The Effect of *Momordica Charantia* L. ("Cundeamor") in Diabetes Mellitus[1]

1. A TEST FOR HYPOGLYCEMIC ACTIVITY IN AN ALCOHOLIC EXTRACT

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MANY PLANTS have long been used in different countries, usually in the form of decoctions, as folk remedies in the treatment of diabetes mellitus. In the unitary conception, diabetes is known to be a metabolic disease due to insufficiency of the insular activity of the pancreas. Since insulin, the insular hormone, has been found an effective and successful therapeutic measure for the relief of the symptoms of the disease, the search for an insulin substitute may seem totally unnecessary and even undesirable. However, there is no doubt that the introduction of a similarly acting drug, which could be administered orally, would have very decided advantages. On the other hand, the continued and indiscriminate use of any such remedy by the public, if ineffective, unavoidably results in detrimental and even fatal procrastination of appropriate treatment. It is therefore of tremendous importance that, if such a remedy is shown to be ineffective by experimentation, the public be cautioned against the potential danger of its use.

A great many substances have been shown to possess hypoglycemic properties. Hill and Howitt[2] list the following: alkalis, phosphate, salts, sodium selenite, creatine, ergotamine, acetylcholine, bile acids, barbituric acid, yeast, pilocarpine, chloralose, spleen extracts, sulphur. The hypoglycemic action of guanidine derivatives is well known and has been thoroughly studied by many authors since Watanabe.[3] The presence of insulin, or of insulin-like substances, in tissues other than the pancreas has also been reported repeatedly. Ivy and Fischer[4] have shown the presence of an insulinotropic principle in the mucosa of the stomach and duodenum;

1. Received for publication March, 1943.

2. D. Hill and F. Howitt, *Insulin, Its Production, Purification and Physiological Action* (England: Hitchinson's Scientific and Technical Publications, 1936).

3. C. K. Watanabe, "Studies in the Metabolic Changes Induced by Administration of Guanidine Bases," *J.Biol.Chem.*, 33:253, 1918.

4. A. C. Ivy and N. F. Fischer, "The Presence of an Insulin-like Substance in Gastric and Duodenal Mucosa and Its Relation to Gastric Secretion," *Am.J.Physiol.*, 67:445, 1924.

Duncan, Shumway, Williams, and Fetter[5] concluded from their studies on the subject that one type of diabetes is due to the lack of activation of the pancreatic islets by the duodenal factor. The occurrence of glycogen in nature suggested to Collip,[6] in 1923, that an insular-hormone-like substance might be present wherever glycogen is found. Clam tissue, yeast, onion tips, barley roots, barley tips, green wheat leaves, sprouted grain, beet tops, and lettuce were shown to exert certain hypoglycemic action, but only after a latent period of several hours to several days; he proposed the name of "glucokinin" for the principle found in extracts obtained from these natural resources. In 1927 Allen[7] prepared an extract from blueberries which he reported as having an insulin-like action, when given orally, and which could be used in mild cases of diabetes; Allen named this active principle "myrtillin." Shpiner[8] gave support to this claim, but Macleod[9] found no corroboration of their findings in depancreatized dogs. Wilder[10] reported its use in one case of severe diabetes in whom it seemed to have some steadying influence on the blood sugar, in two more cases in which the dosage of insulin could be reduced not more than five units, and in ten others in which the results were entirely negative.

In China many a plant is reputed to have antidiabetic properties and many of them have been investigated. King-Li-Pin, Shih-Yuan-Kao, and Li-Teng-Pang (cited by Wilder) found *Rhenania glutinosa* to have the most active hypoglycemic activities. In Australia, likewise, two plants have been reported by Nye and Fritzgerald[11] and by Shellshear[12] to be of value in the treatment of diabetes, but their

5. G. G. Duncan, N. P. Shumway, T. L. Williams, and F. Fetter, "The Clinical Application of Duodenal Extract (Macallum-Laughton) in Diabetes Mellitus," *Am.J.M.Sc.*, 189:403, 1935.

6. J. B. Collip, "The Demonstration of an Insulin-like Substance in the Tissue of the Clam (*Mya arenaria*)," *J.Biol.Chem.*, 55:39, 1923; " 'Glukokinin'—A New Hormone Present in Plant Tissue," *J.Biol.Chem.*, 56:513, 1923; " 'Glukokinin.' " 2d paper, *J.Biol.Chem.*, 57:65, 1923.

7. F. M. Allen, "Blueberry Leaf Extract," *J.A.M.A.*, 89:1577, 1927.

8. L. B. Shpiner, "The Action of Myrtillin in Pancreatic Insufficiency," *Am.J.Physiol.*, 84:396, 1928.

9. J. J. R. Macleod, "Diabetes as a Physiological Problem. Lecture II. Regulation of the Secretion of Insulin," *Lancet*, 219:512, 1930.

10. R. M. Wilder, *Clinical Diabetes Mellitus and Hyperinsulinism* (Philadelphia and London: W. B. Saunders Co., 1940).

11. L. J. J. Nye and M. E. Fritzgerald, "Vinca Treatment and Diabetes," *Med.J.of Australia*, 2:626, 1928.

12. W. G. Shellshear, "The Treatment of Diabetes by Insulin and Prickly Pear," *Med.J. Australia*, 1:329, 1925; "The Prickly Pear and Diabetes," *Med.J.of Australia*, 1:175, 1926.

claims have been denied by Lee and Drew,[13] Corkill and Doudche,[14] and Ingram and Rudd.[15]

In Puerto Rico—as in Cuba and Santo Domingo, we are told—*Momordica charantia* L., "cundeamor," is used far and wide by the public as a folk remedy for diabetes. Hardly a diabetic patient escapes taking it at some time or another during the course of the disease. A vine of the gourd family, generally known in continental United States as wild cucumber or wild balsam apple, "cundeamor" is usually taken as a decoction, one glass after meals three times daily. Some who dislike the bitter taste of the decoction prefer the dried powdered leaves, or leaves and stems, in capsules, taking one or two after meals three times a day. It is claimed that all symptoms of the disease disappear with its use; that it is not necessary to follow any dietary restrictions; and that the glycosuria is controlled.

We have not been able to determine how or when "cundeamor" was first used. Physicians who have been practicing in Puerto Rico and attending diabetic patients since the turn of the century report that it was probably around the year 1910 that people first began to ask and to talk about it. In 1864 Grosourdy[16] published an extensive study of the flora of Puerto Rico and of other Caribbean islands from the standpoint of the medicinal usage of the various plants. Herein he reported the use of "condeamore," or "bejuco de condeamore"—giving it the correct botanical name as well—in "Dr. Malat's balsam, a precious remedy in all kinds of wounds and even a good hemostatic," and as an emmenagogue in the form of a decoction. Grosourdy also stated that "some claim it to be a vermifuge." However, in this voluminous treatise he did not mention diabetes by any of the names by which the disease was then known. We understand that in Venezuela "cundeamor," or "cundiamor"—as it is called there—is also utilized as an emmenagogue. Relying on sources that are not clearly stated, Torres Díaz[17] gives the impression that this plant is used in India for practically every malady, except diabetes.

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13. D. K. Lee and W. R. M. Drew, "Vinca rosea: Its Effect on the Blood Sugar Level of Normal Rabbit," *Med.J.of Australia*, 1:699, 1929.

14. A. B. Corkill and A. Doudche, "An Investigation into the Alleged Therapeutic Properties of Vinca Rosea in the Treatment of Diabetes," *Med.J.of Australia*, 1:213, 1930.

15. W. W. Ingram and G. V. Rudd, "The Influence of Extracts of Prickly Pear on Diabetes Mellitus," *Med.J.of Australia*, 2:360, 1930.

16. R. de Grosourdy, *El Médico Botánico Criollo* (Paris: Librería Francisco Brachet, 1864).

17. L. Torres Díaz, "A Preliminary Study of an Alkaloid-like Material Obtained from Cundeamor or *Momordica charantia* L.," *Puerto Rico J.Pub.Health & Trop.Med.*, 11:812, 1936.

or not their patients used it, provided they followed instructions concerning diet, insulin, and so forth. Torres Díaz states: "An infusion of 'cundeamor' leaves is claimed by some to be effective in the cure of diabetes and even practicing physicians have personally informed the author that they have obtained good results in the cure of this disease by using the plant in one form or the other." This is very obviously either an overstatement of facts or a misquotation of the physicians. We doubt very much whether any physician will speak of the "cure" of diabetes, particularly if no well controlled experiments have ever been carried out. Without offering proof for his statement, Rivera[18] says: "In the empirical use of the plant, it has been observed that a few isolated cases which have been recognized as chronic diabetics have seemed to show improvement on taking the drug orally without any use of insulin. In chronic cases which have developed marked tolerance to insulin, the drug has also seemed of value. The most interesting fact about the use of *M. charantia* is that it can be given orally and dietary restrictions are not very important." There is no evidence to sustain these statements, and it is hoped that the word "fact" in the above quotation refers only to the fact "that it can be given orally."

In 1936 Torres Díaz[19] found an alkaloid-like substance in an alcoholic (95 percent) extract of the leaves and petioles of *Momordica charantia* L., "cundeamor." The amount of the crude alkaloid was set by him at 0.038 percent by weight of the powdered drug. Rivera[20] later reported the separation from the dried powdered plant of an "apparently hypoglycemic substance," a crystalline substance, an alkaloid, a "yellow bitter substance," another crystalline substance, and a glucoside. Subsequently, he[21] reported the effect of an infusion and of several of the above-mentioned substances on the glucose tolerance of normal rabbits, as determined by the Long and Bischoff[22] method, in which a glucose tolerance test is performed with the administration of three grams of glucose per kilogram of body weight; one week later the test is repeated, giving not only the glucose but also the substance to be tested; the blood-

18. G. Rivera, "Preliminary Chemical and Pharmacological Studies of 'Cundeamor,' *Momordica charantia* L. (Part 2)," *Am.J.Pharm.*, 114:72, 1942.

19. L. Torres Díaz, *op.cit.*

20. G. Rivera, "Preliminary Chemical and Pharmacological Studies of 'Cundeamor,' Momordica charantia L. (Part 1)," *Am.J.Pharm.*, 113:281, 1941.

21. G. Rivera, *op. cit.* (18)

22. M. L. Long and F. Bischoff, "Investigation of Insulin-like Properties of Uvarsin Oxycatalyst and *Solanum sanitwongsei* Berries," *J.Pharmacol.& Exp.Therap.*, 38:313, 1930.

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sugar-lowering effect is deduced from the characteristics of the two blood sugar curves thus obtained. One important objection to this method is the fact that it does not take into consideration the possibility that the substance being tested inhibits the absorption of glucose, an inhibitory action which certain substances have been shown to have.[23] Rivera interpreted his findings as indicative of blood-sugar-reducing power in an infusion of the crude drug, in the "hypoglycemic substance," and in the crystalline substance, but none in the alkaloid. Preliminary toxicological observations disclosed that the crude alkaloid was not toxic to rabbits, that hot alcoholic extracts contained a saponin-like substance toxic to gold fish and rabbits, and that the infusion and the powdered drug were not toxic to rabbits.

METHOD

With the means at our disposal we decided during the summer of 1940 to determine what effect, if any, "cundeamor" could have on patients suffering from diabetes, though we realized (Jensen[24]) that the physiological action of the blood-glucose-lowering substances so far tested was quite different from that of insulin itself, in spite of the superficial similarity in effect. We planned to test the hypoglycemic action of the drug first.

Mr. Luis Torres Díaz, Dean of the College of Pharmacy of the University of Puerto Rico, had been interested for some time in the chemistry and pharmacology of the medicinal plants of Puerto Rico and had already contributed to the literature the previously quoted article. When he showed us evidence that a number of diabetics had been taking an alcoholic extract, prepared by him, with the same favorable (*sic*) results obtained from the decoction or the dried powdered leaves and without any toxic or ill effects, we decided to give his extract a trial. This extract was prepared by drying the leaves and petioles of the plant in the sun, reducing them to a fine powder, and extracting with cold 95 percent alcohol. Using althea as excipient, the pills were made to contain 0.10 gm. of the extract. The desired effect was said to have been obtained from three to six pills daily, one or two after each of the three principal meals. Mr. Torres Díaz kindly supplied the pills.

23. R. L. Driver, "Effects of Hexylresorcinol and Other Agents on the Absorption of Sugars, Chloride, and Sulfate from the Alimentary Tract," *Am.J.Physiol.*, 135:330, 1942.

24. H. F. Jensen, *Insulin. Its Chemistry and Physiology* (New York: The Commonwealth Fund, 1938).

No particular selection was made of the cases. All patients were carefully studied to determine their exact status and to eliminate any possibility of the presence of complications that might render them unsuitable for the experiment. Care was also taken in every case not to jeopardize the safety of the patient. While the drug was being administered, strict watch was kept for the appearance of any toxic symptoms or manifestations. Every specimen of urine voided was tested for reducing sugars with Benedict's reagent, and for acetone by the sodium nitroprusside test. The fluid intake and output were carefully measured. Blood sugar determinations were made daily, or almost daily, on samples taken in the fasting state at eight o'clock in the morning, twelve and a half hours after the last meal. Practically all tests were handled by the same technician using the Folin-Wu method.

The diet of these patients was very carefully controlled. With the exception of the patient receiving insulin at the time of this experiment, the diet of the others was divided into thirds on the basis of carbohydrates, proteins, and fats (not on the basis of available glucose), no food being permitted between meals. The patient who was under insulin (Protamine-zinc) therapy had the carbohydrates, proteins, and fats divided into fifths ($^1/_5$-$^2/_5$-$^2/_5$), with 5, 5, and 10 gm. extra carbohydrates at 10 A.M., 3 P.M., and 9 P.M., respectively. The drug was given only when it was reasonably certain that the blood glucose level was more or less stable; the dosage was that which was said to be effective when used empirically, or as a folk remedy.

CASE 1: Elderly woman with diabetes of three years' duration; no treatment for past year but condition aggravated by recent infection; no insulin needed after infection was controlled; test with "cundeamor" when under control without insulin.

G. M. G.—H. No. 43930. Colored female aged 50 years, admitted September 16, 1940. First found to be suffering from diabetes 3 years before entry. Followed diet and took insulin twice daily for 2 years, then gave up both. Some polyuria and anorexia off and on during past year; no known loss of weight. For one month previous to admission, interdigital epidermophytosis of feet with secondary bacterial infection and subacute lymphangitis of leg; edema and a healing small ulcer of leg present. Daily elevation in temperature to 100°–101° F. during first week.

Fasting blood sugar on September 16 was 306 mg. percent; urine positive (4+) for reducing sugars with traces of acetone. Diet of 150 gm. carbohydrate, 70 gm. protein, and 60 gm. fat well received; regular (unmodified)

insulin given every 3 hours during first 24 hours, regular and Protamine-zinc insulin[25] administered during following 24-hour period. In the course of these 48 hours urine became acetone-free first and sugar-free later.

On September 18 fasting blood sugar was 114 mg. percent. On 40 units of P-insulin sugar reappeared in urine but no acetone. On September 21 fasting blood sugar was 228 mg. percent; diet was then reduced to 130 gm. carbohydrate, 60 gm. protein, and 60 gm. fat. With infection under control and urine still showing occasional traces of reducing sugars, fasting blood glucose was 138 mg. percent on September 25. On following day it was 196 mg.; on September 28, 111 mg.; on September 30, 125 mg.; on October 2, 148.1 mg., and on October 4, 125 mg. percent.

Throughout succeeding three weeks dose of P-insulin was gradually reduced; omitted altogether on October 28 with fasting blood sugar at 125 mg. percent. During following 12 days patient perfectly well without insulin; urine consistently negative for reducing sugars, with blood sugar values as follows on October 30, November 1, 4, and 7: 133.3, 117, 138, and 125 mg. percent, respectively. Beginning November 9, with patient still on same diet, 2 "cundeamor" pills were administered after meals three times daily. Fasting blood sugar values during latter therapy, as recorded on November 11, 13, and 18, as follows: 140, 138, and 132 mg. percent, respectively. "Cundeamor" then discontinued and blood sugar values of 133, 133, 160, 125, and 152 mg. percent recorded for November 22, 25, 28, 29, and December 3, respectively.

On November 29 and December 3 another experiment with single large dose of "cundeamor" was performed, but this will be discussed later on in the article.

CASE 2: Middle-aged female having suffered mild untreated diabetes from 1929 to 1937; more severe untreated diabetes from 1937 to 1939, with diabetic ketotic acidosis during last named year; from then on had followed diet and insulin treatment and now readmitted with facial palsy; "cundeamor" test performed when under control with insulin.

M. V. T.—H. No. 44301. Colored female aged 54 years, admitted October 27, 1940. In 1929, while at another hospital, patient discovered suffering from diabetes at which time low carbohydrate diet was prescribed, but no insulin. No symptoms while on diet for 4 years; diet then given up with exception of sugar in all forms; patient thereafter developed symptoms off and on.

When patient was first admitted to Presbyterian Hospital in 1937, loss of 20 pounds had been recorded in one month; controlled with final diet of 150 gm. carbohydrate, 70 gm. protein, 60 gm. fat, and 25–0–20 units of R-insulin. In 1939, after 2 years without insulin, patient readmitted with

25. Hereafter unmodified insulin will be referred to as R-insulin, Protamine-zinc insulin, as P-insulin.

constant polyuria and polydipsia, headaches, chills, dizziness, and precordial oppression. Fasting blood glucose 320 mg. percent; large amounts of reducing sugars, acetone, and diacetic acid in urine. Patient promptly brought under control and discharged after 13 days.

At time of last entry patient claimed to have followed diet closely, to have taken insulin regularly but not under physician's supervision. Two months before entry had a forunculosis, later an alveolar abscess; still later severe upper respiratory infection; recent reappearance of polyuria and polydipsia. Peripheral left facial palsy brought her to hospital. Blood sugar on October 28 was 266 mg. percent; urine showed a strong (4+) reducing sugar reaction but no acetone. Patient placed on diet of 150 gm. carbohydrate, 70 gm. protein, and 80 gm. fat, with 40 units of P-insulin. On October 30, 15 units daily of R-insulin added and given before breakfast.

Fasting blood sugar on November 1 was 166.7 mg. percent; on November 4, 143 mg. percent. Patient continued on P-insulin only, 40 units daily. Urine negative for reducing sugars except for occasional mildly positive (1+) reaction; patient symptom-free except for facial palsy. On November 7 fasting blood glucose was 142.8 and on November 9, 140.8 mg. percent.

Beginning on latter date, 2 "cundeamor" pills administered after meals three times daily, besides the 40 units of P-insulin daily before breakfast. On November 11, after 48 hours of this treatment, fasting blood glucose was 111.1 mg. percent; on November 13, 114.3, on November 15 (after 6 days of "cundeamor" dosage), 103 mg. percent. Dose of P-insulin was not reduced because there had been no symptoms of hypoglycemic reaction. On November 18, fasting blood sugar was 117 mg. percent; that day patient received last dose of "cundeamor." P-insulin immediately reduced to 35 units. On November 20, blood sugar was 121.2 mg. percent and on November 23, when blood sugar was down to 117 mg. percent, P-insulin again reduced to 30 units. November 25 showed blood sugar at 95 mg. percent; again on November 27, at 95.2 mg. percent. Patient given 25 units of P-insulin for next 3 days; blood glucose was 80 mg. percent on November 29 and, when given 20 units daily beginning with December 1, blood sugar was recorded at 98 mg. percent on December 2 and 100 mg. percent on December 4. Patient discharged on same diet and 15 units of P-insulin daily.

CASE 3: Middle-aged female with mild diabetes of six years' duration; "cundeamor" test performed before insulin control.

A. M. M.—H. No. 44352. White female aged 54 years, admitted October 31, 1940. There was found a very strong family tendency to diabetes in patient who had undergone vaginal operation in same hospital in 1930, when the disease had not yet appeared. In 1936, readmitted with symptoms of one year's duration that led to diagnosis of mild diabetes, which was promptly controlled with final diet of 160 gm. carbohydrate, 70 gm. pro-

tein, 120 gm. fat, and 15–0–10 units of R-insulin. At last readmission patient reported not having taken insulin after previous discharge and not having followed diet except for avoidance of sweet foods. Throughout these years, she had noted same symptoms, with varying intensity, complained of in 1936. One week previous to final entry had been unconscious for 2 or 3 hours. No clinical or laboratory evidence of ketotic acidosis.

Fasting blood glucose on November 1 was 181.8 mg. percent; urine only faintly (1+) positive for reducing sugars. On diet of 130 gm. carbohydrate, 60 gm. protein, and 60 gm. fat, blood glucose was 166 mg. percent on November 4, 163.2 mg. percent on November 6, and 153.8 gm. percent on November 8. Throughout this period reaction in urine for reducing sugars fluctuated widely (between 1+ and 4+), with tendency towards stronger reactions in the late afternoon and early evening; no polyuria. On and after November 9, two "cundeamor" pills given after meals three times daily.

During succeeding 14 days blood sugar values were as follows: 183.5, 166.7, 174, 190, 208, and 200 mg. percent on November 11, 13, 15, 18, 20, and 22, respectively. Reaction in urine for reducing sugars during this time continued to vary as widely as before; all symptoms persisted and patient lost weight.

On November 25, day following first injection of 25 units of P-insulin, she suffered a sharp and unexpected drop to 101 mg. percent in blood sugar; a further drop to 75 mg. percent (without hypoglycemic reaction) on November 27 forced reduction of insulin dose to 20 units on November 28 and to 15 units on November 29, when blood sugar was 113 mg. percent. By then all symptoms had disappeared. Subsequently, there were wide fluctuations in patient's blood sugar values, which were unrelated to insulin dosage. Patient finally discharged on 20 units of P-insulin with blood sugar of approximately 130 mg. percent and with several urine specimens still yielding each day faintly positive (1+) reaction for reducing sugars.

CASE 4: Diabetes accidentally discovered in male past middle age; "cundeamor" test given before insulin; readily controlled with insulin; increasing insulin requirements led to discovery of infection in operative wound.

T. R. C.—H. No. 44534. White male aged 58, admitted November 23, 1940 for hernia operation. Admission urinalysis showed strongly positive (3+) reaction for reducing sugars. On November 26, fasting glucose found to be 250 mg. percent. Symptoms of diabetes denied. Glucose tolerance test next day yielded following values: 204, 282, 346, 362, and 354 mg. percent. On diet of 160 gm. carbohydrate, 70 gm. protein, and 90 gm. fat, fasting blood sugar dropped from 212 mg. percent on November 28 to 140 mg. percent on December 2. Urine negative for reducing sugars through day and night of December 1.

On December 2 administration of "cundeamor" pills began, one three times daily after meals; blood sugar showed values of 148, 142, 138, 141, and 131.6 mg. percent during next five days. Reaction for reducing sugars in urine consistently negative at this time. With 15 units of P-insulin blood sugar gradually reduced to 105.3 mg. percent on December 17, when hernia operation was performed. Increasing requirements of insulin after operation led to discovery of wound infection, during which carbohydrate metabolism was extremely variable. Patient finally discharged on original diet and 20 units of P-insulin and 20 units of R-insulin, both to be administered before breakfast.

CASE 5: Acute onset of diabetes in young male; diabetic ketotic acidosis; "cundeamor" test during acidosis; subsequent control with insulin.

L. V.—H. No. 45461. White male aged 32 years, admitted March 10, 1941. Rather acute onset of diabetes 20 days before entry with polydipsia (10 liters daily), polyuria, polyphagia, and loss of 20 pounds in body weight. Severe food poisoning (fish) 2 months previously. One brother died from diabetes at 25 and another has the same disease at 23. Urine strongly positive (4+) for reducing sugars and frankly positive for acetone. Since general condition of patient was excellent, insulin postponed while keeping him under close surveillance.

Patient partook of diet of 150 gm. carbohydrate, 80 gm. protein, and 80 gm. fat; given plenty of salt and fluids. On March 11, blood glucose was 285.6 mg. percent; subsequent blood sugar values were 239.4, 232.6, 212, 195.2, 229, and 239 mg. percent on March 13, 14, 15, 17, 18, and 19, respectively. Glycosuria remained of the same intensity throughout period; acetonuria diminished rapidly after March 16, disappearing altogether by March 19. On latter date and thereafter until March 26, 2 "cundeamor" pills given after meals three times daily. During last treatment urine continued to show strongly positive (4+) for reducing sugars, but no acetone at any time. Blood sugar determinations on March 20, 21, 22, 24, 25, and 26 were 215, 208.4, 226, 245.4, 215, and 238 mg. percent, respectively.

Under 30 units of P-insulin daily, glycosuria disappeared within 48 hours, much more rapidly than it had been intended. Blood sugar levels recorded on March 28 and 29 of 123.5 mg. percent and 94.3 mg. percent, respectively; no hypoglycemic shocks. Dose of P-insulin then reduced to 20 units and diet increased to 180 gm. carbohydrate, 90 gm. protein, and 80 gm. fat. Fasting blood glucose was 86.2 mg. percent on March 31, 155.6 mg. percent on April 1, 143.8 on April 2, and 125.8 on April 3. Occasional urine specimens still faintly positive for reducing sugars. No loss of weight during entire hospital stay.

CASE 6: Recent and moderately severe diabetes in middle-aged female; "cundeamor" test before insulin; apparently high renal threshold without obvious nephritis.

F. C. M.—H. No. 45477. White female aged 48, admitted March 12, 1941. Diabetes discovered 2 months before entry when suffering attack of pruritus vulvae. Although present, polyuria and polydipsia not noted previous to admission; menstrual periods regular. No previous treatment except self-prescribed limitation of carbohydrates in diet. Admission urine positive (3+) for reducing sugars, but not for acetone. On March 13 blood sugar levels were 310, 381, 421, 487.8, and 482 mg. percent during glucose tolerance test. On diet of 150 gm. carbohydrate, 80 gm. protein, and 80 gm. fat, subsequent blood sugar determinations on March 14, 15, 17, 18, and 19 yielded 336, 272, 287.8, 243.8, and 261 mg. percent, respectively. During latter interval every urine specimen positive for reducing sugars (2+ to 4+).

Two "cundeamor" pills given after meals three times daily between March 19 and April 5 with results of blood sugar as follows: March 20, 239 mg. percent; March 21, 247 mg. percent; March 22, 250; March 24, 203; March 25, 232; March 26, 216; March 27, 248.4 mg. percent. On March 28 and 29, and on April 1, 2, 3, 4, and 5, fasting blood glucose was 198, 222.2, 228.6, 184.4, 195.2, 198.3, and 183.4 mg. percent, respectively. Beginning April 6, 20 units of P-insulin administered daily before breakfast; blood sugar reduced to 146 gm. percent by April 10, when patient was discharged. It is to be noted that after March 19, day on which "cundeamor" therapy was instituted, reaction for reducing sugars became only faintly positive (1+) in every specimen voided. After March 27 many specimens completely negative; others faintly positive (1+). After April 2, with blood sugar levels ranging between 198 and 183.4 percent, all specimens negative. No evidence of nephritis.

Case 7: Mild diabetes of over 15 years' duration in an elderly female never under diabetic control; diabetes aggravated by infection during which "cundeamor" test was performed; prompt subsequent control with insulin.

F. R. M.—H. No. 45492. White female aged 70 years, admitted March 13, 1941. Patient known to be diabetic for not less than 15 years, but never under systematic treatment or diabetic control of any kind. Sweets avoided in diet and insulin taken intermittently and more or less haphazardly without expert advice. Admission sought because of fever of 15 days' duration; patient had remained obese throughout illness.

Admission urinalysis gave positive (4+) for reducing sugars; negative for acetone. Blood sugar reached following levels during glucose tolerance test on March 14: 400, 532, 532, 532, and 532 mg. percent. On diet of 120 gm. carbohydrate, 70 gm. protein, and 80 gm. fat, urine continued to be strongly positive (4+) for reducing sugars in every specimen voided; glycemic levels during succeeding 5 days were 360, not taken, 381, 373.8, and 425 mg. percent. Patient having daily febrile elevations to 101° and 102° F. due to pyelitis.

On March 19, 2 "cundeamor" pills administered after meals three times daily and continued until April 6. Blood glucose during next 11 days was 381, 384, 377, not taken, 325, 341, 333, 421, 341.8, 347.8, and not taken, mg. percent. Throughout this period urine continued to give strongly positive reaction (4+) for reducing sugars. During succeeding 7 days of "cundeamor" therapy blood sugar levels were 247.8, 363.6, 310, 320, 347.8, 327.8, and not taken, mg. percent. Urine fluctuated between negative and strongly positive (0 to 4+) for reducing sugars, but was only faintly positive (1 and 2+) in all specimens voided during last 2 days of period. Blood sugar brought down in 4 days from 330.6, 274, and 250 mg. percent to 126.6 mg. percent by administration of 40 units of P-insulin daily. Patient discharged on 20 units of P-insulin, though urine still gave occasional faintly positive reactions (1+) for reducing sugars.

Case 8: Normal young man with high glucose tolerance.

P. M. P.—H. No. 44565. White male aged 21, admitted November 26, 1940 with complaints of constipation and vague gastrointestinal symptoms. Patient found to have only uncinariasis and hyperchlorhydria. Glucose tolerance test performed November 27, giving following blood sugar values: 90, 83, 103, 83, and 80 mg. percent. On November 27, 28, and 29, fasting blood sugar levels were 90, 99, and 63.3 mg. percent on general diet. On latter day patient placed on fixed intake of 3,000 calories with 280 gm. carbohydrate, 80 gm. protein, and 80 gm. fat. On November 30, December 2, 3, 4, and 5 fasting sugar was 83, 88.1, 90.9, and 86.2 mg. percent. On December 5 and thereafter, 1 "cundeamor" pill administered after meals three times daily. Fasting blood sugar on December 6, 7, 9, 10, 11, 12, 13, 14, 16, 17, 18, and 19 found to be 93, 91, 93, 94, 101, 93.4, 97.1, 111, 104.2, 108.1, 90, and 93.2 mg. percent, respectively.

EFFECT OF A SINGLE LARGE DOSE ON THE GLYCEMIC LEVEL

For this experiment a blood sample was taken at eight o'clock in the morning in the fasting state and ten "cundeamor" pills were immediately given with a little water. Thereafter, blood samples for the determination of glucose were taken every half hour for three and one-half or four hours. This procedure was carried out on three of the preceding cases with the following results:

Case 1: On November 29, blood samples taken every half hour for four hours without giving either glucose or "cundeamor." Blood sugar determined on each specimen for purpose of finding out degree to which homeostasis of sugar had been established after diabetes had been controlled by diet only. Results were 125, 138.9, 117, 121.9, 114.3, 106, 114, 111, and 103 mg. percent. Procedure repeated on December 3, patient having been

given 10 "cundeamor" pills immediately after first blood sample was taken. Blood sugar levels were 128, 152, 156, 158, 142, 124, 122, and 118 mg. percent.

CASE 4: In this case above procedure was carried out on December 9, immediately upon termination of other experiment. Ten "cundeamor" pills administered immediately after first blood sample was taken. Results of blood sugar determinations: 105, 121, 117, 111, 106.4, 105.3, 110.6, and 109 mg. percent.

CASE 8: On December 4, nondiabetic patient also given 10 "cundeamor" pills immediately after first blood sample was taken; one sample taken every half hour for four hours. Blood sugar levels as follows: 90.9, 95, 97, 80, 93, 90, 95, 94.6, and 92.6 mg. percent.

COMMENTS AND DISCUSSION

It has not been our aim at this time to determine whether *Momordica charantia* L., "cundeamor," is or is not a good drug to use in the treatment of diabetes, or whether it does or does not affect the course of the disease in any of its stages or phases. We have merely attempted to determine whether, when administered orally, it has any blood-sugar-reducing powers to which any favorable effects can be attributed.

It may seem strange that we should administer this drug to humans without any preliminary animal experiment. This we can justify by the fact that, in the course of the past fourteen years, we have seen hundreds of patients taking "cundeamor" over long periods of time without any pathology that may in any way be attributed to the drug. This observation includes cases of diabetes that have come to autopsy. As for the particular preparation utilized in the experiments, we have direct verbal evidence from patients who have taken it and who have obtained the adduced beneficial effect without any untoward reactions. The dosage used was the same claimed to have been effective.

We realize that there is one incommensurable factor in these experiments, namely, the integrity of the absorptive mechanism of the gastrointestinal tract of the patients. We feel, however, that the uniformity of the results obtained eliminates this particular factor as a possible source of error or misinterpretation. The seven cases of diabetes treated perhaps represent the common types of the disease. Figures 1 and 2 show the blood sugar levels before and during "cundeamor" and under insulin.

Case No. 1 represents a case of diabetes developing in old age,

possibly on an arteriosclerotic basis, severe enough to require insulin yet mild enough to go on for one whole year without it and without much of a diet, yet no complications. Only a recent infection aggravated the patient's disturbed carbohydrate metabolism sufficiently to bring her back to the hospital. After the infection subsided, she continued well on a diet alone with a rather stable blood sugar level slightly above normal. One might consider this the type of case in which a drug having a mild blood-sugar-reducing power would be most effective. It was not, however, yet one received the impression that the drug might have had a steadying influence on the blood sugar level even though it remained at a slightly elevated level.

Case No. 2 is that of a middle-aged female who had had diabetes for some eleven years. The disease at first had been so mild that she had felt well for four years on no other treatment than dietary restrictions consisting of the avoidance of sugar. No other treatment had been necessary for the following four years. However, a sudden drop in weight required the administration and continued use of insulin with the necessary adherence to a diet. The patient's diet and insulin dosage were therefore readjusted, the latter to 40 units of P-insulin. After seven days with a blood sugar level of about 140 mg. percent, six days of "cundeamor" treatment seemed to bring her blood sugar level down to as low as 103 mg. percent. Without reducing the insulin dose, her blood sugar rose to 117 mg. percent after three more days. It was then possible to reduce the dose of insulin to 15 units in the course of the next sixteen days, without "cundeamor."

This case clearly shows how easy it would have been to attribute to "cundeamor"—had this patient been taking it—the reduction of the insulin dosage in the course of sixteen days from 40 units, at which dose the patient had been considered stabilized, to 15 units.

Case No. 3 also represents diabetes of middle age in a patient coming from a diabetic family. For six years she had suffered a severe enough attack to require a small amount of insulin. This she had not done, however, neither had she followed any systematic dietary with the exception of avoiding sugar. The patient's renal threshold seemed rather variable and generally low. "Cundeamor" was given when her blood sugar was fairly stable at a level of about 160 mg. percent. The tendency during fourteen days of this therapy was for the sugar level to climb to a level of about 200 mg. percent. When insulin was administered, the patient proved to be hyper-

sensitive to it. While there is no definite dextrose-insulin ratio that applies to all persons having diabetes, we had not expected a dose of 25 units to bring about the abrupt drop that this patient suffered. Her final dose, however, was 20 units. In a sense, and even though the cause of hypersensitivity to insulin is not known, one would expect an insulin-hypersensitive diabetic patient to react readily to any agent with blood-glucose lowering activity. This patient certainly did not so react to "cundeamor."

Case No. 4 illustrates a moderately severe attack of diabetes, accidentally discovered, in a male just past middle age. On a dietary regime alone his blood sugar dropped from a level around 200 mg. percent to one about 140 mg. percent, at which it became apparently stable. During four days of "cundeamor" treatment, there was no change in the general blood glucose level; on the fifth it dropped 10 mg. Inadvertently, and this is to be regretted, the experiment was discontinued on this same day. On 15 units of P-insulin daily, the patient's blood sugar gradually descended to a level of 105.3 mg. percent in ten days. It is possible, if not likely in the light of the results in other cases, that a reduction in the blood sugar was to be initiated under "cundeamor" therapy precisely when the experiment was stopped on the fifth day. If the latter assumption is correct, the paucity of the effect was very unlike an insulin effect.

Case No. 5 shows diabetes developing acutely in a relatively young male with a strong family tendency to the disease. Rather mild diabetic ketotic acidosis was permitted to subside gradually without insulin and, when the blood sugar was fairly stable at a level around 230 mg. percent, seven days of "cundeamor" treatment failed to bring it down. The response to insulin was a rapid one, as is usually the case in acute diabetes. In a case like this, one might again expect some response to any drug having any hypoglycemic activity.

It is a well-known fact that infections cause an increase in the severity of diabetes mellitus and an increase in insulin requirements. This means a lowered carbohydrate tolerance. Marble[26] has suggested that this may be due to one of four causes in diabetic and nondiabetic individuals: (1) lessened production of insulin possibly brought about by injury to the pancreatic islets of Langerhans; (2) increased production of hormonal anatagonists to insulin possibly due to increased activity of the suprarenal and thyroid glands; (3) destruction of insulin, as if by trypsin and toxins produced by

26. A. Marble, cited by E. P. Joslin, *The Treatment of Diabetes Mellitus, 6th ed.* (Philadelphia: Lea and Febiger, 1937).

bacteria, leucocytes, and pus; (4) interference with the storage of glycogen of which there is some experimental evidence. If "cundeamor" were capable of antagonizing directly any of these mechanisms and of thus increasing carbohydrate tolerance, its effect on a case of diabetes with infection might well be more marked than in diabetes without infection, thus rendering any hypoglycemic activity more readily detectable.

Case No. 7 afforded a good opportunity for such a test. An elderly woman with mild diabetes of fifteen years' duration, which had never been under systematic control, had fever due to pyelitis. She was not seriously ill and had no ketotic acidosis. During a glucose tolerance test her blood sugar behaved peculiarly in that it stayed at a fixed level of 532 mg. percent (from 400 mg. fasting) for three hours. After five days on a fixed diet, her blood sugar remained at a fairly stable level of about 380 mg. percent. During eleven days of "cundeamor" treatment, the blood sugar level gradually decreased to a level of about 325 mg. percent, except for one unexplainable elevation to 421. The glycosuria continued to be marked. During seven more days of "cundeamor" therapy, the blood sugar remained at approximately the same level as during the previous eleven-day period, but with rather wide variations. However, in spite of high glycemic levels, there were urine specimens without glycosuria, all specimens being but mildly positive (1+) for reducing sugars on the last two days of this period. The patient was then promptly controlled with P-insulin. She did not have a high renal threshold for glucose. When her blood sugar was at a level of about 125 mg. percent on 20 units of insulin during her last few days in the hospital, she was still voiding specimens that occasionally gave weakly positive (1+) reactions for reducing sugars.

Here again we might be led to believe that "cundeamor" therapy had brought about a reduction in glycemia from a level of about 380 to one of about 325 mg. percent. It so happened that by the time this drop took place the active infection had considerably, or almost completely, subsided and the temperature was already quite normal. Once more we cannot attribute a drop in the blood sugar level to the "cundeamor" being taken at this time, since such a drop is perfectly explicable in terms of a change in other circumstances. The patient did not have the relative insensitivity to insulin that her moderate obesity and her age would have suggested.

While a diabetic with hyperglycemia, a diabetic with normal glycemia, and a normal person may all react differently to a given

blood-sugar-reducing agent (except insulin, outside of individual sensitivity) so that it is conceivable that one such agent may be capable of reducing diabetic hyperglycemia but not normal glycemia or a normal blood sugar in a diabetic, we decided to try "cundeamor" on a normal person. Case No. 8 had only uncinariasis and hyperchlorhydria. A glucose tolerance test revealed a high tolerance at a rather low level. A low glucose tolerance curve in Puerto Rico often signifies chronic ileo-jejunal insufficiency and failure of absorption of the glucose. This mechanism is similar, or identical, to that usually encountered in sprue, the original description of which Hanes[27] attributed to Thaysen. It does not by any means imply a high carbohydrate tolerance.

However, this patient did not present such a picture. In our experience this syndrome is quite invariably associated with hypochlorhydria or achlorhydria; the patient had hyperchlorhydria. If the curve actually represented a high glucose tolerance with a general tendency to a somewhat hypoglycemic level, its nature could be of mild pituitary hypoglycemia, or Wilder's syndrome. We doubted whether we should use him as a subject for the experiment. However, patients having hypoglycemic levels of endocrine origin are said to be extremely sensitive to insulin.[28] This has been our experience with patients having low blood sugar values and low glucose tolerance curves from deficient absorption. We therefore decided that he might also be hypersensitive to whatever hypoglycemic activity "cundeamor" might have. During the fifteen days in which "cundeamor" was administered, the glycemic level was considerably higher than during the previous five-day period.

The effect of a single large dose of "cundeamor" was tested on three patients, two diabetic and one nondiabetic. Figure 3 shows the corresponding glycemic levels. Case No. 1 was under diabetic control without insulin at which time the fasting blood sugar determinations, made every half hour for four hours, fluctuated between 13.9 mg. above and 23 mg. below an initial blood sugar level at 125 mg. percent. Four days later, with ten "cundeamor" pills given after a first blood sample was obtained, the fasting blood sugar determinations carried out every half hour for four hours fluctuated between 24 mg. above and 10 mg. below an initial glycemic level of 128 mg. percent.

27. F. M. Hanes, in *A Textbook of Medicine*, by R. L. Cecil, 5th ed. (Philadelphia and London: W. B. Saunders Co., 1940).

28. M. A. Goldzieher, *The Endocrine Glands* (New York and London: D. Appleton-Century Co., Inc., 1939).

In Case No. 4, when the same dose of "cundeamor" pills was given, every blood sample (taken every half hour for three and a half hours) contained more glucose than the initial sample. In the nondiabetic subject (Case No. 8), every blood sample also contained more glucose than the initial sample, with the exception of the one taken on the one and a half hour which was 10.9 mg. lower. Rivera[29] claims that in his experiments with rabbits the maximum hypoglycemic effect took place between the first and third hours. The sudden drop in this patient was very brief and was noticed only on the one and a half hour sample.

No untoward effects or toxic manifestations attributable to the drug were detected at any time in any of the patients. No improvement in any of the subjective symptoms of diabetes, which could be attributed to the effect of the drug, was recorded.

CONCLUSIONS

In an effort to determine whether the plant possesses blood-sugar-reducing powers, *Momordica charantia* L., known as "cundeamor" and used in Puerto Rico and other neighboring countries as a folk remedy in the treatment of diabetes mellitus, was given to seven diabetic and one nondiabetic subjects under hospital conditions. It is generally claimed that "cundeamor" controls the symptoms of the disease to the point where dietary restrictions are unnecessary.

An alcoholic extract from this plant, claimed to be equally effective, was used in the dosage said to be capable of producing the desired results. A single large dose was also given to two diabetic patients at low glycemic levels and to one nondiabetic subject, after which their blood sugar levels were determined every half hour for three and one-half to four hours.

The results of this study did not reveal that this particular preparation of the drug possessed any blood-sugar-reducing powers in the dosage used. We found two instances in which any such action was vaguely suggested—Cases 4 and 8. In the first there was a drop of 10 mg. percent on the fifth day; this case was unfortunately not followed up. In the latter case, the initial blood sugar level was lowered by 10.9 mg. percent one and a half hours after a large single dose. Notwithstanding, these cases do not justify the use of the preparation as an insulin substitute. We should add, however, that

29. G. Rivera, *op. cit.*

these negative findings do not altogether disprove the claims made for "cundeamor," since they cover only one aspect of a rather large problem.

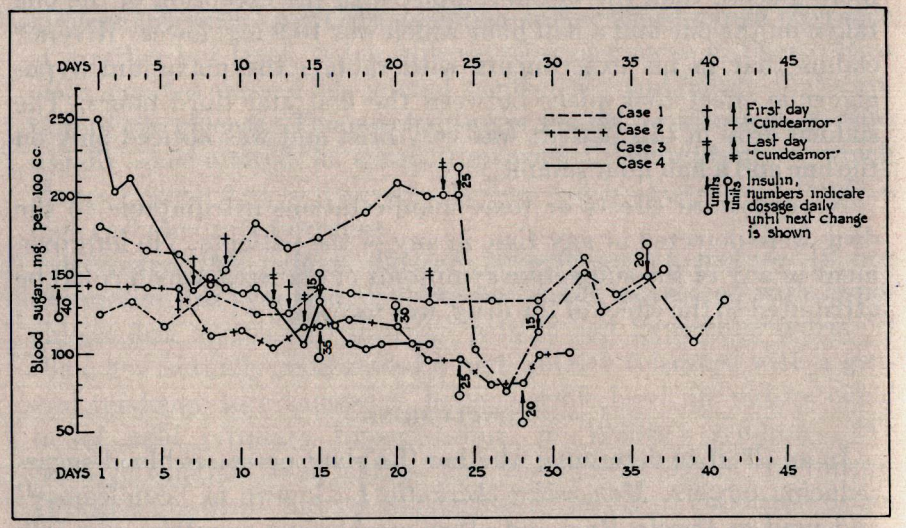

FIGURE 1

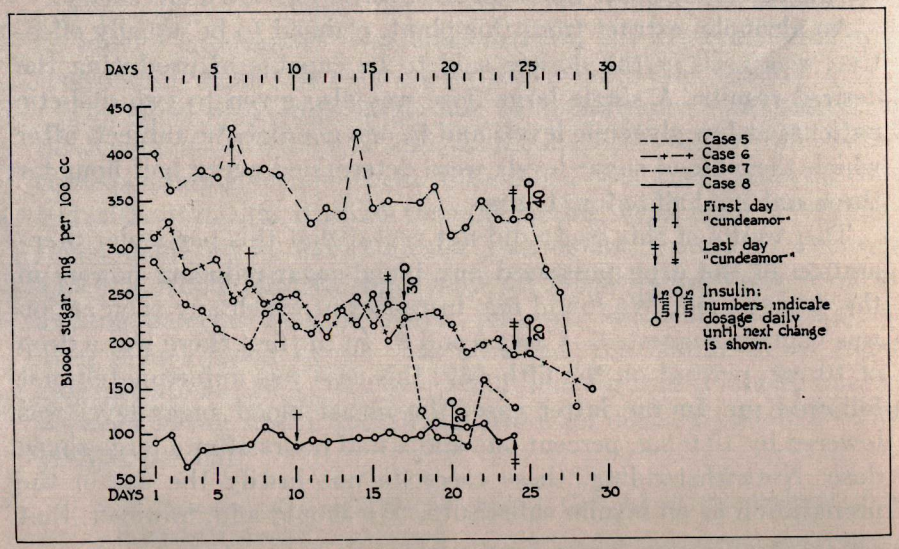

FIGURE 2

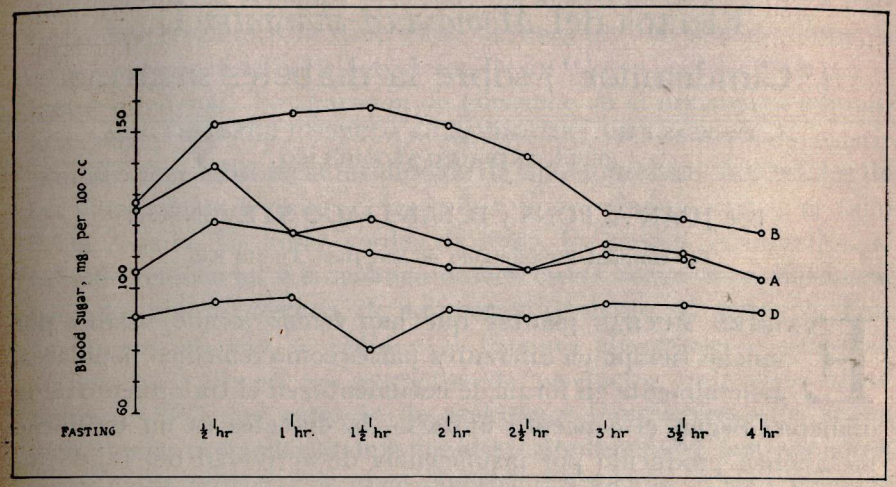

FIGURE 3