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Hyperthyroidism complicated by diabetes mellitus

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by

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Hyperthyroidism Complicated by Diabetes Mellitus.

This particular syndrome was brought to the attention of the medical profession during the latter half of the nineteenth century. The first case of hyperthyroidism and diabetes mellitus (1) was described by Dumontpallier in 1867. In 1874 the second case was described by Brunton in the English literature; in 1878 two cases were reported at the Tubingen clinic by Hartman; in 1891 Budde of Denmark reported two cases; and in 1899 Manges, an American, reported two cases. H. J. John searched the literature and reported 137 cases of hyperthyroidism and diabetes mellitus up to 1927. Joslin and Lahey have reported 75 cases, Wilder 38 cases and Rabinowitz 24 cases. At the University of Kansas Ginsberg (1) reports 6 cases out of 277 cases of hyperthyroidism. At the University of Nebraska, I found 5 cases out of 315 cases of hyperthyroidism cared for from 1917 to January 1, 1932.

Fitz (2) has pointed out that hyperthyroidism complicated by diabetes mellitus is not a common occurrence. Hyperglycemia and glycosuria, on the other hand, are not infrequent findings in cases of hyperthyroidism. Geyelin (8) states that hyperglycemia is a very common accompaniment of hyperthyroidism. He found it occurring in 90% of mild and severe cases studied. He also states, that glycosuria either spontaneous or alimentary is an equally constant symptom. John (9) found non-physiological hyperglycemia in 8.54% following sugar tolerance test in 3,335 cases of hyperthyroidism. Joslin and Lahey (4) report the results of a series of cases in

which they found glycosuria in 38.6% of the 228 exophthalmic goitres studied, and 27.7% of the 83 cases of toxic adenomata. Chvostek (11) states that 69% of the exophthalmic goitres show temporary glycosuria, whereas, Naunyn of Strassburg only records one case with glycosuria in a large series of cases of exophthalmic goitre. At the University of Nebraska I found 4.4% of the cases of hyperthyroidism showing evidence of glycosuria. Out of this group 2.86% were simple glycosurias which cleared up with thyroidectomy, and in several cases with rest and iodine therapy previous to thyroidectomy. Simple glycosurias were found in 0.96% of the toxic adenomata and 1.9% of the exophthalmic goitre cases.

Owing to the intricate relationship of the endocrines there is a possibility of hyperthyroidism being an etiological factor in the development of diabetes mellitus. Wilder (3) states that the incidence is probably too small to consider hyperthyroidism much etiologic significance in diabetes mellitus, however, a mild and possibly inconspicuous or latent spark of diabetes may be fanned into a flame by hyperthyroidism. Wilder reports 1.1% of hyperthyroidism with frank diabetes. Ginsberg (1) reports 2.16% of hyperthyroidism with diabetes in a series of 277 cases at the University of Kansas. Joslin and Lahey (4) reported 1.52% from their own series of cases, and 1.2% from Dr. Cushing's series at Peter Bent Brigham Hospital. The Mayo Clinic, as reported by dyas (5) showed 0.5% in a series of 1800 Cases of hyperthyroidism. Joslin and Lahey (6) later reported 3.15% in a series of 2,406 cases of operated hyperthyroidism. At the University of Nebraska I found 1.5% in a series of 315 cases of hyperthyroidism. In this

group of cases of hyperthyroidism complicated by diabetes mellitus there were more toxic adenomata than exophthalmic goitre involved. There were 0.9% toxic adenomata and 0.6% exophthalmic goitre. Wilder (3) and Joslin (4) found more toxic adenomata than exophthalmic goitres associated with diabetes. They state that such is to be expected because toxic adenomata and diabetes mellitus are diseases of the older adult. Bryan (7) noted diabetes complicating toxic adenomata more often, probably because the patients are older when sclerosis, chronic infections, and obesity operate in the production of diabetes. Exophthalmic goitre, on the other hand, occurs quickly and at an age when there is a greater insulogenic reserve.

The endocrines of the body provide the delicate mechanisms which keep the body in equilibrium. Diseases acting as external forces tend to disturb this equilibrium and at times overthrow the balance altogether with resulting death. The body functions best at a temperature of 98.4 degrees, with five million erythrocytes, and five thousand leucocytes per cubic millimetre, with a gastric juice of 0.2 per cent HCL, alveolar air containing 5 percent CO2, and blood sugar of 0.1 percent. Brown (10) states that the endocrines fall into two groups, namely the accelerating and the retarders of metabolism. In general the accelerating endocrine glands are controlled by the sympathetics and the retarding with the parasympathetics. The accelerators are katabolic and militant in character and the parasympathetics vice versa. Emotions which stimulate the sympathetics activate us to fight or flight

thereby calling forth an increase in blood sugar because active muscle consumes three and one half times as much sugar as resting muscle. This is apparently done through the activity of the thyroid, pituitary and adrenals. The adrenals, which spring from the sympathetic system, are closely associated to the sympathetics. Either stimulation of the sympathetic or injection of adrenaline, therefore, alike increase the blood sugar and lower the carbohydrate tolerance. There is also much the same correlation between the sympathetics and thyroid and pituitary glands. The endocrine glands associated with the parasympathetics are chiefly concerned with assimilation of food and building up of body reserves. The insulogenic cells of the pancreas are activated by the parasympathetics plus a chemical factor and inhibited by the sympathetics. Insulin may be considered as an amboceptor joining the glucose molecule to larger molecules such as protein thus preventing spill of sugar into the urine. There is only enough to handle approximately 0.15% and if the sugar rises above this level usually will cause glycosuria. When the insulin output decreases it leads to glycosuria. The sympathetic action on the pancreas is shown by an experiment in which the adrenals are removed followed by injection of adrenaline. The removal causes persistent flow of pancreatic secretions, and the injection of adrenaline causes decrease. Eppinger and Falta (10) believe diabetes mellitus not due to any one endocrine but a loss of balance between them. They have shown the relationship of the endocrines to the sympathetic system by a

diagram. See figure I.

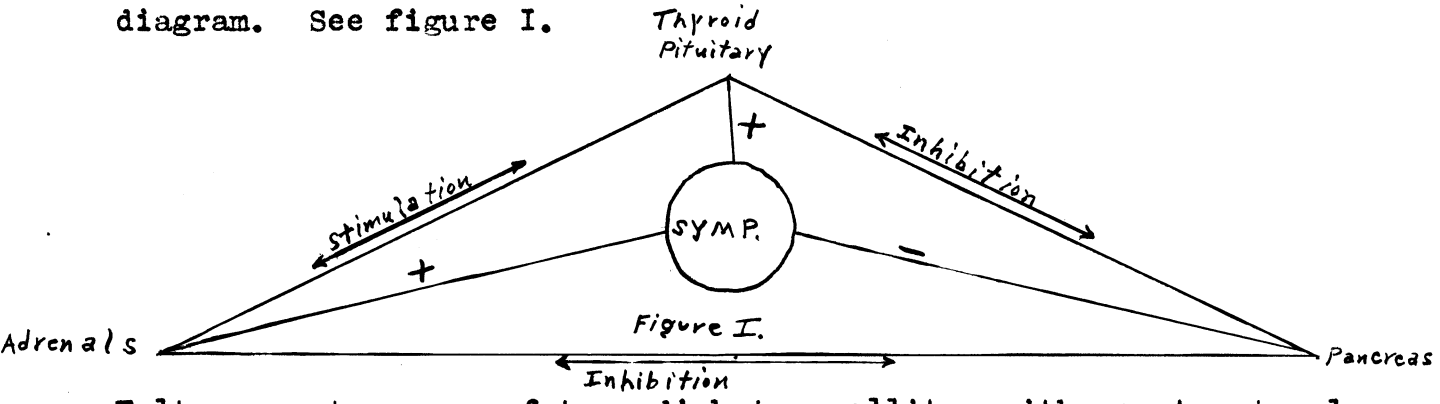


Figure I.

Falta reports cases of true diabetes mellitus with no structural changes in the endocrines but a constant overactivity of the sympathetic system. Boyd (12) likewise feels that there is a close relationship between the endocrines. He states, that the thyroid gland is the leader of the glandular orchestra, and when the thyroid fails to ring true the other ductless glands become jangled and out of tune. Ginsberg (1) states, that an overdose of thyroid in man produces symptoms of sympathetic stimulation. This has lead some to believe that the symptoms of hyperthyroidism are due to overactivity of the adrenal glands. Palpitation, tachycardia, dilated pupils, prominence of eyeballs, concomitant widening of the palpebral fissures, perspiration, and glycosuria are characteristic symptoms found in stimulation of the thyroid or adrenals. Frankel (13) found that the adrenaline output is four to eight times normal in cases of exophthalmic goitre. It is probably upon this basis that the Goetch test, in which eight minums of adrenaline are injected subcutaneously, that the symptoms of hyperthyroidism are increased. Symptoms due to overactivity of the thyroid and underactivity of the pancreatic islands may be identical; as loss of weight, flushed skin, high

metabolism, increased pulse rate, weakness, polyuria, and thirst. There is a possibility of a joint relationship between the thyroid and pituitary glands. Dyas (5) following some experimental work with the thyroid and pituitary glands, points out that the thyroid and pituitary glands are regulators of the supply of insulin to the blood stream. Legiardi and Laura (15) on the other hand believe the thyroid control of sugar metabolism predominant in infancy and pituitary control in adult life. Cramer and Kojima (16) found that excess thyroid feeding lead to hypertrophy of the island cells and atrophic changes in the pituitary gland. Ginsberg (1) found that oral administration of thyroid substance decreased the liver glycogen and increased the size and weight of the adrenals showing possibility of increased activity. Ginsberg's findings coincide with Falta's conception shown in figure I. The antagonistic relationship o the thyroid secretion to insulin is shown by experimental work of Doucheneau (18), Burn and Marks (19) in which they found that thyroidectomy made rabbits more sensitive to insulin. Burn and Marks (19), and Bodansky (20) carried out a series of experiments wherein rabbits were fed thyroid, and dextrose was given intravenously. Glycosuria was produced. If thyroid feeding continued the animals eventually developed hypoglycemia, convulsions and died because there was no more hepatic glycogen to be discharged. If on the other hand the rabbits had their thyroids removed 1/3 to 1/6 dose of insulin would produce hypoglycemia due to the lack of antagonism held upon insulin by the thyroid gland. Parhon,

Marinesio, Falta and Lorand (9) found that removal of the pancreas was followed by signs of over function of the thyroid; while removal of the thyroid was followed by hypertrophy of the pancreatic island cells. Joslin (4) summarizes the relationship of the thyroid to the pancreatic islands by stating that the pancreatic hormone is a subservient to the thyroid, but only so long as the thyroid keeps intact a store of glycogen in the liver. Experimental evidence also shows an intimate relationship between the thyroid and the adrenals. Asher and Flack (14) in 1910 showed experimentally with rabbits that adrenaline in some way enhanced the effect of a given amount of thyroid and vice versa. Macleod (17) states that adrenaline probably stimulates the splanchnic sympathetics which in turn increase glycogenolysis. This has been proven by removal of adrenals and stimulation of the splanchnics without production of hyperglycemia. When the adrenals are intact stimulation of the splanchnics produces hyperglycemia. Experimental work and clinical observations show that the thyroid, pituitary, and adrenals are closely related to each other and the sympathetic nervous system. The parasympathetic group, of which the pancreas is a member, is antagonized by the thyroid, pituitary, and adrenals and the sympathetic system. The evidence presented shows that the sympathetic group produces glycogenolysis and hyperglycemia and the pancreas produces glycogenesis and hypoglycemia.

Diabetes mellitus usually appears secondarily to

hyperthyroidism in this particular syndrome. Joslin (21) reports that primary hyperthyroidism precedes the diabetes in 85%, and secondary hyperthyroidism in 52%. The lower percentage in the latter is probably because secondary hyperthyroidism does not develop until later adult life when the diabetes incidence is higher. John (9) also feels that diabetes usually follows the onset of hyperthyroidism in this particular syndrome. He states that the increased basal metabolic rate with an increased carbohydrate intake lays too much burden upon the island cells, whereupon, degeneration results with the onset of diabetes. Mueller and Rohdenburg (9) have reported cases where thyroid feeding lead to diabetes. Joslin (4) is of the opinion that hyperthyroidism does not produce diabetes in cases where the pancreatic islands are normal. He feels that in cases where diabetes developed there existed an island weakness or diabetic "anlage" which was unable to cope with the added burden of increased thyroid activity. Naunyn and Von Noorden (9) likewise feel that diabetes results in hyperthyroidism because of a pancreatic deficiency in the insulogenic reserve. Falta (23) even feels that there is a pancreatic weakness in any case which shows evidence of glycosuria provided there is no abnormal renal permeability for sugars.

The normal blood sugar tends to fall within quite definite limits. Todd and Sanford (24) consider the normal blood sugar 0.09-0.12 %. Sanger and Hun (25) give the normal blood sugar as 0.07-0.11%. Todd and Sanford (24) state that the blood sugar may rise to 0.17-0.18% before it is spilled into the urine. An abnormally low renal threshold will produce glycosuria when the blood sugar

is within normal limits. Chronic nephritis on the other hand may cause an elevation of the renal threshold so that a blood sugar as high as 0.30% would fail to produce glycosuria.

Janney and Isaacson (26) have established a definite technic for the sugar tolerance test. From a large number of tests they have been able to set down the normal tolerance limits which are widely accepted as standard today. The patient must be fasting at the time the test is given, preferably fifteen hours. Blood must be drawn before the glucose is given. The patient is given orally 1.75 grams of d-glucose per kilo. body weight. The d-glucose is given in the concentration 4 grams in 10 c.c. of water. The exercise must be limited during the test. Draw blood at ½ hour, 1 hour, 1½ hours, 2 hours, 3 hours, and more if necessary. Normally after the glucose is ingested there is a gradual rise until it reaches 0.15% or slightly over at about the end of one hour. It then returns to normal or slightly below normal within two hours.

The sugar tolerance tends to increase or decrease with the various changes in the endocrine relationship. When a sugar tolerance test is done in diabetes mellitus there may be a sharp rise or a more gradual rise of the blood sugar. Usually the curve begins above the normal limits 0.09-0.12% and rises very high and remains elevated after three hours. Occasionally a mild diabetic will have a normal fasting blood sugar, however, in the majority of the cases it will remain above the maximum normal limit. Hyperthyroidism, on the other hand, usually has a normal fasting blood sugar. Following the ingestion of glucose the blood sugar

rises above the normal peak, at times similating a diabetic curve, and remains elevated over two hours. Joslin and Lahey (4) have had a consideralbe number of cases confused giving a diognosis of hyperthyroidism to diabetes and vice versa. They state than an uncomplicated diabetes mellitus must have a fasting blood sugar over 0.15%, and after ingestion of 100 grams glucose or a full meal should rise to 0.20% or more with the production of glycosuria. Geyelon, Coller and Huggins, Sanger and Hun, Conlin, and Marks (8) (23) (25) (27) (16) feel that hyperglycemia and associated glycosuria is a rather frequent finding in cases of uncomplicated hyperthyroidism. Wilder and Sansum (28) have experimentally determined the sugar tolerance of normal patients and patients afflicted with diabetes, and with hyperthyroidism. The patients were given a definite number of grams of d-glucose per kilogram of body weight per hour with equal amounts of water given per mouth to prevent delay of glycosuria when the tolerance limit was reached. A very pure product of glucose was used in order to rule out any toxic effects upon the kidneys which might in any way have altered the kidney permeability. They found that a normal individual would tolerate 0.8 grams per kilogram per hour, and that 0.9 grams would produce glycosuria. In cases of hyperthyroidism 0.5-0.7 grams were the limits. In cases of diabetes, only mild cases being studied, 0.4-0.7 grams were the upper limits. John (9) believed in the cases of hyperthyroidism the glycosuria was due to an increased sugar permeability produced by the hyperactive thyroid. Marks (16) has shown by feeding thyroid to dogs that the renal threshold is not lowered but that a hyperglycemia is produced

which leads to glycosuria.

Interesting pathological findings have been made in cases of patients afflicted with pancreatic disease, thyroid disease, and conditions with combinations of both. Marinesio and Parhon (9) found that removal of the pancreas in dogs was followed by hypertrophy of the thyroid acini, and removal of the thyroid gland followed by hypertrophy of the pancreatic islands. Cramer and Kojima (16) found in cases of excessive thyroid feeding evidence of hypertrophy of the island cells and accompanying atrophic changes in the pituitary gland. Rhodenburg (9) reports a case who suffered marked glycosuria with considerable loss of weight for a period of seven years. After the period of menopause she began to show improvement of sugar tolerance. For a period of three years before her death, which resulted from chronic nephritis, she was able to consume huge quantities of carbohydrates with no evidence of glycosuria. Autopsy showed marked degeneration of the thyroid alveoli with marked hypertrophy of island cells. These findings tend to point toward a definite interrelationship between the thyroid and island cells. Laura (15) found rather peculiar pathology when making autopsys on a series of clinical diabetes. He found cases with pathology in the pancreas and a normal thyro-pituitary system. He likewise found cases with pathology in the thyro-pituitary system and a normal pancreas. Bergstrand (29) reports autopsy findings of a series of six cases of clinical diabetes. Three of the six cases showed distinct pathology of the thyroid referable to exophthalmic

goitre yet the patient had symptoms of diabetes and not exophthalmic goitre. The autopsy findings tend to bear out clinical and experimental findings which point toward an interrelationship between the endocrines with antagonistic action between the pancreatic islands and the thyroid and pituitary glands. They also show that the endocrine findings are not definite entities in all cases of diabetes.

The prognosis varies directly with the severity of the condition at hand, and the ability of the physician in charge to understand the operating forces and make proper corrections. The greater the thyroid activity and the less the ability of the pancreas to compensate the more likely is the patient to plunge suddenly into coma. Joslin (21), Coller and Huggins (23), Wilder (3), Conlin (27), Ginsberg (1), and Mc Kittrick and Root (6) state that coma results more frequently in hyperthyroidism complicated by diabetes than in cases of uncomplicated diabetes. Ginsberg (1) states that coma is 2½ times more frequent than in uncomplicated diabetes. Joslin (21) says that a patient with hyperthyroidism and diabetes is like a diabetic who is over eating and breaking his diet, or the diabetic with fever who is over eating, both being in easy distance of coma. Ginsberg (1) feels that it is due to higher metabolism which produces a low glycogen reserve resulting in ketosis. Coller and Huggins (23) state that there is a high metabolic rate with low glycogen reserve. There is also great amounts of body fat entering into the metabolism in order to meet the metabolic requirements. There is an inability to oxidize a sufficient amount of glucose owing to the existing diabetes, hence ketosis and coma result.

The therapy of hyperthyroidism associated with glycosuria; and hyperthyroidism complicated by diabetes mellitus has two phases, namely Medicinal and surgical. The medicinal phase comprises the use of insulin, iodine, and dietetics, and the surgical phase thyroidectomy.

Cases of hyperthyroidism with simple glycosuria should bear watching even if they do not demand special diabetic regime. John (9), Coller and Huggins (23) and Sainton and Gastand (30) believe that simple glycosuria in hyperthyroidism may be a mild form of diabetes or at least a potential case of diabetes. John (9) states that all cases of hyperthyroidism with simple glycosuria, which are not due to a lowered threshold of the kidney, should be treated with diabetic regime, namely insulin and dietary restrictions. In treating hyperthyroidism which is complicated by diabetes one will need to give larger amounts of insulin than would be necessary in an uncomplicated case of diabetes. Burn and Marks (19) demonstrated experimentally that hyperactivity of the thyroid decreased the efficiency of the insulin unit. Wilder (3), Joslin and Lahey (4), Bryan (7), John (9), McKittrick and Root (6), Fitz (2), and Conlin (27) have made the same observations clinically. McKittrick and Root (6) state that when dietary restrictions and insulin are employed in these cases one should desugarize gradually and not suddenly as is done not uncommonly by over zealous therapists. Bryan (7) states that a diet should be given to meet the metabolic requirements and sufficient insulin

administered to keep the patient sugar free.

Iodine therapy in the form of Lugal's solution is very closely associated to dietetic and insulin therapy. Iodine lowers the metabolic rate, decreases the carbohydrate metabolism, and increases the efficiency of the insulin unit. Lugal's solution should not be an agent for treatment per se, but used only in the preparation of such patients for operation. If iodine is continued over too long a period of time it looses its effectiveness and the coexisting diabetes will become much harder to control. Fitz (2), Wilder (3), McKittrick and Root (6), Bryan (7), Joslin (21), Coller and Huggins (23), and Conlin (27) advocate the use of Lugal's solution in cases of hyperthyroidism with simple glycosuria, or hyperthyroidism complicated by diabetes mellitus.

Thyroidectomy produces an increase of sugar tolerance and a lowering of the basal metabolic rate. The surgical treatment is the only certain method to obtain permanent results in case of hyperthyroidism with diabetes. Coller and Huggins (23) have found through clinical study that thyroidectomy is not followed by the same pleasing results in non-toxic goitres complicated by diabetes mellitus. Friedman and Gottesman (31) found in experimental work on depancreatized dogs that thyroidectomy or ligation of the thyroid arteries lead to improvement of the sugar tolerance. Thyroidectomy employed after proper preparation will result in improvement of the sugar tolerance and more successful diabetic management. This view in upheld by Wilder (3), Fitz (2),

Joslin and Lahey (4), Bryan (7), McKittrick and Root (6), Ginsberg (1), John (9), Dyas (5), Coller and Huggins (23), Conlin (27), Webb (32), Holst (33), and Buchanan (34). John (9) reports that mild cases may recover normal tolerance, severe diabetics become mild cases, and cases of hyperthyroidism with simple glycosuria which are improperly treated post operatively may become diabetics with varying degrees of severity. He believes that thyroidectomy will increase the glycogen reserve in the liver, decrease ketosis, and help maintain proper glycogen reserve in the heart muscle.

In summarizing the therapy question the following routine suggests itself for hyperthyroidism with simple glycosuria or with diabetes mellitus. All patients should be properly prepared before operation by the use of iodine, diet and insulin if necessary. Both types should be subject to thyroidectomy providing the patient can be improved sufficiently to withstand the shock of surgery.

Case Reports

Case I---Miss B. O., age 18, female, single, entered the University Hospital October 26, 1931 complaining of nervousness, palpitation, loss of 15 pounds weight in the last four weeks, polydipsia, polyphagia, and polyuria. The patient was well up untill three years ago when she began to notice fatigue and loss of strength. Following this she began to note increasing nervousness, and palpitation. She entered the University Hospital November, 1930 for a basal metabolic rate determination. This was found to be plus 33 and 21%. After remaining in the hospital for four weeks, and taking Lugal's solution she recovered sufficiently to permit her to go back to school. Soon after starting to school the above named symptoms came on, whereupon she visited the University dispensary. Here she was advised immediate entrance to hospital for thyroidectomy.

Past history: Negative.

Family history: Negative.

Physical Examination:

Eyes showed mild conjunctivitis. The thyroid gland was nodular and enlarged on the right side. Extremities showed slight tremor.

Laboratory findings:

10/26/31 urine showed 1 plus albumin. 10/27/31 urine showed 3 plus sugar, and 16.8 grams quantitatively. The blood sugar was 189 mgm. %. The B.M.R. was plus 19 and 27%. The blood

picture showed hemoglobin of 99%, R.B.C. 5,670,000, W.B.C. 7,200, differential showed 1% young forms, 2% staff forms, 49% segmented, 33% lymphocytes, 4% eosinophiles, 11% monocytes. Stool was neg. Wassermann was negative. 10/28/31 B.M.R. was plus 21%. 10/30/31 Blood sugar was 154 mgm.%. 11/1/31 Sugar tolerance test (see figure II). 11/3/31 Blood sugar 148 mgm %. 11/6/31 Blood sugar 157 mgm %. 11/10/31 Blood sugar 88 mgm %. 11/13/31 Blood sugar 124 mgm %. 11/20/31 Blood sugar 141 mgm %. 11/24/31 Blood sugar 115 mgm %. 11/27/31 Blood sugar 108 mgm %. 12/1/31 Blood sugar 95 mgm %. B.M.R. minus 17 and 14%, pathological report was adenoma of the thyroid. 12/4/31 Sugar tolerance test (see figure III).

Progress:

The patient entered hospital showing glycosuria, and with a blood sugar of 189 mgm %. Was placed on a strict diabetic regime, namely 91 to 100 total "G" with 8 units of insulin given (3-2-3). Patient became sugar free before operation. Thyroidectomy was performed by Dr. Waters 11/14/31 using 1% novocaine locally. The post operative course was satisfactory except for an occasional glycosuria. From 11/28/31 to date of dismissal 12/7/31 remained sugar free with diet and no insulin. Patient was dismissed 12/7/31 with no glycosuria, blood sugar 95mgm%, B.M.R. minus 17 and 14%. Patient to follow diet C86, P53, F135, total "G" 130, calories about 1800. No insulin to be taken unless advised by physician.

Discussion:

The symptomatology suggests both hyperthyroidism and diabetes mellitus. The symptoms of hyperthyroidism preceded those

of diabetes. The sugar tolerance test appears like that of a diabetic according to Joslin and Lahey (4). After insulin and diet used patient became sugar free and was operated. After operation the sugar tolerance improved such that the 8 units of insulin could be discontinued and the patient kept sugar free with diet alone. The last sugar tolerance test made after thyroidectomy showed a normal fasting blood sugar. There was, however, a deficiency in the insulogenic reserve necessitating a diabetic diet.

Figure II.

Hours.

Fasting ½ 1 1½ 2 3

Glucose Tolerance Test 11-1-31.

Miss B. A.

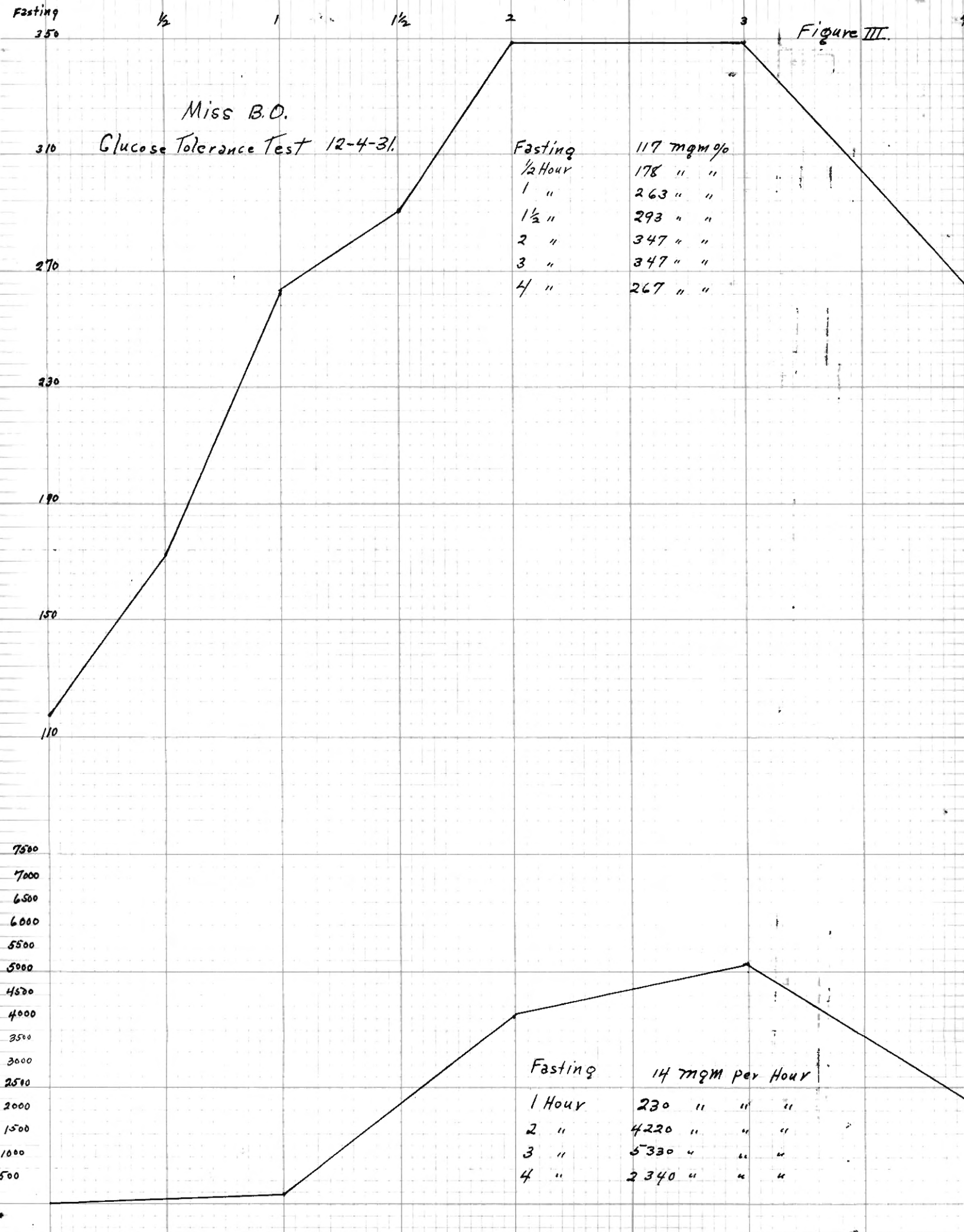
Blood sugars	mgm %
Fasting	168
½ hour	275
1 "	333
1½ "	398
2 "	358
3 "	356
4 "	185

Urine sugar	mgm per Hour
Fasting	110
1 Hour	2970
2 "	8048
3 "	17,630
4 "	8,840

400 360 320 280 240 200 160

18000 17500 17000 16500 16000 15500 15000 14500 14000 13500 13000 12500 12000 11,500 11,000 10,500 10,000 9500 9000 8500 8000 7500 7000 6500 6000 5500 5000 4500 4000 3500 3000 2500 2000 1500 1000 500 0

Figure III.



Miss B.O.

Glucose Tolerance Test 12-4-31.

Fasting	117 mgm %
½ Hour	178 " "
1 "	263 " "
1½ "	293 " "
2 "	347 " "
3 "	347 " "
4 "	267 " "

Fasting	14 mgm per Hour
1 Hour	230 " " "
2 "	4220 " " "
3 "	5330 " " "
4 "	2340 " " "

Case II---Mrs. P. C. age 46, white, female, married, housewife entered the University Hospital 12/4/30 complaining of dry mouth and throat, polydipsia, polyphagia, pruritus vulvae, enlarged thyroid gland, dyspnea on exertion and choking spells. Patient began to become obese 23 years ago following the birth of her first child. About 18 years ago noticed enlargement of the thyroid gland. Ten years ago patient began noticing nocturia, polydipsia and polyphagia. About 5 years ago she began developing ulcers on both legs below the knees. At this time she was placed on a diabetic diet by her private physician. Patient remained on a diet for two years feeling well during that time. She discontinued her diet with no ill effects until one month ago when she began to develop the above named symptoms. Patient came to the dispensary where she was prescribed a temporary diet and advised hospitalization due to a very high blood sugar.

Past History: Negative

Family History: Negative.

Operations and injuries: None.

Eyes and Ears: Eyes have become more prominent during the last 6 months.

Nose and Throat: Negative.

Gastro-intestinal: Negative.

Genito-urinary: Nocturia 4-5 times per night, polyuria.

Menses: Negative.

Weight: Best 190# one month ago, present weight 168#.

Physical examination.

General: Short, obese female, lying quietly in bed.

Head: Negative.

Eyes: Suggestion of exophthalmos.

Ears: Negative

Nose and Throat: Upper gums somewhat ulcerated.

Neck: Small protruding tumor about the size of a golf ball situated in the sternal notch. Mass attached to the thyroid gland.

Heart: Enlarged to left, systolic murmur, regular rate 126, blood pressure 210/110.

Abdomen: Negative

Pelvis: Negative

Extremities: Negative

Laboratory Findings:

12/5/30 urine showed 3 plus albumin, 4 plus sugar, 2 plus acetone, and a few casts. The blood picture was negative. Blood sugar 428 mgm %. 12/6/30 B.M.R. plus 51 and 43 %. Pulse was 128. 12/9/30 Blood sugar 376 mgm %. 12/10/30 B.M.R. was plus 28 and 24%. 12/16/30 Blood sugar 298 mgm %. Wassermann was negative. 12/19/30 B.M.R. was plus 23 and 22%. Blood sugar 264 mgm %. 12/26/30 Blood sugar 186 mgm %. 1/2/31 Blood sugar 168 mgm %. 1/12/31 urine showed trace of sugar. 1/20/31 Blood sugar was 166 mgm %. 1/24/31 Urine showed no sugar, B.M.R. was minus 4 and 0 %. 1/27/31 Blood sugar 138 mgm %. 1/30/31 Blood sugar 130 mgm %.

Progress:

The patient entered 12/4/30 with glycosuria, basal

metabolic rate of plus 43 and 51%, and a fasting blood sugar of 428 mgm %. Following administration of Lugal's solution and diet, and insulin therapy the basal metabolic rate fell to plus 22 and 23%, the urine contained only a small trace of sugar, and the blood sugar dropped to 168 mgm %. Following thyroidectomy 1/10/31 the urine became permanently sugar free, the B.M.R. dropped to minus 4% and 0%, and the blood sugar dropped to 130 mgm % on a diabetic and 6 units of insulin per day. The patient was dismissed with a diet C46, P77, F101, "G" 101, Calories 2000, and 6 U. insulin. The patient has returned to the dispensary for periodical observations. Has improved progressively since discharged from the hospital.

Discussion:

This patient shows definite improvement of sugar tolerance brought about by iodine, diet and insulin. More permanent results were obtained by thyroidectomy.

Case III---Mr. J. R. K. age 46, male, white, entered the University Hospital 11/10/24 complaining of polyuria, polydipsia, polyphagia, pruritus, loss of strength, nervousness, dyspnea on exertion, vertigo, palpitation and exophthalmos. The patient began to loose strength after an attack of influenza February, 1923. He noted change in disposition about 18 months ago. About 13 months ago he became short of breath on exertion. 9 or 10 months ago he

began noticing vertigo. Exophthalmos became noticable 6 months ago. Has had polyuria, polydipsia, polyphagia, and nocturia for several months. Lately patient has developed voracious appetite, cardiac palpitation, pains in the legs, and tremor of the hands.

Past History: Negative

History by Systems: Eyes showed exophthalmos of eyes, neck has mass present, noted pains in legs and tremor of hands.

Weight: Best weight 179#, lowest 138#, and present weight 158#.

Family history: Father died of diabetes mellitus, mother died of goitre and apoplexy.

Physical Examination

Head: Negative

Eyes: Marked exophthalmos

Ears: Negative

Nose and Throat: Negative

Neck: Palpable thyroid.

Heart: Slightly increased rate.

Abdomen: Negative

Extremities: Tremor, excoriation on legs.

Genitalia: Negative.

Laboratory Findings:

11/11/24 Urine showed glycosuria, blood picture was negative, blood sugar 225 mgm %. 12/5/24 Urine showed glycosuria, quantitatively 2.3%. 12/10/24 no glycosuria. 12/20/24 no glycos-

uria. 12/25/24 Trace of sugar in the urine. 12/29/24 No glycosuria. 1/30/25 No glycosuria. 2/1/25 No glycosuria, blood sugar 115 mgm %.

Progress:

Patient entered 11/10/24 with high fasting blood sugar and glycosuria. Patient was put on diet P45, C60, F160, and "G" 102. No insulin was used. Under this regime patient became sugar free before thyroidectomy. Following operation 12/29/24 the patient remained sugar free with diet and the blood sugar dropped to 115 mgm %.

Discussion:

The symptomatology suggests a combination of hyperthyroidism and diabetes mellitus. The fasting blood sugar is high as is found in diabetes mellitus. Thyroidectomy improved the sugar tolerance so that the patient could remain sugar free on a diet. The diabetes remained in mild form, ~~because~~ however, the patient was unable to discontinue the dietetic restrictions.

Case IV---Mr. G. H. S. age 30, male, white, married, farmer, entered the University Hospital 6/20/27 complaining of weakness, increased appetite, and polyuria. Last summer patient was troubled with backache. In March he developed headache and weakness. About one month ago he began to notice a voracious appetite. About that time he noticed polyuria, polydipsia, and dry mouth.

Previous illness: Childhood diseases were measles and mumps. Adult diseases none. Injuries and accidents none.

History by Systems:

Heart--dyspnea on exertion for last 4 or 5 years, palpitation. Genito-urinary--nocturia since present illness.

Weight: Best 135#, present weight 129#.

Family history: Negative.

Physical Examination

Head: Negative

Eyes: Slight exophthalmos

Ears: Negative

Mouth & throat: Negative

Neck: Palpable thyroid

Chest: Heart has lowd, booming first sound but no murmurs.

Abdomen: Negative

Genitalia: Negative

Extremities: Slight tremor of hands.

Laboratory findings:

6/20/27 glycosuria, blood count negative, Wassermann negative, blood pressure 118/68. 6/21/27 glycosuria, basal metabolic rate plus 15%. 6/25/27 sugar tolerance test (see figure IV).

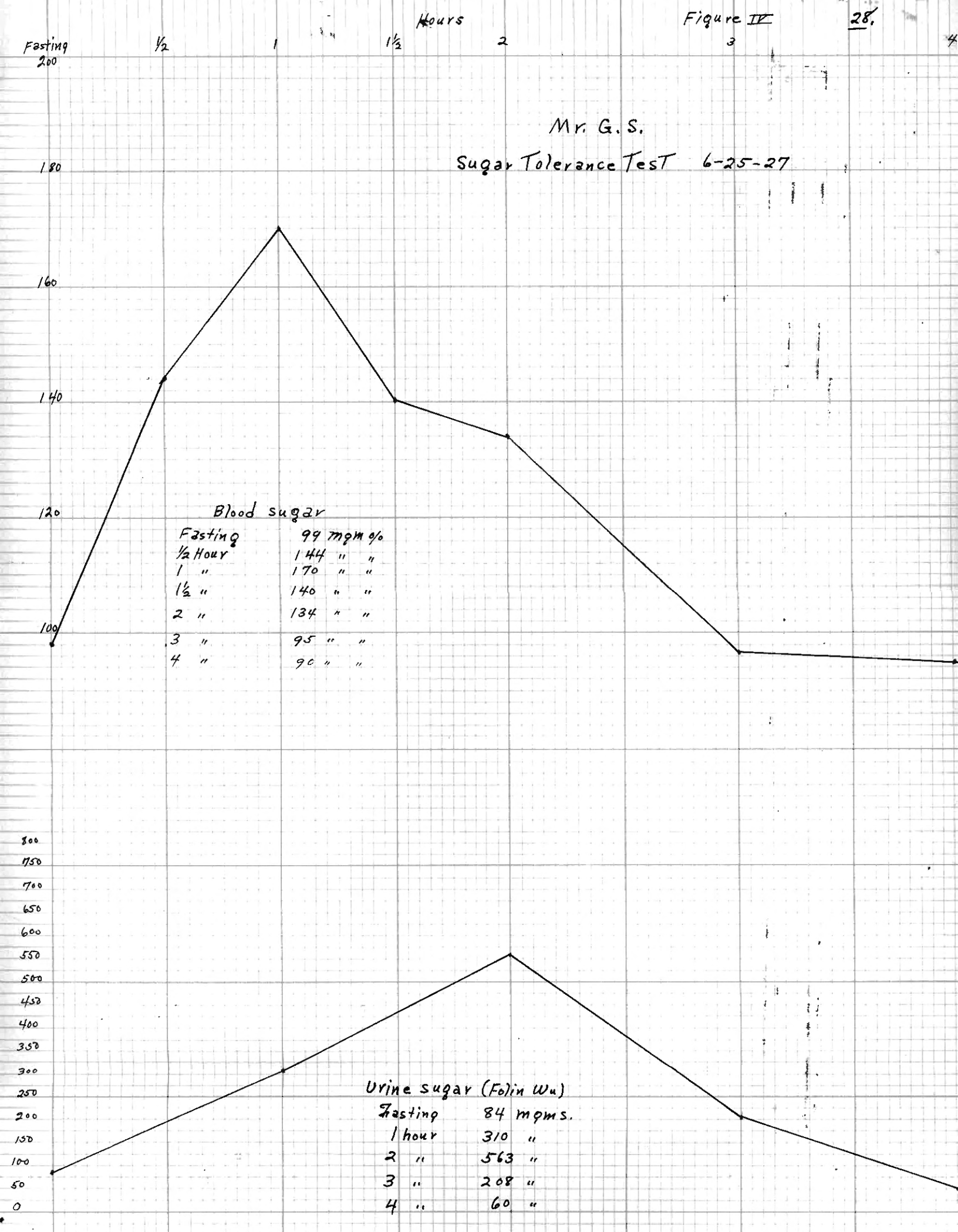
Progress.

Patient refused operation after complete explanation of condition. Left hospital showing evidence of hyperthyroidism and glycosuria.

Discussion.

This case did not show evidence of marked diabetes. The fasting sugar was normal and the rise was gradual much the same as in normal cases. The return to normal line was prolonged an hour showing evidence of a lack of insulogenic reserve. Such a case may become complicated by diabetes if the patient is allowed to eat at will and his basal metabolism is not lowered by thyroidectomy. This case demonstrates the improper management of a hyperthyroid case with simple glycosuria.

Figure IV


Hours
Fasting
1/2
1
1 1/2
2
3
4
200
180
160
140
120
100
Mr. G. S.
Sugar Tolerance Test 6-25-27
Blood sugar
Fasting 99 mgm %
1/2 Hour 144 " "
1 " 170 " "
1 1/2 " 140 " "
2 " 134 " "
3 " 95 " "
4 " 90 " "
800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
Urine sugar (Folin Wu)
Fasting 84 mgms.
1 hour 310 "
2 " 563 "
3 " 208 "
4 " 60 "

Case V. Miss G. T. age 17, white, single, American, school girl entered the University hospital 8/5/27 complaining of enlarging mass in the neck, nervousness, choking sensation, headaches, dyspnea on exertion, tachycardia, hot flashes and profuse perspiration, gradual failing vision and increased appetite. About 6 months agopatient developed edema of the ankles. Following this she developed headaches and nervousness. At this time she noted a mass in the neck which seemed to grow larger. Along with this she noted palpitation, tachycardia, choking, dyspnea, hot flashes and perspiration and increased appetite. Then she began to develop involuntary twitchings and tremor.

Past History: Previous illness were measles, mumps, varicella, pertussis, tonsillitis and influenza. Injuries and accidents--right wrist sprained 3 years ago.

History by systems: Eyes--blurring of vision for past four months.

Heart--edema of ankles, dyspnea, and palpitation.

Weight: 120#, lost 8# in 2 months,

Family History: negative

Physical Examination

Head: Flushed face, involuntary twitchings of head.

Eyes: Decreased vision.

Ears: Negative

Nose & Throat: Negative

Neck: Bilateral enlargement of thyroid, Soft, smooth feel. Marked pulsation in gland.

Lungs: Negative

Heart: Soft systolic murmur. B. P. 128/64.

Abdomen: Negative.

Genitalia: Negative

Rectal: Negative

Extremities: Course tremor of fingers. Reflexes ok.

Laboratory findings: 8/5 urine showed trace of sugar; Wassermann negative; blood count RBC 3,210,000, WBC 4,040, Hemoglobin 70%

8/10 Sugar tolerance test (see figure V).

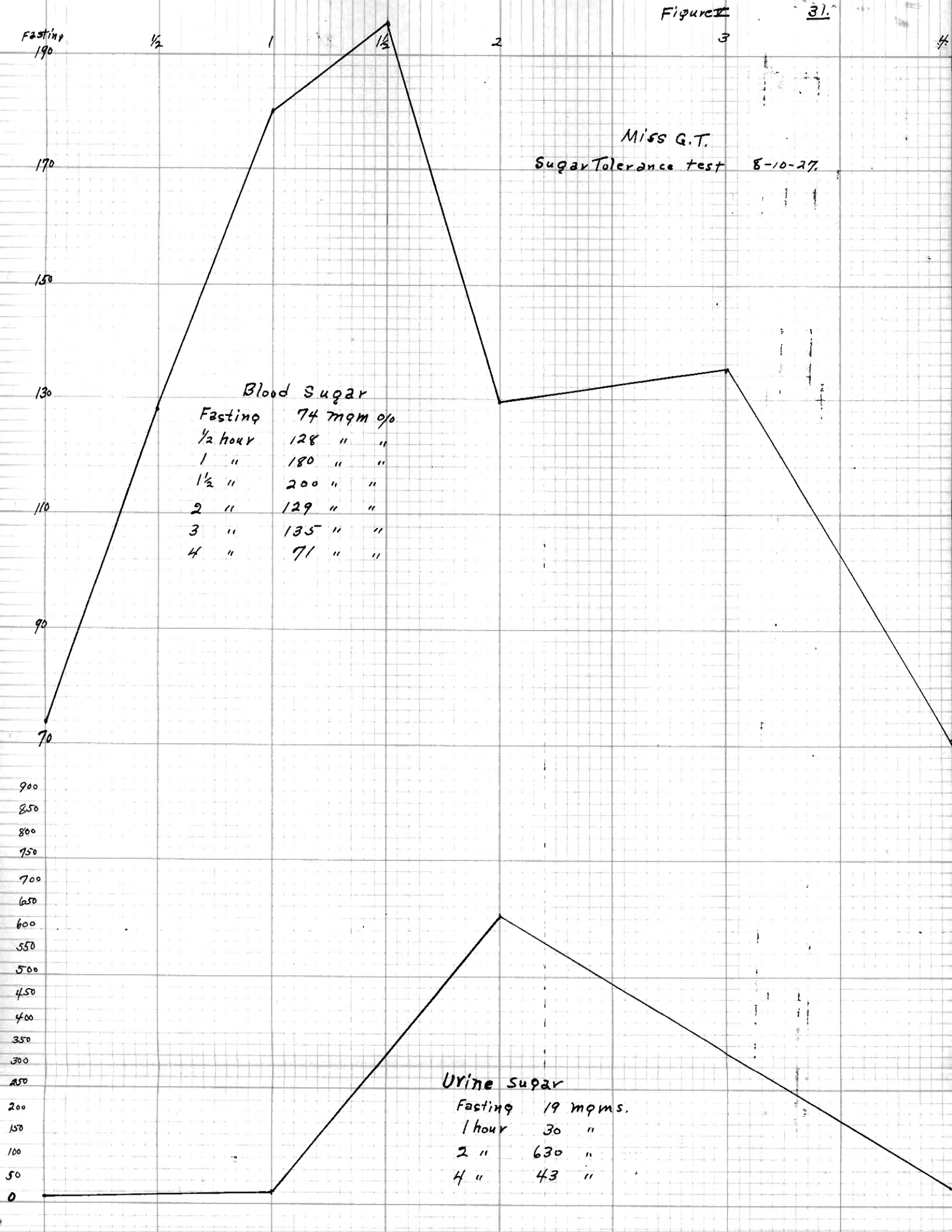
8/12 urine shows trace sugar 8/13 urine shows trace sugar.

8/17 BMR plus 43%. 8/29 BMR plus 18%.

Progress: On entrance patient very nervous, pulse rat e 130 Patient given lugal's solution with definite improvement. Patient was unable to tolerate a high carbohydrate diet without spilling over large quantities of sugar into the urine. Patient later placed in a private room and given more lugal's solution. Following this patient quieted down and pulse rate decreased. On 8/29 patient was operated with gas anesthesia. 8/30 patient became cyanotic and died suddenly of laryngeal edema.

Discussion:

The sugar tolerance test (figure V) demonstrates the type found in hyperthyroidism. According to Joslin and Lahey (4) the fasting blood sugar should be within normal limits as is found in this case. The rise shows a decreased insulogenic reserve. The Folin-Wu urine test showed an increase over normal which usually rises very little. Had this patient lived her sugar tolerance probably would have improved permanently.



Miss G.T.

Sugar Tolerance test 8-10-27.

Blood Sugar

Fasting	74 mgm o/o
½ hour	128 " "
1 "	180 " "
1½ "	200 " "
2 "	129 " "
3 "	135 " "
4 "	71 " "

Urine Sugar

Fasting	19 mgms.
1 hour	30 "
2 "	630 "
4 "	43 "

Case VI---Mrs. D. S. age 27, white, married, housewife, entered the University Hospital complaining of nervousness, palpitation, loss of weight, dyspnea, weakness, hot flashes, profuse sweating, enlargement of the thyroid, and failing vision. The patient began noticing the forenamed symptoms about 2 years ago. Began noticing loss of weight about 6 months ago. Since that time her weight has dropped from 195 to 121#.

Previous history: Had measles, pertussis, mumps and tonsillitis.

Family history: Mother living, age 50, has goitre. Father dead.

Physical Examination

Head: Negative

Eyes: Moderate exophthalmos.

Ear, Nose & Throat: Negative.

Neck: Thyroid enlarged bilaterally, thrill and bruits present.

Heart: Rapid, 120 per minute, lowd, harsh systolic murmur. at the apex referred to great vessels in the neck. Apex beat 9 cm. to the left of the mid-sternal line.

Laboratory findings:

7/16 B.M.R. was plus 60%. 7/20/27 Urine showed specific gravity of 1.020, trace sugar, no albumin, negative microscopic. Blood count showed hemoglobin 80%, RBC 4,620,000, WBC 11,250, polymorphonuclear leucocytes 62%, and lymphocytes 38%. 7/21 Wassermann was negative, blood pressure 120/80, and glucose tolerance test (see figure VI). 8/28 B.M.R. plus 30%.

Progress:

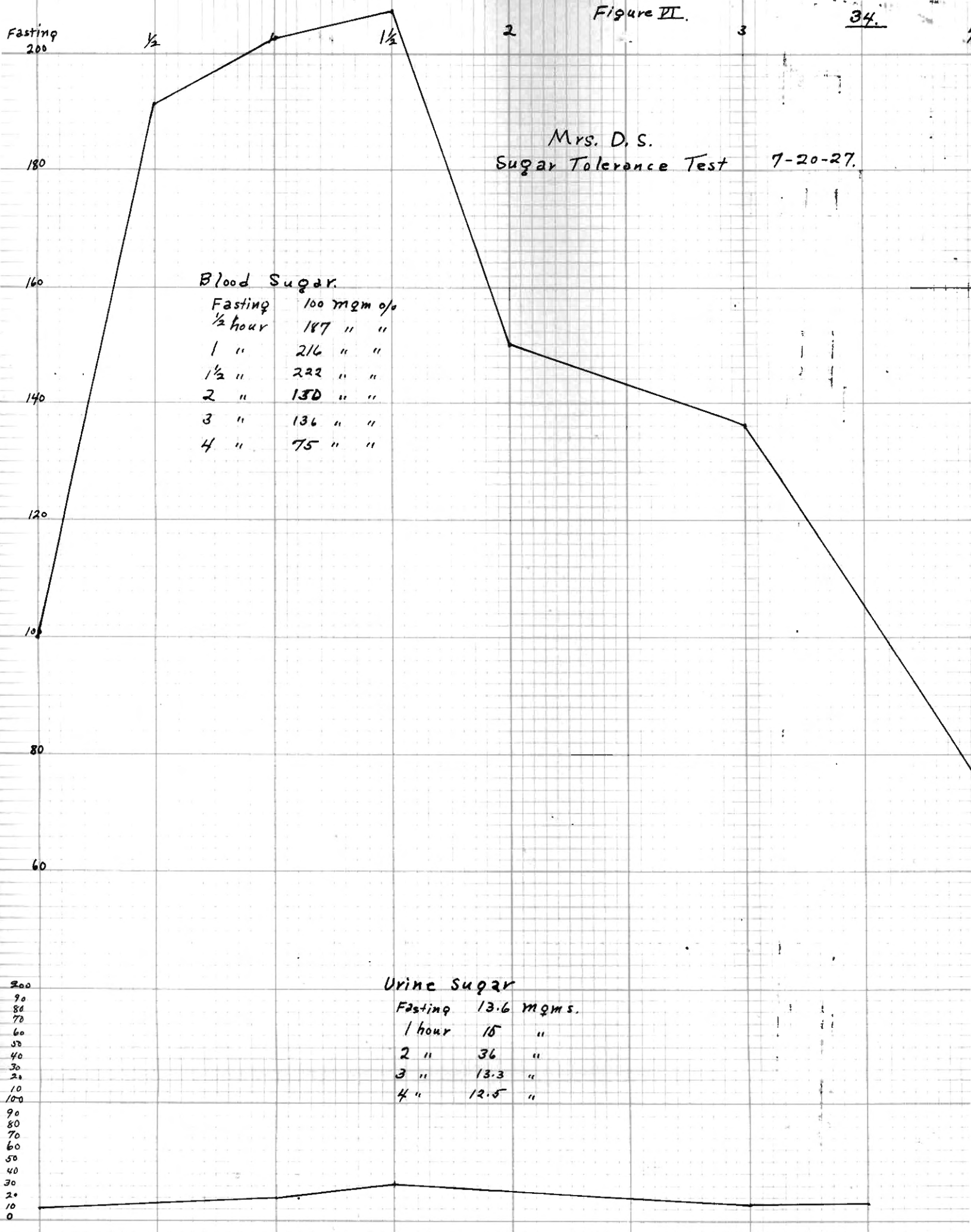
After Lugal's solution the basal metabolic rate dropped from plus 60% to plus 30%. After thyroidectomy the B.M.R.

dropped to minus 2% and the glycosuria disappeared.

Discussion:

This case represents a case of exophthalmic goitre with simple glycosuria. The administration of Lugal's solution improves the condition markedly by lowering the basal metabolic rate. Thyroidectomy improved the sugar tolerance and the glycosuria disappeared permanently.

Figure VI.



Mrs. D. S.
Sugar Tolerance Test 7-20-27.

Blood Sugar.

Fasting	100 mgm o/o
½ hour	187 " "
1 "	216 " "
1½ "	222 " "
2 "	130 " "
3 "	136 " "
4 "	75 " "

Urine Sugar

Fasting	13.6 mgms.
1 hour	15 "
2 "	36 "
3 "	13.3 "
4 "	12.5 "

Case Summary.

The first three cases represent cases of hyperthyroidism complicated by diabetes mellitus. All three cases were rendered sugar free by use of diet, insulin, and Lugal's solution. The sugar tolerance was permanently improved by thyroidectomy. The patients were able to carry on as mild diabetics. The latter three cases represent cases of hyperthyroidism with simple glycosuria. The glycosuria disappeared temporarily with rest and Lugal's solution. Thyroidectomy improved the tolerance permanently in the last case. The two previous cases did not demonstrate the results of thyroidectomy because one refused operation and the other died on the day following operation. The sugar tolerance curves demonstrated normal fasting blood sugars and alimentary hyperglycemias resulting from decreased sugar tolerance brought about by the overactivity of the thyroid gland.

Conclusions:

1. The first case of hyperthyroidism complicated by diabetes mellitus was reported in 1862.

2. Glycosuria in cases of hyperthyroidism was reported in 4.4 to 90% of cases.

3. Hyperthyroidism complicated by diabetes is not a common syndrome. The frequency is reported as 1.1 to 3.15%. I found 1.5% among the hyperthyroidism cases at the University Hospital. Was found to exist more often in toxic adenoma, namely 0.9% in toxic adenoma and 0.6% in exophthalmic goitres.

4. There probably is a definite endocrine relationship. Falt believes the thyroid, pituitary and adrenal associated with the sympathetic system and the pancreatic islands with the parasympathetics. Stimulation of the sympathetic or any of the associated glands inhibits the action of the pancreatic cells hence producing glycogenolysis and hyperglycemia.

5. Diabetes mellitus follows hyperthyroidism in the large majority of the cases where this syndrome exists.

6. The sugar tolerance is definitely lowered in hyperthyroidism, and diabetes, however, unlike the usual case of diabetes the fasting sugar is within normal limits.

7. Pathological findings bear out experimental and clinical findings in which there is a definite relationship between the endocrines. It also shows that diabetes not always due to pancreatic pathology but there may be a normal pancreas with pathology in the thyroid-pituitary system. The reports also show that clinical observations cannot always be attributed to specific endocrine pathology.

8. Hyperthyroidism and diabetes more likely to develop ketosis and coma than uncomplicated diabetes.

9. Hyperthyroidism decreases the insulin unit. Iodine decreases the metabolic rate and carbohydrate intake thus making diet and insulin more effective.

10. All cases of simple glycosuria should be watched for development of diabetes. They should be operated as soon as the patient is prepared.

11. Thyroidectomy produces permanent improvement in the sugar tolerance thereby abolishing simple glycosuria, and rendering cases of diabetes mellitus more easy to control.

12. The six case reports demonstrate glycosuria, three of which are complicated by diabetes mellitus.

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