other hand, the injection of saline into patients with hyperthyroidism presents a more interesting picture (chart 2). Here there is a definite dissociation between the arterial and the venous sugar. The arterial sugar rises higher than the venous sugar, which rises but little or may even be decreased. Such an injection causes shock to the liver, to which it answers by releasing its labile glycogen into the circulation. That this is in reality the liver sugar and not the tissue sugar is shown by the fact that the arterial blood sugar rises, whereas the venous sugar is not changed. There is thus a certain surplus in the arterial blood which is caught by the tissues and does not reach the venous blood. It is a well-known fact that dextrose itself is the best stimulant for the utilization of dextrose by the tissues. Charvát's former work¹⁰ showed that the burning of dextrose in the tissues of patients with hyperthyroidism is very active.

In the case of diabetic patients the picture is somewhat changed. In such a case the arterial sugar does not rise as markedly as is the case in hyperthyroidism and the curve often approaches that of normal persons. The venous sugar, on the other hand, is higher than the arterial sugar (chart 2). According to Gjurič's view, in cases of severe diabetes the tissue rather than the liver binds the sugar in a labile manner and releases it easily into the venous blood, which consequently is higher than the arterial sugar. In this manner

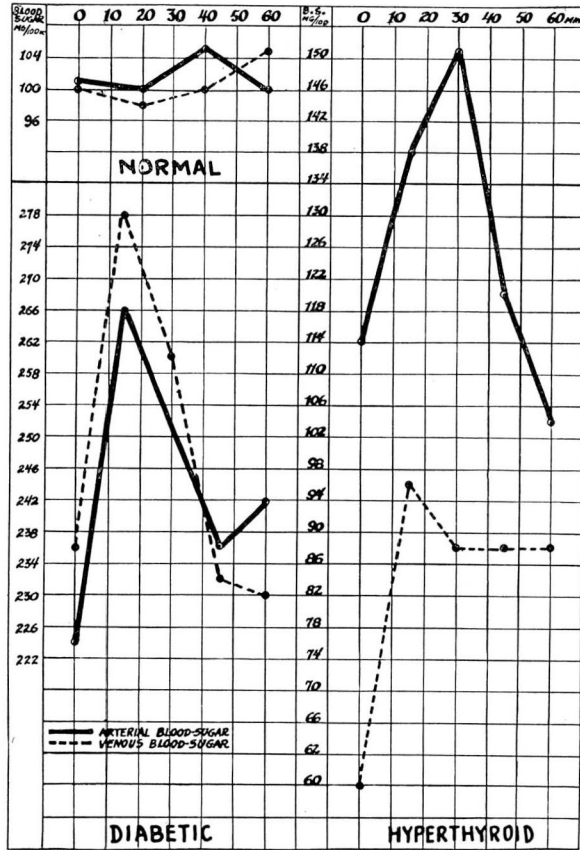


Chart 2.—Curves after the injection of 1 cc. of physiologic solution of sodium chloride per kilogram of body weight. (After Charvát and Gjurič.)

the glycoregulatory disturbance of the patient with hyperthyroidism differs markedly from that in diabetes.

That the liver is not the chief factor in the production of hyperglycemia in hyperthyroidism is suggested by the following points:

1. The incidence of hyperglycemia in hyperthyroidism is too low.
2. The incidence of hyperglycemia in hyperthyroidism is irregular; severe cases usually show no hyperglycemia; mild cases may show pronounced hyperglycemia. If the liver were the primary factor, the degree of hyperglycemia would be proportionate to the severity of the hyperthyroidism.
3. In general, the renal threshold in patients with hyperthyroidism is low,⁴ but the excretion of sugar bears no relation to the

severity of the hyperthyroidism. If the storage function of the liver were at fault, glycosuria would automatically disappear after thyroidectomy, but this does not happen. In 35.3 per cent of the 166 cases reported here, the patients have to continue to take insulin, for even though the condition of the liver has improved, the pancreas still does not function sufficiently.

Ketone Bodies. Thyrotoxic persons who are given a carbohydrate-free diet for two days show a marked increase of ketone bodies in the blood. In the normal person the fasting value of ketone bodies never exceeds 3.5 mg. per hundred cubic centimeters of aceto-acetic acid and 5.5 mg. per hundred cubic centimeters of beta-oxybutyric acid. In the thyrotoxic patient the ketone bodies rise as high as 16 mg. per hundred cubic centimeters of aceto-acetic acid and 18 mg. per hundred cubic centimeters of beta-oxybutyric acid. The patient with hyperthyroidism has a lowered glycogen reserve available for metabolism.

Levulose. Strauss¹¹ first introduced the determination of alimentary levulosuria as a method for testing the liver function. Isaac and Adler¹² showed experimentally that of all the organs and cells of warm-blooded animals only the liver is capable of transforming levulose into dextrose. According to Isaac, the alimentary levulosuria is dependent on the fact that the part of the levulose which is not converted into glycogen or is not burned, in case of functional inability of the liver to convert levulose into dextrose, passes as levulose into the blood and is excreted as urine.

Kugelmann¹³ offered the following conclusion: "We can now say with certainty that the thyrotoxic liver not only suffers severe injury in its glycogen depots but has also lost the capacity to change large amounts of levulose into dextrose and to utilize them later." (See chart 3, which represents Kugelmann's experiments along this line.)

Insulin. Ten units of insulin given intravenously to man causes a rise of blood sugar of from 15 to 20 mg. per hundred cubiccentimeters of blood in the first ten minutes, after which it falls. Bürger¹⁴ demonstrated that this primary rise of blood sugar is dependent on the glycogen function of the liver. In none of the cases of exophthalmic goiter studied by the Bürger method by Kugelmann was his initial hyperglycemia seen. This is a further proof of poverty in glycogen in the hyperthyrotic liver.

Rathery, Kourilsky and Laurent¹⁵ have shown that the blood sugar in depancreatized, starved, and starved and phlorhizinized dogs is distributed in the same proportions during the maximum

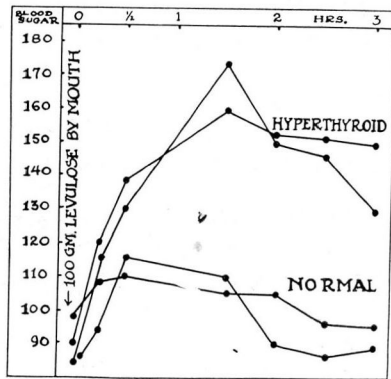


Chart 3.—Blood sugar curves of the administration of 100 Gm. of levulose. (After Kugelmann.)

effect of insulin as in normal animals. The discharge of glycogen from the liver is not influenced by its glycogen content. In dogs under similar experimental conditions, the hyperglycemia immediately following the administration of insulin upsets irregularly the relationship between the blood sugar in different vascular areas.

It would seem that with a little help from insulin the liver gradually resumes its capacity to bind more dextrose and keep a more even blood sugar level. Were it the state of hyperthyroidism alone which brings about the functional change that manifests itself in hyperglycemia, then one would expect the degree of hyperglycemia to bear a direct relation to the severity of the hyperthyroidism, and the incidence of hyperglycemia in cases of hyperthyroidism would be greater than it is. This is not so, however, for some of the most severe derangements of carbohydrate metabolism are found in some of the mildest cases of hyperthyroidism, and many of the most severe and even toxic states of hyperthyroidism show no disturbance of carbohydrate metabolism. Insulin brings about improvement in all cases by its direct action, by its protein-sparing action, through its influence on the storage of glycogen or on the diminution of the ketone bodies, or as the result of all four of these. The fact that disturbed carbohydrate metabolism rights itself in only the mild cases suggests that the protein-sparing function may play a role in the carbohydrate metabolism.

As for the clinical effect of insulin on hyperthyroidism, one may reason that it perhaps improves the patient's general metabolic condition, giving him a better chance to store glycogen in the liver and thus to combat acidosis; to store glycogen in the heart muscle and thus to give it a better chance to do its work; to spare protein by the increased oxidation of dextrose, and to store glycogen in the

muscles and thus eliminate the instability of the organism in general. There is perhaps nothing specific about the action of insulin.

It is a good preoperative measure to give a patient 250 cc. of 10 per cent dextrose made up in saline solution intravenously, together with from 10 to 20 units of insulin, depending on the patient's condition. When the dextrose is buffered with insulin, hyperglycemia does not result even in diabetic cases, as I have shown in my observations on the intravenous administration of dextrose in cases of diabetes and in cases of acidosis as well as in ordinary surgical cases.¹⁶ Such a procedure, therefore, is both logical and helpful, both before and after operation, for the first three days following the operation is the critical period for the patient and a little prevention goes far.

Postoperative Acidosis. Acidosis is a well recognized complication of the postoperative course after thyroidectomy. The pulse rate in such cases is high, and the patient can become semicomatose or stuporous immediately after operation. Is the acidosis in these cases of the same type as diabetic acidosis? Diabetic acidosis is due to the inability of the organism to burn dextrose, this in turn producing an incomplete combustion of fats with the resultant accumulation of ketone bodies in the blood stream (acetone, diacetic acid, beta-oxybutyric acid) and consequent acidosis. In uncomplicated hyperthyroidism, however, there is no such inability to burn dextrose, but there are rather an inability to store glycogen and a general increase of the metabolic process, so that all the available carbohydrate, including the glycogen reserve of the liver and muscles, is often utilized with resultant hypoglycemia. Holman¹⁷ cited a case of hyperthyroidism in which the basal metabolic rate was plus 29 and plus 35 per cent, on two occasions. After thyroidectomy the pulse rate rose to between 180 and 250 immediately after operation, this very high rate lasting for sixty hours. Twenty-four hours after the operation the patient was in a semicomatose condition, and her blood sugar at that time was found to be only 48 mg. per hundred cubic centimeters. Dextrose solution, 20 per cent, was administered, and immediately the patient became conscious. Six hours later the patient again went into a deep stupor. She was again given dextrose, and again immediately became conscious. It is clear that in this case the stupor was due to hypoglycemia, a condition similar to the hypoglycemia of an insulin reaction. This is a condition that should be borne in mind. Blood sugar studies during the post-operative period are often of great value as they tell the needs of the patient at that time.

Basal Metabolism. The relationship of the basal metabolic rate to the dextrose tolerance in a series of cases of thyroid disease is shown in table 10. It will be noted that in 60.6 per cent of the cases

TABLE 10
Relation of Basal Metabolic Rate to Dextrose Tolerance Tests in 66 Cases of Thyroid Disease (John)

	Normal Basal Meta- bolic Rate	Increased Basal Rate, Percentage									Total	Per- cent- age
		10	20	30	40	50	60	70	80	90		
Number of cases....	3	11	8	11	10	10	4	4	4	1	66	
Diabetic.....	2	5	3	7	5	8	3	4	2	1	40	60.6
Normal.....	1	6	5	4	5	2	1	0	2	0	26	39.4

analyzed the dextrose tolerance curve was diabetic or prediabetic in type, while the basal metabolic rates ranged from minus 3 to plus 90 per cent. The case in which the metabolism was minus 3, however, was one of simple goiter and not one of hyperthyroidism. In 39.4 per cent of the cases the dextrose tolerance curve was normal in type, and the basal metabolic rate in these cases varied from minus 3 to plus 80 per cent. On the basis of this study it seems evident that the height of the basal rate bears no relation to the carbohydrate metabolism. The mild derangements of the carbohydrate tolerance that have been observed in this series of cases may be but functional disturbances. They may disappear only in part when hyperthyroidism is eliminated either by operation or by other treatment, thus showing that there is something other than the hyperthyroidism that is playing a part.

COMMENT

I think that the explanation of the disturbed carbohydrate metabolism associated with hyperthyroidism is not found in the state of hyperthyroidism per se, but that it is due rather to some other factor which I believe is a "diabetic anlage" that was present in the patient before the hyperthyroidism developed; infection or obesity would have brought about the same disturbance. Thus Naunyn,¹⁸ in 1917, made the following statement: "I consider it justifiable to draw the conclusion that the thyroid causes glycosuria only where there exists a predisposition (anlage) to diabetes."

The following statement has been made by von Noorden:¹⁹ "Pure hyperthyroidism in the presence of a fully normal chromaffin system and a normal pancreas will very seldom produce an alimentary and spontaneous transitory glycosuria."

It is possible that in hyperthyroidism, in which one is dealing with such an unstable nervous system, the nervous regulatory mechanism may also enter into the picture. But even so, the same problem is presented. Why is it that hyperglycemia occurs in some of the mildest cases of hyperthyroidism and is not present in many of the most severe cases?

Again one may raise the question whether in hyperthyroidism one may be dealing also with hypersuprarenalism, a condition that is known to produce hyperglycemia. In some of the mild cases in which the hyperglycemia disappears after thyroidectomy, the hyperglycemia might well be due to this cause. However, were the hyperglycemia due primarily to hypersuprarenalism, one would find a much higher incidence of hyperglycemia than is found and this again would be relative to the severity of hyperthyroidism, which is not the case.

The question that is unsettled today is whether any of the factors mentioned could induce diabetes when there is no "diabetic anlage" to start with. I think not, but it is not known at present, as the background on which to base a proper interpretation of the facts that confront one and with which one has to deal is lacking.

The incidence of diabetes in hyperthyroidism is 2.1 per cent. The incidence of diabetes at large is given as 1 per cent. There is thus a 100 per cent increase of diabetes in cases of hyperthyroidism. I am inclined to think that a big factor here is the question of over-eating, which is automatically brought about by the increased metabolism demanding more calories, and as the patient starts losing weight he automatically tries to compensate for this by eating more. This throws a great load on the insulogenic apparatus, which, if normal and with a good reserve, stands it well; if the reserve is small, it easily becomes exhausted and diabetes results. The condition is similar to obesity (over-eating), in which, too, the incidence of diabetes is high, and the two are analogous pictures, their end-result being the same, though in one the patient is thin and in the other fat. Also the incidence of diabetes in hyperthyroidism is high from the fifth decade on, when one has to consider the problem of arteriosclerosis and endarteritis, which no doubt are contributory factors to functional changes in the insulogenic apparatus.

The medical problem involved in mild cases of disturbed carbohydrate metabolism is to protect persons with a decreased carbohydrate tolerance, rather than to let them drift along, unprotected toward diabetes. They should be under surveillance until the physician has satisfied himself that stability has been established.

In most of these cases the glycosuria disappears after thyroidectomy, and the carbohydrate tolerance is restored to normal; in others, this does not happen. It is important, therefore, to make postoperative examinations in order to determine whether or not the carbohydrate metabolism has been restored to normal, and when this has not happened to institute such measures as are indicated. It is much easier to keep a diabetic patient in the mild stage of diabetes on a mild dietary routine (for that is all that is necessary in most mild cases) than to treat him successfully after a severe stage of diabetes has developed.

SUMMARY

1. No dextrose tolerance curve is specific for hyperthyroidism. That is, a definite diabetic type of curve may be present in a mild case of hyperthyroidism and a normal curve may be present in a very severe case of hyperthyroidism.

2. A single blood sugar estimation, when such a patient is first seen, is no criterion for the evaluation of or even for a diagnosis of diabetes in such a patient. This serves merely as a lead which should be followed up further and the true state of the patient determined. Even a high blood sugar may be just an incidental finding that clears up quickly, and another much lower blood sugar may persist as a definite diabetic condition.

3. The diagnosis of diabetes in cases of hyperthyroidism can be made only when such a patient has been studied over a sufficiently long time to determine a persistence of the defective carbohydrate metabolism. Without such a time element, many faulty diagnoses of diabetes are bound to occur.

4. Thyroidectomy lowers the total metabolism and in consequence improves the carbohydrate tolerance. In cases in which little or no improvement follows thyroidectomy this is due to the fact that lack of proper diabetic treatment or insufficient treatment has followed the operation, or else that intercurrent infections have produced further damage to the pancreas.

5. If diabetes develops after thyroidectomy, it is due either to other extraneous factors such as produce diabetes in other cases or to the fact that an insufficient amount of thyroid tissue has been removed and an active stage of hyperthyroidism persists. In the latter case, when more of the gland is removed, the diabetes is improved.

6. Hyperthyroidism plays a fundamental etiologic role in the disturbances of endocrine equilibrium in cases with a diabetic

anlage in which diabetes can be precipitated. The factor here may be the heavy ingestion of food which accompanies active hyperthyroidism, thus placing a heavy load on the insulogenic function.

7. Glycosuria and hyperglycemia (either fasting or more often two and one-half hours after a meal) are not uncommonly present in hyperthyroidism. When found they should not be disregarded, but their significance and their relationship to the carbohydrate metabolism should be determined by appropriate tests.

8. The presence of hyperglycemia two and one-half or more hours after a meal, if it persists, is usually an expression of an insufficient insulogenic function.

9. The intervention of the menopause in a case of hyperthyroidism may cause hypertrophy of the islands of Langerhans with the resultant cure of a coincident diabetes. This probably, however, is a rare occurrence, for but few cases are reported in the literature (Rohdenburg²⁰).

10. The glycogen depletion of the liver in hyperthyroidism increases the tendency to acidosis and makes a mild case of diabetes temporarily appear as a severe case. This factor is aggravated in cases in which diabetes is present. The ingestion or the intravenous administration of dextrose before or after operation, with or without insulin, according to the indication in the individual case, would seem to be a logical procedure. The factors that influence the glycogen depletion are probably the following:

(a) Toxic influences which directly affect the parenchyma of the liver cells.

(b) A high metabolic rate which causes increased consumption of carbohydrate and depletes the insulogenic stores, with resultant depletion of the glycogen store in the liver. Such a depletion is also shown in uncomplicated cases of hyperthyroidism which do not show a high blood sugar.

11. Hypersuprarenalism may also play a part in the production of hyperglycemia.

12. Patients with hyperthyroidism in whom a frank diabetic condition of severe type is not present, but merely a mild degree of disturbance of the carbohydrate metabolism, may have but "functional" diabetes or again they may have early diabetes. If appropriate treatment is not given, a frank diabetic state may develop.

13. The administration of thyroid preparations is not without danger. It may precipitate hyperthyroidism, and may even produce diabetes.

14. In my series of 100 dextrose tolerance tests in 82 cases of hyperthyroidism and 10 cases of colloid goiter, fasting glycosuria was present in 19 cases and absent in 81 cases. Sixty-six per cent of the curves indicate an impaired tolerance.

15. From the observations of these patients it would appear that the renal permeability is decreased in the active stage of hyperthyroidism. The renal threshold for dextrose was below 120 mg. per hundred cubic centimeters of blood in 35.6 per cent of the patients studied. The average renal threshold in cases of hyperthyroidism was 147 mg. per hundred cubic centimeters of blood.

REFERENCES

- 1 Joslin, E. P., and Lahey, F. H.: Diabetes and Hyperthyroidism, *Am. J. M. Sc.*, 176:1-22, 1928.
- 2 John, H. J.: Carbohydrate Metabolism in Hyperthyroidism, *Endocrinology* 11:497-581, 1927.
- 3 Sattler: Die Basedowische Krankheit, Leipzig, Wilhelm Engelmann, 1909, vol. 1, p. 384.
- 4 John, H. J.: Study of 1,100 Glucose Tolerance Tests, *M. J. & Rec.*, 131; 287; 351; 398, 1930.
- 5 Editorial: Hepatic Lesions Associated with Exophthalmic Goiter, *Ann. Int. Med.*, 4:501, 1930.
- 6 Weller, C. V.: Hepatic Lesions Associated with Exophthalmic Goiter, *Tr. A. Am. Physicians*, 45:71-76, 1930.
- 7 Simonds, J. P., and Brandes, W. W.: The Effect of Experimental Hyperthyroidism and of Inanition on the Heart, Liver and Kidneys, *Arch. Path.*, 9:445-460, 1930.
- 8 Asher, L.: The Function of Thyroid and Its Relation to Other Organs, *Med. Klin.*, 27:757-760, 1931.
- 9 Charvát and Gjuríč: The Question of Liver and Tissue Glyco-Regulation, *Rozpr. II třídy české Akad.*, 1926, no. 26, p. 36.
- 10 Charvát, J.: Metabolic Reflexes, *Časop. lék. česk.*, 67:533-537, 1928.
- 11 Strauss, J.: Untersuchungen über alimentäre spontane und diabetische Glykosurien, *Ztschr. f. klin. Med.*, 39:202, 1900.
- 12 Isaac, W., and Adler, E.: Clinical Value of Liver Function Tests, *Illinois M. J.*, 52:490-493, 1927.
- 13 Kugelmann, B.: Disturbances in the Carbohydrate Metabolism in Morbus Basedowii, *Klin. Wchnschr.*, 9:1533-1534, 1930.
- 14 Bürger, M.: The Clinical Significance of the Hyperglycemic Effect Principle in Pancreas, *Klin. Wchnschr.*, 10:351-354, 1931.
- 15 Rathery, F.; Kourilsky, R., and Laurent, Y.: Hyperglycemia Following Insulin in Dogs Under Different Conditions, *Compt. rend. Soc. de biol.*, 103:864-881, 1930.
- 16 John, H. J.: The Use of Intravenous Glucose in Diabetic Patients, *Surg., Gynec. & Obst.*, 50:769-773, 1930.

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- 17 Holman, E. F.: Hypoglycemia in Exophthalmic Goiter, Bull. Johns Hopkins Hosp., 34:69-70, 1923.
- 18 Naunyn, Bernhard: Der Diabetes mellitus, Vienna, A. Hölder, 1906, p. 99.
- 19 Von Noorden, C. H.: Zuckerkrankheit und ihre Behandlung, ed. 7, Berlin, A. Hirschwald, 1917, p. 41.
- 20 Rohdenburg, G. L.: Spontaneous Disappearance of Diabetes, Endocrinology, 6:519-522, 1922.