MEDICAL GRAND ROUNDS September 16, 1976

INSULIN RESISTANCE STATES AND INSULIN ALLERGY

Case 1 D.C. PMH #18-79-61

This 48 year old black woman was first diagnosed as having diabetes in 1962. She was treated with oral agents until December, 1975 when she was switched to insulin because of poor control. In January of 1976 her FBS was 380 $mg \cdot dl^{-1}$ while taking 50 units of NPH insulin daily (and supposedly following an 1800 calorie diabetic diet). In February of 1976 she was admitted to Parkland in diabetic ketoacidosis. She had an uneventful recovery and was discharged on 55 units of NPH insulin daily. In March 1976 the FBS was 425 $mg \cdot dl^{-1}$ and insulin was increased to 50 units of NPH insulin in the morning and 15 units in the evening. In April, 1976 she was again admitted in ketoacidosis without apparent precipitating cause. Plasma glucose was 390 $mg \cdot dl^{-1}$, CO_2 was 6 $meq \cdot liter^{-1}$ and pH was 7.09. Physical exam was unremarkable except for marked obesity (219#) and a modest diabetic retinopathy with microaneurysms. She was treated with IV fluids and 1000 units of regular insulin. Ketoacidosis was reversed in about 16 hours. Because of difficulty in controlling the plasma glucose, increasing amounts of NPH insulin were given (90 units AM, 50 units PM). Despite this she lapsed into ketoacidosis again in the hospital on 5th hospital day (CO_2 7 $meq \cdot l^{-1}$). On the 9th hospital day another episode of ketoacidosis occurred (CO_2 9 $meq \cdot l^{-1}$) in the face of over 100 units of regular and NPH insulin.

She was started on prednisone 80 mg per day and therapy was changed to 40-45 units of regular pork insulin three times daily before meals. On this regimen urines became ketone free and blood sugars ranged from 115 to 269 $mg \cdot dl^{-1}$. Since discharge from the hospital she has done well. Prednisone has been gradually decreased to 10 mg per day but insulin dosage has not decreased. Fasting plasma glucose in the clinic has ranged from 166 to 300 $mg \cdot dl^{-1}$, but she has had no ketosis and no nocturia has been present.

Insulin binding capacity of plasma was 2.5 $units \cdot l^{-1}$.

Case 2 E.B.

This 67 year old man was seen in consultation with Dr. Howard Heyer at Presbyterian Hospital. He had had diabetes for 15 years. Initial treatment had been with oral agents, but secondary failure resulted in the necessity of insulin treatment. He also had severe atherosclerotic heart disease with congestive heart failure. In late 1972 insulin resistance appeared and his physician in a Dallas suburb increased the dose to over 400 units a day including up to 200 units of regular insulin. When hospitalized at Presbyterian a

history of hypoglycemic attacks was obtained and the Somogyi effect was suspected. Insulin dosage was cut and he was discharged on 80 units of Lente insulin in the morning and 65 units in the evening. The patient did well for several weeks on this regimen but in January of 1973 he developed increasing polyuria (nocturia X 10) and was readmitted to Presbyterian Hospital. Blood sugar was greater than 700 $mg \cdot dl^{-1}$ and CO_2 was 18 $meq \cdot l^{-1}$. He was treated with fluids and regular insulin. Over the next several days 150 to 180 units of insulin a day were required to control the blood sugar. He was then started on 80 mg of prednisone daily. On the second day thereafter only 25 units was required. He was discharged on 50 units of Lente insulin per day. Prednisone was gradually decreased and insulin sensitivity was maintained on 5 mg/day. When steroids were discontinued the patient did well for 3 weeks at which time insulin resistance abruptly resumed. He responded rapidly to re-initiation of prednisone. A subsequent attempt to discontinue therapy was again followed by resumption of insulin resistance three weeks later. He was carried on 5 mg of prednisone daily until his death from myocardial infarction.

COMMENTS AND SELECTED BIBLIOGRAPHY

1. Receptors and hormone action

During the past several years there has been a great deal of scientific interest in the binding of hormones to receptors located on the surface of the cell and, in certain instances, intracellularly. This interest was generated by the recognition that hormonal activation of a target tissue requires interaction of the hormone with some constituent of the cell. The concept has arisen that hormone binding to a receptor is the initial step in hormone action; it is further often implicitly assumed that the binding step is rate-limiting in the sequence of events leading to ultimate hormone effect. (This assumption may not always be valid. See below). Since a number of the insulin resistance syndromes require an understanding of hormone-receptor interactions, a brief review is indicated.

a. Methodology: The basic methodology is quite simple. The hormone to be studied is given a radioactive label (usually ^{125}I or ^{131}I) and prepared with high specific activity. Ideally less than one atom of iodine is added per molecule to minimize the potential for altered biologic activity. The second step is to prepare the receptor material. This may be intact cells, purified plasma membranes or purified and solubilized receptors themselves. Receptor material and labeled hormone are then incubated for given periods of time under selected conditions of temperature, pH and osmolality (which may or may not be physiologic). It is generally assumed that hormone-receptor interaction represents a simple, reversible bimolecular reaction which obeys the laws of mass

action, i.e.

$$H + R \rightleftharpoons HR \qquad (1)$$

where H = hormone and R = receptor. It follows that such a reaction will eventually reach equilibrium and that a Keq can be written in terms of molar concentration.

$$Keq = \frac{[\,HB\,]}{[H][B]} \qquad (2)$$

The important point to note is that at equilibrium a dynamic steady state exists in which the quantity of hormone bound is constant while individual hormone molecules freely exchange between free and bound pools.

At the end of the incubation period bound and free radioactivity are separated by one of several methods; e.g. centrifugation, gel filtration, talc or silica adsorption of free hormones or polyethylene glycol precipitation of bound hormone. Non-specific binding of hormone must be assessed; specificity is usually defined as radioactivity displaced from receptors by a large excess of unlabeled hormone (which exchanges with the bound labeled material and dilutes the specific activity of the released hormone in the large excess of unlabeled material such that rebinding is minimized). Radioactivity remaining is considered non-specific and that displaced, specific. (See Fig 1)

Figure 1

INSULIN BINDING TO FAT CELLS

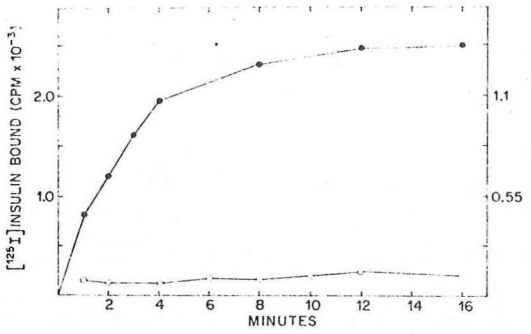


FIG. 4. Rate of binding of [^{125}I]insulin to isolated fat cells at 24°C. Fat cells (3×10^5/ml) were incubated with 6.8×10^{-11} M [^{125}I]insulin in the presence (○) and absence (●) of native insulin (40 μg/ml). The left ordinate describes the uptake of radioactivity; the right, the corresponding concentration of the complex that was used to calculate the kinetic constants.

(from P. Cuatrecasas, Proc. Nat. Acad. Sci. USA 68:1264-1268, 1971)

1. Roth, J. Peptide hormone binding to receptors: a review of direct studies in vitro. Metabolism 22:1059-1073, 1973.
2. Cuatrecasas, P. Insulin receptor of liver and fat cell membranes. Fed. Proc. 32:1838-1846, 1973.
3. Cuatrecasas, P. Membrane receptors. Annu. Rev. Biochem. 43:169-214, 1974.

b. Analysis: As will be apparent from equations (1) and (2) above, hormone-receptor binding can be analyzed in essentially the same manner as a kinetic analysis of enzyme reactions. The appropriate general formulas are:

$$r = \frac{nkA}{1 + kA} \tag{3}$$

and

$$v = \frac{Vmax\ (1/km)S}{1 + (1/km)S} \tag{4}$$

where r is the moles of bound small molecule (e.g., hormone) per mole protein, n the number of binding sites on the protein molecule, k the intrinsic binding constant (the classic association constant) and A the molar concentration of free (non-bound) small molecule. The initial velocity of the reaction is described by v, with Vmax, Km and S representing, in the usual sense, maximal velocity, the Michaelis constant and substrate respectively. Equation (3) can be replotted in straight line fashion as follows:

$$\frac{r}{A} = kn - kr \tag{5}$$

Such a graph is commonly known as a Scatchard plot (4) although the principles had been established considerably earlier (5,6). When r/A is plotted against r, a straight line results provided the receptor represents a single class of binding sites with the same intrinsic binding constant. In most hormone-receptor studies the r, A symbolism is replaced by B and F, standing for bound and free hormone respectively. Thus the plot is B/F versus B rather than r/A versus r. In such a plot the intercept on the horizontal axis is n, the number of binding sites and the slope of the line is -k. The intercept on the vertical axis is nk. Several graphical representations of eq. 3 are drawn in Fig 2. The classic Scatchard representation is the 3rd panel on the right.

Figure 2

THE SCATCHARD PLOT (ref 6)

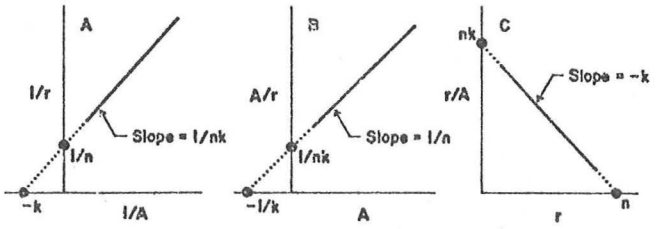


FIGURE 1: Graphical representation of the three commonly used linear transformations of the binding equation for a single site or a single class of sites. The slopes and intercepts of the three straight lines are indicated.

4. Scatchard, G. The attractions of proteins for small molecules and ions. Ann. N.Y. Acad. Sci. 51:660-672, 1949.
5. Klotz, I. M. The application of the law of mass action to binding by proteins. Interactions with calcium. Arch. Biochem. Biophys. 9:109-117, 1946.
6. Klotz, I. M. and D. L. Hunston. Properties of graphical representations of multiple classes of binding sites. Biochemistry 10:3065-3069, 1971.

In practice such curves are often curvilinear rather than straight lines. Under these circumstances analysis is difficult. The curvilinear plot could represent binding to several different classes of receptors with different binding affinities or site-site interaction could occur, where binding of hormone to one site influences the binding of hormone to adjacent sites. Such interactions have been called "negative or positive cooperativity" (7) and are analogous to the familiar oxygen-hemoglobin binding reactions where the binding of the first molecule of oxygen alters the affinity of the subsequent association reaction.

Fig 3 shows the typical Scatchard plot for insulin. On the left is the raw data showing displacement of radioactive insulin as the concentration of non-labeled insulin is increased and on the right the calculated bound-free values are plotted.

Figure 3 (ref 9)

SCATCHARD PLOT OF INSULIN BINDING

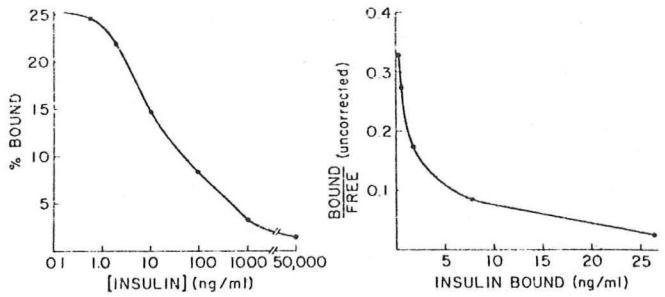
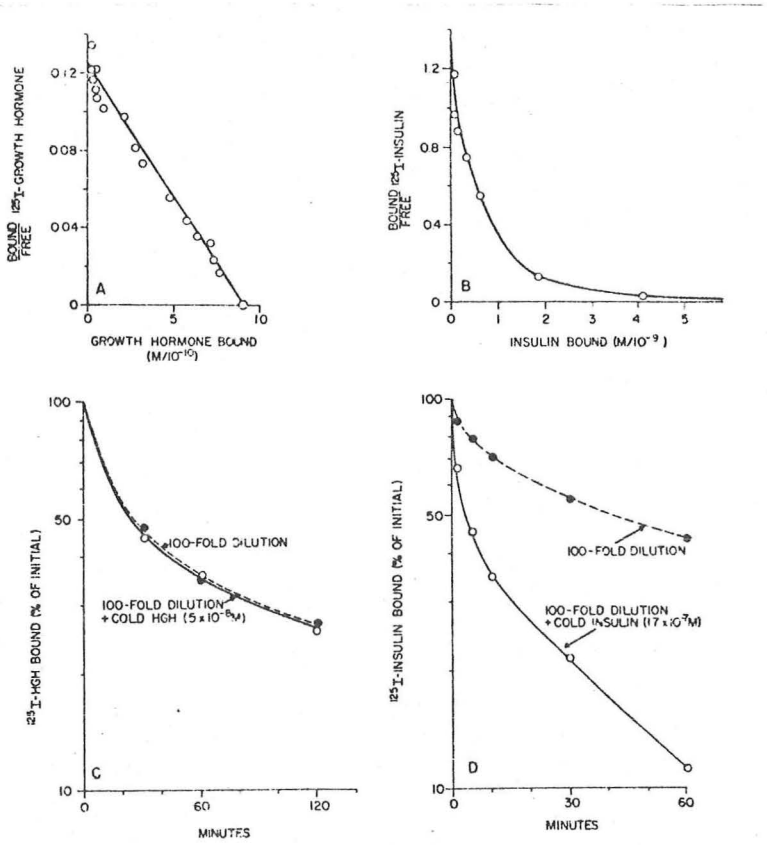


FIG. 1. *Left*, per cent of total ^{125}I-insulin bound to liver membranes as a function of total insulin concentration. Liver membranes (0.6 mg per ml) were incubated with ^{125}I-insulin (100 pM) at 30° for 60 min. Bound and free hormones were separated as described under "Materials and Methods." *Right*, Scatchard plot of the data on the *left* uncorrected for nonspecific binding and degradation.

Without going into detail, Roth and coworkers (7,8) believe that insulin-receptor interactions are best described by the concept of negative cooperativity and that many other hormones and biologically active compounds act similarly (glucagon, ACTH, oxytocin, TSH, epinephrine, estrogens, acetylcholine and Ca^{++}). Part of the evidence for this concept is shown in Fig 4, where the dissociation of radioactive growth hormone and insulin from their receptors is measured in the presence and absence of unlabeled hormone. Note that the Scatchard plot for growth hormone is linear. When excess insulin is present the dissociation is much more rapid with insulin while growth hormone dissociation is not altered by excess hormone. (It is of interest that the association of growth hormone appears to indicate a single class of binding sites, but dissociation is curvilinear. The explanation is not known). The importance of this concept, if true, is enormous. It says that when circulating insulin concentrations are high, binding to the target tissue is decreased.

Figure 4 (ref 7)



7. DeMeyts, P., J. Roth, D. M. Neville, Jr., J. R. Gavin, III and M. A. Lesniak. Insulin interactions with its receptors: experimental evidence for negative cooperativity. Biochem. Biophys. Res. Commun. 55:154-160, 1973.
8. DeMeyts, P., A. R. Bianco and J. Roth. Site-site interactions among insulin receptors. Characterization of the negative cooperativity. J. Biol. Chem. 251:1877-1888, 1976.
9. Kahn, C. R., P. Freychet and J. Roth. Quantitative aspects of the insulin-receptor interaction in liver plasma membranes. J. Biol. Chem. 249:2249-2257, 1974.

c. Cautions: While the studies of hormone-receptor interactions are extremely interesting and the concepts derived from them generally correct, it should be emphasized that many scientifically unacceptable results are appearing in the literature (e.g., ref 10) in which radioactive hormones and other materials are added to crude tissue prepa-

rations and results are interpreted in terms of receptors. The problem comes from the fact that almost all these materials are biochemically "sticky" and that they bind to non-specific biological and non-biological material. In fact, as emphasized by Cuatrecasas and Hollenberg (11), the non-specific binding can behave with characteristics suggestive of specificity, saturability and negative cooperativity, probably because of ligand-ligand interactions. In assessing binding studies one should require evidence for the following:

1. Labeled hormone is biologically active and identical with non-labeled hormone.
2. Full equilibrium has been achieved (may require hours at low temperatures).
3. Specificity of the receptor for the hormone is demonstrated.
4. The affinity constant is very high (K_m is very low) consistant with known hormone concentrations in plasma.
5. Specific binding is high compared to non-specific binding at low hormone concentrations.
6. The number of binding sites per cell is low (less than 10^6).
7. Dissociation of intact hormone is demonstrable.
8. Raw data (actual dpm bound specifically and non-specifically) are given.

10. Enna, S. J., E. D. Bird, J. P. Bennett, Jr., D. B. Bylund, H. Y. Yamamura, L. L. Iversen and S. H. Snyder. Huntington's chorea: changes in neurotransmitter receptors in brain. N. Engl. J. Med. 294:1305-1309, 1976.
11. Cuatrecasas, P. and M. D. Hollenberg. Binding of insulin and other hormones to non-receptor materials: saturability, specificity and apparent "negative cooperativity". Biochem. Biophys. Res. Commun. 62:31-41, 1975.

Two other points should be made. The first is that very few in vitro systems show coupling of the initial step of hormone binding to receptor with the effects of the hormone inside the cell. (An exception is the LDL receptor system of Brown and Goldstein in which all steps from binding to intracellular events are known (12)). This makes it extremely difficult to interpret the physiological meaning of altered receptor number or affinity. Essentially no peptide hormone coupling system has been deciphered. Although most authors assume a change in adenyl cyclase and cyclic AMP concentration to be the second step, it is now clear that in some systems complete dissociation between hormone effects and cyclic AMP can be demonstrated. This is true even for the original epinephrine-glycogenolysis system (13,14,15).

The second point is that many studies of hormone-receptor interactions are done with isolated lymphocytes or monocytes. While the receptors on these cells appear to act like receptors in known target tissues, the fact that they are not normally target tissues should raise reservations about interpretations, particularly if comparative studies with known responsive cells have not been carried out (16).

12. Brown, M. S. and J. L. Goldstein. Receptor-mediated control of cholesterol metabolism. Science 191:150-154, 1976.
13. Talbert, M. E. M., F. R. Butcher and J. N. Fain. Lack of correlation between catecholamine effects on cyclic adenosine 3':5'-monophosphate and gluconeogenesis in isolated rat liver cells. J. Biol. Chem. 248:5686-5692, 1973.
14. Pointer, R. H., F. R. Butcher and J. N. Fain. Studies on the role of cyclic guanosine 3':5'-monophosphate and extracellular Ca^{2+} in the regulation of glycogenolysis in rat liver cells. J. Biol. Chem. 251:2987-2992, 1976.
15. Exton, J. H., N. J. Hutson, S. C. Harper and F. D. Assimacopoulos. Studies on the alpha-adrenergic activation of hepatic glucose output. I. Studies on the roles of α and β-adrenergic receptors and of adenosine 3':5'-monophosphate in the stimulation of glucose output by epinephrine in isolated hepatocytes. J. Biol. Chem. In press.
16. Archer, J. A., P. Gorden and J. Roth. Defect in insulin binding to receptors in obese man: Amelioration with calorie restriction. J. Clin. Invest. 55:166-174, 1975.

2. Insulin resistance states

The term "insulin resistance" is used rather loosely in the literature and as a consequence firm classifications are difficult to establish. In some cases the "insulin resistance" has no apparent physiological consequence and can be detected only by specific testing. In others severe hyperglycemia and ketosis may result. A further problem is that pathogenetic mechanisms are only now being dissected. One of the most intriguing aspects of insulin resistance is that a number of the syndromes are associated with acanthosis nigricans. The relation of this skin disorder to the insulin resistance is completely unknown. A reasonable working classification of the insulin resistance states might be the following:

Table 1

Insulin resistant states

I. Insulin resistance without acanthosis nigricans

1. Obesity.
2. Diabetes mellitus with insulin antibodies.
3. Werner's syndrome.

II. Insulin resistance with acanthosis nigricans

1. Insulin resistance with receptor abnormality.
   a. Antibody to insulin receptor.
   b. Receptor deficiency.

2. Lipodystrophic states
   a. Generalized lipodystrophy (congenital or acquired).
   b. Partial lipodystrophy (congenital or acquired).
   c. Partial familial lipodystrophy with dominant transmission.

3. Syndrome of familial insulin resistance, somatic abnormalities and pineal hyperplasia.

4. The Alström Syndrome.

Before discussing these syndromes, it should be pointed out that previous considerations of insulin resistance have included a number of other conditions such as infection (17), endocrinopathies (acromegaly, Cushing's disease, therapeutic hormones) (18-20), diabetic ketoacidosis (21), maturity onset diabetes (22) and liver disease (23). In these situations the insulin resistance is mild if it is present at all. They will not be considered here.

17. Field, J. B. Insulin resistance in diabetes. Annu. Rev. Med. 13:249-260, 1962.
18. deBodo, R. C. and N. Altzuler. Experimental pituitary diabetes. Diabetes 5:194-202, 1956.
19. Olefsky, J. M., J. Johnson, F. Liu, P. Jen and G. M. Reaven. The effects of acute and chronic dexamethasone administration on insulin binding to isolated rat hepatocytes and adipocytes. Metabolism 24: 517-527, 1975.
20. Alavi, I. A., B. K. Sharma and V.K.G. Pillary. Steroid-induced diabetic ketoacidosis. Am. J. Med. Sci. 262:15-23, 1971.
21. Field, J. B., F. Tietze and D. Stetten, Jr. Furthur characterization

of an insulin antagonist in the serum of patients in diabetic acidosis. J. Clin. Invest. 36:1588-1593, 1957.
22. Ginsberg, H., G. Kimmerling, J. M. Olefsky and G. M. Reaven. Demonstration of insulin resistance in untreated adult onset diabetic subjects with fasting hyperglycemia. J. Clin. Invest. 55:454-461, 1975.
23. Olefsky, J. M. and G. M. Reaven. Decreased insulin binding to lymphocytes from diabetic subjects. J. Clin. Invest. 54:1323-1328, 1974.
24. Collins, J. R. and O. B. Crofford. Glucose intolerance and insulin resistance in patients with liver disease. Arch. Intern. Med. 124:142-148, 1969.

I. Insulin Resistance Without Acanthosis Nigricans

1. Obesity:

The most common form of insulin resistance is simple obesity. One of the earliest demonstrations of this resistance was that of Rabinowitz and Zierler (25) who showed that the insulin stimulating effect on glucose uptake and its inhibiting effect on lipolysis in adipose tissue were blunted in obesity.

Figure 5

FOREARM INSULIN RESPONSE IN OBESITY

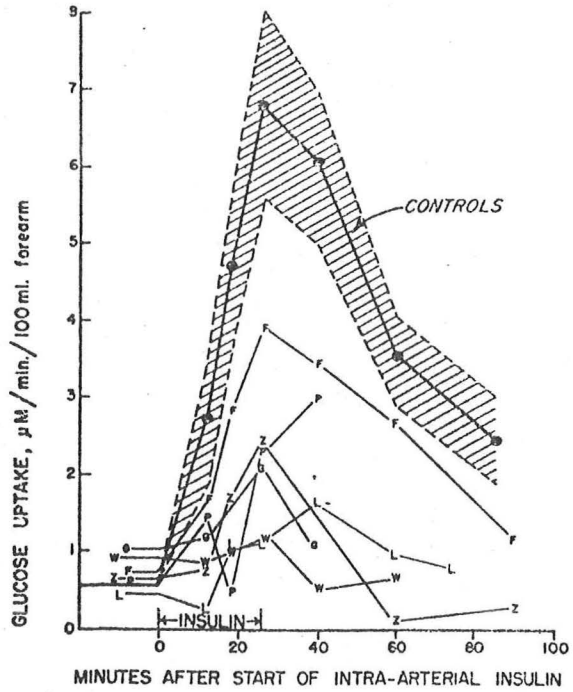


FIG. 1. EFFECT OF INSULIN ON FOREARM GLUCOSE UPTAKE IN OBESE SUBJECTS. Shaded area represents mean ± SE of mean among 10 control subjects (7). Individual lines indicate glucose uptake in obese subjects, identified by initials.

It was subsequently recognized that circulating levels of insulin were increased by obesity both in the fasting state and particularly after a glucose load or meal. Fig 6 represents a graph of the relation between body weight and plasma insulin concentrations.

Figure 6 (ref 26)

SERUM INSULIN AND BODY WEIGHT

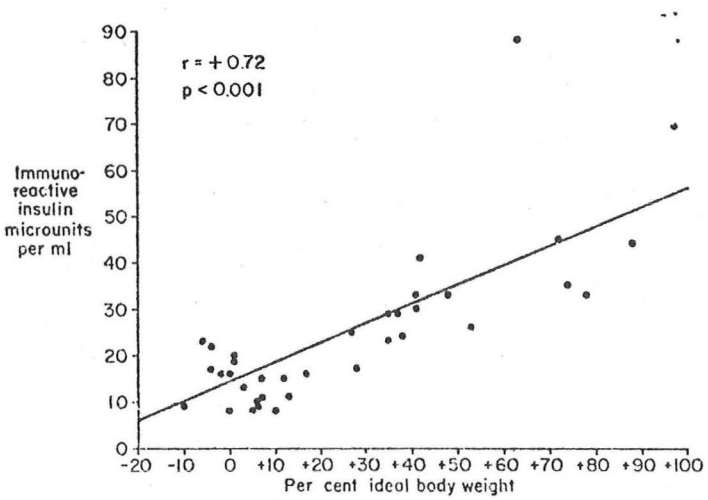


FIG. 1. CORRELATION OF FASTING SERUM IMMUNOREACTIVE INSULIN AND OBESITY EXPRESSED AS PER CENT OF IDEAL BODY WEIGHT.

Fig 7 shows the insulin response to a glucose load in lean and obese normal subjects and lean and obese diabetics. From a practical standpoint the insulin resistance has no importance in normals, but it is extremely detrimental in diabetes. If the genetic tendency to diabetes is present the superimposition of obesity, with concomitant insulin resistance, may cause deterioration into a symptomatic hyperglycemic state. Put in another way, reduction of the obese diabetic may alleviate or remove carbohydrate intolerance. It also is not surprising that large quantities of insulin are required to control hyperglycemia in obese maturity onset diabetic patients who cannot be treated with oral hypoglycemic drugs because of primary or secondary failure of the latter agents.

Figure 7 (ref 26)

INSULIN RESPONSE TO ORAL GLUCOSE

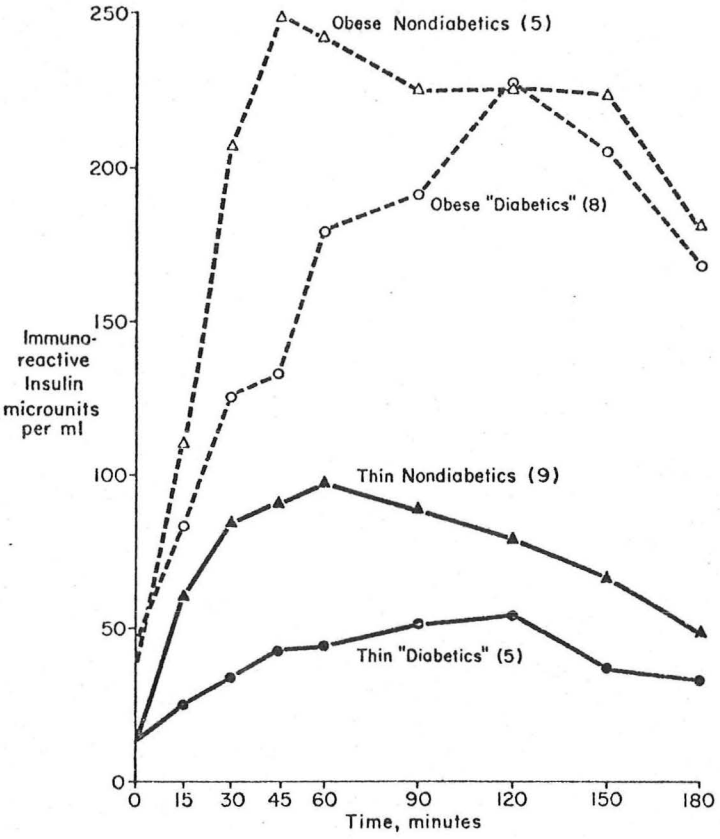


FIG. 3. THE MEAN ABSOLUTE INSULIN RESPONSES IN THIN AND OBESE NONDIABETIC AND DIABETIC SUBJECTS DURING 3-HR (100 G) ORAL GLUCOSE TOLERANCE TESTS.

The mechanism of the insulin resistance in obesity is not completely worked out and controversy exists between workers in the field. In 1975 Amatruda, Livingston and Lockwood (27) reported that insulin receptor number was normal in large adipocytes taken from obese humans and that the affinity of these cells for insulin was likewise not impaired. Subsequently a number of studies have claimed decreased receptor number in obesity, together with diminished affinity for insulin (28,29). (Fig 8,9).

Figure 8 (ref 31)

SCATCHARD PLOTS OF INSULIN BINDING IN OBESITY

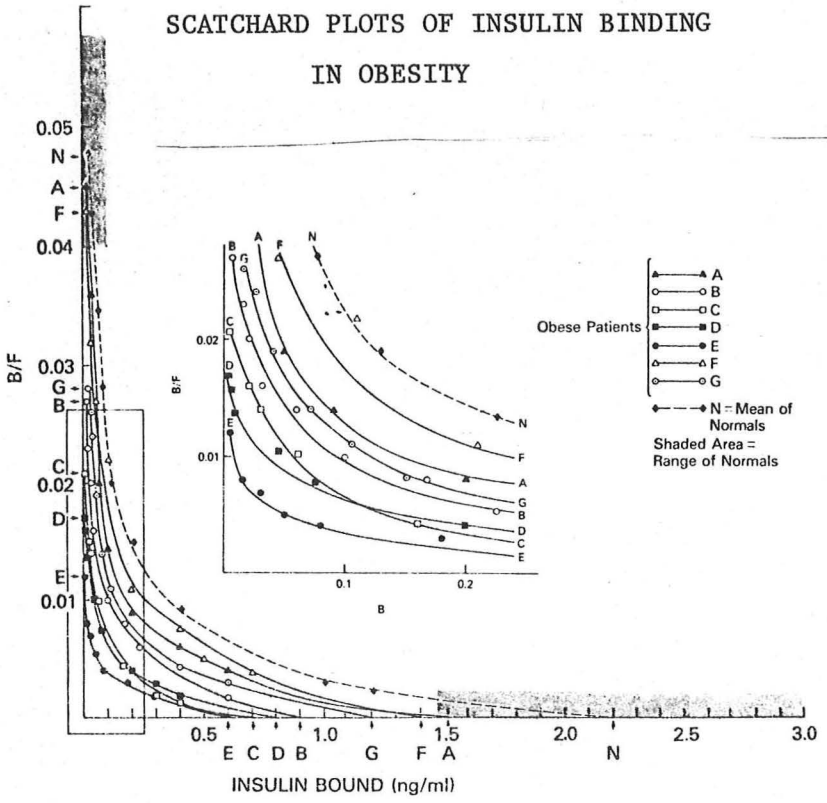
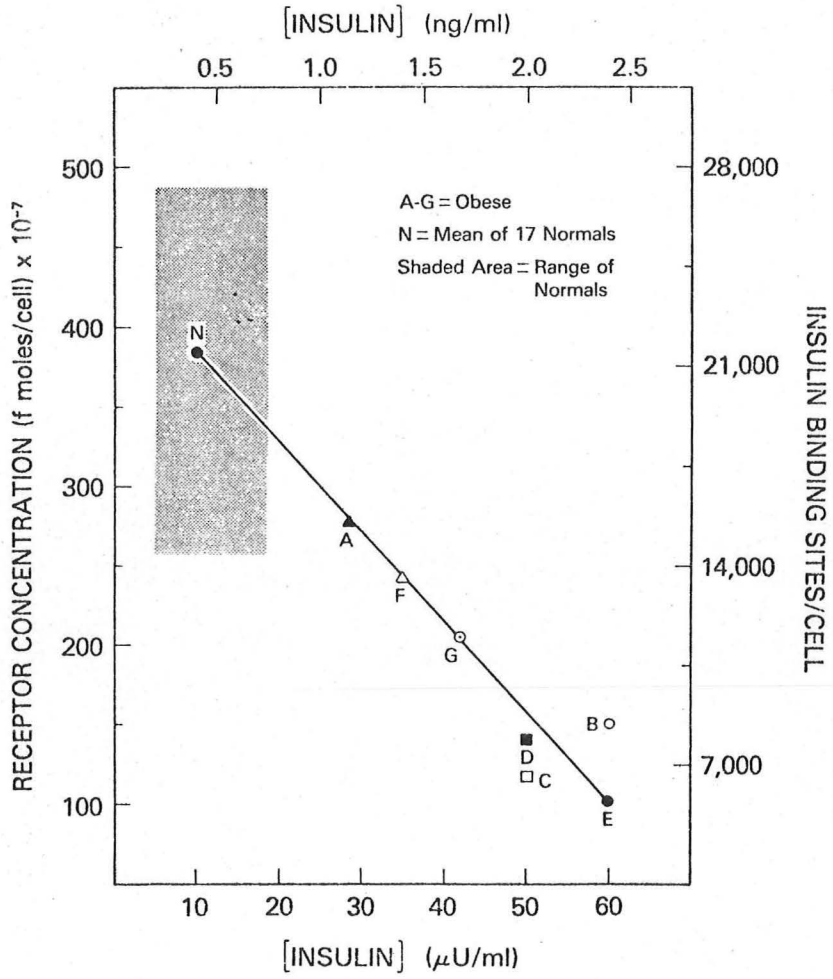


Figure 9 (ref 31)



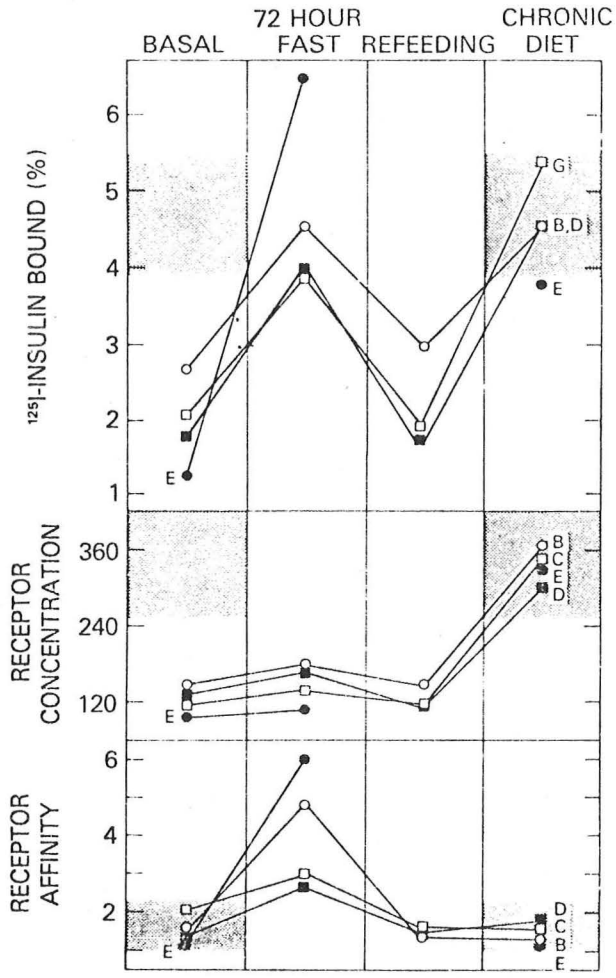
DECREASED RECEPTOR CONCENTRATION IN OBESITY

However, not all obese subjects show the defect; only those subjects which have insulin resistance as indicated by elevated plasma insulin levels and diminished glucose disappearance in a tolerance test appear to have significant diminution in receptor number (28,29). The problem has been complicated by the recent observations of Archer, et al (30) and Bar, et al (31) which showed that a short term fast or more prolonged caloric restriction both affected insulin-receptor interactions, but in different ways.

As shown in Fig 10, a 48-72 hour fast increased insulin binding to normal without increased receptor number (at low insulin concentrations) indicating an increased affinity of the receptor for insulin. Refeeding reversed the pattern. With a chronic diet and weight reduction the amount of insulin bound was also increased to normal. However, in this instance receptor number increased without a change in receptor affinity.

Figure 10 (ref 31)

EFFECT OF FASTING AND DIET ON INSULIN RECEPTORS IN OBESITY



The critical question is whether the elevated circulating insulin concentrations are the cause or the result of insulin resistance. The NIH group, and a number of other laboratories, favor the former concept; i.e., they believe that insulin "down regulates" its own receptor. Thus, in their view, hyperinsulinism in obesity is primary and insulin resistance is caused by it. The reason for the presumed primary elevation of insulin is not known, although in the ob/ob mouse, a genetically determined obese species, it has been shown that insulin removal by the liver is impaired allowing higher concentrations of the hormone to pass into the systemic circulation from the portal vein (32).

That this viewpoint may be overly simplified is suggested by two observations. First, in a carefully controlled study, Czech (33) has shown that functional insulin resistance in large adipocytes (recall that obesity is associated with both an increased number and an increased size of fat cells) is beyond the insulin receptor step. At low glucose concentrations in the media, where transport of hexose into the cell is limiting (0.2 mM), basal and insulin-stimulated glucose uptake was equivalent in large and small adipocytes. At high glucose concentrations the metabolism of glucose was no longer insulin responsive, indicating an intracellular (probably enzymic) site for the insulin resistance. From a clinical point of view the concept of insulin induced-insulin resistance is troublesome since it is clear that the insulin resistance of obesity can be overcome by giving sufficiently large amounts of the hormone. For this reason some caution should be exercised at present in accepting completely the idea that insulin resistance in obesity is solely accounted for by hyperinsulinism and its effect on receptor number and affinity. (Explanations for current discrepancies can be postulated, but will not be explored here since data to resolve the questions are not yet available).

25. Rabinowitz, D. and K. L. Zierler. Forearm metabolism in obesity and its response to intraarterial insulin. Characterization of insulin resistance and evidence for adaptive hyperinsulinism. J. Clin. Invest. 41:2173-2181, 1962.
26. Bagdade, J. D., E. L. Bierman and D. Porte, Jr. The significance of basal insulin levels in the evaluation of the insulin response to glucose in diabetic and non-diabetic subjects. J. Clin. Invest. 46: 1549-1557, 1967.
27. Amatruda, J. M., J. M. Livingston and D. H. Lockwood. Insulin receptor:role in the resistance of human obesity to insulin. Science 188: 264-266, 1975.
28. Olefsky, J. M. Decreased insulin binding to adipocytes and circulating monocytes from obese subjects. J. Clin. Invest. 57:1165-1172, 1976.
29. Harrison, L. C., F. I. R. Martin and R. A. Melick. Correlation between insulin receptor binding in isolated fat cells and insulin sensitivity

in obese subjects. J. Clin. Invest. 1976. In press.
30. Archer, J. A., P. Gorden and J. Roth. Defect in insulin binding to receptors in obese man. Amelioration with calorie restriction. J. Clin. Invest. 55:166-174, 1975.
31. Bar, R. S., P. Gorden, J. Roth, C. R. Kahn and P. DeMeyts. Fluctuations in the affinity and concentration of insulin receptors on circulating monocytes of obese patients: effects of starvation, refeeding and dieting. J. Clin. Invest. 1976. In press.
32. Karakash, C., F. Assimacopoulos-Jeannet and B. Jeanrenaud. An anomaly of insulin removal in perfused livers of obese-hyperglycemic (ob/ob) mice. J. Clin. Invest. 57:1117-1124, 1976.
33. Czech, M. P. Cellular basis of insulin insensitivity in large rat adipocytes. J. Clin. Invest. 57:1523-1532, 1976.

2. Diabetes mellitus with insulin antibodies:

This disorder is the most important of the insulin resistant syndromes because it is quite common and because it is functionally significant, causing marked difficulty in control of hyperglycemia or precipitation of diabetic coma. In practice insulin resistance has been defined (in diabetes) as the requirement of 200 units of insulin a day in the absence of infection or other known cause of decreased insulin sensitivity. While arbitrary, this definition has some usefulness (see therapy below). It has long been known that administration of exogenous insulin results in the production of insulin binding and neutralizing antibodies (34,35). This antibody is present in almost all patients within 60 days after the initiation of insulin therapy (34-36) and is IgG in type (37). Binding antibodies for insulin of the autoimmune type have also been reported (38). The titer of circulating antibodies fluctuates in individual patients for reasons which are not clear. The concentration of antibodies appears to relate in crude fashion to this form of insulin resistance (see below).

34. Berson, S. A. and R. S. Yalow. Quantitative aspects of the reaction between insulin and insulin-binding antibody. J. Clin. Invest. 38:1996-2016, 1959.
35. Anderson, O. O. Insulin antibody formation. I. The influence of age, sex, infections, insulin dosage and regulation of diabetes. Acta Endocrinol. 71:126-140, 1972.
36. Christiansen, AA. H. and J. Krøll. Determination of insulin binding to human IgG by quantitative radioimmunoelectrophoresis. Scand. J. Immunol. 2:suppl. 1:133-138, 1973.
37. Patterson, R., J. O'Rourke, M. Roberts and I. Suszko. Immunologic reactions against insulin. I. IgG anti-insulin and insulin resistance. J. Immunol. 110:1126-1134, 1973.
38. Hirata, Y., M. Tominaga, J-I Ito and A. Noguchi. Spontaneous hypoglycemia with insulin autoimmunity in Grave's disease. Ann. Int. Med. 81:214-218, 1974.

The incidence of insulin resistance in insulin treated diabetics is not known with certainty. Between 1940 and 1960 some 30,000 patients were seen and followed at the Joslin Clinic and 34 cases of insulin resistance occurred (39), indicating an occurrence rate of about 0.1% (although the authors of this report suspected the overall incidence might be less because of selection occasioned by referral of difficult cases to Joslin). References 39 and 40 represent the major series in the literature on the subject. From them and the review by Field (17) the clinical features of insulin resistance in diabetes can be summarized. It should be noted that both of the large clinical series appeared before recent descriptions of specific subsets of insulin resistance were recognized and could, therefore, include several types of insulin resistance. However, the bulk of the patients would appear to belong to category 1 since acanthosis nigricans was not a feature. Males and females appear to be affected equally and the syndrome can begin at any age (it has been reported in a 4 year old child), though there is a tendency to occur more frequently in later years (Table 2).

Table 2 (ref 39)

Age at onset of insulin resistance

Age in Years	Joslin Clinic		Literature	
	Number	Per Cent	Number	Per Cent
Less than 20	2	5.9	4	7.3
20-39	7	20.6	7	12.7
40-59	13	38.2	16	29
60 and greater	12	35.3	28	51
Total	34	100	55	100
Range	13 to 74 years		13 to 78 years	

Insulin resistance may begin within a few weeks of the start of therapy or many years later (Table 3). The incidence of concomitant insulin allergy is not precisely known, but probably is in the range of 20-30% (39). There appears to be no relation to generalized allergic susceptibility in affected patients. Onset of resistance may be abrupt, with ketoacidosis, but is usually gradual with uncontrollable hyperglycemia being the major problem. As indicated in Table 4, the amount of insulin required for therapy may be very high.

Table 3 (ref 39)

Duration of insulin treatment prior to onset of insulin resistance

Years	Joslin Clinic		Literature	
	Number	Per Cent	Number	Per Cent
0-0.5	7	23.4	20	39.2
0.6-0.9	13	43.4	8	15.7
1-4.9	4	13.3	16	31.4
5-9.9	4	13.3	4	7.8
10-20	2	6.6	3	5.9
Total	30	100	51	100
Range	2 months to 12 years		0 to 15 years	

Table 4 (ref 39)

Maximal 24 hour insulin dose during insulin resistance

Units	Joslin Clinic		Literature	
	Number	Per Cent	Number	Per Cent
200-499	17	50	10	18.2
500-999	7	20.6	13	23.6
1000 or more	10	29.4	32	58.2
Total	34	100	55	100
Range	220 to 5,700 units		212 to 38,000 units in 24 hours (97,740 units in 56 hours)	

It was pointed out by Berson and Yalow (41) that the insulin required in treatment was not closely related to insulin binding capacity, although the capacities in 19 resistant patients were all much greater than non-resistant patients also on insulin (the latter usually have binding capacities of 1.0-2.5 units insulin bound/liter plasma (42)).

Table 5 (ref 41)

Insulin dosage and insulin binding capacities in insulin resistant patients

Patient	Insulin dose	Insulin binding
	units/day	units/liter
1	120	57
2	480	60
3	200	70
4	300	85
5	300	>100
6	250	105
7	150	106
8	190	122
9	350	140
10	500	180
11	145	195
12	150	210
13	800	210
14	700	250
15	500	500
16	700	1,250
17	2,400	270
18	2,957	750
19	14,000	4,700

Measurement of insulin binding capacities is complicated by the fact that much of the antibody may be bound to insulin and circulating as immune complexes. Total capacity can only be measured by splitting off and removing the bound insulin (43). The relatively low binding capacity of patient 1, who should have insulin resistance as a consequence of both obesity and insulin antibodies, might be due to the fact that most of the antibody was saturated with insulin at the time of measurement. (See Table 6)

Table 6 (ref 43)

Free and total antibody in a patient with diabetes

Date	Plasma insulin	Free antibody	Bound antibody	Total
	uU/ml		titer*	
12-4-67	15,000	5	10	15
3-5-68	11,800	21	20	41
3-21-68	12,000	25	9	34
12-30-68	5,700	22	3	25
3-3-69	2,500	20	2	22

*titer = reciprocal of serum dilution that bound 50% of added ^{131}I insulin.

In the series of Oakley, Jones and Cunliffe (40) patients were tested for insulin antibody by passive cutaneous anaphylaxis (PCA) and hemagglutination techniques. Twenty-nine of 41 patients showed positive PCA and 15 of 22 had significant titers of antibody by hemagglutination.

39. Shipp, J. C., R. W. Cunningham, R. O. Russell and A. Marble. Insulin resistance: clinical features, natural course and effects of adrenal steroid treatment. Medicine 44:165-186, 1965.
40. Oakley, W. G., V. E. Jones and A. C. Cunliffe. Insulin resistance. Br. Med. J. 2:134-138, 1967.
41. Berson, S. A. and R. S. Yalow. Insulin inhibitors and insulin resistance. N.Y. State J. Med. 60:3658-3665, 1966.
42. Andreani, D., M. Iavicoli, G. Tamburrano and G. Menzinger. Comparative trials with monocomponent (MC) and monospecies (MS) pork insulins in the treatment of diabetes mellitus. Horm. Metab. Res. 6:447-454, 1974.
43. Jayarao, K. S., W. P. Faulk, J. H. Karam, G. M. Grodsky and P. H. Forsham. Measurement of immune complexes in insulin-treated diabetes. J. Immunol. Meth. 3:337-346, 1973.

As an aside it is interesting to note that the presence of insulin antibodies is not always considered detrimental. Dixon, Exon and Malins (44) classified 72 insulin dependent diabetics on clinical grounds as stable, unstable or insulin resistant and measured insulin binding capacity of the plasma. They concluded that most unstable patients had low insulin antibody levels. Twenty-four of 39 stable patients had significant antibody levels while in 15 the concentration

was low. The latter were considered to have significant residual pancreatic function (though this was not proven). The concept is that insulin bound to antibody represents a buffering pool to ameliorate both insulin excess and insulin deficiency by binding and releasing hormone as needed. While the speculation is attractive, it should be accepted with caution for the present.

On the other hand insulin antibodies may do more than cause insulin resistance. Faulk, et al (45,46) have described a syndrome of lymphadenopathy, hepatosplenomegaly, leukopenia and Coombs positive hemolytic anemia in which the RBC were coated with a non-complement fixing monoclonal IgG anti-insulin. Serum contained high concentrations of insulin:anti-insulin complexes with little free antibody available. Red cell survival was decreased and hemolysis was accelerated by treatment with de-alaninated pork insulin (30 days → 23 days → 16 days). Hemoglobin reached 6 grams %. Over 90% of IgG from plasma cells had anti-insulin specificity. Interestingly, insulin requirements went up on prednisone.

44. Dixon, K., P. D. Exon and J. M. Malins. Anti-insulin antibodies and the control of diabetes. Q. J. Med. 176:543-553, 1975.
45. Faulk, W. P., E. J. Tomsovic and H. H. Fudenberg. Insulin resistance in juvenile diabetes. Am. J. Med. 49:133-139, 1970.
46. Tomsovic, E. J., W. P. Faulk and H. H. Fudenberg. Anaphylaxis and red cell survival studies in a child with insulin resistant diabetes mellitus. Acta Paediatr. Scand. 60:647-652, 1971.

Treatment: In general treatment is undertaken when insulin dosage reaches 200 units a day, but may be started earlier, particularly if ketoacidosis is a problem. Therapy of the syndrome requires the use of prednisone in large amounts. While prednisone is probably only effective if the insulin resistance is due to antibodies (40) and while some of the non-antibody syndromes may present as the former, a trial of steroids should be undertaken in all forms of idiopathic insulin resistance. Therapy should be started with large quantities, usually 80-100 mg, in divided doses and continued at this level until a response is obtained. The dose can then be cut rapidly (10-20 mg decrements every 3-7 days) until maintenance level (5-10 mg/day) is reached. Response is often obtained within 48-72 hours (protocol case 2; Fig 11) but may take longer. No hard figures are available to indicate how long a trial should be continued before being terminated as a failure.

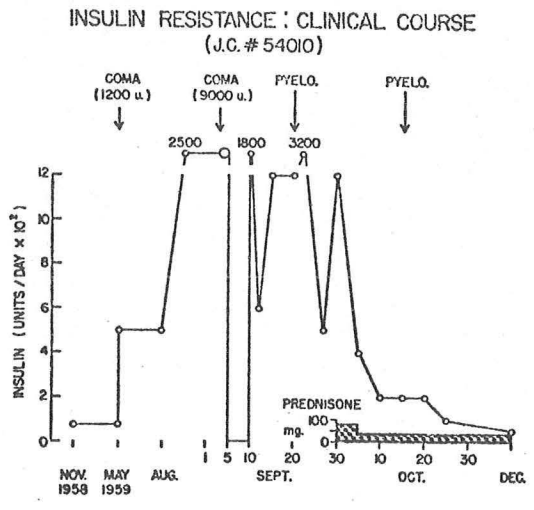


Figure 11 (ref 39)

Since the half life of IgG antibody is approximately 3 weeks in normal subjects, a 4 week interval would seem reasonable. It should be noted that insulin resistance may last for prolonged periods, requiring maintenance steroid therapy for years (Table 7).

Table 7 (ref 39)
Duration of insulin resistance

Months	Joslin Clinic		Literature	
	Number	Per Cent	Number	Per Cent
Less than 1	8	23.5	13	31.7
1-6	12	35.3	16	39
7-12	6	17.7	7	17.1
Greater than 12	8	23.5	5	12.2
Total	34	100	41	100
Range	6 days to 14 years		2 days to 4 years	

Typical results of such therapy are shown in Table 8.

Table 8 (ref 40)
Clinical response to prednisone in insulin resistance due to antibodies

Patient	Insulin dose (units/day)	
	Before Rx	After Rx
1	816	96
2	720	120
3	1,264	84
4	1,440	-
5	960	120
6	640	90
7	4,800	104
8	1,000	40
9	200	80
10	1,120	84
11	640	96
12	480	148
13	496	80
14	208	56
15	576	36
16	672	84

During the acute phase of treatment, particularly if ketoacidosis is present, intravenous regular insulin should be used for therapy. Since the rise in insulin concentration is very rapid (47), free insulin can escape the plasma compartment even in the face of high circulating antibody concentrations. The slower absorption from intramuscular or subcutaneous sites may allow all the insulin picked up in plasma to be bound. (See Figs 12 and 13).

Figure 12 (ref 47)

PLASMA INSULIN AND GLUCOSE FOLLOWING IV INSULIN (0.1 U/kg)

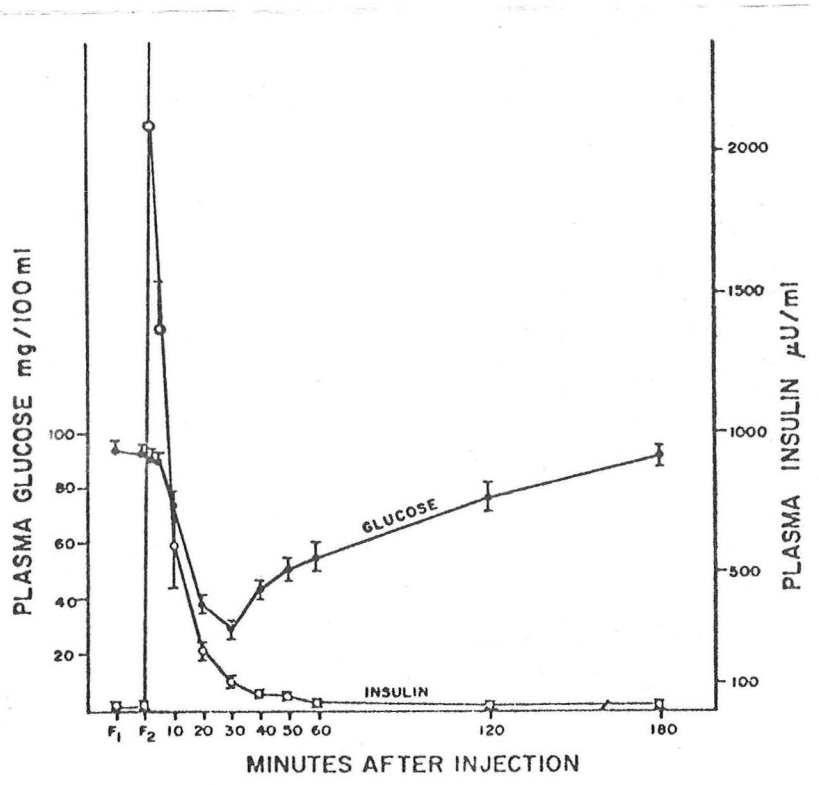
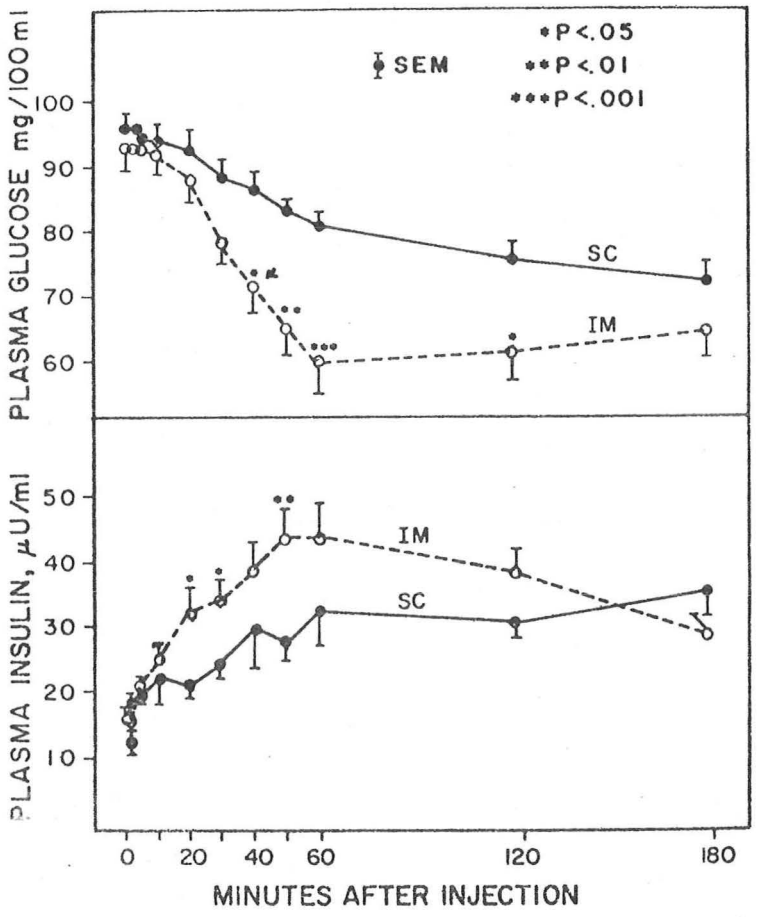


Figure 13 (ref 47)

PLASMA INSULIN AND GLUCOSE FOLLOWING IM AND SC INSULIN (0.1 U/kg)



It had been hoped that monocomponent insulin would be helpful in treatment, but antibody formation, while quantitatively less, is still significant with the purified hormone (42). Even so, difficult cases should probably be switched to monocomponent insulin as an adjunct to steroid therapy.

47. Guerra, S. M. and A. E. Kitabchi. Comparison of the effectiveness of various routes of insulin injection:insulin levels and glucose response in normal subjects. J. Clin. Endocrinol. Metab. 42:869-874, 1976.

3. Werner's syndrome:

This autosomal recessive illness has a high incidence of diabetes (44%) although the latter is usually mild. Occasional ketoacidosis has been reported. The patients show little response to exogenous insulin and have high circulating levels of endogenous insulin. The metabolic picture is similar to that seen in obesity except that fasting hyperglycemia is more frequent (48). The etiology of the insulin resistance is unknown. Clinical features of the syndrome are:

Table 9

Werner's syndrome - clinical features

1. Symmetrical growth retardation
2. Absent adolescent growth spurt
3. Premature graying of the hair
4. Atrophy and hyperkeratosis of skin
5. Generalized loss of hair
6. Cataracts
7. Leg ulcers
8. Diabetes mellitus
9. Atrophy of muscle, fat and bone
10. Soft tissue and vascular calcification
11. Hypogonadism
12. High incidence (10%) sarcomas and meningiomas

48. Epstein, C. J., G. M. Martin, A. L. Schultz and A. G. Motulsky. Werner's syndrome. A review of its symptomatology, natural history, pathologic features, genetics and relationship to the aging process. Medicine 45:177-221, 1966.

II. Insulin Resistance with Acanthosis Nigricans

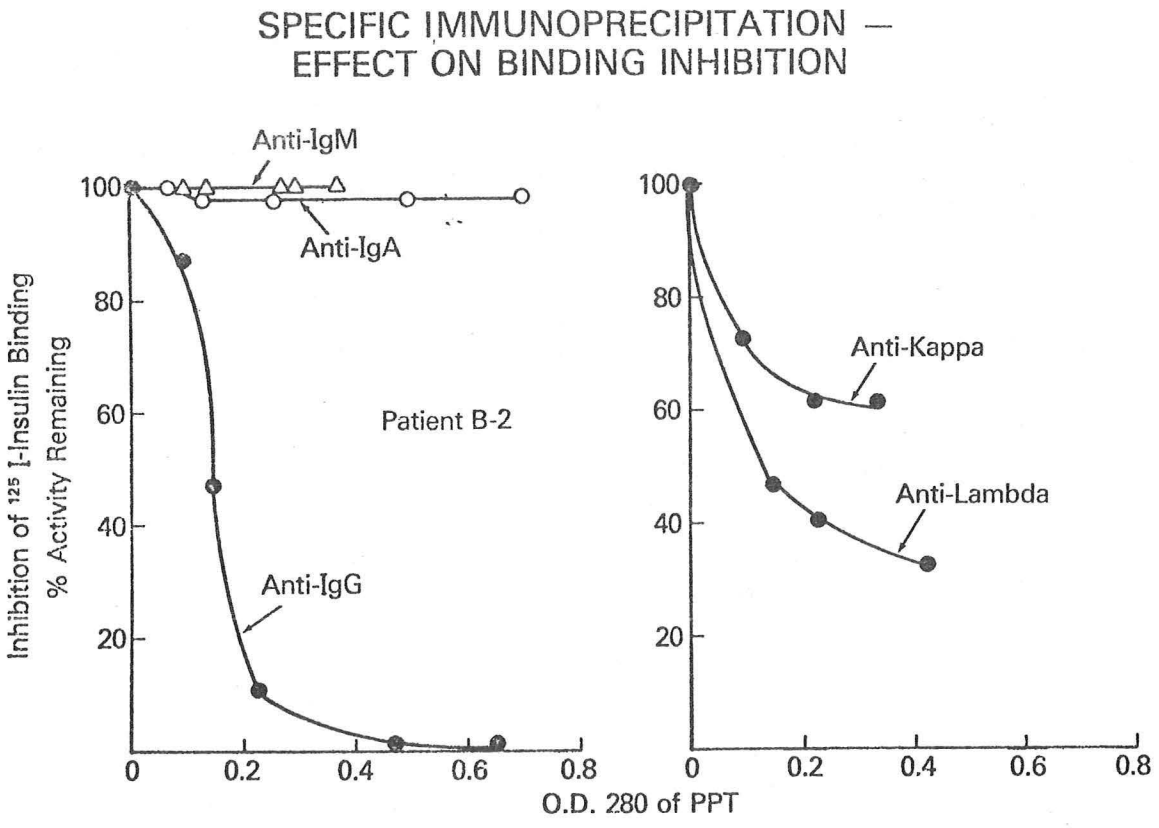
1. Insulin resistance with receptor abnormality

In 1961 Field and colleagues (49) described a patient with marked insulin resistance who had acanthosis nigricans and high concentrations of biologically active insulin in the plasma. It was shown that the patient's tissue in vitro was resistant to insulin action. This probably represented the first carefully studied case of insulin resistance due to receptor abnormality (although receptors were not known at the time). Recently the NIH diabetes group has provided new insight into the mechanism of this type of insulin resistance and has described two discrete types of insulin resistance due to receptor abnormality (50,51).

Since the number of patients is small (3 in each group) it is not yet clear whether the defects represent specific clinical syndromes or whether different clinical syndromes may have, as a common feature, the receptor defect. Type A patients are tall young females with a tendency to hirsutism and abnormalities of the reproductive tract (polycystic ovaries, clitoral enlargement, irregular menses). Coarseness of the features was also commented on. All three patients had hyperinsulinism, insulin resistance, and diminished number of insulin receptors on circulating monocytes.

Type B patients are older women and have evidence of an immunologic disease. The clinical picture derived from the 3 patients of Kahn, et al (51) and other apparently similar patients reported in the literature would appear to consist of severe insulin resistance, increased gamma globulin, positive anti-DNA and anti-nuclear antibodies (but not positive LE preparations) acanthosis nigricans, alopecia, arthralgias, leukopenia, proteinuria, and enlarged salivary glands. In this type of insulin resistance receptor affinity is abnormal and it has recently been shown that the defect is due to the presence of specific anti-receptor antibodies circulating in the plasma (52). Activity is predominantly in the IgG fraction but some activity is found in IgM. Since the inhibitory immunoglobulin reacts with both anti-kappa and anti-lambda antisera, it is polyclonal in nature (Fig 14). Activity is retained in the $F(ab)_2$ fraction after pepsin digestion.

Figure 14 (ref 52)



While the syndromes have separate clinical features, functionally the defects act identically; i.e. there is basal and stimulated hyperinsulinism (Fig 15) and marked resistance to exogenous insulin (Fig 16). Hyperglycemia may or may not be present.

Figure 15 (ref 51)

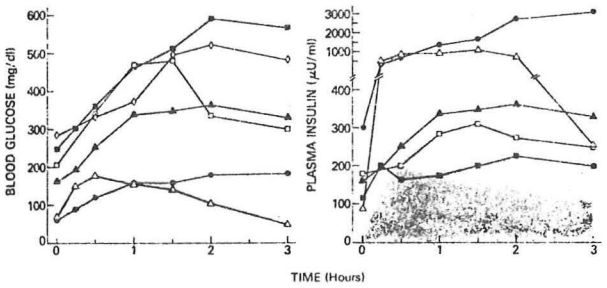


Figure 1. Oral Glucose Tolerance Tests, Performed as Described in Materials and Methods, in Patients with Insulin Resistance and Acanthosis Nigricans.
The symbols connected by solid lines represent ■, B-3; ◇, B-2; □, A-1; ▲, A-2; △, B-1; and ●, A-3. The shaded area is the mean ± 2 S.D. for 27 normal controls.

Figure 16 (ref 51)

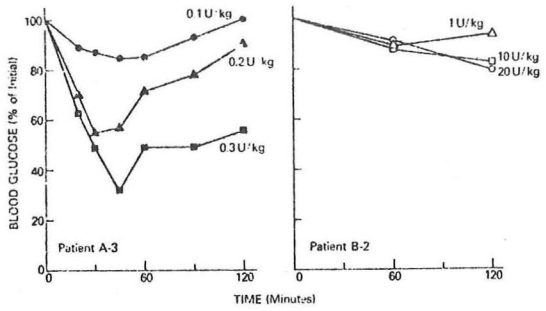


Figure 3. Graduated Insulin Tolerance Tests, Performed as Described in Materials and Methods at Least Two Days Apart, on Patients A-3 and B-2.

Insulin binding is markedly decreased (Fig 17) and is unaffected by fasting (which restores insulin sensitivity in obesity) (Fig 18).

Figure 17 (ref 51)

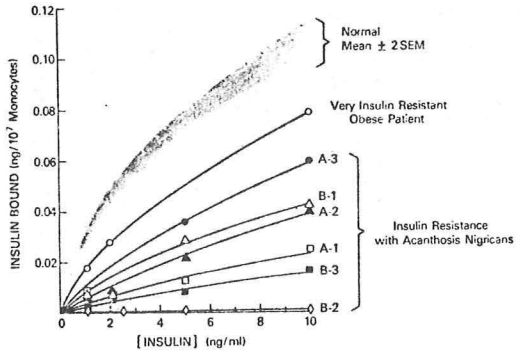


Figure 4. Insulin Binding to Circulating Monocytes in Patients with Insulin Resistance and Acanthosis Nigricans.

Figure 18 (ref 51)

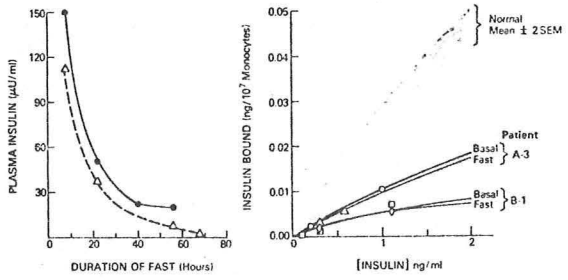


Figure 5. Effect of Fasting on Plasma Insulin and Insulin Binding to Monocytes in A-3 and B-1.

In the panel on the left the plasma insulin levels (● represents B-1, and ▲ A-3) are plotted as a function of the duration of fasting. On the right, the insulin-binding data from basal studies and studies at the end of the fasting period are presented.

It is important to note that anti-insulin antibodies were present only in extremely low concentration (51,52) and were insufficient to account for the resistant state. The insulin resistance may be extreme (up to 177,500 units/day). It is of interest that the syndrome tends to disappear spontaneously (51,53). Under these circumstances the acanthosis nigricans also improves or disappears. (Note: while acanthosis nigricans is commonly found in insulin resistance, insulin resistance is not a common feature of acanthosis nigricans - only 5-10%. See Medicine 47:33-51, 1968).

An overview of the two syndromes is shown in Table 10.

Table 10

Characteristics of receptor defective states

Characteristics	Type A	Type B
Specific	Young women Acanthosis nigricans Accelerated growth Hirsutism Sexual abnormalities Coarse features Decreased receptor number	Older women Acanthosis nigricans Arthralgias Alopecia Enlarged salivary glands Increased gamma globulin Anti-nuclear, anti-DNA antibodies Proteinuria Leukopenia Antibody to insulin receptor
Common	Insulin resistance Hyperinsulinism (basal and stimulated) Decreased insulin binding to receptors No anti-insulin antibodies No improvement with fasting Spontaneous remission	

It is uncertain how symptomatic Type A patients should be treated. Symptomatic Type B patients should be given a trial of adrenal steroids.

49. Field, J. B., P. Johnson and B. Herring. Insulin resistant diabetes associated with increased endogenous plasma insulin followed by complete remission. J. Clin. Invest. 40:1672-1683, 1961.
50. Flier, J. S., C. R. Kahn, J. Roth, and R. S. Bar. Antibodies that impair insulin receptor binding in an unusual diabetic syndrome with severe insulin resistance. Science 190:63-65, 1975.
51. Kahn, C. R., J. S. Flier, R. S. Bar, J. A. Archer, P. Gorden, M. M. Martin and J. Roth. The syndromes of insulin resistance and acanthosis nigricans. N. Engl. J. Med. 294:739-745, 1976.
52. Flier, J. S., C. R. Kahn, D. B. Jarrett and J. Roth. Characterization of anti-insulin receptor antibodies: a cause of insulin resistant diabetes in man. J. Clin. Invest. In press.
53. Bruce, D. H., W. Bernard, and W. G. Blackard. Spontaneous dis-

appearance of insulin-resistant diabetes in a patient with a collagen disease. Am. J. Med. 48:268-272, 1970.

2. Lipodystrophic states

Classification of lipodystrophic states is confused, with different authors using different terminology. I have chosen to use a simple 3 part classification. Generalized and partial lipodystrophy appear to be essentially the same syndrome with only the extent of fat depletion setting off one syndrome from the other. In generalized lipodystrophy essentially all peripheral fat tissue is missing, while in the partial form fat is present in some areas but not all. The most common form of the latter is progressive cephalothoracic lipodystrophy in which the upper half of the body shows no adipose tissue and the lower half has normal or increased adiposity. Interestingly, transplanation of tissue from the upper body to the lower results in appearance of adipocytes and vice-versa. The disease can be either congenital (it appears to be transmitted in autosomal recessive fashion) or acquired following some unrelated illness. Seip, in the definitive review of the subject, (54) indicates that the disorder likely arises in the central nervous system. While all patients do not demonstrate the complete syndrome, the basic clinical features are shown in Table 11 (54,55).

Table 11

Clinical features of lipodystrophic states

1. Generalized or partial absence of peripheral adipose tissue
2. Accelerated linear growth, absent adolescent growth spurt
3. Hepatomegaly (fatty liver → cirrhosis)
4. Frequent splenomegaly and cardiomegaly
5. Hypertrichosis → hirsutism
6. Acanthosis nigricans
7. Hypertrophy of external genitalia
8. Mental retardation (mild to marked)
9. Probable true muscle hypertrophy in congenital forms
10. Generalized lymphadenopathy
11. Varicose veins
12. Renal disease (K-W disease)

A high percentage of the patients develop "diabetes" (at puberty in the congenital form) which is characterized by insulin resistance and the inability to produce ketone bodies. No ketoacidosis has ever been reported. The patients frequently have marked hypertriglyceridemia which may be accompanied by eruptive xanthoma. Both chylomicrons and VLDL increase in the blood indicating a disposal defect. Free fatty acid levels may increase during fasting, but the source of the fatty acids is plasma triglyceride rather than adipose tissue. The role of a "diabetogenic" peptide found in the urine of lipodystrophic patients is not clear. The term "lipoatrophic diabetes" is synonymous with the above syndromes and probably should be abandoned.

The cause of the insulin resistance is not known. Basal and stimulated plasma insulin concentrations are usually high, though late in the disease they may fall. The clinical picture best fits a receptor defect, but this has not been studied as yet. The metabolic abnormalities are summarized in Table 12.

Table 12

Metabolic derangements in lipodystrophy

1. Insulin resistance
2. Elevated plasma insulin
3. Hyperglycemia (ketosis resistant)
4. Hypertriglyceridemia (chylomicrons + VLDL)
5. Hypermetabolism (↑ BMR)

It is of interest that basal glucagon levels are normal and that glucose suppressibility of the alpha cell hormone is intact.

A new form of lipodystrophy has recently been described in which familial transmission appears to follow a dominant pattern with variable expressivity (56,57). In addition to a genetic difference, the distribution of fat was unique since limbs and trunks showed lipoatrophy, but the face was full with normal adipose tissue. Other features appear identical with the more common forms.

54. Seip, M. Generalized lipodystrophy. Ergeb. Inn. Med. Kinderheilkd. 31:59-95, 1971.
55. Brubaker, M. M., N. E. Levan and P. J. Collipp. Acanthosis nigricans and congenital total lipodystrophy. Arch. Dermat. 91:320-325, 1965.
56. Dunnigan, M. G., M. A. Cochrane, A. Kelly and J. W. Scott. Familial lipoatrophic diabetes with dominant transmission. Q. J. Med. 169: 33-48, 1974.
57. Lillystone, D. and R. J. West. Lipodystrophy of limbs associated with insulin resistance. Arch. Dis. Child. 50:737-739, 1975.

3. Syndrome of familial insulin resistance, somatic abnormalities and pineal hyperplasia

This fascinating syndrome was first described in 1956. As indicated in Table 13, the patients are peculiar looking with dental precocity and malformed teeth. They have acanthosis nigricans, thick nails, dry skin and hirsutism. There is a peculiar sexual precocity with enlargement of the external genitalia. Before the age of 3 clitoris and vaginal labia may be of adult size and the vagina sufficiently large to allow a pelvic examination. One young male had a penis 3 inches long at the age of 4. At autopsy the major finding is pineal hypertrophy (58,59,60).

Table 13

Clinical features of the pineal hypertrophy syndrome

1. Peculiar facies
2. Early dentition with mishapen teeth
3. Acanthosis nigricans
4. Hirsutism
5. Dry skin, thick nails
6. Genital enlargement
7. Severe insulin resistance with ketoacidosis
8. Increased plasma insulin concentrations
9. Recurrent sepsis
10. Pineal enlargement

The insulin resistance of this syndrome is very severe, and keto-acidosis is common. Interestingly (Table 14), the insulin resistance may not be complete, since free fatty acid levels fall following oral glucose loads. All of these children die at an early age (usually before 10 years).

Table 14

Results of oral glucose tolerance tests in patients and parents

Subject	Age (yr)	Estimation	Minutes after glucose					
			0	30	60	90	120	150
Case 1	7·3	Glucose (mg/100 ml)	265	387	370	310	286	246
		Insulin (μU/ml)*	212	–	440	–	–	–
		NEFA (mEq/l)	1·56	0·70	0·84	0·72	0·62	1·77
Case 2	3·1	Glucose (mg/100 ml)	42	154	144	122	109	84
		Insulin (μU/ml)	556	3208	3136	2875	3187	2656
		NEFA (mEq/l)	1·98	1·93	0·53	0·44	0·58	0·88
	4·9	Glucose (mg/100 ml)	90	232	250	231	174	104
		Insulin (μU/ml)	1050	4050	3125	4300	3350	1600
		NEFA (mEq/l)	0·88	0·50	–	0·29	0·26	0·47
	6·8	Glucose (mg/100 ml)	259	460	469	362	218	252
		Insulin (μU/ml)	498	535	725	909	393	288
Mother	30	Glucose (mg/100 ml)	61	101	98	90	67	51
		Insulin (μU/ml)	48	310	312	240	115	69
Father	32	Glucose (mg/100 ml)	78	128	103	34	55	74
		Insulin (μU/ml)	16	130	136	23	8	11
		NEFA (mEq/l)	0·45	0·19	0·17	0·26	0·47	0·71

*After removal of circulating antibody.
NEFA, plasma nonesterified fatty acids.

58. Rabson, S. M. and E. N. Mendenhall. Familial hypertrophy of pineal body, hyperplasia of adrenal cortex and diabetes mellitus. Am. J. Clin. Pathol. 26:283-290, 1956.
59. Barnes, N. D., P. J. Palumbo, A. B. Hayles and H. Folgar. Insulin resistance, skin changes and virilization: A recessively inherited syndrome possible due to pineal gland dysfunction. Diabetologia 10:285-289, 1974.
60. West, R. J., J. K. Lloyd and W. M. L. Turner. Familial insulin-resistant diabetes, multiple somatic anomalies, and pineal hyperplasia. Arch. Dis. Child. 50:703-708, 1975.

4. The Alström syndrome

This rare syndrome has been reviewed in detail by Goldstein and Fialkow (61). It is an autosomal recessive disease which is characterized by profound childhood blindness due to retinal degeneration. Other features are summarized in Table 15 and include nerve deafness, insulin resistance and hyperglycemia. Interestingly the patients may have resistance to vasopressin, resulting in a diabetes insipidus-like state, and, in males, hypogonadism with high circulating gonadotropin levels occurs. They thus appear to have multiple end organ unresponsiveness to hormones. It has been pointed out that the patients superficially resemble the Laurence-Moon-Biedl syndrome. However, the Alström patients are not mentally deficient and do not have polydactyly, while LMB patients only rarely have nerve deafness, diabetes or nephropathy. The insulin resistance is not functionally a major problem.

Table 15

Clinical features of the Alström syndrome

1. Childhood blindness (retinal degeneration)
2. Infantile obesity
3. Insulin resistance with hyperglycemia
4. Nerve deafness
5. Chronic nephropathy
6. Acanthosis nigricans
7. Hypertriglyceridemia
8. Hyperuricemia
9. Baldness
10. Hyperostosis frontalis interna
11. Hypogonadism in males (high gonadotropins)
12. Aminoaciduria
13. Nephrogenic diabetes insipidus

The sequence of appearance of the major features is shown in Fig 19.

61. Goldstein, J. L. and P. J. Fialkow. The Alström Syndrome. Report of 3 cases with further delineation of the clinical, pathophysiological and genetic aspects of the disorder. Medicine 52:53-71, 1973.

Figure 19 (ref 61)

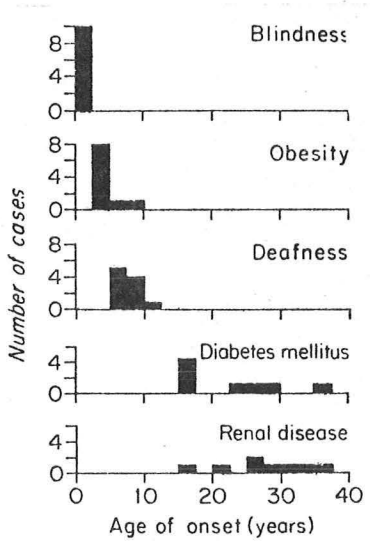


FIG. 7. Distribution of the ages of onset of each of the major clinical manifestations of the Alström syndrome.

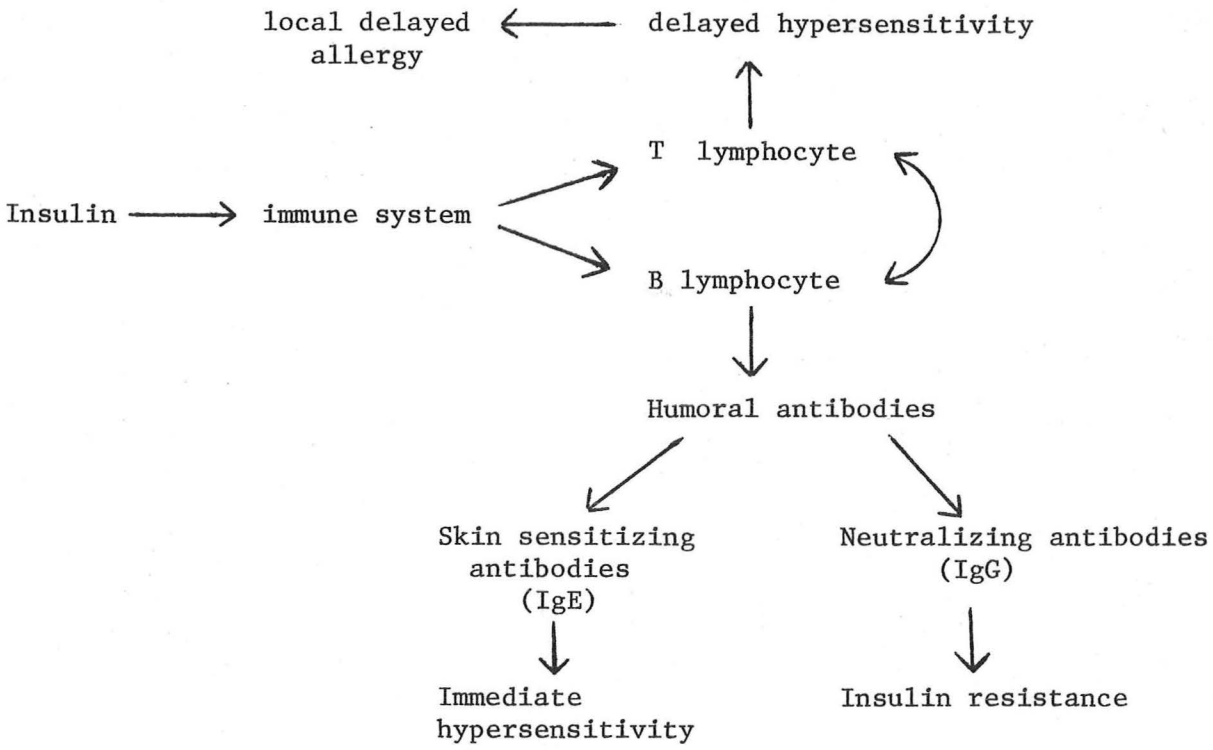
3. Insulin allergy

Dermal reactions to insulin have been observed in 20-50% of patients on therapy (62-64). Essentially 3 types of reactions occur (64).

1. Immediate, mild, local stinging
2. Delayed local reaction with brawny swelling lasting up to 30 hours
3. Generalized reaction with urticaria and erythema

The type 3 (systemic) reaction can be associated with anaphylactic shock and collapse. Other types of reaction, such as the Arthus phenomenon and positive LE preps have also been reported (64). The antibody responsible is an IgE (65). Systemic reactions are most often seen in patients previously treated with insulin who for one reason or another have stopped therapy for awhile and then resumed. The reaction may occur as early as the second injection and almost always before the tenth injection on resumption of therapy. It can occur in patients never previously treated with insulin (66). Interestingly, a history of allergy to environmental substances is usually absent. Both insulin resistance and insulin allergy can co-exist in the same patient (65,67). A simplified scheme to account for these findings is shown:

Scheme 1



If a patient with systemic allergy requires insulin therapy, desensitization should be carried out. While this can be done with commercial insulin, it is far preferable to use monocomponent insulin (Fig 20).

Figure 20

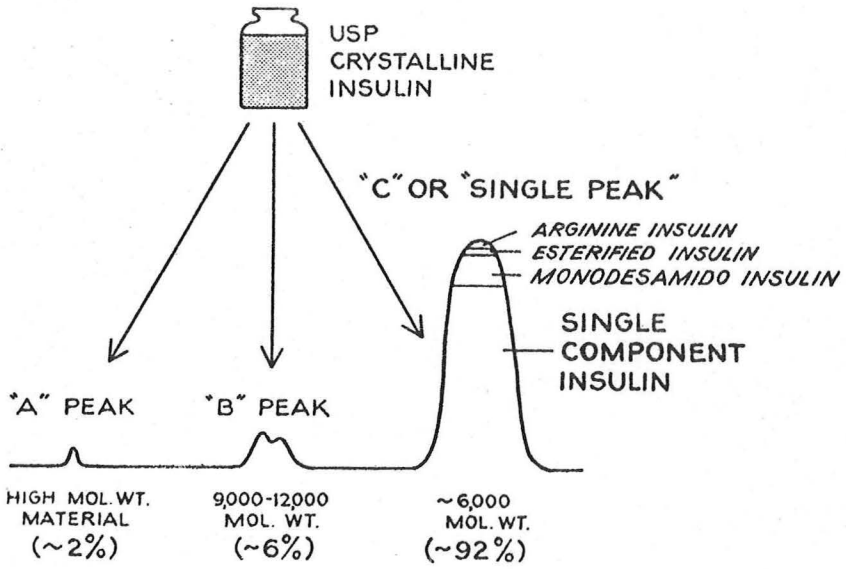


FIGURE 1

Diagrammatic representation of G-50 Sephadex gel chromatography.

Two schedules for desensitization are shown. The first (Table 15) requires several days, while that of Galloway (Table 16) can be done in 1 day.

Table 16 (ref 68)

Table 2.—Representative Insulin Desensitization Schedule*

Day	Time	Units of Insulin	Route Administered
1	7:30 AM	0.00001	Intradermal
	12 noon	0.0001	Intradermal
	4:30 PM	0.001	Intradermal
2	7:30 AM	0.01	Intradermal
	12 noon	0.1	Intradermal
	4:30 PM	1.0	Intradermal
3	7:30 AM	2.0	Subcutaneously
	12 noon	4.0	Subcutaneously
	4:30 PM	8.0	Subcutaneously
4	7:30 AM	12.0	Subcutaneously
	12 noon	16.0	Subcutaneously
	4:30 PM	20.0	Subcutaneously
5	7:30 AM	25.0	Subcutaneously
6	7:30 PM	30.0	Subcutaneously

* Commercial insulin (beef or pork) was administered. Long-acting insulin preparations may be considered on day 2, at 4:30 PM.

Table 17 (ref 69)

Desensitization *

Time Hour	Dose Units	Route of Administration
0	1/1000	Intradermal
½	1/500	Intradermal
1	1/250	Subcutaneous
1½	1/100	Subcutaneous
2	1/50	Subcutaneous
2½	1/25	Subcutaneous
3	1/10	Subcutaneous
3½	1/5	Subcutaneous
4	1/2	Subcutaneous
4½	1	Subcutaneous
5	2	Subcutaneous
5½	4	Subcutaneous
6	8	Subcutaneous

Use 2-10 units every 4-6 hours for next 24-36 hours before switching to Lente or Lente and Regular.

* Material will be supplied by Lilly.

Once the patient is desensitized insulin therapy should never be interrupted. IgE levels fall rapidly on desensitization. (Fig 21)

Figure 21 (ref 68)

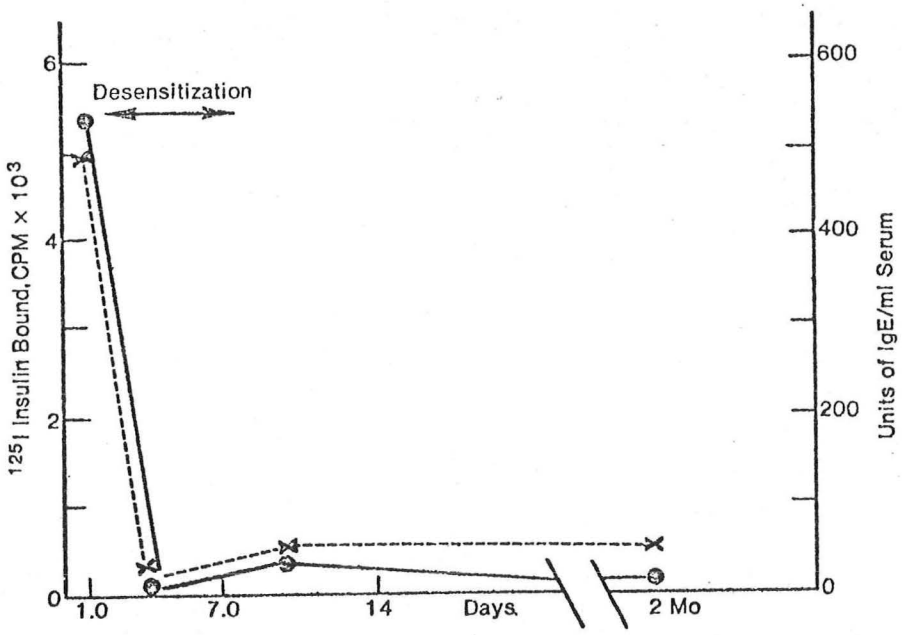


Fig 1.—Rapid decline in IgE antiinsulin binding following desensitization (patient 1). Counts per minute (CPM) of ^{125}I-labeled insulin bound by 1 ml serum (solid line and solid circles); serum IgE concentration (dashed line and crosses).

62. Arkins, J. A., N. H. Engbring and E. J. Lennon. The incidence of skin reactivity to insulin in diabetic patients. J. Allergy 33: 69-72, 1962.
63. Lieberman, P., R. Patterson, R. Metz and G. Lucena. Allergic reactions to insulin. JAMA 215:1106-1112, 1971.
64. Porter, R. D. and C. R. Hartman. Arthus reactions from insulin. Association with lupus erythematosus cell phenomena. JAMA 214:1884-1885, 1970.
65. Patterson, R., C. J. Mellies and M. Roberts. Immunologic reactions against insulin. II. IgE anti-insulin, insulin allergy and combined IgE and IgG immunologic insulin resistance. J. Immunol. 110: 1135-1145, 1973.
66. Dacon-Voutetakis, C., TH. Themoides, E. Roma, A. Kalpini-Mavrou and E. Economou-Mavrou. Systemic allergic reaction to initial insulin therapy in a juvenile diabetic. Acta Paediatr. Scand. 64: 773-776, 1975.

67. Dolevich, J., J. D. Schnatz, R. F. Reisman, Y. Yogi and C. E. Arbesman. Insulin allergy and insulin resistance. Case report with immunologic studies. J. Allergy 46:127-137, 1970.
68. Mattson, J. R., R. Patterson and M. Roberts. Insulin therapy in patients with systematic insulin allergy. Arch. Int. Med. 135:818-821, 1975.
69. Galloway, John A. Personal communication.

4. Lipoatrophy

This subject will not be discussed except to say that it is a common accompaniment of insulin therapy (24% of patients taking insulin for 1 year). Treatment is effective by simply substituting monocomponent insulin and injecting into the site.

70. Teuscher, H. Treatment of insulin lipoatrophy with monocomponent insulin. Diabetologia 10:211-214, 1974.