

Two cases of true allergy to insulin are reported and discussed.

Insulin Allergy

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ADVERSE REACTIONS TO injected insulin may be allergic or non-allergic. Hypoglycemia is the most frequent untoward reaction encountered. "Insulin presbyopia" is a usually transient loss of visual accommodation that occurs in patients with newly diagnosed diabetes when control with insulin is rapidly achieved. It is attributed to changes in the physical properties of the crystalline lens resulting from reduction of blood sugar.¹ Lipodystrophy, atrophy of fat at sites of frequent insulin injection, occurs in some patients. Others may develop thickening of skin and subcutaneous tissue often to a sizable degree.² Mild local reactions consisting of swelling,

erythema, and stinging at the injection site occur frequently in patients who have never previously taken insulin. Such reactions usually disappear in a few weeks despite continued insulin treatment. Whereas some³ consider them irritant reactions, others⁴ believe they are mild allergic reactions. Insulin resistance is frequently, but not always, associated with large amounts of plasma insulin-binding antibodies.⁵ Table I lists some adverse reactions to insulin.

Commercially employed insulin usually contains mixtures of beef and pork insulins and is capable of provoking immediate allergic reactions.⁶ The immunologic mechanism involved in these reactions is not clear.⁷ Immunoglobulin E (IgE), thought to be responsible for most immediate hypersensitivity reactions⁸ is believed to play a major role in insulin allergy as well.⁹ Local reactions of increasing severity may appear causing extreme pain, marked induration, urticaria, and erythema at the injection

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TABLE I. ADVERSE REACTIONS TO INSULIN

Hypoglycemia
"Insulin Presbyopia"
Lipodystrophy
Lipohypertrophy
Mild local reactions—?irritant; ?allergic
Insulin resistance
True allergic reactions—immediate type

site. Maculopapular rash, large local bullae, and localized purpura without thrombocytopenia have been reported.⁴ Systemic manifestations are generally cutaneous, circulatory, or gastrointestinal. Cutaneous reactions are most common⁴ and include paresthesias, urticaria, angioedema, erythemas, pruritus, morbilliform, scarlatiniform, or vesicular eruptions.⁴ Circulatory reactions include pallor, flushing, palpitations, and circulatory collapse. Nausea, vomiting, abdominal cramps and diarrhea are among gastrointestinal reactions encountered.⁴ Lymphadenopathy, or asthma may occur, and anaphylactic shock is reported occasionally.^{4,10} Porter and Hartman¹¹ recently reported a patient with insulin hypersensitivity manifested by the Arthus phenomenon, lupus erythematosus cells, eosinophilia, and hypergammaglobulinemia. Table II contains a summary of the types of allergic reactions to insulin that occur.

Systemic reactions to injected insulin that we observed in two patients recently are illustrated in the following case reports.

TABLE II. TYPES OF ALLERGIC REACTIONS TO INSULIN

Local Reactions	
Pain	Bullae
Induration	Maculopapular rash
Urticaria	Non-thrombocytopenic purpura
Erythema	
Systemic Reactions	
Cutaneous	
Paresthesias	Pruritus
Urticaria	Morbilliform eruption
Angioedema	Scarlatiniform eruption
Erythema	Vesicular eruption
Circulatory	
Pallor	Palpitations
Flush	Circulatory collapse
Gastrointestinal	
Nausea	Abdominal cramps
Emesis	Diarrhea
Other reactions	
Lymphadenopathy	Arthus phenomenon
Asthma	L. E. phenomenon
Anaphylactic shock	Eosinophilia

Case Report

A 59-year-old white female was admitted to the hospital on August 29, 1969, for evaluation of angina pectoris and to control her diabetes. In May, 1968, when she developed a 15-pound weight loss, polydipsia, and polyuria, diabetes mellitus was diagnosed. She responded to tolbutamide initially, but in December, 1968, her physician prescribed insulin because her diabetes had become difficult to control. Following the fifth dose of isophane beef-pork insulin (NPH) 20 units per dose, urticaria, dyspnea, and tachycardia were noted. Beef-pork insulin zinc suspension (Lente) was substituted for the isophane insulin and she had a more severe urticarial reaction, accompanied by angioedema, dyspnea, and tachycardia, which required hospitalization. It was discovered later that she had used insulin for a short period of time about 20 years previously. She had a history of hay fever and of several rashes attributed to drugs, but details were not forthcoming.

Fasting blood sugar on admission was 150 mg/100 cc. Direct skin tests to beef and pork antigens were negative. Direct skin tests were strongly positive to both beef and pork insulins. No attempt at desensitization was made because the endocrinology consultant did not advise it and the patient was reluctant to agree to it. She was discharged on diet, phenformin (DBI-TD®) and acetohexamide (Dymelor®). Continued poor diabetes control may necessitate desensitization in the near future.

Case Report

A 32-year-old white female was admitted to the hospital on August 28, 1970, complaining of allergy to insulin. She had had known diabetes for nine years. Before she began taking insulin, trials of tolbutamide (Orinase®) and chlorpropamide (Diabinese®) had resulted in urticaria and laryngeal edema. Insulin was started in 1963, and she experienced no difficulty with it until May, 1970, when she began to have large local reactions at sites of injection. Later generalized urticaria, often with wheezing developed with each injection. This was somewhat modified by use of diphenhydramine (Benadryl®), 50 mg every two hours. She was taking 20 units of regular beef-pork insulin and 40 to 50 units of beef-pork isophane (NPH) insulin daily. No history of interruption in the insulin treatment program was obtained. Trials of pure beef insulin zinc suspension (Lente) and pure pork insulin suspension (Lente) produced similar

allergic reactions, despite the fact that the pure pork insulin was such a highly purified semi-synthetic product that it produced only one peak on chromatography.

Fasting blood sugar on admission was 243 mg/100 cc. Direct skin tests were negative to beef and pork antigens, but positive to beef insulin and pork insulin. Treatment included diet and phenformin (DBI-TD), 25 mg daily. When last seen she was progressing satisfactorily. No attempt at desensitization was considered.

Comment:

Both patients were tested directly by the scratch method to beef antigen, pork antigen, beef insulin, pork insulin, and saline control. All were negative. Intradermal tests using 0.02 cc of 0.4 unit of regular insulin per cubic centimeter produced positive reactions with both beef and pork insulins. In each case the reaction consisted of a flare and wheal with pseudopod formation. No reactions were observed when intradermal tests to beef and pork antigens were made. Passive transfer of

skin reactivity was successfully accomplished in both patients. Neither patient had evidence of insulin resistance. Table III outlines some clinical features of the two patients studied.

Lieberman et al⁷ have found that *in vitro* histamine release was not demonstrated when insulin was added to peripheral leukocytes of five patients with true insulin allergy. The reason for this could not be explained. Moreover, *in vitro* confirmation of an IgE antibody against insulin was not demonstrated by autoradiographic techniques in the same five patients, probably because of the small amount of antibody present. However, the antibody in one patient, studied by specific absorption techniques was found to be IgE.⁹

Unlike Lieberman et al⁷ and Dolovich et al,⁶ one of our patients (Case 2) developed true insulin allergy while having taken insulin for years without interruption. In their patients, as well as in our Case 1, insulin injections had been resumed after having been

TABLE III. FEATURES OF TWO PATIENTS WITH INSULIN ALLERGY

	CASE I	Case II
Age and Sex	59 F	32 F
Age at onset of diabetes	58	25
Initial diabetic complaints	Wt. loss, Polydipsia, Polyuria	Polydipsia, Polyphagia, Polyuria.
Fasting blood sugar—range in mg/100 cc	80-306	170-246
Insulin dose when allergic reaction began	20 units	40 units
Type of insulin	Beef-pork Isophane (NPH)	Beef-pork Regular and Isophane (NPH)
Allergic reaction	Urticaria, dyspnea, tachycardia	Urticaria, wheezing.
Lapse in insulin treatment	Yes	No
Length of insulin treatment before reaction began	5 days	7 years
Personal or Family History of allergy	Hay fever, Drug eruptions	Drug eruptions, Aplastic anemia, Mother had allergy to penicillin.
Direct skin tests to insulin	Positive	Positive
Passive transfer possible	Yes	Yes
Course	Poor control on diet and oral hypoglycemic agents.	Controlled with diet and oral hypoglycemic agents.
Desensitization attempted	No	No

discontinued previously.

No attempt to desensitize either of our patients has been necessary to date. One patient (Case 1) may require it since her diabetes has been difficult to control on her present program.

Discussion

Insulin is a complete protein and an active antigen capable of producing sensitization, and allergic reactions to it have been reported repeatedly.⁴ Insulin is a polypeptide containing, in most species, 51 amino acids arranged in two chains; one contains 21 amino acids (A chain), the other contains 30 amino acids (B chain). The two chains are united by two disulfide bridges.³¹ Pork insulin differs from human insulin by only one amino acid, but beef insulin differs by three.³¹ This may explain the greater antigenicity of beef insulin in humans compared to pork insulin.³² Patterson et al⁹ found reactivity directed against insulins of several species including human insulin in the serum of a patient, but not against the patient's own insulin.

Commercial production of insulin from the pancreases of animals was soon achieved following isolation of insulin by Banting and Best in 1922.¹² The insulin first used for treatment of diabetes was contaminated with other pancreatic proteins, so reports of allergic reactions that followed were not unexpected. Following the work of Abel¹³ and Scott¹⁴ crystalline insulin became available for clinical use, but allergic reactions to this form also occurred. Tuft¹⁵ was the first to study insulin allergy carefully. He showed that a patient allergic to crude insulin preparations was also allergic to re-crystallized insulin, but not to protein extracts of the animal from which the insulin was derived. He found a skin-sensitizing antibody and a precipitin in the serum of his patient. The precipitin disappeared

swiftly, but the reagin persisted at least three months.

Banting et al,¹⁶ observed insulin resistance in a patient given large doses of injected insulin for psychiatric treatment. They clearly demonstrated anti-insulin factor in the serum and localized it to the serum globulin. Utilizing the Shultz-Dale technique, Lewis¹⁷ found that strips of uterus of animals sensitized to beef insulin reacted to beef insulin, but not to beef pancreas or beef serum. Moreover uteri of animals sensitized with either beef or pork insulin responded to tests with both insulins. Wasserman and Mirsky¹⁸ and others^{19,20} induced anaphylaxis with insulin from a different species in sensitized guinea pigs. Hanauer and Batson⁴ reported a case of anaphylactic shock following insulin injection and found seven such cases in the literature in English.

Although circulating antibodies to insulin are present within a few months after starting insulin treatment, the insulin-binding capacity of the serum remains low in most diabetic patients.²¹ Insulin-resistant diabetes may be present with or without associated insulin allergy.²² Lowell^{23,24} reported the course of a patient in whom allergy to beef insulin alternated with insulin resistance. Serum levels of skin-sensitizing and insulin-neutralizing antibody activity varied independently of each other and the latter were high during periods of insulin resistance. Others^{29,30} have reported the coexistence of insulin allergy and insulin resistance. More recently²⁵ circulating antibodies to insulin of the IgG, IgA, and IgM classes have been observed in the sera of diabetics.⁶ Skin-sensitizing antibody activity present in the serum of naturally allergic subjects is now known to be a function of the IgE class of antibody.⁸ IgE probably mediates insulin allergy as well. Blocking antibody ac-

tivity which is present in the sera of naturally allergic subjects after injection of antigen and limits the interaction of antigen with reaginic antibody, is largely of the IgG class.²⁶

Dolovich et al⁶ recently described a subject who was controlled for a long period without insulin treatment. When insulin was resumed, the patient suffered a generalized allergic reaction to insulin followed by a period of insulin resistance, during which the allergic reaction subsided. Patterson et al⁹ reported findings which indicate that the reaginic antibody of an insulin-allergic subject was in an immunoglobulin class other than IgA, IgG, and IgM. More recently, Lieberman, et al⁷ reported insulin allergy in five patients, two of whom responded successfully to desensitization. Results indicated that insulin allergy may be directed against the insulin molecule itself or against protein contaminants in the commercially available preparation. It can be mediated by IgE, they postulated.

Skin tests are usually employed to diagnose insulin allergy, but they may not be accurate. Lieberman et al⁷ found that 40 percent of 50 diabetic patients who were taking insulin had positive skin tests to insulin, but no evidence of systemic reactions. Moreover, reactions can occur in patients with negative skin tests to insulin.²⁷

While desensitization may be successful in insulin allergy, it should be employed with extreme caution. Anaphylaxis may be produced by the desensitization. Also precautions against hypoglycemic reactions are mandatory if frequent doses are given to desensitize. Initial dose for desensitization should be from 0.00001 unit of insulin⁷ to 0.001 unit.⁴ Rapid desensitization²³ may be required if diabetic acidosis is present. Where no emergency exists the procedure may be done more slowly.⁷

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