HYPERINSULINISM, A DEFINITE DISEASE ENTITY

ETIOLOGY, PATHOLOGY, SYMPTOMS, DIAGNOSIS, PROGNOSIS AND TREATMENT OF SPONTANEOUS INSULOGENIC HYPOGLYCEMIA (HYPERINSULINISM)

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Hyperinsulinism, also called the "hunger" disease because hunger, associated with weakness, nervousness and other manifestations of hypoglycemia, is the most constant symptom, has been known to exist for ten years.[1] At least a hundred cases have been reported by American and European clinicians, surgeons and pathologists who have made thorough studies of all phases of hypoglycemia due to the hypersecretion of the islet cells of the pancreas. Sufficient data have accumulated in medical literature to warrant the discussion of hyperinsulinism as a definite disease entity. In this paper the effort will be made to outline the etiology, pathology, symptoms, diagnosis and treatment of hyperinsulinism as derived from published reports of many cases and from ten years' study of the disease.

DEFINITION

Hyperinsulinism, the antithesis of diabetes mellitus (hypoinsulinism), may be defined as a disease of the pancreas resulting from the spontaneous excessive secretion of insulin by the islands of Langerhans and characterized clinically by hypoglycemia with its concomitant symptoms, i. e., hunger, weakness, nervousness, tremors, sweating, trembling and mental lapses. Unconsciousness and convulsions may occur in the severe cases.

Dysinsulinism is a condition, or disease, associated with the uncontrolled secretion of the islet cells of the pancreas resulting in hyperglycemia, alternating with or followed by hypoglycemia, and characterized clinically by symptoms of hypo-insulinism (diabetes mellitus), and at times by the syndrome of hyperinsulinism.

Hypo-insulinism (diabetes mellitus) is essentially a disease of the pancreas resulting from the deficient secretion of insulin by the islands of Langerhans and is characterized clinically by hyperglycemia, polyuria, polyphagia, polydipsia, emaciation and weakness. Gangrene of the lower extremities, carbuncles and acidosis, with and without coma, may occur in the neglected cases of hypo-insulinism.

FREQUENCY

No doubt, hyperinsulinism has existed as long as has diabetes and was not recognized, just as hyperthyroidism, now known to be a frequent disease, for a long time was considered a nervous disorder and was not recognized as a disease of the thyroid. Physicians now practicing medicine can remember when the first cases of appendicitis were recognized and operations performed; and it may be predicted that in the near future hyperinsulinism will become recognized as a comparatively frequent disease which in most cases is amenable to treatment, either by dieting or by surgery.

A chronological review[2] of the cases of hyperinsulinism reported in the United States and Canada up to 1931 indicates that hyperinsulinism not only is a frequent condition but that it may cause a wide range of symptoms which heretofore have been diagnosed as being due to other causes but which in reality are manifestations of insulogenic hypoglycemia. Marsh[3] in 1930 reported nine cases of hyperinsulinism, which occurred in his private practice. Jean Sigwald[4] and Rathery report a number of cases of hyperinsulinism ("hypoglycémie par hyper-pancréatie"). Sigwald also reviews a number of reported European cases and presents a large series of experiments on animals in which he describes the manifestations of hypoglycemia induced by varying doses of insulin. Sippe and Bostock,[5] in Sidney, Australia, in a review of the general subject of hypoglycemia, report twenty-five cases as having occurred in their private practice and in the Brisbane General Hospital. In discussing the frequency of chronic hypoglycemia they say: "In a large series of cases met with in general medical practice, the percentage of cases of hypoglycemia was 0.47 and that of diabetes 0.51. Thus it will be seen that hypoglycemia is practically as common as hyperglycemia."

Cammidge in 1930 reported 200 cases of "chronic hypoglycemia." He is of the opinion that the condition is of hepatogenous origin, though he considers that the pancreas may be a contributing factor in producing the hypoglycemia.

Judging from the number of cases of hyperinsulinism now being reported by many clinicians and from blood sugar studies in 3,076 cases, in my series of 6,641 adult patients largely ambulatory with gastro-intestinal and nutritional disorders, it seems probable that hyperinsulinism is almost as frequent as the opposite secretory disorder of the insulin-forming cells of the pancreas, hypo-insulinism (diabetes mellitus). Of the recorded fasting blood sugars on 3,076 patients, 535 were diabetic. Of the remaining 2,541 nondiabetic patients, 242 had hyperglycemia; i. e., fasting blood sugars above 0.120 per cent. No doubt many of these were cases of true diabetes, but most of the patients were under observation for only two or three days and the opportunity was not given for further study in their cases. Of the 2,541 nondiabetic cases, 218 showed hypoglycemia of varying degrees. Of these, 86 showed unmistakable symptoms of hyperinsulinism and dextrose tolerance tests or repeated fasting blood sugars confirmed the diagnosis. Fifty-eight of the cases of hypoglycemia presented symptoms of hyperinsulinism but were considered borderline cases, while seventy-four patients found to have hypoglycemia in the routine fasting blood sugar examinations had no symptoms of hyperinsulinism. It is probable that some of the latter two groups, if thoroughly studied, would prove to be hyperinsulinism.

Careful history taking, fasting blood sugars, dextrose tolerance tests, and blood sugar studies at the time of many heretofore unexplained nervous attacks, and in periods of unconsciousness with and without convulsions will prove that many of them are due to hyper-

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1. Harris, Seale: (*a*) The Etiology and Prevention of Diabetes—Hyperinsulinism by Exhausting the Islands of Langerhans May Be a Factor in the Production of Diabetes, Virginia State M. A., October, 1923; (*b*) Virginia M. A. Monthly **50**: 672 (Jan.) 1924; (*c*) Hyperinsulinism and Dysinsulinism, J. A. M. A. **83**: 729-733 (Sept. 6) 1924.

2. Harris, Seale: Hyperinsulinism: Review of Cases Reported in United States and Canada, Endocrinology **16**: 29-42 (Jan.-Feb.) 1932.

3. Marsh, H. E.: Hyperinsulinism with Report of Cases, Wisconsin M. J. **30**: 340-342 (May) 1931.

4. Sigwald, Jean: L'hypoglycemie, Paris, Doin & Cie., 1932.

5. Sippe, Clive, and Bostock, John: Hypoglycemia: A Survey and a Report of Twenty-Five Cases, M. J. Australia **1**: 217-219 (Feb. 18) 1933.

insulinism. The physician with laboratory facilities who keeps up with medical literature will find many cases of hyperinsulinism in his regular practice.

Since a number of cases of epilepsy and epileptiform attacks have been found to be associated with hyperinsulinism, every patient having petit mal and grand mal attacks should have thorough blood sugar studies made before he is stigmatized with the diagnosis of epilepsy. It is believed that many cases now diagnosed as idiopathic epilepsy soon will be classified as belonging to the severe type of hyperinsulinism, in which recurring attacks of unconsciousness and convulsions are symptoms.

ETIOLOGY

Since hyperinsulinism and diabetes (hypo-insulinism) are secretory disorders of the pancreas, it seems probable that the same causes may produce the two; and of these a previous, usually unrecognized, pancreatitis is perhaps the most important factor. The fact that several patients have been observed who have diabetes and hyperinsulinism (dysinsulinism) indicates that the two have a common origin. In one of my cases of subacute pancreatitis there was disturbed carbohydrate metabolism with symptoms of hyperinsulinism.

Probably the most important underlying or predisposing cause of the pancreatitis that precedes hyperinsulinism and diabetes is a diet deficient in vitamins. About twenty years ago, McCollum, Simmonds [6] and Parsons expressed the opinion that the rôle of food in the etiology of many diseases "involves increased susceptibility to infection, due to lowered resistance caused by faulty diet." McCarrison's [7] classic experiments seem to have proved that foods of low vitamin content predispose to all abdominal infections. Other nutritionists, Barnett Sure [8] in particular, stress the rôle of diets deficient in vitamins A and B in the etiology of abdominal infections. The anatomic and circulatory relations of the pancreas would seem to make it particularly vulnerable to secondary involvement from gallbladder, intestinal and other abdominal infections.[9] If it is accepted as a fact that faulty diets predispose to the infections that play a part in the etiology of pancreatitis, sugar-saturated, vitamin-starved Americans, i. e., those who live largely on white flour bread, white potatoes, white rice, lean meats, sugar saturated coffee, and sugar-laden desserts, with candy and soft drinks between meals, would seem to be prone to become victims of pancreatic disorders, including hyperinsulinism and diabetes.[10] With a damaged pancreas as a factor, and since the ingestion of carbohydrates stimulates insulogenesis,[11] it seems probable that the excessive use of sugars and starches in the American diet may play another important part as an exciting cause in the incidence of hyperinsulinism.

Focal infections from the mouth, tonsils, colon, rectum, prostate, and the uterus and its adnexa may be the primary causes of the pancreatitis that precedes hyperinsulinism. Likewise, the general infections such as typhoid, influenza and the diseases of childhood, particularly mumps, may involve the pancreas as a complication, and the pancreatitis may be unrecognized.

In one of my cases of epilepsy associated with hyperinsulinism the first attack occurred about four weeks after an abdominal injury from which the patient was in bed three weeks suffering from abdominal pain and tenderness, nausea and vomiting, symptoms that suggest injury to the pancreas. It therefore seems that trauma may be a factor in the etiology of hyperinsulinism.

Three diabetic patients with hyperglycemia have given clear histories of previous hypoglycemic symptoms, indicating that the first manifestation of dysfunction of the pancreas was hyperinsulinism, and diabetes was a sequence. One of these patients, with a history of hyperinsulinism before she became obese and developed diabetes, has a son who has typical symptoms of mild hyperinsulinism.[12] This suggests that the familial tendency exists in hyperinsulinism as in diabetes (hypoinsulinism). Sippe and Bostock express the opinion that "the hypoglycemic entity possesses a definite hereditary tendency."

Worry and other emotional disturbances, and overwork—particularly prolonged physical exertion, thus exhausting the suprarenals, which seem to act conjointly with the islet cells of the pancreas—may play a part in producing excessive and uncontrolled insulogenesis.

A number of the severe cases of hyperinsulinism have been proved to be due to adenomas of the pancreas (insulomas). In other cases, carcinoma of the islands of Langerhans has been found at operation or at necropsy. It seems probable that neoplasms of the pancreas may be as important factors in the etiology of hyperinsulinism as adenomas and other tumors of the thyroid are in the pathogenesis of hyperthyroidism.

PATHOLOGY

In several cases of hyperinsulinism in which operation has been done, normal appearing pancreases have been found. Histologic studies have not revealed any pathologic changes in those cases. It therefore seems that, as in diabetes, hyperinsulinism may occur without any demonstrable lesion of the pancreas.

Hyperplastic islet cells were found by Phillips [13] at necropsy on a Negro who died in a hypoglycemic attack. Phillips cited the case of Dubreuil and Anderodias [14] of giant islands of Langerhans in a child born of a diabetic mother. Phillips also cited a case reported by Gray and Feemster [15] of "compensatory hypertrophy and hyperplasia of the islands of Langerhans in the pancreas of a child born of a diabetic mother." The blood sugar of the child on the day it died was 0.067 per cent. It seems probable that at least in the severe cases of hyperinsulinism that have existed for some time there may be hyperplasia of the islet cells, though as in other glandular organs the insulogenic cells may function excessively without any evident change in the cell structure.

The first pathologically proved case of hyperinsulinism was reported by Wilder, Allan and Robertson.[16] A

6. McCollum, E. V.: The Newer Knowledge of Nutrition, New York, Macmillan Company, 1922. McCollum, E. V., and Simmonds, Nina: Food, Nutrition and Health, published by the authors.
7. McCarrison, Robert: Faulty Food in Relation to Gastro-Intestinal Disorder, J. A. M. A. **78**: 1 (Jan. 7) 1922.
8. Sure, Barnett: The Vitamins in Health and Disease, Baltimore, Williams and Wilkins Company, 1933, p. 185.
9. Harris, Seale: Pancreatitis as Related to Gastro-Intestinal and Gallbladder Infections, with Particular Reference to the Etiology of Diabetes, J. A. M. A. **81**: 1496-1499 (Nov. 3) 1923.
10. Harris, Seale: Sugar-Saturated Vitamin Starved America, Am. Med. **23**: 840 (Nov.) 1928.
11. John, H. J.: The Lack of Uniformity in the Insulin Reaction, Am. J. M. Sc. **172**: 96 (July) 1926.
12. Harris, Seale: South. M. J. **36**: 250 (June) 1933.
13. Phillips, A. W.: Hypoglycemia Associated with Hypertrophy of the Islands of Langerhans, J. A. M. A. **96**: 1195 (April 11) 1931.
14. Dubreuil, G., and Anderodias: Ilots de Langerhans giants chez un noveau né, issu de mére glycosurique, Compt. rend. Soc. de biol. **83**: 1490, 1920.
15. Gray, S. H., and Feemster, L. C.: Compensatory Hypertrophy and Hyperplasia of the Islands of Langerhans in the Pancreas of a Child Born of a Diabetic Mother, Arch. Path. & Lab. Med. **1**: 348 (March) 1926.
16. Wilder, R. M.; Allan, F. N.; Power, M. H., and Robertson, H. E.: Carcinoma of the Islands of the Pancreas, Hyperinsulinism and Hypoglycemia, J. A. M. A. **89**: 348 (July 30) 1927.

physician, aged 40, had recurring attacks of unconsciousness and convulsions (blood sugar, 0.030 per cent). Exploratory laparotomy revealed an inoperable carcinoma of the pancreas. The patient died a month later. Necropsy showed a carcinoma of the islands of Langerhans with metastatic nodules in the liver, which showed a distinct resemblance to the islet cells of the pancreas. An extract from the metastatic nodules in the liver injected into rabbits showed insulin activity. The report of this case presents one of the most thorough studies of hyperinsulinism that is recorded in medical literature.

Neoplasms of the islet cells of the pancreas associated with hyperinsulinism have also been studied and reported by Thalhimer and Murphy,[17] McClenahan and Norris,[18] Warren,[19] Howland and Campbell and their associates,[20] Graham and Womack,[21] Smith and Seibel,[22] and Bast, Schmidt and Sevringhaus.[23] Smith and Seibel's study of five adenomas found by operations and by autopsy on hypoglycemic patients probably present the most comprehensive report that has been made on the pathology of adenomas found associated with hyperinsulinism.

SYMPTOMS

The Mild Type.—In the mild cases of hyperinsulinism the patient complains most frequently of excessive hunger, weakness, nervousness, anxiety or irritability, one or two hours before meals. All these subjective symptoms are relieved by eating, only to recur three or four hours after meals and often during the night. In addition, there may be trembling, flushed face, or pallor, particularly around the lips, profuse perspiration and tachycardia. These symptoms may be exaggerated by exercise, overwork, either mental or physical, worry and other emotional disturbances. Recurring headaches and inability to concentrate the mind on work late in the afternoon have been observed. Fatigability and insomnia are frequent complaints. Vertigo, dyspnea, "smothering spells," cardiac palpitation and precordial

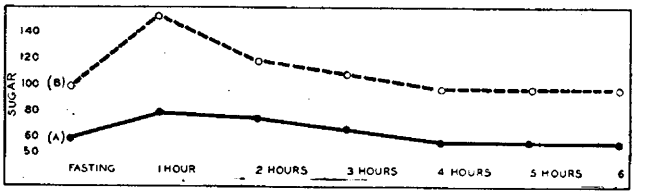

Chart 1 (case 1).—Hyperinsulinism. Complaint: hunger and weak spells. *A*, blood sugar curve, May 25, 1931, eight years after the diagnosis of hyperinsulinism had been made. *B*, average normal blood sugar curve. The blood sugar levels (hypoglycemia) were almost constant during ten years' observation. In the charts the sugar is given in milligrams per hundred cubic centimeters of blood.

pain have been noted and have been relieved by dieting, with frequent feedings between meals.

CASE 1.—H. J. R., a man, aged 52, a mechanic who was 5 feet 10½ inches (180 cm.) tall and weighed 139 pounds (63 Kg.) minimum, 186 pounds (84.4 Kg.) maximum, was seen, Oct. 5, 1923, with the following symptoms: extreme hunger, weakness, nervousness, trembling and profuse perspiration just before the noon and evening meals and at night. The "hunger spells" were relieved by eating. The symptoms were controlled by a low carbohydrate diet and frequent feedings. With lapses in diet the "hunger spells" come on, which are relieved by eating.

In the mild cases the fasting blood sugar usually ranges between 0.075 and 0.060 per cent, and the dextrose tolerance curve is of the low flat type that even in one hour does not go higher than 0.110 per cent and in two or three hours has fallen to 0.060 per cent and in some cases lower. Normal fasting blood sugars have been noted at times with patients who have hypoglycemic symptoms, but at other times the level in the same patients is abnormally low. Therefore, repeated

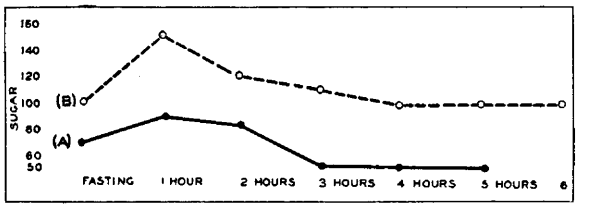

Chart 2 (case 2).—Moderately severe hyperinsulinism following unregulated reduction regimen: psychasthenia or actual psychosis. *A*, low flat blood sugar levels, particularly one and two hours after 100 Gm. of dextrose was given. *B*, average normal blood sugar level.

fasting blood sugar tests should be made before the diagnosis of hyperinsulinism is made or is abandoned. In some cases, not all, the patient's hypoglycemic symptoms are reproduced when his blood sugar falls to its lowest level after a dextrose tolerance test.

Mild cases of hyperinsulinism have also been reported by Gibson and Larimer,[24] John,[25] Liu Shih-Hao and Chang Hsiao-Chien,[26] Pribram,[27] Hoxie and Lisherness,[28] Winans,[29] Waters,[30] Sexton,[31] Marsh,[3] Sippe and Bostock,[5] and others. The authors mentioned, in their published reports of their cases, have described many of the symptoms outlined as occurring in the mild types of hyperinsulinism.

Moderately Severe Type.—In the moderately severe cases of hyperinsulinism the symptoms outlined as occurring in the mild type may be present in an exaggerated form. The hunger, weakness, nervousness, trembling and sweating are more pronounced, and eating gives relief for only one or two hours when more food is demanded, in order that the victim can continue to perform his regular duties. This type appears more frequently in women who complain that they are so weak before breakfast that they cannot do anything. They feel better after breakfast for an hour or two and then become so weak that they have to go to bed; or they learn that they can eat and in a few minutes feel strong enough to go back to work. The vicious circle of getting hungry and weak and eating keeps up until the victim becomes obese. Many of the moder-

17. Thalhimer, William, and Murphy, F. D.: Carcinoma of the Islands of the Pancreas: Hyperinsulinism and Hypoglycemia, J. A. M. A. **91:** 89 (July 14) 1928.
18. McClenahan, W. U., and Norris, G. W.: Pancreatic Adenoma with Hypoglycemia, Am. J. M. Sc. **177:** 93 (Jan.) 1929.
19. Warren, Shields: Adenomas of Islands of Langerhans, Am. J. Path. **2:** 335 (July) 1926.
20. Howland, Goldwin; Campbell, W. R.; Maltby, E. J., and Robinson, W. L.: Dysinsulinism: Convulsions and Coma Due to Islet Cell Tumor of the Pancreas with Operation and Cure, J. A. M. A. **93:** 674 (Aug. 31) 1929.
21. Womack, N. A.; Gnagi, W. B., Jr., and Graham, E. A.: Adenoma of the Islands of Langerhans: Successful Operative Removal, J. A. M. A. **97:** 831-836 (Sept. 19) 1932.
22. Smith, Margaret G., and Seibel, M. G.: Tumors of the Islands of Langerhans and Hypoglycemia, Am. J. Path. **7:** 723-745 (Nov.) 1931.
23. Bast, T. H.; Schmidt, E. R., and Sevringhaus, E. L.: Pancreatic Tumor with Status Epilepticus, Acta chir. Scandinav. **71:** 82-102, 1932.
24. Gibson, R. B., and Larimer, R. N.: Hypoglycemic Symptoms Provoked by Repeated Glucose Ingestion in Case of Renal Diabetes, J. A. M. A. **82:** 468 (Feb. 9) 1924.
25. John, H. J.: Hyperinsulinism, Ohio State M. J. **21:** 99 (Feb.) 1925; Hyperinsulinism, Surg., Gynec. & Obst. **44:** 190 (Feb.) 1927.
26. Shih-Hao, Liu, and Hsiao-Chien, Chang: Hypoglycemia, Arch. Int. Med. **36:** 146 (July) 1925.
27. Pribram, Ernst: Chronic Glycopenia: Clinical Picture, Analysis of Its Causes and Suggestions for Its Therapy, J. A. M. A. **90:** 2001 (June 23) 1928.
28. Hoxie, G. H., and Lisherness, G. M.: Hypoglycemia, Am. J. M. Sc. **173:** 220 (Feb.) 1927.
29. Winans, H. M.: Chronic Hypoglycemia, South. M. J. **23:** 402 (May) 1930.
30. Waters, W. C., Jr.: Spontaneous Hypoglycemia: The Rôle of Diet in Etiology and Treatment, South. M. J. **24:** 249 (March) 1931.
31. Sexton, D. L.: South. M. J. **24:** 251 (March) 1931.

ately severe cases reported have shown overweight; the effort to reduce has exaggerated the symptoms of hyperinsulinism to such an extent that some of the patients had attacks of what has been diagnosed as hysteria of the grave type, and some have been thought to be psychotic.

CASE 2.—Mrs. A. E. W., aged 43, 5 feet 2 inches (157.5 cm.) tall, had reduced from 210 to 133 pounds (from 95 to 60 Kg.) in the past year. About two or three hours after meals and during the night she had spells of weakness, nervousness, mental lapses and irritability and was unable to do her housework. She was mentally depressed and had ideas, or delusions, of persecution. The question of sending her to a psychopathic hospital was considered. She would feel better and stronger after eating but had been dieting to reduce by not eating supper. Glycosuria was present at times. The patient was very much improved by a low carbohydrate, moderately high fat diet for three meals and orange juice or tomato juice every one or two hours between meals. Her mental and physical condition was much improved.

In some of the moderately severe cases there are brief mental lapses, resembling petit mal attacks. In fact, several cases have been reported in which petit mal attacks had been found associated with hyperinsulinism and in which the attacks were controlled by dieting. In the more severe cases there may be brief periods of actual unconsciousness, and transient hemiplegias may occur.

In the moderately severe type the fasting blood sugar level usually ranges from 0.060 to 0.050 per cent, though in some cases it may be above 0.060 per cent, or fall below 0.050 per cent. The symptoms may or may not be reproduced by a dextrose tolerance test when the blood sugar runs lower than 0.055 per cent.

Moderately severe cases of hyperinsulinism have been reported by many other clinicians whose published articles have described the symptoms mentioned in this article. Among the authors whose contributions have enriched the literature on the symptoms of hyperinsulinism may be mentioned: Jonas,[32] Sprunt,[33] Gammon and Tenery,[34] Heyn,[35] Cammidge,[36] Sendrail and Planques,[37] Stenström,[38] Rathery and Sigwald,[39] Escudero,[40] Ravid,[41] Shepherdson[42] and Krause,[43] and others, some of whose names have been listed, have reported mild cases.

The Severe Type.—The severe cases of hyperinsulinism are manifested by attacks of unconsciousness, either with or without convulsions. In some cases there is associated violent delirium. In one of the cases reported by Wilder[44] "the patient developed violent deliria, disturbances of sleep and somnambulism. He had to be confined to a straight jacket because of repeated attacks of manic delirium which were provoked whenever his blood sugar level fell below normal." Wilder concludes by saying: "It is probable that many of these cases are being dismissed with such diagnoses as hysteria, or epilepsy, or schizophrenia; and that more cases of hyperinsulinism will come to light when blood sugar determinations are made with greater frequency. The nervous manifestations of hyperthyroidism formerly led to this disease being included among the neuroses."

CASE 3.—A. H. B., a man, aged 22, a college student, 5 feet 9½ inches (177 cm.) tall, weighing 136 pounds (61.7 Kg.), seen, April 25, 1933, had had almost daily attacks of physical and mental exhaustion since November, 1931, when he became very nervous—"frightened and shaky"—an hour or two before meals. He drank four cups of coffee and two glasses of coca cola a day for relief of and to prevent attacks. Frequently he would become so weak that he would have to lie down before his noon meal. He always felt fine after eating. The symptoms grew worse until October, 1932, when he became dizzy and then unconscious for about twenty minutes; there were no convulsions. He had five attacks of unconsciousness after that. The anxious, nervous, weak feelings between meals have continued.

The patient was hospitalized for two weeks on a diet of 60 Gm. of carbohydrate, 60 Gm. of protein and 150 Gm. of fat, with food every one or two hours between meals and when he awoke at night. He has been free from symptoms except that slight weakness occurred one night about 11 o'clock,

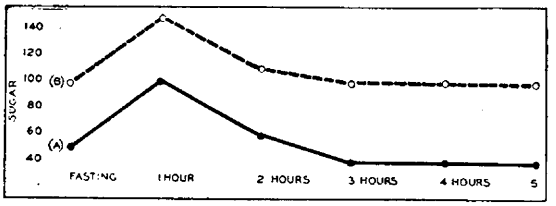

Chart 3 (case 3).—Severe hyperinsulinism: recurring attacks of unconsciousness. *A*, hyperinsulinism blood sugar curve. *B*, average normal blood sugar curve. When the blood sugar fell to 0.040 per cent the symptoms of the hunger attacks were reproduced; i. e., the patient became very weak and pale, particularly around the lips. He was very nervous and trembled but obtained immediate relief from eating.

but he was relieved immediately by taking orange juice. He has learned to weigh and measure food and calculate his menus to carry out the diet at home. He returned for a check up, May 29. He has had no symptoms except one time when he could not get orange juice or other food between meals. He then became weak and trembled but was relieved by eating. The fasting blood sugar was 0.066, compared with 0.05 per cent when the treatment was begun.

In many of the cases of the severe type a diagnosis of epilepsy had been made but abandoned when the attacks of convulsions were found to be associated with hypoglycemia, as in the cases of Neilson and Eggleston.[45] Several cases of what appeared to be true "idiopathic" epilepsy, in which the patients bit their tongues or received burns and other injuries while unconscious, were found to have been associated with hyperinsulinism.[46]

Sevringhaus, Schmidt and Bast[23] reported a case of hyperinsulinism with hypoglycemia (blood sugar, 0.040 per cent) in which the patient was in status epilepticus. Removal of a tumor (carcinoma) of the tail of the pancreas relieved the hypoglycemic symptoms.

In a number of the severe cases of hyperinsulinism the patients have appeared as if they were intoxicated

32. Jonas, Leon: Hypoglycemia, M. Clin. North America **8**: 949 (Nov.) 1924.
33. Sprunt, T. P.: South. M. J. **24**: 251 (March) 1931.
34. Gammon, G. D., and Tenery, W. C.: Hypoglycemia: the Clinical Syndrome, Etiology and Treatment: Report of a Case Due to Hyperinsulinism, Arch. Int. Med. **47**: 829 (June) 1931.
35. Heyn, L. J.: Hyperinsulinism, J. A. M. A. **98**: 1441 (April 23) 1932.
36. Cammidge, P. J.: Hypoglycemia, Lancet **2**: 1277 (Dec. 20) 1924; Spontaneous Hypoglycemia, Practitioner **119**: 102 (Aug.) 1927; Chronic Hypoglycemia, Brit. M. J. **1**: 807-848 (May 3) 1930.
37. Sendrail, M., and Planques, J.: The Condition of Hypoglycemia, Gaz. d. hôp. **100**: 1105 (Aug. 20), 1137 (Aug. 27) 1927.
38. Stenström, T.: Spontaneous Hypoglycemic Reactions in a Nursing Woman, Deutsches Arch. f. klin. Med. **153**: 181, 1926.
39. Rathery, F., and Sigwald, Jean: Spontaneous Hypoglycemia: L'hypoglycemia, (Sigwald) Paris, Doin & Cie, 1932, p. 147.
40. Escudero, cited by Sigwald: L'hypoglycemia, p. 143.
41. Ravid, J. M.: Transient Insulin Hypoglycemic Hemoplegias, Am. J. M. Sc. **175**: 756 (June) 1928.
42. Shepherdson, H. C.: The Efficacy of High Fat Diets in the Treatment of Chronic Hypoglycemia, Endocrinology **82**: 182 (March-April) 1932.
43. Krause, F. (Düsseldorf): Hyperinsulinism with Symptom Complex of Hypoglycemia, Klin. Wchnschr. **9**: 2346 (Dec. 13) 1930.
44. Wilder, R. M.: Progress in Study of Internal Secretions, Internat. Clin. **1**: 293 (March) 1930.
45. Neilson, J. M., and Eggleston, E. L.: Functional Dysinsulinism with Epileptiform Seizures: Treatment, J. A. M. A. **94**: 860 (March 22) 1930.
46. Harris, Seale: Epilepsy and Narcolepsy Associated with Hyperinsulinism, J. A. M. A. **100**: 321-328 (Feb. 4) 1933.

from alcohol but would become normal after taking food. Some have complained of "crazy spells," and actual psychotic symptoms have been observed by several clinicians. In one of Graham's [47] cases the psychosis was relieved by the removal of two small adenomas, which appeared to be the cause of the hyperinsulinism.

Abdominal pain has been pronounced in several reported cases. The pain of severe hyperinsulinism has simulated appendicitis, gallbladder infection and duodenal ulcer, so that exploratory operations, with removal of the appendix and gallbladder and gastroenterostomies, have been performed without relieving the abdominal pain. The pain of hyperinsulinism usually is exaggerated during the attacks, though it may be present more or less constantly. In some cases it is more marked one or two hours after meals. The pain usually is in the upper part of the abdomen, sometimes radiating to the left. Tenderness over the pancreas may be elicited on deep pressure in some cases. It is probable that pain and tenderness over the upper part of the abdomen in hyperinsulinism occurs most frequently in cases in which there are adenomas or other tumors of the pancreas; but in a narcoleptic patient in whom abdominal pain was a prominent symptom, no pathologic changes of the pancreas were found at operation, which relieved not only the hypoglycemia but also the pain.[46] This patient, in addition to the abdominal pain, had the typical Gélineau [48] syndrome of narcolepsy; i. e., attacks of unconsciousness associated with cataplexy.

In severe cases of hyperinsulinism there is usually a history of mild symptoms for several years before the attacks of unconsciousness and convulsions supervened. In other words, in the severe cases of hyperinsulinism the symptoms may progress from those ordinarily observed in the reaction following an overdose of insulin to the symptoms observed in the moderately severe cases and then into the unconscious or convulsive period. Usually there are mild symptoms and often petit mal attacks between the attacks of unconsciousness and convulsions in the severe type.

Some of the most severe cases of hyperinsulinism appear to be of the acute fulminating type in which the patient goes into hypoglycemic coma and remains unconscious for hours before death occurs. In other patients, spontaneous recovery occurs after he has been unconscious for hours. In the severe cases of the epileptiform type, the patient may go for weeks or months without seizures and then have several grand mal attacks in a few hours. In most of the severe cases of hyperinsulinism reported there has been the tendency for the hypoglycemic attacks to become more frequent and progressively more serious unless relieved by dietary management or by surgery. As in the mild and moderately severe types of hyperinsulinism, in the severe cases the hypoglycemic attacks may be induced by mental or physical strain, worry, grief and other emotional disturbances.

The blood sugar levels in the severe type of hypoglycemia usually are very low, below 0.050 per cent. Readings of 0.040, 0.035 and 0.027 per cent have been found; in Weil's [49] case the blood sugar fell to zero. Woodyatt [50] and Millard Smith [51] have reported zero levels in hypoglycemia from overdoses of insulin, but both patients recovered after sugar administration. In two of Neilson and Eggleston's [45] cases of "epileptiform convulsions" the fasting blood sugar level was not very low, only 0.069 and 0.064 per cent. The dextrose tolerance test usually brings out much lower blood sugar levels than are found in the same patient when fasting blood sugars have been made. In several instances the convulsions and mental and nervous symptoms have been induced when the blood sugar fell very low from four to six hours after the 100 Gm. of dextrose was given. In one of my epileptic patients, a woman who had grand mal attacks during menstruation, in a dextrose tolerance test between catamenial periods the lowest blood sugar level was 0.060 per cent. She became weak and had to go to bed but had no convulsions. In the dextrose tolerance test made during menstruation, when a seizure was expected the blood sugar level went to 0.050 per cent, at which time she had a typical epileptic convulsion.

The severe cases of hyperinsulinism that have been reported have attracted more attention than have the milder types, perhaps for the reason that the symptoms have been serious and usually clear cut, and the results of medical and surgical treatment have been dramatic. Pathologic studies from specimens removed by operation, or at autopsy, have been productive of proof that hyperinsulinism is a definite disease entity due in many cases to neoplasms. Among those who have made important contributions to the study of the severe type of hyperinsulinism, associated with attacks of unconsciousness, with or without convulsions, may be mentioned Wilder and his associates,[16] Allan,[52] Thalhimer and Murphy,[17] the Finneys,[53] Hartman,[54] Howland, Campbell, Maltby and Robinson,[20] Neilson and Eggleston,[45] Carr, Parker, Grave, Fisher and Larrimore,[55] Schmidt and Carey,[56] Phillips,[13] Weil,[49] McGavern,[57] Womack, Gnagi and Graham,[21] Sevringhaus, Schmidt and Bast,[23] Holman,[58] Guy-Larache, Lelourdy and Bussiere,[59] Stenström,[38] Pettersson,[60] Krause,[43] and Sippe and Bostock.[5]

DYSINSULINISM

The uncontrolled secretion of insulin, excessive at times and resulting in hypoglycemia, which may alternate with or be followed by hypofunction of the islet cells with hyperglycemia, is manifested by inconstant symptoms of both hyperinsulinism and diabetes mellitus (hypo-insulinism). In some cases the hypoglycemic symptoms predominate and in others hyperglycemic phenomena are more pronounced. The symptoms of dysinsulinism may be mild and irregular, moderately

47. Graham, E. A., and Womack, N. A.: The Application of Surgery to the Hypoglycemic State Due to Islet Tumors of the Pancreas, Surg., Gynec. & Obst. **56**: 728-742 (April) 1933.
48. Gélineau: De la narcolepsie, Gaz. d. hôp. **53**: 626, 1880.
49. Weil, Clarence: Functional Hyperinsulinism—Epileptiform Convulsions Accompanying Spontaneous Hypoglycemia, Internat. Clin. **4**: 33-50 (Oct.) 1932.
50. Woodyatt, R. T.: J. Metabol. Research **2**: 793 (Nov.-Dec.) 1922; cited by Joslin, E. P.: Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1928, p. 45.
51. Smith, Millard: Boston M. & S. J. **195**: 663 (Sept. 30) 1926; cited by Joslin: Treatment of Diabetes Mellitus, p. 46.
52. Allan, F. N.: Carcinoma of the Islands of Pancreas with Hyperinsulinism, Proc. Staff Meet., Mayo Clin. **2**: 89 (April 27) 1927; Hyperinsulinism, ibid. **3**: 367 (Dec. 19) 1928; Hyperinsulinism, Arch. Int. Med. **44**: 65 (July) 1929.
53. Finney, J. M. T., and Finney, J. M. T., Jr.: Resection of the Pancreas, Ann. Surg. **88**: 584 (Sept.) 1928.
54. Hartman, F. L.: Hypoglycemia, M. Clin. North America **12**: 1035 (Jan.) 1929.
55. Carr, A. D.; Parker, Robert; Grave, Edward; Fisher, A. D., and Larrimore, J. W.: Hyperinsulinism from B-Cell Adenoma of the Pancreas: Operation and Cure, J. A. M. A. **96**: 1363 (April 25) 1931.
56. Schmidt, E. G., and Carey, T. N.: Terminal Hypoglycemia, Arch. Int. Med. **47**: 128 (Jan.) 1931.
57. McGavern, B. E.: Epileptoid Attacks and Hyperinsulinism, Endocrinology **16**: 293 (May-June) 1932.
58. Holman, Emile: Partial Pancreatectomy in Chronic Spontaneous Hypoglycemia, Surg., Gynec. & Obst. **56**: 591-600 (March) 1933.
59. Guy-Larache, Lelourdy and Bussiere, cited by Sigwald, L'hypoglycemia, pp. 140-141.
60. Pettersson, A. S.: A Case of Spontaneous Hypoglycemic Coma, Acta med. Scandinav. **69**: 232, 1928.

severe and bizarre, or so severe that attacks of unconsciousness and convulsions and hypoglycemic coma and death may occur in patients known to have diabetes.

Symptoms of dysinsulinism may be brought out in dieting diabetic patients, particularly in the mild overweight cases; but severe diabetes may coexist with severe hyperinsulinism. In such cases the hypoglycemic symptoms usually present the more serious problem.

My first case diagnosed as dysinsulinism was in January, 1924.[1c] An obese woman who a year before, when she weighed 210 pounds (95 Kg.) had had glycosuria, was sent to me as a diabetic patient. She had reduced, by dieting, to 160 pounds (72.6 Kg.), and complained of having "spells of weakness and nervousness" at about 1 or 2 o'clock in the morning. She had found from experience that eating would relieve the symptoms, so that she kept an orange or a glass of milk on the table by her bed. Her blood sugar during an attack was 0.047 per cent. She was relieved promptly by frequent feedings of a low carbohydrate diet, consisting largely of the 5 and 10 per cent vegetables and fruits, with sufficient proteins and fats. Since then I have had three other cases of dysinsulinism.

CASE 4.—C. H. M., a man, aged 41, a laundry manager, 5 feet 5 inches (165 cm.) tall, weighing 127 pounds (57.6 Kg.), seen, Nov. 16, 1930, complained of polyuria, glycosuria, and a nervous, weak feeling in the middle of the morning and afternoon, which was relieved by taking food. The fasting blood sugar was 0.060 per cent. Glycosuria was present constantly for two years, 4 Gm. being excreted in twenty-four hours. The hypoglycemic symptoms were relieved on a weighed and measured diet of 120 Gm. of carbohydrate, 60 Gm. of protein and 180 Gm. of fat, with food every two hours, but the glycosuria persists. The patient increased his weight 12 pounds (5.4 Kg.). The fasting blood sugar, Oct. 16, 1932, was 0.085 per cent.

In the last few years, several similar cases have been reported and the low blood sugars have been attributed to hypersecretion of insulin by Jonas,[32] John,[25] Harrop,[62] Neilson and Eggleston,[45] Howland and Campbell and their associates [20] and Weil.[49]

DIAGNOSIS

A tentative diagnosis may be made from the symptoms; i. e., hunger, weakness, nervousness and the like (insulin reaction) in mild cases, and recurring attacks of mental lapses, convulsions, unconsciousness and coma in the severe cases. If the patient is relieved by reducing the carbohydrates and increasing the fats in his diet, with frequent feedings, the diagnosis of hyperinsulinism may be assumed. A positive diagnosis can be made only from repeated fasting blood sugar studies and carbohydrate tolerance tests showing hypoglycemia; i. e., blood sugar concentration below 70 mg. per hundred cubic centimeters, and by excluding all other causes of hypoglycemia except the excessive secretion of insulin by the islet cells of the pancreas.

The patient receiving a dextrose tolerance test should be observed very carefully to determine his reaction to the low blood sugar levels in from three to five hours after the ingestion of the 100 Gm. of dextrose. In some such cases the symptoms of which the patient complains are reproduced. In one of the epileptic patients a typical grand mal seizure occurred while the patient was undergoing a dextrose tolerance test, when the blood sugar level fell to 0.050 per cent. Lennox and Cobb [63] in two out of seven times produced grand mal attacks in an epileptic patient by giving him insulin. In one of the seven times he was mentally confused but had no convulsion when the blood sugar level was 0.025 per cent. At other times the patient had epileptic attacks when his blood sugar was normal. Gammon and Tenery [34] reproduced the symptoms of hypoglycemia in their case of hyperinsulinism by giving the patient 10 units of insulin. It is hardly necessary to give insulin as a diagnostic procedure in hyperinsulinism because the blood sugar levels after a dextrose tolerance test usually are sufficiently low to give the patient mild hypoglycemic symptoms.

Every possible cause of hypoglycemia besides pancreatic disease should be considered, including studies of all the other organs of internal secretion, excluding them as factors if possible before making the diagnosis of hyperinsulinism in an epileptic or narcoleptic patient.

Since hyperinsulinism has been manifested by symptoms of hysteria of a psychoneurasthenia, neurocirculatory asthenia, psychoses, brain tumors, epilepsy, narcolepsy, status epilepticus, epileptiform convulsions, appendicitis, gallbladder infection, duodenal ulcer and other diseases, a differential diagnosis from those conditions can be made by blood sugar studies. Hyperinsulinism is invariably associated with hypoglycemia. It should be remembered, however, that, in patients who have hypoglycemic symptoms, fasting blood sugars are not always low. Therefore, repeated and varied

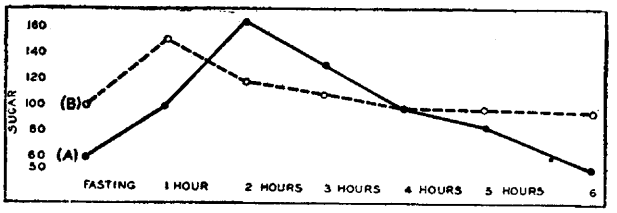

Chart 4 (case 4).—Dysinsulinism: mild diabetes and hypoglycemic symptoms. *A*, low fasting blood sugar rising slowly above normal with slow drop to subnormal level. *B*, average blood sugar curve.

blood sugar studies should be made before hypoglycemia is excluded in suspected cases of hyperinsulinism. It should be remembered also that the patient with hyperinsulinism may have other diseases that may or may not affect the hypoglycemic symptoms. Thus, two cases of hyperinsulinism in syphilitic patients have been observed in which antisyphilitic treatment did not affect the blood sugar levels or the symptoms of hypoglycemia.

Cases of marked degrees of hypoglycemia due to organic diseases, or functional disturbances of other organs besides the pancreas, have been reported as having been due to (*a*) deficient glycogenesis in the liver, from poisons such as arsphenamine or other arsenicals, phenylhydrazine, phosphorus or other hepatotoxins (Cross and Blackford [64]), and from massive tumor of the liver (Nadler and Wolfer [65]); (*b*) inadequate mobilization of glycogen due to deficient secretion of the suprarenals, as in the case reported by Anderson,[66] in which the autopsy revealed an adenoma of the left suprarenal gland, and in Addison's disease (Wadi [67]); (*c*) pituitary dysfunction (Cushing,[68] Josef

63. Lennox, W. G., and Cobb, Stanley: Epilepsy, Medicine **7**: 105-290 (May) 1928.

64. Cross, J. B., and Blackford, L. M.: Fatal Hepatogenic Hypoglycemia Following Neoarsphenamine, J. A. M. A. **94**: 1739-1743 (May 31) 1930.

65. Nadler, W. H., and Wolfer, J. A.: Hepatogenic Hypoglycemia Associated with Primary Liver Cell Carcinoma, Arch. Int. Med. **44**: 700 (Nov.) 1929.

66. Anderson, H. B.: A Tumor of the Adrenal Gland with Fatal Hypoglycemia, Am. J. M. Sc. **180**: 71 (July) 1930.

67. Wadi, W.: Ueber Hypoglykämie bei Morbus Addisonii, Klin. Wchnschr. **7**: 2107 (Oct. 28) 1928, cited by Cross and Blackford.[64]

68. Cushing, Harvey: The Pituitary Body and Its Disorders, Philadelphia, J. B. Lippincott Company, 1912.

Wilder[69]); (*d*) thyroid dysfunction, a possible factor in the etiology of hypoglycemic convulsions (Zubirán[70]), and (*e*) ovarian dysfunction, as in the case of hyperinsulinism of Weil,[49] in which a woman with very low blood sugar levels constantly and frequently had the symptoms of an insulin reaction between her catamenial periods, but had convulsions only just before and during menstruation.

PROGNOSIS

The prognosis of hyperinsulinism depends on the degree and character of the associated pancreatic lesion. It is good in the functional cases when an intelligent patient will carry out dietary instructions.

On account of the bulimia and the polyphagia that is pathognomonic of hyperinsulinism, obesity often results. Prolonged overfunction, with exhaustion, of the islet cells may be followed by hypo-insulinism (diabetes mellitus). Clinical evidences suggest that the patient with hyperinsulinism is a potential diabetic patient. I have had three diabetic patients with histories of unmistakable symptoms of hyperinsulinism before the symptoms of diabetes were observed. Therefore, early diagnosis and early dietary management may prevent the patient with mild or moderately severe hyperinsulinism from becoming diabetic; the clinician may thus aid in combating the increasing death rate from diabetes.[71]

Spontaneous recovery from the attacks of convulsions and unconsciousness due to hyperinsulinism usually takes place, but a number of deaths have been reported from hypoglycemic coma, in some of which unsuspected adenomas of the pancreas have been found at autopsy.

In the severe cases that cannot be controlled by dieting, the hope of cure is offered by surgery; i. e., partial resection of the pancreas, or removal of insuloma. Early diagnosis is important in neoplasms of the pancreas, because delayed surgery may result in the condition becoming inoperable.

TREATMENT

The problem of dieting in hyperinsulinism is much the same as in diabetes mellitus (hypo-insulinism) in that each patient has to be dieted to suit his particular needs. It is necessary to arrange a diet that will nourish the patient properly, providing sufficient amounts of carbohydrates, proteins and fats, with due consideration to its vitamin content. As far as the quantity is concerned, it should have a lower carbohydrate content than in diabetes, with sufficient calories from fats to maintain normal body weight and physical vigor. The protein content depends on the age and weight of the individual, from 60 to 75 Gm. for an adult weighing 70 Kg. (154 pounds).

The adult patient of average height and weight with hyperinsulinism should have about 2,250 calories, from 90 to 120 Gm. of carbohydrates, from 60 to 75 Gm. of proteins and the remainder in fats (cream and butter), divided into from five to seven feedings a day.

In the underweight, asthenic patient with hyperinsulinism, a high fat diet of 90 Gm. of carbohydrate, from 200 to 300 Gm. of fat, and from 60 to 75 Gm. of protein, divided into five or six feedings a day, will keep the blood sugar at a sufficiently high level to prevent hypoglycemic symptoms and will build up the patient's general health and state of nutrition.

Careful blood sugar studies should be made on each patient for a few days after being placed on a diet for hyperinsulinism, during which time his food should be weighed and measured. It is just as necessary to teach the patient with hyperinsulinism food values and to calculate and arrange the menus suited to his particular case, as it is to teach "diabetic arithmetic" to patients with hypo-insulinism (diabetes mellitus).

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69. Wilder, Josef: A New Hypophysis Disease Picture: Hypophyseal Spontaneous Hypoglycemia, Deutsche Ztschr. f. Nervenh. **112**: 192-250, 1930.

70. Zubirán, S.: A Case of Hypoglycemia, Medicina, Mexico **9**: 306-310 (April) 1929.

71. Harris, Seale: Combating the Increasing Death Rate from Diabetes, Mississippi Doctor 20-24 (March) 1933.

ABSTRACT OF DISCUSSION

DR. RUSSELL M. WILDER, Rochester, Minn.: This subject has interested me greatly since I had the opportunity, with Allan, Power and Robertson, to study the case of island carcinoma to which Dr. Harris has referred. The existence of a state of hyperinsulinism was definitely proved in that case by obtaining insulin-like extracts from the hepatic metastases of the tumor. The report of this observation has been followed by a number of other reports of similar cases. In some of these, island tumors have been found and the resection of them has resulted in the complete relief of the syndrome of hypoglycemia. In others, no tumors were discovered. Reviewing the subject recently (*Internat. Clin.* **2**:1 [June] 1933) I was able to cite sixteen cases presenting tumors of the islands of Langerhans. Fourteen had been associated with symptoms of hypoglycemia; nine were diagnosed clinically and treated surgically. Multiple tumors were present in a case reported by Franck, in one reported by Smith and Seibel, and in one of the cases at the Mayo Clinic. In five additional cases of hypoglycemia, hypertrophy of the islands had been noted; but such hypertrophy is frequently seen when there is no evidence of excessive insulin production. In seven other cases of hypoglycemia, two examined at autopsy and five at surgical operations, the pancreas appeared to be normal. Information is thus available concerning twenty-nine cases of this hypoglycemia syndrome in which the opportunity has been given to examine the pancreas. Tumors were noted in only fifteen of them. The clinical differentiation between cases with and those without tumor has been for us impossible. The severity of the symptoms has been great in both groups of cases. The dextrose tolerance test has not been helpful. Extreme degrees of variation in the height of the blood sugar curve and in the rapidity and degree of its descent have been seen in both groups of cases. Dr. Harris suggests that patients with hyperinsulinism may be potentially diabetic and that diabetes may follow a period of hyperinsulinism. We have seen the reverse of this in two cases—diabetes first and hypoglycemia later. I am not entirely prepared to accept the idea of a faulty pancreas in those cases of hypoglycemia which present no neoplasm. It is true that typical diabetes mellitus is not infrequently seen with no morphologic abnormality of the pancreas. By analogy, hyperfunction of the islands of Langerhans might be expected even in the absence of their anatomic alteration. However, hyperglycemia, as contrasted to true diabetes mellitus, can be produced by a variety of disturbances without any evident involvement of the pancreas, and similarly hypoglycemia may be brought about by a variety of causes. Dr. Harris in 1923 happily suggested the possibility of the clinical state of hyperinsulinism, but the diagnosis of his early cases, those on which he based his suggestion, was substantiated only by the fact that the blood sugar was low and that food gave relief. There was no proof of an excess of insulin. Cammidge, observing similar cases about the same time, inferred with equal reasonableness that the liver was responsible. The organ chiefly concerned with the regulation of the blood sugar is the liver, and the secretion of the pancreas is only one of various factors that influence its ability to handle sugar. Recent observations indicate that similar quanta of insulin have different effects under differing conditions. I refer particularly to the extreme insulin sensitiveness of hypophysectomized animals (Barnes). Similar insulin sensitiveness has been produced experimentally by thyroidectomy, by denervation of the suprarenal capsules and by splanchnec-

tomy (de Takáts). Our knowledge, then, is still too fragmentary to accept the assumption of an excessive insulin production merely on the basis of hypoglycemia. Particularly is this true in the rather numerous cases presenting milder degrees of what Dr. Harris calls hyperinsulinism. A pertinent discussion of this matter appears from the pen of the editor of the May issue of the *Annals of Internal Medicine*. The present evidence, as stated in this editorial, seems to indicate that tumor of the islands is among the rarest causes of hypoglycemia, and for the present it would seem more in accordance with our actual lack of knowledge to designate all cases of hypoglycemia in which no definite proof of cause exists as spontaneous or idiopathic hypoglycemia rather than as hyperinsulinism.

DR. HENRY J. JOHN, Cleveland: While hypoglycemia, with its classic symptomatology, is the outstanding manifestation of hyperinsulinism, many persons in perfect health have marked hypoglycemia and no symptoms. Hyperinsulinism is not merely hypoglycemia. I feel, as Dr. Wilder does, that there is some other factor of importance. There are two types of hyperinsulinism, the exogenous and the endogenous. Years ago I published reports of two cases presenting the exogenous type of hyperinsulinism. Both patients had glycosuria and hyperthyroidism, but neither of them had diabetes. Their treatment at home had consisted of large doses of insulin, which had produced the classic hypoglycemic symptoms. In endogenous hyperinsulinism there is hyperfunction of the islands themselves or else an adenoma which either secretes too much insulin or stimulates the islands to secrete an excess of insulin. The treatment for hyperinsulinism has progressed through various phases. The first and most obvious method of relief was learned from the patients themselves. Even before the condition was known as an entity, the patients had learned that the ingestion of carbohydrates relieved them. When hyperinsulinism was definitely recognized as such, the problem presented was just the opposite of that encountered in diabetes, and so frequent carbohydrate feedings and an extra feeding at bedtime were administered to these patients. It was not the ideal treatment, because the excessive carbohydrate was continually stimulating the pancreas to produce more and more insulin, the very condition that the treatment was supposed to combat. The next step was to modify the diet, giving the patient less carbohydrate and more fat, in order to retard absorption of the carbohydrate and the resultant hyperglycemia and thus to eliminate the acute stimulation of insulin production and hypoglycemia. A third method of treatment was surgical removal of a portion of the pancreas, in order to reduce the number of secreting islands in an effort to decrease the excessive production of insulin. Another step in the treatment of hyperinsulinism is the administration of insulin, which I have tried recently with exceptionally good results in one case. The rationale for this method of treatment is briefly as follows: The ingestion of food produces hyperglycemia, which in turn stimulates the insulogenic apparatus to insulin secretion, and this is followed by a drop in the level of blood sugar. In normal persons the intake of dextrose and the secretion of insulin are nicely balanced, but in patients with diabetes or with hyperinsulinism there is some defect in the mechanism in one or the other direction.

DR. GÉZA DE TAKÁTS, Chicago: During the past few years an attempt has been made to produce an increased secretion of insulin in the dog by producing a hypertrophy and hyperplasia of the islet tissue. This was found to be possible in the animal and to a certain extent also in the human juvenile diabetic patient. One may find, however, in the cases of hyperinsulinism not only an excessive insulin secretion but also an increased sensitivity to insulin. Tests for insulin susceptibility have not been determined frequently enough in patients with diabetes but on the basis of a few well observed cases it can be said that there is a wide variation in the individual with diabetes and also in the so-called normal individual as to susceptibility to insulin. It is quite possible, then, that some of these patients with spontaneous hypoglycemia do not actually secrete an excessive amount of insulin, but they become, because of nervous or glandular mechanisms, temporarily sensitive to insulin. Thus it is known that epinephrine insufficiency and pituitary insufficiency will produce a hypersensitivity to insulin. Splanchnic section in diabetic patients also increases insulin sensitivity. From the surgical standpoint the attack on the pancreas is not any more dangerous than any upper abdominal operation on the well controlled patient. I should like to emphasize, contrary to the usual opinion, that the danger of pancreatic necrosis is very slight. Pancreatic secretion is inactive in the pancreas, and an aseptic operation will not activate the pancreatic ferments. As a matter of fact, the cases reported in which the adenoma of the pancreas has been removed show that there was not one single instance of postoperative pancreatic necrosis.

DR. SEALE HARRIS, Birmingham, Ala.: I am sorry that I didn't have the time to discuss the diagnosis of hyperinsulinism in the fifteen minutes allowed for presenting a paper. In my paper I stress the fact that a positive diagnosis of hyperinsulinism can be made only from repeated fasting blood sugar studies and carbohydrate tolerance tests showing hypoglycemia, namely, a blood sugar concentration below 70, and by excluding all other causes of hypoglycemia except the excessive secretion of insulin by the islet cells of the pancreas. It is not possible at times to exclude all the other causes of hypoglycemia except hyperinsulinism, any more than can be done in making a diagnosis of diabetes from hyperglycemia and glycosuria. It seems likely that there are many mild cases of hyperinsulinism just as there are mild cases of diabetes; and I think that hyperinsulinism occurs perhaps as frequently as hypo-insulinism (diabetes mellitus), the opposite secretory disturbance of the islet cells of the pancreas. Hypoglycemia may be due to deficient glycogenesis. A number of cases of hypoglycemia have been reported as resulting from massive tumor of the liver. Inadequate mobilization of glycogen due to deficient secretion of the suprarenals is also a cause of hypoglycemia, as in the case reported by Anderson, in which there was marked hypoglycemia and the autopsy revealed an adenoma of the left suprarenal gland. Hypoglycemia may be due to thyroid dysfunction, and to hypophyseal dysfunction, as Cushing has pointed out. There are other causes of hypoglycemia. The important thing in making a diagnosis of hyperinsulinism is to study the cases carefully and to come to an accurate diagnosis from repeated blood sugar studies, excluding all other causes of hypoglycemia except the excessive secretion of insulin by the islet cells of the pancreas. One can guess pretty definitely in the mild cases of hyperinsulinism from such clinical symptoms as hunger, weakness, nervousness and distress three or four hours after eating, which are relieved by taking food, that one is dealing with hypoglycemia; and a very large proportion of such cases are due to an excessve secretion of insulin by the islet cells. Of course, one should not stop at symptoms but should study the cases carefully, making blood sugar studies and eliminating all other factors in hypoglycemia, except the excessive secretion of the islet cells of the pancreas, before a positive diagnosis of hyperinsulinism is made.

Coughs.—I would particularly ask your attention to coughs. . . . There is the revolting, hawking, morning, pharyngeal cough of chronic pharyngitis best manifest in the alcoholic. There are the annoying habit coughs of children which cause no harm excepting to the inexperienced mother; the painful, voiceless coughs of grave laryngeal disease; the brassy cough of thoracic aneurysm; and the phthisical cough, which I find difficult to describe, although it has quite definite features of its own. It is not so effortful but, in late cases, as productive as the bronchitic cough; being less tenacious, the sputum is more easily ejected; the cough is moister and unattended by rhonchus; in the very advanced case it may have a hollow, weary quality. We have also the unmistakable paroxysm of whooping cough, with its repeated expiratory efforts, usually (but not always) culminating in the final inspiratory stridor. How often I have pricked up my ears during a ward round and caught the eye of my house physician in relation to his latest unsuspected admission as "bronchitis" to one of the cots. I used the adjective "unmistakable" in connection with the cough of pertussis, but it is worth remembering that a foreign body in the bronchus or a small undischarged pulmonary abscess may give rise to severe and prolonged paroxysms of coughing which are not very dissimilar.—Ryle, J. A.: The Training and Use of the Senses in Clinical Work, *Guy's Hosp. Gaz.* **47**:421 (Oct. 28) 1933.