

Idiopathic Insulin-Resistant Diabetes Mellitus*

Report of a Case Associated with Insulin Allergy

ERNEST O. FRIEDLANDER, M.D. and M. DAVID BRYANT, JR., M.D.

Togus, Maine

EVER since insulin has been used in the treatment of diabetes mellitus, the failure of certain patients with diabetes to respond in the expected manner to apparently physiologic substitution therapy has aroused the curiosity of many investigators. Whereas high insulin requirements have been observed under a number of conditions complicating the clinical picture of diabetes, cases of true insulin resistance have been rather uncommon. Root [1] defined a case of insulin-resistant diabetes as one requiring 200 or more units of insulin daily for more than forty-eight hours, in the absence of acidosis and infection. About sixty such cases have been reported in the world literature. We have studied a case of insulin resistance and insulin allergy over a period of four years. Certain aspects of this case pertaining to the use of tolbutamide have been previously published elsewhere [2].

CASE REPORT

A fifty-six year old white man was first noted to have diabetes mellitus in May 1951. He was given a diabetic diet of 1,800 calories and 20 units of NPH insulin daily. His insulin requirements could be gradually reduced and by January 1952 he was well controlled by diet alone. He did well until December 1953 when his diabetes became worse. He was given 40 units of NPH insulin and 25 units of crystalline insulin daily. Despite a gradual increase of his daily insulin dose to 120 units, the blood sugar on his first admission to the hospital in March 1954 was 400 mg. per 100 ml. and he showed 4-plus glycosuria and 2-plus ketonuria. Physical examination was essentially within normal limits except for the presence of multiple, firm, non-tender, movable, subcutaneous nodules in the abdominal wall which the patient stated were the sites of previous insulin injections.

Laboratory data other than those pertaining to carbohydrate metabolism revealed no abnormalities.

Urinary 17-ketosteroid excretion was normal. A roentgenogram of the chest was within normal limits.

There was no evidence of any infection. Despite a gradual increase of the daily insulin dose to 400 units, glycosuria and ketonuria persisted and the patient lapsed into severe acidotic coma on the ninth hospital day. Only after 9,500 units of crystalline insulin had been given within the ensuing three days did the acidosis subside. For the next three weeks his daily insulin requirements ranged from 1,800 to 6,000 units of crystalline insulin. A mild upper respiratory infection and a small area of cellulitis observed during this time may have been partly responsible for the patient's enormous insulin needs. However, after all symptoms and signs of an infection had subsided the daily insulin requirements still remained high. Figure 1 illustrates the average daily insulin dose as calculated for each week of hospitalization.

During the sixth and seventh weeks of hospitalization three doses of nitrogen mustard, 7 mg. each, were administered in an attempt to depress the formation of insulin antibodies. A marked drop in the daily insulin requirement was subsequently noted, followed by a resurgence about five weeks later. (Fig. 1.) During the sixteenth week of hospitalization administration of 80 units of ACTH gel daily was started and continued for ten weeks. During this time the daily insulin dose was reduced from 750 units to 250 units, and finally remained fairly stable at 125 units. (Fig. 1.)

In addition to his insulin resistance the patient showed signs and symptoms of insulin allergy, manifested by local reactions at the site of injection as well as generalized urticaria following intramuscular and intravenous injections of insulin. Intradermal injection of insulin and passive transfer tests confirmed the presence of insulin allergy. A biopsy specimen of the liver revealed no evidence of cirrhosis or hemochromatosis. The patient was discharged from the hospital in January 1955. He was then receiving a diabetic diet of 3,000 calories and 75 units of Lente insulin plus 50 units of crystalline insulin before breakfast.

* From the Veterans Administration Center, Togus, Maine.

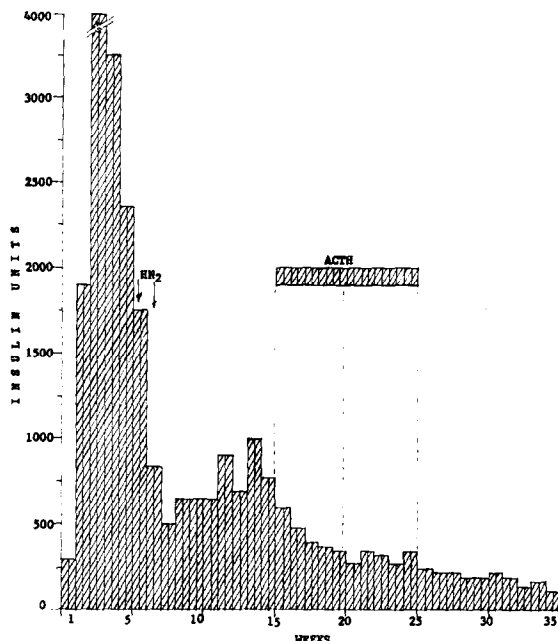


FIG. 1. Average daily insulin dose calculated on a weekly basis during hospitalization in 1954.

He was readmitted to this hospital in August 1956, after his daily insulin requirements had again climbed to about 1,000 units a day and ketonuria had reappeared. With appropriate insulin dosage the ketonuria subsided promptly, but very large amounts of insulin were necessary to keep the blood sugar and glycosuria reasonably well controlled. No evidence of any other underlying disease could be found. The urinary excretion of 17-ketosteroids and glucocorticoids was within normal limits.

The daily insulin dosage varied greatly from day to day and on one occasion was as high as 4,100 units. Only crystalline insulin (500 units or 100 units per ml.) was used. Following administration of tolbutamide* the daily insulin requirements gradually dropped to 475 units. After discontinuance of tolbutamide the daily insulin dose rose again to 900 units. In order to eliminate any delay in insulin absorption all insulin was given intravenously. The patient's diabetes was well controlled when the entire daily dose was administered in one intravenous injection at 7:30 A.M. This response was attributable to the marked retardation of the hypoglycemic effect of the intravenously given insulin and its slow dissociation from the insulin-binding factors in the serum, as shown later on. This therapeutic regimen was no longer feasible when the insulin-binding power decreased in the course of the treatment. After the daily insulin dose of 900 units had remained stable for over two weeks, tolbutamide was resumed and again a

* Kindly supplied as orinase® by the Upjohn Company, Kalamazoo, Michigan.

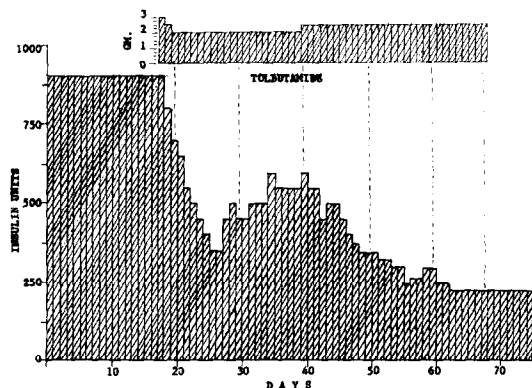


FIG. 2. Daily insulin requirement before and after tolbutamide.

marked drop in the daily insulin requirement was observed. Figure 2 illustrates the prompt reduction of the daily insulin dose following tolbutamide administration [2]. Upon discharge from the hospital in May 1957 the patient required 150 units of crystalline insulin daily. When he was readmitted in December 1957, tolbutamide was again given in a dose of 2.5 gm. daily. Within ten days the daily insulin dose could be reduced from 165 units to 110 units and has remained stable since.

COMMENTS

In the absence of diabetic acidosis, infection, hormonal overactivity or any other condition known to cause abnormally high insulin requirements, our case can be classified as one of idiopathic insulin resistance associated with insulin allergy.

Skin-sensitizing antibodies, present in insulin allergy, were demonstrated by a strong local reaction following the intradermal injection of 0.02 units of crystalline insulin. The passive transfer test for these antibodies performed according to Prausnitz-Küstner was also strongly positive.

The simultaneous occurrence of resistance and allergy to insulin has been reported in a number of cases. However, the association between these two conditions is by no means constant. In their review of the pertinent literature Davidson and Eddleman [3] found only seventeen cases of insulin allergy among fifty cases of insulin resistance. On the other hand, insulin allergy without resistance has been observed in 7.3 per cent of diabetic patients receiving insulin [4], Lowell [5] proved the existence of two different antibodies to crystalline insulin, one being responsible for skin sensitivity, generalized urticaria and other allergic manifestations, the

other causing insulin resistance. With the help of zone electrophoresis of the serum the skin-sensitizing antibody has been localized in the beta-globulin fraction [6] whereas the insulin-neutralizing antibody has been found to be associated with the gamma globulin fraction [7], specifically with the gamma-2-globulin fraction [8,9].

These factors inhibit the hypoglycemic effect of exogenous insulin and have been variously described as insulin antibodies, inhibitors and binding factors. Studying the effect of serum from insulin-resistant patients on the combination of insulin with the rat diaphragm preparation, Marsh and Haugaard [10] found that the "binding factor" had to be present at the same time the diaphragm was exposed to insulin in order to exert its antagonistic action. In contrast to their observation, Field, Stetten and Woodson [11] proved the presence of a different insulin antagonist in the serum of patients in diabetic acidosis that was rapidly and firmly bound to the diaphragm independent of insulin and then interacted with insulin to abolish its effect. This factor had an electrophoretic mobility similar to the alpha-globulins and was not present in the gamma globulin fraction. Thus these authors have shown that inhibition of insulin activity during diabetic acidosis is fundamentally different from that seen in idiopathic insulin resistance.

Insulin-binding factors have been found in all insulin-treated subjects and only in those [12]. Berson and co-workers [13] found that in insulin-treated patients insulin- I^{131} was bound to an acquired globulin which satisfied the criteria for an antibody and which they called "insulin-transporting antibody." Its appearance was observed after three to four months of insulin medication. According to these authors the maximal capacity for insulin-binding in non-resistant subjects rarely exceeded 10 units of insulin per liter of plasma, whereas it amounted to 80 to 400 units per liter of plasma in four insulin-resistant patients [14]. The insulin-binding antibody retains the insulin, which normally disappears from the blood quite rapidly, much longer and prevents it from entering the cell. Studies with I^{131} -labeled insulin have demonstrated that in insulin-treated persons 15 per cent to 90 per cent of injected insulin is still present in the blood one hour after injection, whereas only about 8 per cent is found in persons who have not been previously treated with

insulin. Normal degradation of insulin is similarly delayed [15]. Thus the binding factors interfere with the biological activity of insulin, which depends upon the quantity of the hormone available at the cellular level and not upon its concentration in the blood. When these factors are present in excessive quantity, insulin resistance results.

Why such large amounts are produced in some cases and under certain circumstances is still obscure. Insulin itself is a weak antigen, but impurities and additions to prolong its action may give rise to the initial formation of insulin antibodies [16,17]. A similar phenomenon was observed by Gordon et al. [18] following injection of other hormones. They found that purified hormone preparations were less antigenic than crude ones. These investigators concluded that true immunological reactions played a role in the production of antihormones following injection of hormone preparations containing antigenic material. Immunizations or infection may also raise the titer of insulin antibodies in the form of an anamnestic reaction. Rausch-Stroomann [16] found an increased insulin-antibody titer fifteen to sixty minutes after injection of a large insulin dose. Further insulin administration may thus serve as a booster, especially if it is given intermittently or had been discontinued for some time. This was observed in many of the published cases of insulin resistance and was considered an important factor in the development of resistance by some authors [9,19]. In the case herein described insulin therapy was interrupted for about one year, after 20 units of NPH insulin had been given initially for eight months. We concur in the assumption of other investigators [7,15,19-21] that insulin resistance is a true immunological phenomenon.

Our case showed what others have observed, namely, localization of the insulin-binding antibodies in the gamma globulin fraction of the serum. This was accomplished by starch block electrophoresis and addition of insulin- I^{131} . An interesting quantitative relationship between the insulin-binding power of the gamma globulin fraction of our patient's serum and the severity of his insulin resistance could be established. At a time when 98 per cent of the added insulin- I^{131} was bound to gamma globulin, the daily insulin dose was 800 units. When only 42 per cent of insulin- I^{131} was attached to the gamma globulin fraction, the daily insulin requirement had

TABLE I
PLASMA BINDING OF INSULIN- I^{131} *

Sample	Binding of Insulin- I^{131} to Gamma Globulins (%)	Daily Insulin Dose (units)
Patient's serum 9-26-56.....	98	800
Patient's serum 1-18-57.....	42	270
Serum of non- insulin-resist- ant diabetic patients.....	<6	20-60

* Starch block electrophoresis; insulin concentration 0.2 units per ml.

dropped to 270 units. (Table I.) The oft-described ability of the serum of insulin-resistant patients to protect mice from the hypoglycemic action of insulin was also demonstrated in our patient. A sample obtained when the daily insulin requirement was 800 units was capable of protecting mice from the lethal effects of 0.07 units of insulin. Only one of seven mice died when given that amount of insulin and 1 ml. of the patient's serum, while forty-one of forty-nine animals died when given the same amount of insulin and 1 ml. of normal serum.

While the aforementioned tests and also the measurement of insulin activity by the rat diaphragm technic [10,22] require elaborate laboratory facilities, insulin sensitivity tests and blood sugar profiles afford a simple method of detecting abnormal inhibition and retardation of insulin activity. In our case we have found blood sugar profiles extremely helpful for the demonstration of insulin-binding factors as well as for the management of the diabetes. Perusal of the literature reveals that this diagnostic tool has been rarely used in cases of insulin-resistant diabetes. By this clinical method one can often arrive at a more accurate estimate of insulin-resistance than by the rat diaphragm technic, insulin- I^{131} -binding method or the mouse protection test. Since all these tests are based on the presence of free binding factors, their saturation by previously administered insulin may yield falsely negative results in highly insulin-resistant patients [3,11,18]. Some investigators were unable to demonstrate the insulin-neutralizing activity of the serum in about 50 per cent of insulin-resistant patients [23].

TABLE II
INSULIN SENSITIVITY TEST*

Sample	Blood Sugar (mg./100 ml.)		
	Before	30 Minutes Later	60 Minutes Later
Before tolbutamide.	240	240	235
After tolbutamide for 9 days.....	240	230	220
After tolbutamide for 50 days.....	170	130	65

* Blood sugar response to intravenous injection of 100 units of crystalline insulin.

Collens and Banowitch [24] considered the insulin sensitivity test more important for the diagnosis of resistance than the actual amount of insulin required. Insulin sensitivity tests, performed during different phases of our patient's clinical course, reflected the immense insulin resistance and its decrease after treatment with tolbutamide. The test dose of insulin used (1.5 units per kg.) was of necessity fifteen times as large as the usual dose of 0.1 unit per kg. (Table II.) No tolbutamide was given during the twenty hours preceding the tests.

On several occasions the blood sugar was determined about every two hours throughout the day while the patient remained on his regular meal schedule and received his usual insulin injections. Two blood sugar profiles obtained before tolbutamide medication, when the daily insulin doses were 1,000 units and 1,200 units, respectively, reveal the amazing inhibition or retardation (or both) of the hypoglycemic effect of large amounts of insulin intravenously given. Even after intravenous injection of 1,200 units of crystalline insulin (500 units per ml.) the blood sugar reached its lowest level only as late as eight hours after the injection with two meals consumed by the patient in the interval. Following the evening meal the blood sugar was still maintained below the initial morning value. (Fig. 3A.) In contrast to this marked retardation of insulin activity two blood sugar profiles obtained during the second course of tolbutamide administration, when the daily insulin dose had dropped to 400 units of insulin and less, showed considerably less delay of the hypoglycemic effect of the insulin administered intravenously. In both curves the lowest blood sugar level was

reached as early as four hours after the intravenous injection of much smaller amounts of insulin, namely 400 units and 220 units, respectively. (Fig. 3B.)

Inasmuch as only that amount of insulin which is not prevented from entering the cell by insulin-binding factors can exert its biologic effect, the management of insulin resistant diabetes should aim at providing enough free insulin for satisfactory control of the diabetic state. Therapeutic measures should be directed at the following points: (1) saturation of the insulin-binding factors by large, preferably intravenously given, insulin doses, (2) avoidance of further stimulation of insulin-antibody formation by the exclusive use of crystalline insulin, and (3) inhibition of or interference with the formation of insulin antibodies.

Dituri [25] found the insulin-antibody titer highest in the morning and lowest in the evening. It has been our experience and also that of others [26] that it is therefore important to administer a large insulin dose in the morning in order to saturate the insulin-binding factors. This large dose is usually well tolerated due to the rapid binding of the injected insulin. Its subsequent slow dissociation from the antibody complex often effects satisfactory control of the diabetes throughout the entire day. By giving the insulin intravenously one can avoid its often unpredictable absorption from the tissues due to additional blocking of the insulin by binding factors present in the tissue fluid. However, when, in the course of treatment the increasingly prompt effect of the intravenously administered insulin does not permit large enough amounts to be given in this way, one can take advantage of this additional delay of insulin activity and mimic the effect of depot insulin by giving large amounts of crystalline insulin subcutaneously or intramuscularly. This circumstance made the use of long-acting insulins in our case unnecessary. We believe that in cases of insulin resistance only crystalline insulin should be given as it is less apt to stimulate antibody formation than long-acting insulin preparations which contain more antigenic material.

Alleviation of insulin resistance by suppression of insulin-antibody formation has been attempted by several means. Some investigators [7,18,21,24,27,28] saw good results following the use of ACTH or adrenocortical steroids, with complete remission in some cases, while others [6,9] noticed no improvement. According to

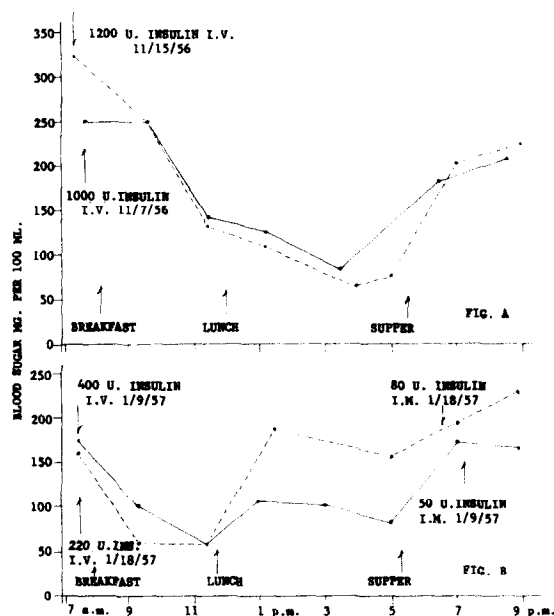


FIG. 3. Blood sugar profiles without (A) and with tolbutamide (B).

Colwell and Weiger [7] ACTH and adrenocortical steroids probably interfere with the excessive formation of gamma globulin and block the anamnestic production of specific insulin antibody. Dammin and Bukantz [29] reported depression of antibody production in rabbits by the use of nitrogen mustard and Geller et al. [30] reduced the insulin requirement of their insulin-resistant patient 90 per cent by the injection of 12.4 mg. nitrogen mustard on two consecutive days. In our patient a marked decrease of the average daily insulin dose was noted following three injections of 7 mg. nitrogen mustard in April 1954. (Fig. 1.) A spontaneous remission cannot be excluded, however, since another therapeutic trial during a relapse of the patient's insulin resistance in June 1956 was entirely unsuccessful. As can be seen from Figure 1, the response to ACTH was quite satisfactory in that the average daily insulin dose could be reduced to 34 per cent of the initial value during a ten-week course of ACTH, and after withdrawal of the hormone dropped further to 16 per cent of the amount required before ACTH was started. The most decisive improvement of insulin resistance was achieved by the use of tolbutamide (orinase). During the past eighteen months our patient received three courses of tolbutamide without any untoward effect. On the first two occasions the daily

insulin requirement decreased 75 per cent, on the third occasion 33 per cent. (Fig. 2.) It has been previously proposed that the insulin-sparing effect of tolbutamide in this case has been due to its inhibitory action on the insulin-binding factors [2]. This assumption has been confirmed by the diminished plasma binding of insulin-I¹³¹ following tolbutamide administration. (Table I.)

SUMMARY AND CONCLUSIONS

A patient with initially mild diabetes mellitus is described in whom after discontinuance of NPH insulin for a year, severe insulin resistance and moderate insulin allergy developed following resumption of treatment with NPH insulin.

The several distinct plasma factors responsible for insulin allergy, idiopathic insulin resistance, and insulin resistance associated with diabetic acidosis are discussed. Idiopathic insulin resistance is regarded as a true immunological phenomenon.

A good correlation between the plasma binding of insulin-I¹³¹ and the severity of insulin resistance is shown. Blood sugar profiles are considered a valuable diagnostic tool for the evaluation and satisfactory control of insulin resistant diabetes.

The management of insulin resistant diabetes mellitus is outlined and the effects of nitrogen mustard, ACTH and tolbutamide (orinase), as observed in the treatment of the case reported are described.

Acknowledgment: We are greatly indebted to Dr. James B. Field at the National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland, for the determination of the insulin-I¹³¹-binding power of our patient's serum and the mouse protection test.

ADDENDUM

Since this paper was written the patient's daily insulin requirements rose again to 400 units. This rise could not be reversed by the administration of tolbutamide. The patient was then given prednisone for four and a half months. The first drop in the daily insulin requirement was observed on the tenth day of prednisone administration. From then on the daily insulin dose could be gradually reduced to 50 units. After discontinuance of prednisone the diabetes has

remained well controlled with 50 to 60 units of insulin a day.

REFERENCES

1. ROOT, H. F. Insulin resistance and bronze diabetes. *New England J. Med.*, 201: 201, 1929.
2. FRIEDLANDER, E. O. Use of tolbutamide in insulin-resistant diabetes. Report of a case. *New England J. Med.*, 257: 11-14, 1957.
3. DAVIDSON, J. K., III and EDDLEMAN, E. E., JR. Insulin resistance. Review of the literature and report of a case associated with carcinoma of the pancreas. *Arch. Int. Med.*, 86: 727-742, 1950.
4. COLLENS, W. S., LERNER, G. and FIALKA, S. M. Insulin allergy. Treatment with histamin. *Am. J. M. Sc.*, 188: 528-533, 1934.
5. LOWELL, F. C. Evidence for the existence of two antibodies for crystalline insulin. *Proc. Soc. Exper. Biol. & Med.*, 50: 167-172, 1942.
6. LOVELESS, M. H. and CANN, J. R. Distribution of blocking antibody in human serum proteins fractionated by electrophoresis convection. *J. Immunol.*, 74: 329-339, 1955.
7. COLWELL, A. R. and WEIGER, R. W. Inhibition of insulin action by serum gamma globulin. *J. Lab. & Clin. Med.*, 47: 844-861, 1956.
8. SEHON, A. H., KAYE, M., MCGARRY, E. and ROSE, B. Localization of insulin-neutralizing factor by zone electrophoresis in serum of insulin-resistant patient. *J. Lab. & Clin. Med.*, 45: 765-770, 1955.
9. KAYE, M., MCGARRY, E. and ROSENFELD, I. Acquired insulin resistance: case report. *Diabetes*, 4: 133-137, 1955.
10. MARSH, J. B. and HAUGAARD, N. Effect of serum from insulin-resistant cases on the combination of insulin with the rat diaphragm. *J. Clin. Invest.*, 31: 107-110, 1952.
11. FIELD, J. B., STETTEN, D., JR. and WOODSON, M. L. Studies on humoral antagonists in diabetic acidosis. *Diabetes*, 5: 391-396, 1956.
12. SKOM, J. H. and TALMADGE, D. W. Non-precipitating insulin-binding antibodies. *J. Lab. & Clin. Med.*, 48: 943, 1956.
13. BERSON, S. A., YALOW, R. S., BAUMAN, A., ROTHSCCHILD, M. A. and NEWERLY, K. Insulin-I¹³¹ metabolism in human subjects: Demonstration of insulin-binding globulin in the circulation of insulin treated subjects. *J. Clin. Invest.*, 35: 170-190, 1956.
14. BERSON, S. A. and YALOW, R. S. Kinetics of reaction between insulin and insulin-binding antibody. *J. Clin. Invest.*, 36: 873-874, 1957.
15. WELSH, G. W., III, HENLEY, E. D., WILLIAMS, R. H. and COX, R. W. Insulin-I¹³¹ metabolism in man: plasma-binding, distribution and degradation. *Am. J. Med.*, 21: 324-338, 1956.
16. RAUSCH-STROOMANN, J. G. and SAUER, H. Zur Frage der Insulinresistenz durch Antikörperbildung. *Klin. Wchnschr.*, 31: 551-555, 1953.
17. STEIGERWALD, H. and SPIELMANN, W. Nachweis von Insulinantikörpern bei Diabetikern mit Insulinresistenz im Hämagglutinationstest und Coombs-test. *Klin. Wchnschr.*, 34: 80-84, 1956.

18. GORDON, A. S., KLEINBERG, W. and CHARIPPER, H. A. The reticuloendothelial system and hormone refractoriness. *J. Exper. Med.*, 70: 333-345, 1939.
19. YANKLOWITZ, T., MASSRY, S. and GITTER, S. Insulin resistant diabetes with insulin antibodies. A case report. *Diabetes*, 5: 457-461, 1956.
20. DEFILLIPIS, V. and IANNAZONE, A. Insulin-neutralizing activity of gamma-globulin derived from the serum of an insulin-resistant patient. *Lancet*, I: 1192, 1952.
21. KLEEGER, J., DIENGOTT, D. and GOTTFRIED, J. A case of insulin resistance treated with corticotropin. *J. Clin. Endocrinol.*, 16: 680-686, 1956.
22. VALLANCE-OWEN, J., HURLOCK, B. and PLEASE, N. W. Plasma insulin activity in diabetes mellitus, measured by the rat diaphragm technique. *Lancet*, 2: 583-587, 1955.
23. FIELD, J. B. Personal communication.
24. COLLENS, W. S. and BANOWITZ, M. M. Insulin resistance; report of an unusual case with requirements up to 7840 units in 24 hours. *Metabolism*, 4: 355-363, 1955.
25. DITURI, B. Insulin-resistant diabetes after total pancreatectomy. *New England J. Med.*, 251: 13-16, 1954.
26. ESKIND, I. B., FRANKLIN, W. and LOWELL, F. C. Insulin-resistant diabetes mellitus associated with hemochromatosis. *Ann. Int. Med.*, 38: 1295-1305, 1953.
27. HOWARD, J. E. Proceedings of the second ACTH conference, vol. 1, p. 327, 1951.
28. GITELSON, S. Insulin resistance (a review). *Harefuah*, 49: 200-202, 1955.
29. DAMMIN, G. J. and BUKANTZ, S. C. Modification of biological response in experimental hypersensitivity. *J. A. M. A.*, 139: 358-362, 1949.
30. GELLER, W., LADUE, J. S. and GLASS, G. B. J. Insulin resistant diabetes precipitated by cortisone and reversed by nitrogen mustard. *Arch. Int. Med.*, 87: 124-127, 1951.