

## ASSOCIATION OF HYPERTHYROIDISM WITH DIABETES

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FROM THE CLEVELAND CLINIC

THE association of diabetes with hyperthyroidism is by no means of rare occurrence, although one would be inclined to think so from the sporadic reports in the literature which give but little indication of the actual incidence of this combination of diseases. For this reason, and because it illustrates the importance of an early recognition of the onset of diabetes in these cases, I am reporting here the case of a patient in whom severe hyperthyroidism preceded the onset of diabetes by nearly a year. In this case such a severe stage of diabetes developed that the patient became extremely emaciated. The hyperthyroidism and severe myocarditis persisted even after both lobes of the thyroid gland had been removed, these conditions disappearing only after the removal of a little nodule of thyroid tissue which clinically was about the size of a small marble. When I first saw him this patient was a mere skeleton, too weak to lift his arm, with a basal metabolic rate of about plus 70 per cent., and a blood sugar content of about 400 mg. per 100 c.c. The important feature in this case was that the diabetes was masked, for though glycosuria was present, yet the fasting blood sugar first was at the normal level, a finding which emphasizes the fact that a fasting blood sugar estimation is not a true criterion for the early diagnosis of diabetes; a blood sugar estimation two and one-half hours after a heavy carbohydrate meal being a far better routine procedure.

CASE.—The patient was an unmarried man, thirty-three years of age. There was no significant item in the family history. Of the usual diseases of childhood he had had measles, mumps, whooping cough, and chickenpox. He had also had a Neisserian infection. Aside from these diseases he had been in good health until the early part of 1925, when he first noticed that he was gradually becoming increasingly nervous and later that his eyes were becoming increasingly prominent. A gradual loss of weight accompanied the development of these symptoms and his neck gradually enlarged in front. He had some dyspnoea and also tachycardia, which was increased by exertion. Two years before he came to the Clinic his weight had been 130 pounds, but when first seen (December 29, 1925) his weight was 115 pounds. His pulse rate at this time was 140, blood-pressure 130/60.

Physical examination revealed a thin, nervous man with a bilateral thyroid enlargement and with marked exophthalmos. He had a rapid heart which was slightly enlarged to the left, but there were no thrills, shocks or friction rubs and no murmurs. Otherwise the physical examination revealed nothing of importance, excepting paralysis of the left vocal cord with great œdema of the arytenoid on that side and also some affection of the right cord (false cord). The subsequent course of this patient can best be followed by an examination of Table I and of the charts given in Figs. 1-5.

In this case we were dealing with a very severe case of hyperthyroidism presenting all the cardinal symptoms, the high basal metabolic rate persisting

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even after a second lobectomy. At the suggestion of Doctor Marine we instituted the feeding of thymus, which was continued for nearly three months after the second lobectomy without any apparent effect. During this

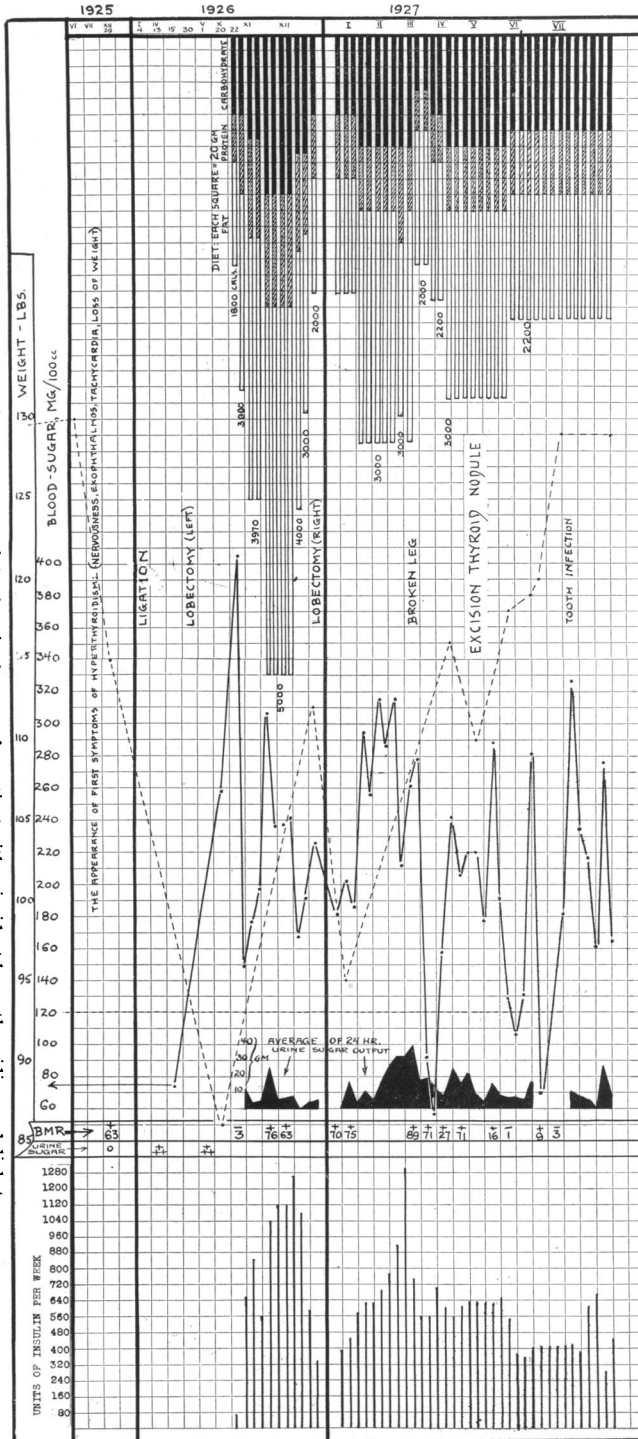
TABLE I.  
Summary of History of Patient with Coincident Hyperthyroidism and Diabetes

Year	Date	Weight	Glycosuria	Blood sugar mg. per 100 c.c.	B. M. R. per cent.		Operations	24 hr. N. output gm.	Symptomatology
					+	-			
1925	June	130							
	July								Appearance of symptoms of hyperthyroidism—nervousness, exophthalmos, rapid heart, loss of weight. First seen at the Clinic.
1926	Dec. 24	115	neg.		63				
	Jan. 4						Ligation, left		
	Jan. 7						Ligation, right		
	Jan. 10								Discharged from hospital to return for lobectomy. Reentered hospital.
	April 13		3 plus						Pulse irregular.
	April 15			73			Lobectomy, left		
	April 30								
	May 1		3 plus						
	May 11								Discharged from hospital, second lobectomy to be done later. Reentered hospital markedly emaciated.
	Oct. 19			258					
	Oct. 20			405					
	Oct. 22	86			3				Diabetic treatment started. See chart. See photograph 1 (Fig. 6).
	Oct. 23								
	Oct. 29	89.5							
	Oct. 30	91							Heart irregular. Arrhythmia.
	Nov. 8	92.5							
	Nov. 18				76				
	Nov. 27				37				
	Dec. 9				63				See photograph 2 (Fig. 6).
	Dec. 29						Lobectomy, right		
1927	Jan. 18	97			70				
	Feb. 9	103.5			75				See photograph 3 (Fig. 6).
	Feb. 24							12.7	
	Feb. 27							13.44	Feeding with thymus started.
	Feb. 28						Broke left fibula		
	March 3							14.3	
	March 7							11.79	Heart irregular. Arrhythmia.
	March 10							11.34	
	March 12				89				
	March 14							9.5	
	March 16				71				
	March 17							7.84	
	March 21							21.	
	March 24							13.03	Serum calcium 12 mg. per 100 c.c.
	March 28							12.01	
	March 31							7.4	
	April 4	115						9.65	
	April 7				27				
	April 11							10.75	
	April 15				43				
	April 21							14.64	Heart irregular. Arrhythmia.
	April 25	116.75			71				
	May 1							13.5	
	May 2	111.5					Removal of thyroid nodule		
	May 9	110						4.9	Heart more regular.
	May 16	112						8.5	
	May 25	113.75			16				
	May 31	118						9.8	
	June 9								See photograph 4 (Fig. 6). Glucose tolerance test. See chart.
	June 21					1			Heart quite regular, rhythmic and normal in every way.
	June 22				9				
	June 24	120							
	July 27					3	Infected teeth extracted		Severe reaction due to extraction of teeth, face badly swollen.
	Aug. 29	129							Discharged from hospital.

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time, while attempting to open a window, the patient broke his left fibula. Some time after the second operation a small nodule was noted on the right side in the thyroid region. This was removed on May 2, 1927, and was found to consist of thyroid tissue. (See pathological reports.) After the removal of this portion of thyroid tissue, the patient began to improve markedly; the basal metabolic rate promptly became normal and remained so; the heart quieted down and he began to gain strength. The outstanding features in this case are that: The hyperthyroidism preceded the onset of diabetes by nearly a year. The patient first noted the symptoms of thirst and polyuria in September, 1926. Glycosuria had

Fig. 1.—Chart showing a summary of the data in the case of a patient with coincident hyperthyroidism and diabetes.



been discovered five months before, in April, 1926, while he was in the hospital, just before his first lobectomy, but on the following day his fasting blood sugar was only 73 mg. per 100 c.c. so that the presence of the glycosuria was disregarded, since this is a common finding in cases of hyperthyroidism. Glycosuria was again found on May 1, 1926, shortly before the patient was

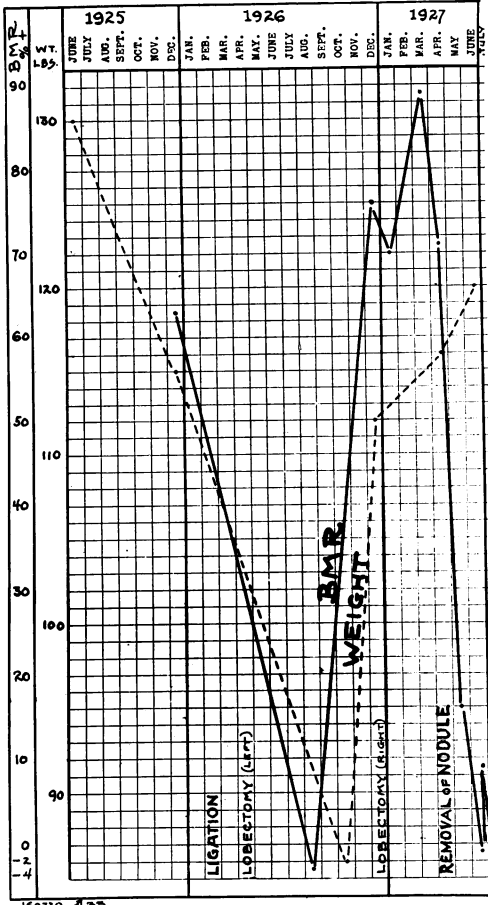


FIG. 2.—Chart showing the variations in the basal metabolic rate and in the weight of a patient with coincident hyperthyroidism and diabetes.

two-fold: (1) the diabetic condition must be controlled, and (2) the patient must be prepared for a second lobectomy. The man was given large amounts of insulin daily (see Figs. 3 and 4) and began to improve immediately, as is shown by Photograph B in Fig. 6, which was taken less than two months later. During this period his weight had increased from 86 to about 95 pounds. He grew very hungry and his diet was increased from 1800 to 3000 calories, but this did not seem to satisfy his hunger, so that it was further increased to 4000, and finally to 5000 calories before his appetite was satisfied. Even on this high diet (200 gm. carbohydrate, 140 gm.

discharged from the hospital after the first lobectomy, but was again disregarded. When the patient reentered the hospital for his second lobectomy he had had the symptoms of thirst and frequency of urination for about six weeks, he was markedly emaciated, his weight having dropped to 86 pounds (see Photograph A in Fig. 6), and he was extremely weak and exhausted. The morning after his admission his fasting blood sugar was 258 and two days later it was 405 mg. per 100 c.c.

The lesson one can draw from the above history is that glycosuria in hyperthyroidism cannot be disregarded, and that even a fasting blood sugar will not always tell the story, for it masked the true situation in this case. A blood sugar determination made two and one-half hours after a meal might have revealed the diabetic condition, and a glucose tolerance test certainly would have done so.

The problem which was before us in October, 1926, was

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protein) on many days there was no sugar in the 24-hour specimen of urine (see Fig. 1). On one day the sugar output was 50 gm., but most of the time it was only 5 or 6 gm. in 24 hours, which indicated that the man was utilizing his food, as was shown also by his steady gain in weight. The

TABLE II.

*Observations of Pulse Rate of Patient with Coincident Hyperthyroidism and Diabetes*

Year	Date	Pulse average	Operation
1925	December 29	80	
1926	January 1	120	Ligation, left.
	January 7	109	Ligation, right.
	April 12	130	
	April 19	125	
	April 26	95	Lobectomy, left.
	October 19	145	
	October 26	90	
	November 2	100	
	November 9	100	
	November 16	100	
	November 23	110	
	November 30	130	
	December 7	120	
	December 14	120	
	December 21	130	
December 28	120	Lobectomy, right.	
1927	January 1	150	
	January 8	110	
	January 15	110	
	January 22	100	
	January 29	120	
	February 5	110	
	February 12	110	
	February 19	110	
	February 26	115	
	March 5	120	
	March 12	100	
	March 19	95	
	March 26	100	
	April 2	100	
	April 9	95	
	April 16	95	
	April 23	95	
	April 30	100	
	May 7	130	Nodule of thyroid tissue removed.
	May 14	95	
	May 21	90	
	May 28	90	
	June 4	90	
	June 10	85	
June 17	90		
June 24	82		

average sugar output did increase in 1927, when the patient was on a much lighter diet. Once the craving for food was satisfied, we were able to cut down the diet considerably until, when he was finally discharged, he was receiving 2200 calories (carbohydrate, 120 gm.; protein, 80 gm.; fat, 155 gm.) and three daily doses of insulin of 10, 20, and 20 units, respectively.

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When the patient was first here he had tachycardia, and his heart was enlarged to the left; and later murmurs, arrhythmia, reduplication of sound and oedema developed. Digitalis and Lugol's solution did not seem to improve the condition of the heart until after the final nodule of thyroid tissue had been removed, when the whole situation changed rapidly and the heart rapidly improved. (Table II.) I am adding here the notes made by Doctor Anderson, who has been examining the man periodically; and also

the electrocardiogram. (Fig. 7.)

"December 12, 1925: Pulse 140. Heart enlarged to left, no thrills, shocks nor friction; no murmurs.

"December 16, 1926: Heart regular, pulse 132. Left border in anterior axillary line.

"March 5, 1927: Pulse 138. Heart enlarged. Systolic murmur with a reduplicated sound.

"April 13, 1927: On digitalis and Lugol's solution since above note. Pulse 94. Faint systolic murmur at apex. No signs of failure except that feet are slightly swollen.

"June 22, 1927: Heart normal in size, rate 80, no murmurs can be elicited. No failure signs, except that the ankles are still oedematous."

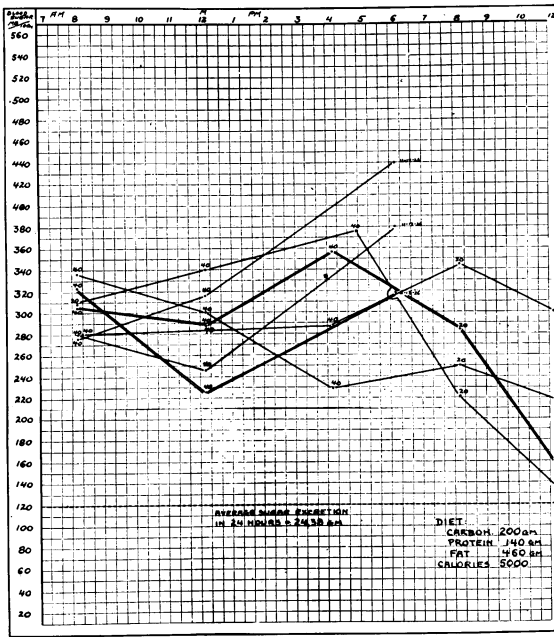


FIG. 3.—Chart showing the blood-sugar fluctuations on six successive days in the case of a patient with coincident hyperthyroidism and diabetes, while he was on a diet of 5000 calories. Insulin dosage is given above dots which indicate height of blood-sugar.

PATHOLOGICAL REPORTS (FIG. 8)

"April 30, 1926: First lobectomy.

"Gross Description.—One lobe of the thyroid weighing 65 gm. on section presented a moderately firm but rather colloid appearing cut surface.

"Microscopical Description.—Sections through the gland showed it to be composed of enlarged acini lined for the most part by slightly to moderately proliferating cuboidal epithelial cells, which in several instances were thrown into papillary folds. There was relatively slight colloid content throughout.

"Pathological Diagnosis.—Rather moderate hyperplasia.

"December 29, 1926: Second lobectomy.

"Gross Description.—Specimen consisted of a portion of thyroid tissue, weighing 15 gm., 40 x 25 mm. It was deeply lobulated, fairly firm and on section presented a pinkish-gray, glistening surface.

"Microscopical Description.—Sections showed follicular hyperplasia with infolding of acinar walls which had papillary projections into the lumina. Lining cells were columnar in type. In some areas the acini were small, lined with broad columnar cells and had no secretory product in the lumina.

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*“Pathological Diagnosis.*—Moderate hyperplasia.

*“May 2, 1927:* Nodectomy.

*“Gross Description.*—Specimen consisted of a portion of thyroid tissue, weighing 35 gm., and measuring 70 x 30 mm. It was deeply lobulated, flabby and had a dark red, moist cut surface.

*“Microscopical Description.*—Sections showed follicular hyperplasia and infolding of acinar walls, which were lined with columnar epithelium. The stroma was scanty and showed distinct lobular markings.

*“Pathological Diagnosis.*—Slight hyperplasia.”

### GENERAL DISCUSSION

In Table III I have summarized cases of coincident hyperthyroidism and diabetes which I have found in the literature, including therein my own

TABLE III.  
*Cases of Coincident Diabetes and Hyperthyroidism Reported in the Literature*

Author	No. of cases	Total series of cases of hyperthyroidism	Outcome		Year	
			Cured or improved	Dead		
Dumontpallier . . .	1	80		1	1867	
Brunton . . . . .	1					1874
Hartmann . . . . .	2					1878
Budde . . . . .	2					1891
Manges . . . . .	1					1899
Müller . . . . .	2					1906
Thompson . . . . .	3					1906
Sattler . . . . .	56 (from literature)				25	1909
Crile . . . . .	1			1		1915
O'Day . . . . .	4			4		1916
Rohdenburg . . . . .	2			2		1920
Fitz . . . . .	9		1800 (Mayo Clinic) 315 (Mass General Hosp.)			1921
Holst . . . . .	10 (glycos.)			10 (by thyroid-ectomy)		1921
Cambridge . . . . .	1			1		1923
Buchanan . . . . .	1			1		1924
Charvat . . . . .	1		1		1926	
John . . . . .	40	3171	38	2	1927	

series which is to be reported elsewhere. For about two years I have been making a special study of the carbohydrate metabolism in such cases of hyperthyroidism as showed, (1) glycosuria, (2) fasting blood sugar above normal (120 mg. per 100 c.c.), or (3) blood sugar above normal two and one-half or more hours after a meal. This study has consisted chiefly in the study of the glucose tolerance in these cases and basal metabolism estimations. Of the 93 cases of hyperthyroidism which have been included in this study, in forty the glucose tolerance curve was not normal, that is, the curve did not return to the normal level within two and one-half hours after the ingestion of 100 grams of glucose. In a normal individual the curve returns to the normal level within one or one and one-half hours. In some of these cases the height and length of the curve showed a frankly diabetic condition to be present.

It is somewhat difficult to interpret the borderline curves—that is, those which are not frankly diabetic in character but nevertheless do indicate some

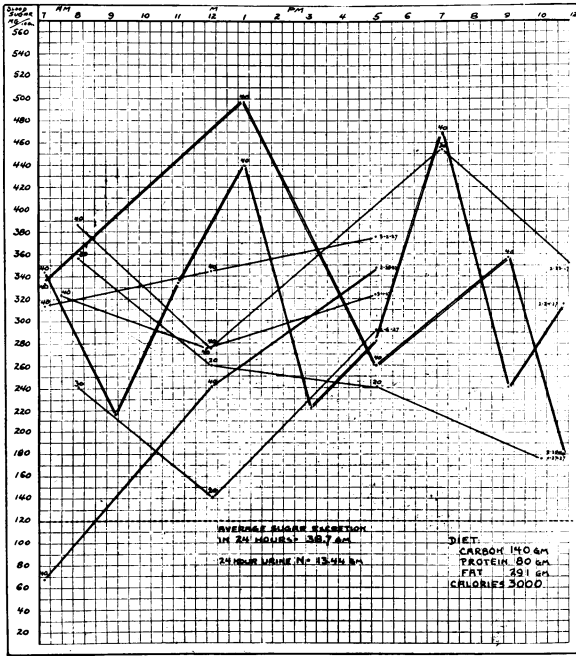


FIG. 4.—Chart showing the blood-sugar fluctuations on eight days during a period of five weeks in the case of a patient with coincident hyperthyroidism and diabetes, while he was on a diet of 3000 calories. The insulin dosage is given above the dots which indicate the height of the blood-sugar.

disturbance of the carbohydrate metabolism. One may consider that they indicate an impairment of the insulogenic function which may be and often is corrected when the hyperthyroidism is controlled, by whatever means; yet, if uncared for, these cases may drift into a diabetic stage, as I have seen happen in a few cases. I am inclined to consider these as cases of functional diabetes” in which the condition may be corrected under appropriate treatment. In some cases a normal status is reestablished without treatment, but since no one can say in

advance in which cases this will happen, the only safe procedure is to institute an anti-diabetic regimen. Glycosuria is not an infrequent finding among cases of hyperthyroidism. The presence of glycosuria in itself alone is not, by any means, a proof of a diabetic state, but it does indicate the need of further investigation. In hyperthyroidism we are dealing not only with the normal renal threshold to which blood sugar must rise before it can appear in the urine, but also with the fact that in some cases of hyperthyroidism the renal permeability is increased, an increase which Allen has described as being of toxic origin. I have noted this phe-

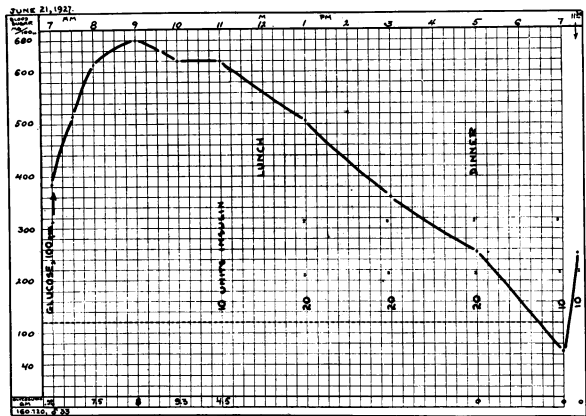


FIG. 5.—Chart showing the curve obtained in a glucose tolerance test made June 21, 1927, seven weeks after the final operation, in a case of coincident hyperthyroidism and diabetes.



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nomenon by comparing glucose tolerance tests made during the acute stage of hyperthyroidism with those made from four to six months after thyroidectomy. This comparison has shown that the sugar excretion during the

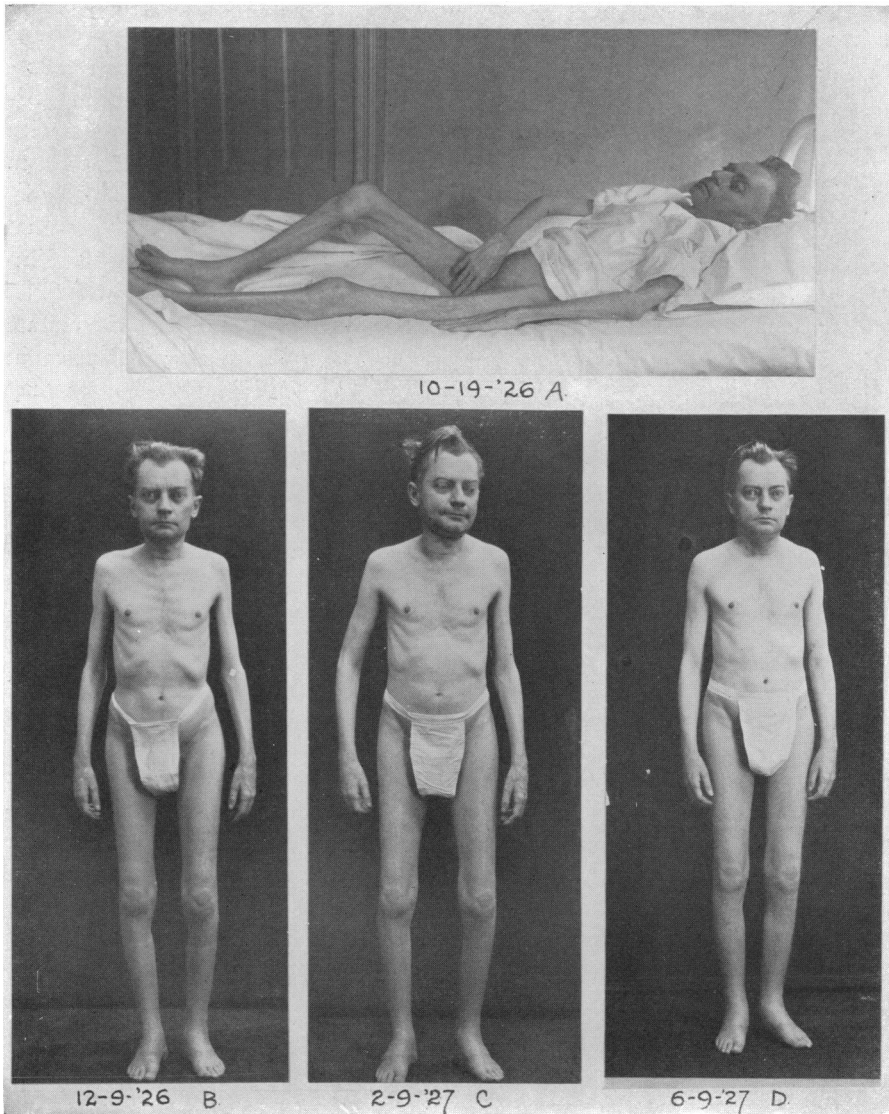


FIG. 6.—Photographs of patient with coincident hyperthyroidism and diabetes. A, photograph made at the time of the discovery of the diabetic condition; B, C, after treatment with insulin had been instituted; D, one month after the final operation.

acute stage of the disease was much larger than after the thyroidectomy, though the coincident blood sugar curves were identical. Increased renal permeability is evidenced by high incidence of a low renal threshold in cases of hyperthyroidism as compared with that in average run of cases. (Table IV.)

As one studies the relationship of diabetes to hyperthyroidism, it becomes

quite evident that in the majority of cases hyperthyroidism precedes diabetes, and a study of the carbohydrate metabolism in these cases leads one to think that hyperthyroidism must be one of the predisposing factors in the development of diabetes. This does not mean, however, that the most severe cases of hyperthyroidism are most predisposed to diabetes, for apparently that is not the case. In a very severe case of hyperthyroidism the glucose toler-

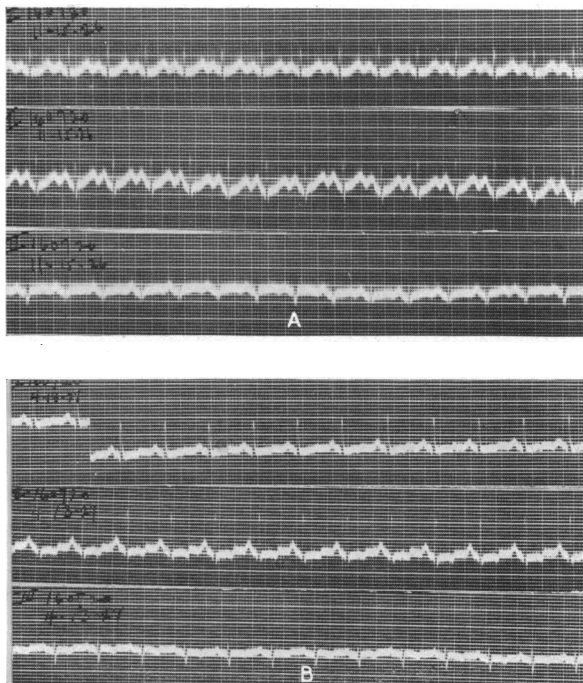


FIG. 7.—Electrocardiographic tracings made in a case of coincident hyperthyroidism and diabetes. A, tracing made November 15, 1926, before the second lobectomy; B, tracing made April 12, 1927, before final operation—removal of a small nodule of thyroid tissue.

ance may be quite normal, while a patient with mild hyperthyroidism may be frankly diabetic. It seems rather that hyperthyroidism is simply a factor which is sufficient to precipitate the onset of diabetes in individuals who, we may say, are already on the road to diabetes, so that the coincident occurrence of any other factor such as infection, over-eating, etc., would have the same influence. It is a well known fact that patients with hyperthyroidism consume an enormous amount of food, to compensate for the increased metabolism, and they thus throw a heavy burden on the

insulogenic function of the islands of Langerhans which, if already weakened, will easily become exhausted, with resultant diabetes. Years ago von Noorden<sup>3</sup> called attention to this fact.

CONCLUSIONS

1. Personal observations and cases reported in the literature lead to the conclusion that the association of diabetes with hyperthyroidism is not a

TABLE IV.  
*Renal Threshold in 73 Cases of Hyperthyroidism and Simple Goitre as Shown by Glucose Tolerance Tests*

Blood sugar mg. per 100 c.c.	60-70	71-80	81-90	91-100	101-110	111-120	121-130	131-140	141-150	151-160	161-170	171-180	181-190	191-200	201-210	211-220	221-230	231-240	241-250	251-260	261-270	271-280	281-290	294
Number of cases . . . .	3	3	0	6	3	11	7	4	4	7	5	4	1	1	3	2	4	1	1	1	1	0	0	1



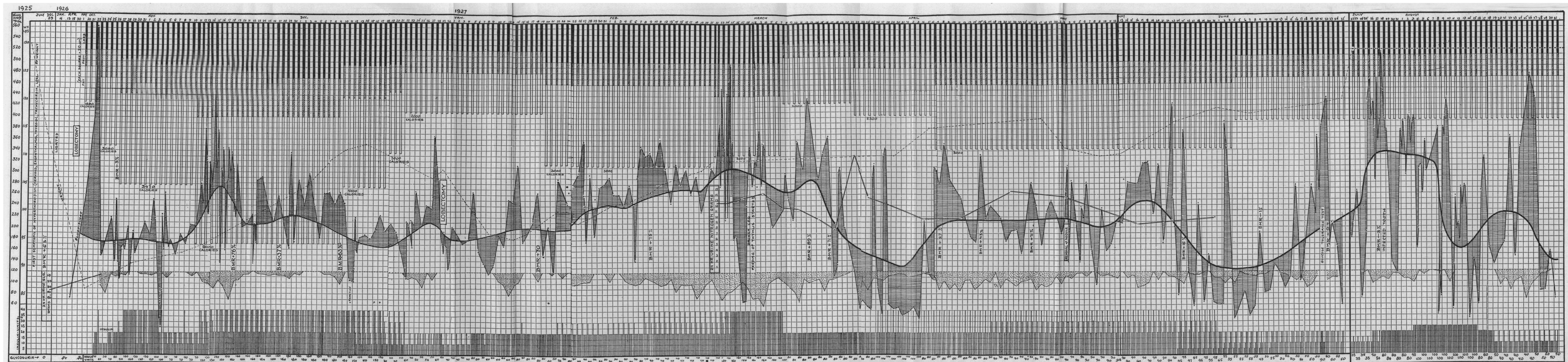


FIG. 9.—Chart showing daily data and progress in the case of a patient with coincident hyperthyroidism and diabetes. The diet is shown at the top of the chart in long columns, the black portion representing the carbohydrate, the shaded portion the protein, and the clear portion the fat. The fluctuations in the blood-sugar during each day are shown in a heavy black line, intersected by dots which show the actual readings. The scale is given on the left side of the margin. The insulin dosage is indicated in the vertical column at the bottom of the chart.



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rare occurrence; and that when this association does occur the diabetes usually develops after the onset of the hyperthyroidism.

2. The appearance of glycosuria in a case of hyperthyroidism should never be disregarded, but a blood sugar determination two and one-half hours after a heavy carbohydrate meal or else a glucose tolerance test should be made in order to determine whether or not the glycosuria indicates a diabetic or prediabetic status.

3. The treatment of diabetes associated with hyperthyroidism does not vary from the treatment of diabetes without this complication, with the

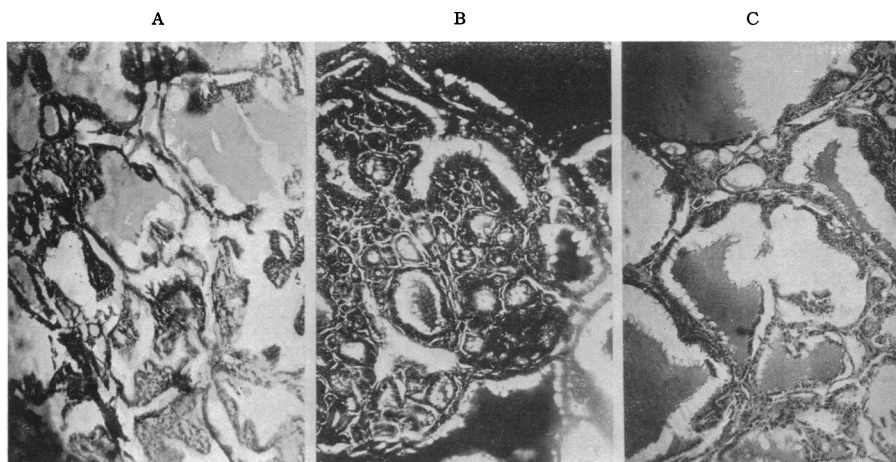


FIG. 8.—Photomicrographs made in a case of coincident hyperthyroidism and diabetes. A, section from specimen in first lobectomy; B, section from specimen in second lobectomy; C, section from specimen of nodule removed in final operation.

exception that, because of the increased metabolism in cases of severe hyperthyroidism, a diet of much higher caloric value than the usual diabetic diet is necessary, and consequently much more insulin is required.

4. Thyroidectomy improves carbohydrate tolerance in all cases of diabetes associated with hyperthyroidism in which diabetes is mild in character; in most of these cases insulogenic function is restored to normal status.

*Addendum.*—The patient whose case is reported in this article returned to the Clinic, July 22, 1927, approximately one month after he was discharged from the hospital, complaining of abscessed teeth. They were extracted and a severe reaction followed, his face becoming badly swollen, etc. There was a marked rise in the blood-sugar for a period of nearly two weeks and the insulin dosage had to be increased, as is usually the case when an infection occurs in a case of diabetes. The basal metabolic rate, however, was not increased and the patient was discharged from the hospital August 29, on the same diet and the same dosage of insulin which he had had before the infection. In Fig. 9 are given the complete data of this case during the three years that the patient has been under observation.

### REFERENCES

- <sup>1</sup> John, H. J.: Carbohydrate Metabolism in Hyperthyroidism, *Endocrinology* (to be published).
- <sup>2</sup> Allen, F. M.: *Glycosuria and Diabetes*, Cambridge, 1913, p. 1051.
- <sup>3</sup> Von Noorden: *Zuckerkrankheit*, 7th ed., 1917, p. 41.