5. White, A. C., et al. Absorption and antimicrobial activity of penicillin V (phenoxymethyl penicillin). In *Antibiotics Annual: 1955-1956*. Edited by H. Welch and F. Martí-Ibáñez. 994 pp. New York: Medical Encyclopedia, Inc., 1956. Pp. 490-501.
6. Nichols, R. L., Jones, W. F., and Finland, M. Plasma penicillin levels from oral penicillins V and G and intramuscular penicillin G. *Proc. Soc. Exper. Biol. & Med.* **90**:688-692, 1955.
7. Quinn, E. L., Colville, J. M., Cox, F., Jr., and Truant, J. Phenoxymethyl penicillin (penicillin V) therapy of subacute bacterial endocarditis. *J.A.M.A.* **160**:931-936, 1956.
8. Martin, W. J., Nichols, D. R., and Heilman, F. R. Observations on clinical use of phenoxymethyl penicillin (penicillin V). *J.A.M.A.* **160**:928-931, 1956.
9. Martin, R., Chabbert, Y., Sureau, B., and Cayla, E. À propos de deux endocardites lentes à streptocoques traitées par la pénicilline V orale. *Presse méd.* **64**:1655-1657, 1956.
10. Jones, W. F., and Finland, M. Blood levels from orally administered penicillins G and V: relation to food intake. *New Eng. J. Med.* **253**:754-760, 1955.
11. Eagle, H., Fleishman, R., and Levy, M. "Continuous" vs. "discontinuous" therapy with penicillin: effect of interval between injections on therapeutic efficacy. *New Eng. J. Med.* **248**:481-488, 1953.
12. Heck, W., Hinshaw, H. C., and Hobson, L. Reduced neurotoxicity of mixture of streptomycin and dihydrostreptomycin. In *Transactions of the Twelfth Conference on the Chemotherapy of Tuberculosis Held on February 9 to 12, 1953, at the Fulton County Medical Society, Atlanta, Georgia: Prepared and edited by Veterans Administration Area Office, Atlanta, Ga., and Central Office, Washington, D.C.: With cooperation of National Tuberculosis Association*. 430 pp. Washington, D.C.: Veterans Administration, 1953. Pp. 294-297.
13. Geraci, J. E., and Martin, W. J. Antibiotic therapy of bacterial endocarditis. IV. Successful short-term (two weeks) combined penicillin-dihydrostreptomycin therapy in subacute bacterial endocarditis caused by penicillin-sensitive streptococci. *Circulation* **8**:494-509, 1953.
14. Hall, B., Dowling, H. F., and Kellow, W. Successful short-term therapy of streptococcal endocarditis with penicillin and streptomycin. *Am. J. M. Sc.* **230**:73-81, 1955.
15. Hunter, T. H., and Paterson, P. Y. Bacterial endocarditis. *Disease-a-Month*, pp. 1-48, November, 1956.

SEVERE DIABETES WITH REMISSION

Report of a Case and Review of the Literature

REED HARWOOD, M.D.*

BOSTON

DIABETIC acidosis is generally believed to be the result of an acute and severe degree of insulin insufficiency. Patients who recover from this acute condition almost invariably need insulin injections for the rest of their lives. The patient whose history is reported below is unusual because his diabetes has improved to the extent that he has been able to maintain normoglycemia and good health without the help of insulin for nearly two years.

CASE REPORT

J.N., a 24-year-old engineering student, was referred to my office on May 12, 1955, with severe diabetes. He had been well until 10 days previously, when he began to notice a rapidly progressive thirst, polyuria and weakness; his weight dropped from 79.4 to 68.0 kg. (175 to 150 pounds).

The past history was not remarkable except for severe acne since the age of 15. His dietary habits were those of the average American youth, but in recent months he had adopted the custom of spending his evenings drinking beer in considerable quantities and eating pretzels with his fellow students.

A maternal aunt had diabetes.

He appeared ill and weak; he was markedly dehydrated, and respirations were slightly increased in rate and depth. There was a strong odor of acetone on the breath. He had severe acne vulgaris involving the face, neck and thorax. The temperature, pulse and blood pressure were normal. There was no evidence of disease of the optic fundi, pharynx, thyroid gland, heart, lungs, abdomen or extremities. No neurologic abnormalities were noted.

Urinalysis revealed a ++++ test for sugar and a ++++ test for acetone, as well as a ++++ test for albumin, and the sediment was loaded with granular casts.

He was taken to the Emergency Ward of the Massachusetts General Hospital, where initial studies showed a blood sugar of 330 mg. per 100 ml., and a serum carbon dioxide content of 8.5 milliequiv. per liter. The serum pH was 7.18, and the nonprotein nitrogen was 28 mg. per 100 ml.

During the next 9 hours he received 130 units of crystalline insulin, and 4 liters of fluids parenterally, mostly as an 0.85 per cent solution of sodium chloride. The blood sugar fell to 53 mg. per 100 ml. after 4 hours of treatment, and the acidosis was quickly corrected. He was regulated on a diet of 300 gm. of carbohydrate, 130 gm. of protein and 120 gm. of fat (2800 calories), and he was discharged from the hospital 2 weeks later, well controlled on 80 units of lente insulin. At this time the albuminuria and cylindruria had cleared, and the weight was 70.8 kg. (156 pounds).

He was seen at weekly or fortnightly intervals for the next 3 months. The urine remained entirely free of sugar, and the blood sugar during this period, taken usually at 5 p.m., ranged from 67 to 82 mg. per 100 ml. He had no symptoms of hypoglycemia, but because of the consistently low blood sugar tests, the dose of lente insulin was gradually reduced to 50 units.

On August 23, 3 months after discharge from the hospital, he had a moderately severe hypoglycemic attack, with profuse sweating, tremor, weakness and mild confusion, that was quickly relieved by the administration of sweetened orange juice. The dose of insulin was reduced to 25 units daily. Three days later he appeared in my office suffering from another mild hypoglycemic attack, and reported that in the interim he had felt poorly, as if continually on the verge of an insulin reaction. The symptoms of headache and weakness were promptly relieved by 20 gm. of glucose by mouth. The blood sugar at this time was 92 mg. per 100 ml. He was then instructed to omit insulin entirely until glycosuria recurred, but to make no change in the diet. The expected return of glycosuria failed to occur, however, and he has had no insulin since that date, 23 months ago. During this period he has felt very well, and has had no illness except for occasional upper respiratory infections. His weight dropped from 71.2 to 62.6 kg. (157 to 138 pounds) during the 1st few months without insulin; a review of his eating habits disclosed that he had reduced his intake in an effort, as he said, to "spare his pancreas." The actual intake was estimated to contain 150 gm. of carbohydrate, 82 gm. of protein, and 85 gm. of fat (1693 calories). An x-ray film of the chest was normal. The blood sugar, taken at monthly intervals at around 5 p.m., ranged from 82 to 100 mg. per 100 ml. Four months after the omission of insulin, a glucose-tolerance test with 100 gm. of glucose was performed, after 3 days of preparation on a diet containing 300 gm. of carbohydrate. The true venous blood sugar values were as follows: fasting, 75 mg., at 1 hour, 150 mg., and at 2 hours, 80 mg. per 100 ml. Simultaneous determinations of blood pyruvate and lactate showed the changes characteristically seen in the nondiabetic person: the pyruvate rose from 1.0 to 2.0 mg., and the lactate rose from 7.5 to 10.0 mg. per 100 ml.

During the next year this patient continued to do well. Because of the weight loss, his diet was increased to 240 gm. of carbohydrate, 105 gm. of protein and 117 gm. of fat (2433 calories), and he subsequently regained 3.6 kg. (8 pounds). In this period 4 late-afternoon blood sugar tests

*Instructor in medicine, Harvard Medical School; associate physician and chief of Diabetes Clinic, Massachusetts General Hospital.

done at 3-month intervals were, respectively, 89, 82, 79 and 84 mg. per 100 ml. As time went on, he liberalized his diet to the extent of frequently eating a very large supper, including a sweet dessert, when hungry. In December, 1956, 16 months after the omission of insulin, the glucose-tolerance test was repeated, with the following results (true venous blood sugar): fasting, 97 mg., at ½ hour, 186 mg., at 1 hour, 200 mg., and at 2 hours, 260 mg. per 100 ml. Heavy glycosuria was noted at the end of the test. A physical examination at this time was negative; the acne had improved considerably, and the patient looked and felt extremely well. His weight remained at 66.2 kg. (146 pounds). Because of the unfavorable outcome of the 2d glucose-tolerance test, he resumed his strict diet (approximately 2400 calories). One month later a late-afternoon blood sugar was 87 mg. per 100 ml., and his weight was 64.9 kg. (143 pounds). Two subsequent blood sugar tests were 87 and 80 mg. per 100 ml.; the latter test was performed in May, 1957, 21 months after insulin therapy was stopped.

Review of the Literature

Marked amelioration of the diabetic state as a result of treatment was first described by the English physician, John Rollo,[1] in 1796. In the following century, the dietary treatment of diabetes — restriction of carbohydrate and also of protein and fat — was systematized by the studies of Cantani, Bouchardat and Naunyn. All these investigators succeeded in arresting the downward progress of severe diabetes by various degrees of starvation, and were able to report cases in which the patient, after being controlled by the strictest dietary measures, gradually gained carbohydrate tolerance to the point where he could remain aglycosuric for years on a normal diet.[2] Allen,[3] reviewing in 1913 the literature on the curability of diabetes, quotes Naunyn as saying, "Diabetes mellitus may recover, but this happens very seldom, and I know of no case in which the cure of the disease has occurred after any long duration." Allen drew a distinction between improvement and cure of diabetes, and pointed out the need for caution in reporting cures because of the intermittent nature of some cases of diabetes. "A cured diabetic," he wrote, "is one who can go and live like other people on the ordinary quantities of starch and sugar and remain permanently free from his former disease. . . . By such a test, numerous alleged cures are ruled out." In modern times Newburgh and Conn[4] reported the "disappearance" of diabetes in obese patients after adequate weight reduction. Their patients not only became asymptomatic and sugar free but also regained normal glucose-tolerance curves. Some of these patients later abandoned the diet and again became obese; it was noted that their carbohydrate tolerance was eventually lost and that diabetic symptoms recurred. In a subsequent paper Newburgh[5] reported that a small percentage of his obese diabetic patients who co-operated fully and succeeded in reducing their weight to normal, *failed* to achieve normal glucose-tolerance curves — a finding that cast some doubt on his theory that the diabetes of obesity was a different disease from ordinary diabetes.

Numerous writers have reported the disappearance of diabetes in rare cases of juvenile diabetes. John[6] cites a patient of Joslin, a boy of seven who was treated by diet alone and remained sugar free for fifteen years, and a patient of van Norden, also seven years old, whose severe diabetes was finally controlled by a diet of oatmeal and vegetables, so that he was able five years later to maintain good health and freedom from glycosuria on a normal diet. It is not clear, however, that these cases represent "cure" of diabetes. Joslin et al.[7] reported in 1935 that in response to a yearly follow-up inquiry of 1000 juvenile diabetic patients, 38 stated that they were "well, aglycosuric, eating freely and using no insulin." In analyzing this group Joslin excluded 24 cases for various reasons, among them a possibly faulty original diagnosis, but concluded that the remaining 14 patients "have at least markedly atypical, perhaps temporarily and spontaneously arrested diabetes." Details of the severity of the disease and the type of treatment are not included in this report. In a later edition of his textbook Joslin[8] makes no reference to these 14 cases and writes: "We have sought zealously for cures and have not found them, and one of our best possible examples of subsidence or even cure of the disease . . . later proved to be false." Duncan[9] refers to 2 juvenile patients with acute onset of symptoms (1 of these had ketosis[10]) whom he has followed for many years after all detectable signs of diabetes had disappeared; he also reports that marked remissions after adequate treatment are fairly common among the group with milder diabetes.

Numerous studies on the pathology of diabetes and on its production in the laboratory animal are pertinent to an understanding of remissions in diabetes. MacCallum,[11] in 1907, describing the autopsy findings of 2 children who died of acute diabetes, noted changes in the pancreas that he interpreted as representing compensatory hypertrophy and also regeneration of the islands of Langerhans. He believed that the newly formed islets arose from the acinar ductile epithelium. Cecil[12] soon after reported that he found evidence of hypertrophy of the islets and newly formed islet tissue in 34 out of 100 autopsies on diabetic patients. Warren and Root[13] wrote in 1925: "The pathology which we find in the pancreas at autopsy rarely represents the initial damage to the organ, but rather the result of a long struggle between regenerative activity of the pancreas and the degenerative changes caused by the diabetogenic factor. The pancreas is not a static organ like the brain or myocardium, unable to repair itself after injury." Gray and Feemster[14] noted marked hypertrophy and hyperplasia of the islands of Langerhans of the infant of a diabetic mother. It is significant that the woman experienced a considerable diminution of her insulin requirement in the latter half of pregnancy.

Homans,[15] in 1914, studied the effects of subtotal pancreatectomy in the cat. He found that this procedure, although not always producing diabetes, usu-

ally resulted in a disappearance of the secretory granules of the islets in the pancreatic remnant, suggesting overactivity of the islets. The same procedure occasionally produced fatal diabetes, with marked degeneration of the remaining islet tissue. Allen[16] made similar observations in dogs after subtotal pancreatectomy. In addition he noted that the type of diet used after the operation had an important effect on the subsequent clinical course and on the histologic findings in the pancreas. In dogs given a diet rich in starches a progressive loss of carbohydrate tolerance developed, leading eventually to death in diabetic acidosis, with marked hydropic degeneration of the pancreatic islets. The animals that were given a low-starch, high-fat diet, on the other hand, gradually regained a normal tolerance for carbohydrate, and in such experiments hypertrophy and hyperplasia of the islets were found. Copp and Barclay[17] showed that administration of insulin after subtotal pancreatectomy in the dog also prevented hydropic degeneration of the remaining islets and tended to promote recovery in islets that showed this lesion.

Several other methods of producing and preventing diabetes in the laboratory animal should be mentioned. Haist, Campbell and Best,[18] in 1940, reviewed this subject and concluded that extensive partial pancreatectomy or the prolonged administration of anterior pituitary extract led to exhaustion and degeneration of the islets, largely through overwork, and produced a markedly diminished insulin content of the pancreas, with clinical diabetes. If the animal was fasted, fat fed or given insulin, islet-cell degeneration did not occur, and diabetes failed to appear.

Dohan and Lukens[19] produced diabetes in the cat by the intraperitoneal injection of glucose. They concluded that the hyperglycemia induced by this method caused the islet damage and the resultant permanent diabetes.

In the light of this experimental work, the clinical reports of remissions in human diabetes become significant. Boyd and Robinson[20] reported the case of a nine-year-old child with diabetes who was rescued from chronic invalidism by the discovery of insulin. His insulin requirement at first was 90 units, but gradually fell to 30 units. At the age of thirteen he was well and strong, when he was killed in an accident. Post-mortem examination showed marked regeneration of the islands of Langerhans. Leyton,[21] discussing the possibilities of recovery from diabetes, wrote: "Most advise the administration of the minimum dose of insulin which will render the patient free from glycosuria whilst on a fixed diet; I give the maximum dose of insulin which the patient can stand whilst on a fixed diet." He described 9 patients with "recovery" from diabetes whose insulin dose had to be reduced and finally omitted because of hypoglycemic attacks, and who were able to maintain normoglycemia on a reasonable diet for six months to two years. His data show that these were merely marked remissions, not recoveries, since hyperglycemia could be provoked in each by an infection or a glucose meal. He believed that failure to produce similar remissions in his other diabetic patients could be ascribed to delay in treatment, infection, lack of co-operation or technical difficulties in keeping the blood sugar below 150 mg. per 100 ml., especially at night.

Within the last fifteen years a number of papers have stressed the possibilities of marked amelioration of severe diabetes with early and vigorous treatment. McDaniel and his colleagues[22] reported marked diminution in the daily insulin requirement during the early months of regulation, so that there is great temptation to omit insulin — an error, according to them, because "within a period of weeks or months the diabetic condition reasserts itself in full force." Jackson, Boyd and Smith,[23] with an extensive experience in the care of diabetic children, stated that during the period of metabolic control, the daily insulin requirement could be reduced by two thirds in patients with early diabetes and by a third in protracted cases. They pointed out that the common practice of maintaining minimal glycosuria (that is, chronic mild hyperglycemia) makes this reduction of insulin requirement impossible. Brush[24] has had a similar experience in his group of 39 juvenile patients with diabetes. By pushing insulin to the point of mild hypoglycemia and by very careful dietary management, he succeeded in getting the daily insulin requirement down to 10 units or less in almost all cases, whereas in control series by other authors, who were less bold in the use of insulin, satisfactory control was attained with an average dose of 30 units. White[25] also reports frequent marked amelioration of diabetes in her juvenile patients.

Lukens and Dohan[26] described 19 adult patients who improved to the extent of being able to omit insulin and to maintain normoglycemia on an adequate diet, at least for a short time. At the time of publication 7 were still in remission, which had endured for one to ten years. All those tested during remission still had positive glucose-tolerance tests. Most of the patients who relapsed did so as the result of gross neglect of the diet.

A. F. Hartmann[27] presents 2 cases of children with an abrupt onset of diabetic acidosis and coma, which was followed by rapid subsidence of the signs of diabetes with treatment. These children were maintained without insulin and on an adequate diet for several months before severe diabetes recurred. Hartmann ascribes the eventual severe diabetes to subsequent hyperglycemic stimulation of the beta cells (presumably by dietary excesses), to infections, to emotional upsets and to the overproduction of insulin antagonists.

In 1953 Cheng, Jahraus and Traut[28] described the experience of a sixty-year-old woman after severe

diabetic acidosis. On admission the blood sugar was 1120 mg. per 100 ml., and the carbon dioxide combining power was 10 vol. per cent. She required 1425 units of insulin in the first twenty-four hours to bring about recovery from coma. Subsequently, she improved to the extent that she required no insulin and was able to maintain a normal blood sugar on a free diet, but her glucose-tolerance curve remained mildly diabetic. In another remarkable case reported by del Greco and Scapelatto[29] in the same year, a sixty-two-year-old man, recovering from pneumonia and a penicillin reaction, consumed 2 kg. of cane sugar and 3 kg. of honey in a period of two days. Severe diabetes with acidosis quickly developed; the blood sugar was 640 mg. per 100 ml., and the carbon dioxide combining power was 18 vol. per cent. After treatment with insulin brought about recovery from diabetic coma, a remission of the diabetes was subsequently observed. Treatment with insulin was discontinued, and he was allowed a normal diet. Glucose-tolerance tests were still negative two years later.

Discussion

It is apparent from this review of the literature that marked remissions can frequently be achieved in cases of diabetes of the middle-aged and the obese simply by means of prolonged dietary restriction and weight reduction, and that equally impressive remissions can occur in rare cases in the more severe, insulin-deficient diabetes of the young and asthenic patient, occasionally by the method of severe restriction of the diet but more usually by the prompt and vigorous administration of insulin. The data obtained from the production of diabetes in the laboratory animal, in addition to knowledge of the pathology of diabetes, provide a convincing explanation of these remissions: the beta cells of the pancreatic islets, under certain circumstances that produce hyperglycemia, can be stimulated to the point of exhaustion; the pancreas responds to the stimulus by hypertrophy of the islets and by formation of new islets from the acinar ducts, and will do so provided the stimulus is not so overwhelming or so prolonged as to lead to irreversible destruction of the islets. The process of exhaustion and degeneration of the beta cells can be arrested and reversed by measures that lessen the stimulus and relieve the hyperglycemia — usually by restriction of food intake and the administration of insulin, but also occasionally by the removal of a diabetogenic tumor such as an adrenal tumor[30] or a pheochromocytoma[31] or a hyperfunctioning diabetogenic gland, as in thyrotoxicosis.[32] When the stimulus is removed, the exhausted beta-cell apparatus has a chance to recover; adequate production of insulin becomes possible, and normal tolerance for glucose is restored.

It may be asked why this phenomenon of remission is not more commonly encountered. The reasons are probably multiple. In the first place, it is generally agreed that the beta-cell apparatus of the diabetic patient is inherently weak and has suffered a certain amount of irreversible damage even before hyperglycemia and glycosuria have been discovered. A few of Newburgh's[5] patients failed to regain tolerance despite faithful adherence to the prescribed diet and despite a weight loss that, for the majority of other patients, was adequate to restore normal tolerance; in all probability they represent a group in which the hyperglycemia had been of such a degree and duration as to impair permanently the ability of the pancreas to recover. In other cases the failure may be ascribed to the notorious inability of the patient to submit to the rigors of the diet. Few physicians today are willing to resort to a measure that Cantani,[33] in the mid-nineteenth century, occasionally employed: that of locking the patient in a room for several weeks so that the regimen of semistarvation could not be violated. However, confinement to a hospital today not infrequently produces a striking amelioration in the diabetic state of the obese and unco-operative patient: I have seen numerous patients who repeatedly require little or no insulin during a hospital stay, but need 60 units or more immediately before and soon after each such episode. In the hospital food supplies are usually locked up, and diabetic meals are measured.

Remissions of diabetes in those requiring insulin from the beginning of treatment are much less common. Nevertheless, every diabetes clinic has a significant number of patients who need insulin initially for several weeks or months, but who eventually are able to maintain satisfactory control for many years on diet alone. The diabetes of such patients is mild, and their remissions are only partial, as attested by their own reports of the brief appearance of glycosuria after a single piece of pie or an emotional upset, or during an acute infection.

In the more severe type of diabetes seen in the young or asthenic patient, significant remissions are really quite rare. In such cases it is assumed that the damage to the pancreatic islets is more serious. Nevertheless, the reports of marked amelioration cited above suggest that remissions in this insulin-deficient type of diabetes could be achieved more frequently than is realized. The experience of Jackson and his co-workers[23] and of Brush[24] shows that a marked diminution of insulin dosage is possible provided treatment is started promptly and pursued with sufficient vigor. The work of McDaniel et al.,[22] White[34] and Hartmann[27] and sporadic reports from the earlier literature indicate that amelioration of severe diabetes to the extent of complete omission of insulin for months or years can occasionally be achieved.

That such amelioration is not commonplace is attributable to several factors. In addition to the

obvious initial severity of the pancreatic damage and the probable continuation of the factors that produced it, there is the usual difficulty in obtaining complete adherence to the restrictions of the diet. Moreover, most physicians, in my experience, fear to be blamed for provoking attacks of hypoglycemia, and, viewing the patient's obvious good health and vigor, they prefer a moderate hyperglycemia and minimal glycosuria to the risk of an occasional "insulin reaction." Most patients who have once experienced a disagreeable or frightening hypoglycemic episode will take steps to make sure that it never happens again — that is, they will eat more food or reduce the dose of insulin, aiming for the continual presence of slight glycosuria. Thus, the majority of patients with severe diabetes are systematically undertreated, and the resulting mild hyperglycemia makes amelioration of their diabetes impossible.

It should be emphasized here that "cure" of diabetes is rarely mentioned as a possibility today. The dictum "once a diabetic, always a diabetic" is almost unanimously accepted. The patient whose history is presented above still has diabetes, as shown by the positive glucose-tolerance test obtained sixteen months after insulin treatment was stopped; it is highly probable that the diabetes will eventually become severe again, judging from the experience of other authors. The degree of his recovery after severe diabetic acidosis is most unusual, for diabetic acidosis itself indicates a very severe degree of insulin insufficiency. A few cases of similar recovery have been reported, as I have shown, after diabetic acidosis in childhood and there are the 2 cases cited above of recovery in adults[28,29]; however, my search of the literature and other sources[10,25,35-37] has failed to disclose any other cases of such recovery after acidosis in adults. I regret that I cannot claim credit for my patient's recovery or offer a complete explanation for its occurrence. The patient followed instructions faithfully; the blood sugar showed a unusual lack of fluctuation, being slightly subnormal throughout the three months that insulin was used, the dose of insulin was reduced only when hypoglycemic symptoms seemed imminent or had actually occurred, and the outcome was not anticipated. The brief duration of the acute symptoms and the whole-hearted co-operation of the patient doubtless favored the recovery. It is hoped that this report will encourage others to aim for remission in their treatment of early diabetes.

Summary

A case history is presented in which a young man on recovery from diabetic acidosis soon went into a remission that permitted him to live on a mildly restricted diet without insulin up to the time of publication, twenty-three months later. Search of the literature discloses few cases of similar recovery after acidosis in an adult, but suggests that restoration of function of the islands of Langerhans in early diabetes is always a possibility, and that attempts to achieve this by the strictest control with diet and insulin should make such remissions a more common occurrence.

266 Beacon Street

References

1. Rollo, J. *Cases of Diabetes Mellitus: With the results of certain acids, and other substances, in the cure of the lues venera.* Second edition. 628 pp. London: J. Callow, 1806.
2. Allan, F. N. History of treatment of diabetes. *J. Am. Dietet. A.* **6**:1-9, 1930.
3. Allen, F. M. *Studies Concerning Glycosuria and Diabetes.* 1179 pp. Boston: W. M. Leonard, 1913.
4. Newburgh, L. H., and Conn, J. W. New interpretation of hyperglycemia in obese middle-aged persons. *J.A.M.A.* **112**:7-11, 1939.
5. Newburgh, L. H. Control of hyperglycemia of obese "diabetics" by weight reduction. *Ann. Int. Med.* **17**:935-942, 1942.
6. John, H. J. Spontaneous disappearance of diabetes. *J.A.M.A.* **85**:1629-1631, 1925.
7. Joslin, E. P., Root, H. F., White, P., and Marble, A. *Treatment of Diabetes Mellitus.* Fifth edition. 620 pp. Philadelphia: Lea & Febiger, 1935.
8. *Idem. Treatment of Diabetes Mellitus.* Ninth edition. 771 pp. Philadelphia: Lea & Febiger, 1952.
9. Duncan, G. G. *Diabetes Mellitus: Principles and treatment.* 289 pp. Philadelphia: Saunders, 1951.
10. *Idem.* Personal communication.
11. MacCallum, W. G. Hypertrophy of islands of Langerhans in diabetes mellitus. *Am. J. M. Sc.* **133**:432-440, 1907.
12. Cecil, R. L. On hypertrophy and regeneration of islands of Langerhans. *J. Exper. Med.* **14**:500-519, 1911.
13. Warren, S., and Root, H. F. Pathology of diabetes: with special reference to pancreatic regeneration. *Am. J. Path.* **1**:415-430, 1925.
14. Gray, S. H., and Feemster, L. C. Compensatory hypertrophy and hyperplasia of islands of Langerhans in pancreas of child born of diabetic mother. *Arch. Path.* **1**:348-355, 1926.
15. Homans, J. Degeneration of islands of Langerhans associated with experimental diabetes in cat. *J. Med. Res.* **30**:49-68, 1914.
16. Allen, F. M. Experimental studies on diabetes. I. Production and control of diabetes in dog: gross anatomic relations of pancreas and diabetes. *J. Exper. Med.* **31**:363-402, 1920.
17. Copp, E. F. F., and Barclay, A. J. Restoration of hydropically degenerated cells of pancreatic islands in dogs under insulin treatment. *J. Metabolic Res.* **4**:445-451, 1923.
18. Haist, R. E., Campbell, J., and Best, C. H. Prevention of diabetes. *New Eng. J. Med.* **223**:607-615, 1940.
19. Dohan, F. C., and Lukens, F. D. W. Experimental diabetes produced by administration of glucose. *Endocrinology* **42**:244-262, 1948.
20. Boyd, G. L., and Robinson, W. L. Evidence of regeneration of pancreas in insulin treated case of diabetes. *Am. J. Path.* **1**:135-146, 1925.
21. Leyton, O. Nine cases of recovery from diabetes mellitus. *Proc. Roy. Soc. Med.* (Sect. Med.) **23**:37-49, 1929-1930.
22. McDaniel, L. T., Marble, A., and Joslin, E. P. Can diabetes be "cured" by early, vigorous treatment? *Connecticut M. J.* **4**:710-718, 1940.
23. Jackson, R. L., Boyd, J. D., and Smith, T. E. Stabilization of diabetic child. *Am. J. Dis. Child.* **59**:332-341, 1940.
24. Brush, J. M. Initial stabilization of diabetic child. *Am. J. Dis. Child.* **67**:429-444, 1944.
25. White, P. Personal communication.
26. Lukens, F. D. W., and Dohan, F. C. Remissions of diabetes mellitus. *Pennsylvania M. J.* **48**:24-28, 1944.
27. Hartmann, A. F. In M & R Laboratories. *Fat Metabolism.* (Report of Twelfth M & R Pediatric Research Conference.) 73 pp. Columbus, Ohio: M & R Laboratories, 1954. Pp. 19-25.
28. Cheng, T. O., Jahraus, R. C., and Traut, E. F. Extreme hyperglycemia and severe ketosis with spontaneous remission of diabetes mellitus. *J.A.M.A.* **152**:1531-1533, 1953.
29. del Greco, F., and Scapellato, L. Transient diabetes with coma following short term excessive consumption of carbohydrate: case report. *Diabetes* **2**:457-461, 1953.
30. Sprague, R. G., Priestly, J. T., and Dockerty, M. B. Diabetes mellitus without other endocrine manifestations in case of tumor of adrenal cortex. *J. Clin. Endocrinol.* **3**:28-32, 1943.
31. Duncan, L. E., Jr., Semans, J. H., and Howard, J. E. Adrenal medullary tumor (pheochromocytoma) and diabetes mellitus: disappearance of diabetes after removal of tumor. *Ann. Int. Med.* **20**:815-821, 1944.
32. Wilder, R. M. Hyperthyroidism, myxedema and diabetes. *Arch. Int. Med.* **38**:736-760, 1926.
33. Allen, F. M. Arnoldo Cantani: pioneer of modern diabetes treatment. *Diabetes* **1**:63, 1952.
34. White, P. Natural course and prognosis of juvenile diabetes. *Diabetes* **5**:445-450, 1956.
35. Guest, G. M. Personal communication.
36. Wilder, R. M. Personal communication.
37. Best, C. H. Personal communication.