

ALLERGY GRAND ROUNDS

Allergic reactions to insulin

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The development of heterologous insulin to control diabetes mellitus ranks as one of the great achievements of medical science. However, as with other therapeutic modalities, insulin therapy has not been without unwanted adverse effects. Reported untoward reactions to insulin have included: hypoglycemia, scar formation, and lipodystrophy (hypertrophy and atrophy),¹ "insulin edema,"² and immune reactions.³ The latter would not be unexpected since insulin is a foreign protein and therefore capable of eliciting a variety of immunologic responses. We have found it convenient to group proved or suspected immune responses as seen in Table I.

This discussion will concentrate on the relatively more common local and systemic responses, both of which have been described since the earliest writing on insulin therapy.^{11, 12} The reported frequency of *local* cutaneous reactions has ranged from 14 to 55.8%.¹³ These figures are probably artificially high, however, since they are based upon the incidence of reactions as determined by close clinical observation of patients mainly during the first several days of therapy. The incidence of clinically significant reactions is unknown but certainly much lower. These reactions which may be quite painful consist of erythema, induration, pruritus, and occasional wheal formation at the injection site. The local reaction usually occurs early in the course of insulin therapy. It may occur immediately after injection, increase in intensity for 12-24 hr and then subside, or may begin 6-8 hr after injection, reach peak intensity in 24-48 hr, and subside after several days. An occasional patient may have a dual response consisting of an immediate response, which improves temporarily, only to be followed several hours later by the delayed response. These reactions often

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TABLE I. Proved or suspected immune responses to insulin

I. More common reactions	
A. Local—limited to injection site	
1. Immediate	
2. Delayed	
3. Dual (combination of above)	
B. Systemic—urticaria and angioedema with or without shock, gastrointestinal or respiratory symptoms	
C. Insulin resistance	
II. Rare	
A. Serum sickness ^{4, 5}	
B. Purpura	
1. Nonthrombocytopenic ⁶	
2. Thrombocytopenic ⁷	
C. Lymphadenopathy, hepatosplenomegaly, Coombs (+) hemolytic anemia ⁸	
D. Arthus phenomenon with LE cells, eosinophilia, and hypergammaglobulinemia ⁹	
E. "Insulin autoimmune syndrome" ¹⁰	

TABLE II. Insulin amino acid sequence differences among various species¹⁷

	A chain		B chain
	8	10	30
Man	Thr	Ileu	Thr
Pig	Thr	Ileu	Ala
Rabbit	Thr	Ileu	Ser
Beef	Ala	Val	Ala

disappear with continued insulin administration. However, they may persist and be a harbinger of a systemic reaction.³ In one of the largest series of patients with systemic reactions to insulin, 14 of 15 patients had clinically apparent local reactions preceding their systemic response.¹⁹ On the other hand, the percentage of patients exhibiting local reactions who later develop systemic reactions is unknown, but is probably very small. Skin testing with insulin may reproduce these responses, i.e., immediate, late, or dual.

Systemic reactions to human insulin are undoubtedly rare; their exact incidence is unknown. Their importance, however, lies not in their frequency but in the fact that they may prohibit insulin therapy and may be life-threatening, demanding prompt attention. These are mediated by IgE.¹⁴

The insulin molecule consists of two polypeptide chains (A and B) held together by two disulfide bonds. The acidic chain A has 21 amino acids. The B chain (which is basic) has 30 amino acids. There is also an intrachain disulfide bridge between positions 6 and 11 in the A chain.¹⁷ Although there can be considerable species-specific variation in amino acid sequence, some animal species differ very little from human insulin.¹⁷ This of course has therapeutic and immunologic implications. Differences between human and structurally related insulins of other species are seen in Table II. The only sites of amino acid variability among the species noted are positions 8 and 10 of the alpha chain and position 30 of the beta chain. Human and porcine insulin are almost identical, differing only at position 30 of the beta chain. Pork insulin is probably therefore, at least in most instances, the least allergenic preparation. Skin testing data in insulin-allergic patients seem to confirm this postulate. Patients taking

TABLE III. Results of intradermal testing with 0.02 c.c. of various U 100 insulin preparations

Insulin preparation	20 min	8 hr	24 hr	48 hr
Beef				
SP reg*	12-mm wheal	10-mm erythema	12-mm induration	8-mm induration
SC reg	13 mm	9 mm	10 mm	7 mm
SP lente	6 mm	5 mm	11 mm	5 mm
SC lente	14 mm	9 mm	7 mm	2 mm
Pork				
SP reg	10-mm wheal	5-mm erythema	8-mm induration	5-mm induration
SC reg	5 mm	Neg	2 mm	Neg
SP lente	8 mm	Neg	5 mm	1 mm
SC lente	6 mm	5-mm erythema, pruritus	6 mm	2 mm
Beef-pork				
SP reg	7-mm wheal	Neg	8-mm induration	2-mm induration
SP lente	12 mm	8-mm erythema, pruritus	11 mm	3 mm
Human				
SC reg	10-mm wheal	5-mm erythema, pruritus	2-mm induration	Neg
Diluent	Neg	Neg	Neg	Neg

*SP, Single peak; SC, single component.

mixtures of beef-pork insulin at the time of their systemic reaction usually exhibit a lesser degree of cutaneous reactivity to pork than to beef insulin on skin test titrations.¹⁴ Most commercial preparations consist of a mixture of both beef and pork insulin.

CASE REPORTS

To further clarify the nature of the local cutaneous and systemic reactions to insulin two illustrative cases have been chosen for discussion. Case 1 is a patient with severe, persistent local reactions. The severity of the local reactions exhibited by this patient is extremely rare, but the case does illustrate the problems such local reactions can present in their extreme form. The second case illustrates a systemic reaction treated successfully with desensitization.

Case 1. Severe local reaction

W. M., a 55-yr-old white man, had a 23-yr history of diabetes mellitus. Insulin therapy was begun when the diagnosis was made. However, shortly after the initiation of treatment with 20 U of NPH U 80 insulin he began to notice local swelling with pain, erythema, and pruritus at the injection site. These reactions would begin 15 min after injection, reach a peak at 12 hr, then slowly subside. Insulin was continued for several weeks even in the face of large local reactions, but was terminated after an episode of generalized urticaria and angioedema occurring within 30 min of an injection. The dose of insulin was not increased prior to the systemic reaction. For the next 15 yr the patient was poorly controlled with oral agents and diet (tolbutamide 1 gm twice a day, phenformin 300 mg per day, and a 1,000-calorie diet). Then several attempts were made to reinstitute insulin therapy. On each occasion, the patient would do well for 3 to 4 days, then develop severe local reactions. Attempts to alleviate the reactions by varying injection technique and diets and substituting various insulin preparations were unsuccessful. The reactions were so severe that insulin had to be discontinued in favor of oral hypoglycemic agents. However, significant hyper-

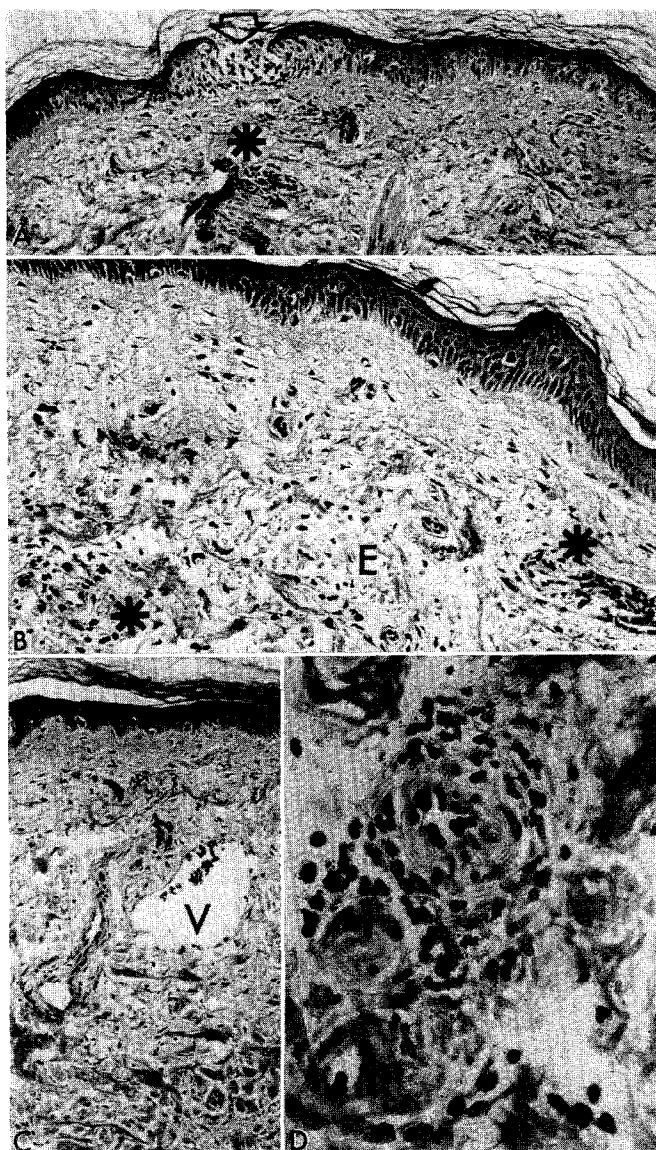


FIG. 1. In **A** an intraepidermal vesicle (arrow) is present just above the vasculitis (*) (24-hr specimen). In **B** marked edema (**E**) in the reticular dermis and leukoclastic angiitis (*) are seen (24-hr specimen). In **C** a marked dilatation of superficial blood vessels (**V**) is observed (6-hr specimen). In **D** swollen endothelial cells occlude the lumen of some vessels and destruction of degranulated leukocytes gives rise to a picture of leukoclastic angiitis (24-hr specimen). (**A**, **B**, and **C**, $\times 100$; **D**, $\times 400$.)

glycemia persisted and the patient subsequently developed diabetic retinopathy, angina pectoris with "two heart attacks," hypertension, and recurrent paresthesias of both feet. Because of this poor diabetic control, the patient was referred to the allergy service to investigate the possibility of reinstituting insulin therapy.

He denied any history of asthma, allergic rhinitis, or food intolerance. There was no family history of atopy. Physical examination revealed: a height of $75\frac{1}{2}$ inches, weight



FIG. 2. A 20-min specimen. One erythrocyte (**RBC**) is found in perivascular space of a medium-sized vessel. One mast cell (**M**) shows almost complete degranulation. **E**, Endothelial cell; **SM**, perivascular smooth muscle. ($\times 15,000$.)

200 pounds, blood pressure 140/90 mm. Hg, pulse 72, respiration 16. The patient was in no distress. Pertinent findings included: several areas of exudate and scar formation in the left fundus and decreased deep tendon reflexes in both lower extremities with decreased light touch perception over all toes. Initial laboratory data were all negative or within normal limits except for a fasting blood sugar of 280 mg/100 ml and 3+ glycosuria.

Skin tests to a battery of insulin preparations (kindly supplied by Eli Lilly and Company, Indianapolis, Ind.) were applied intradermally. These are summarized in Table III. There was an initial wheal-and-flare response typical of immediate hypersensitivity which resolved within 1 hr. Frank erythema, induration, and pruritus were then noted at 6-8 hr, followed by mild erythema and induration at 24 hr. Reactions were resolving by 48 hr and undetectable by 3 days. Representative biopsy specimens were obtained at 30 min, and 6, 24, and 48 hr for light (Fig. 1) and electron microscopy (Figs. 2 to 4).

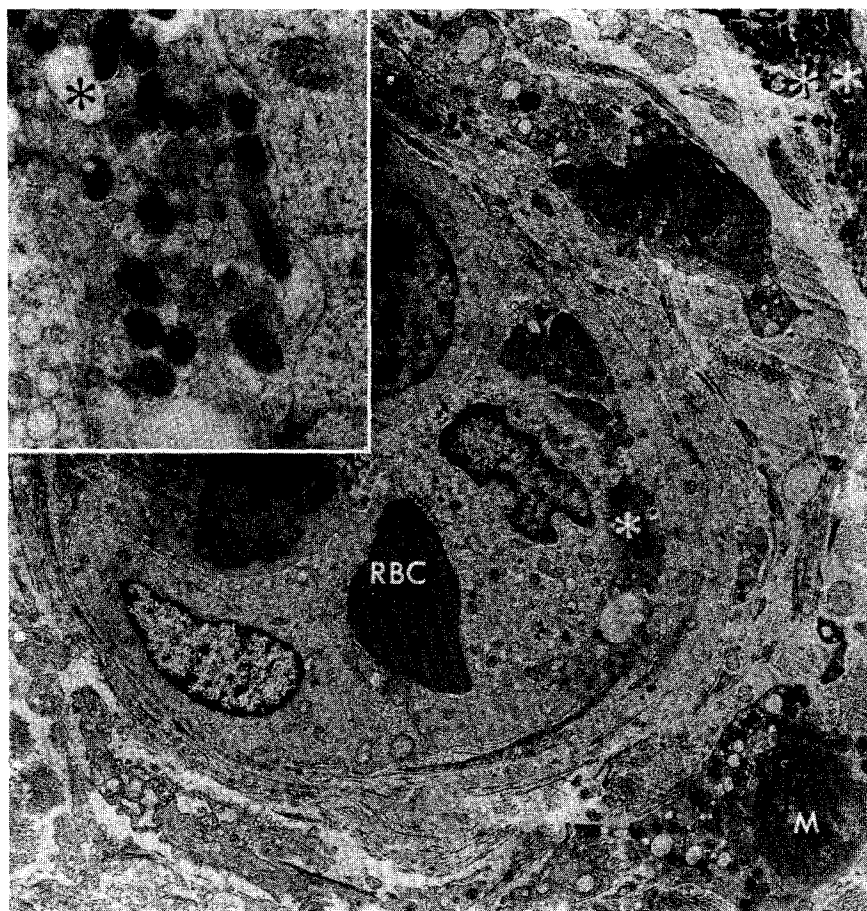


FIG. 3. A 7-hr specimen. Intravascular (*) as well as extravascular (**) degranulation of neutrophilic leukocytes. **M**, Degranulating mast cell; **RBC**, erythrocyte. ($\times 5,750$.) Inset: A higher magnification of intravascular degranulation of a neutrophil (*). ($\times 30,000$.)

Light microscopic studies were consistent with an allergic leukoclastic vasculitis similar to that seen in type III (Arthus) immunopathologic reactions (Fig. 1). Ultrastructural changes observed on electron microscopic studies (Figs. 2 to 4) were also consistent with a type III response. In addition, mast cell degranulation, observed at 20 min, implicated a type I, IgE-mediated reaction, consistent with skin test data.

Because both skin test and histologic observations suggested a type I "introductory reaction" followed by a type III (Arthus) response, it was felt that diphenhydramine, by inhibiting the "introductory response," might successfully eliminate the entire reaction. It was therefore elected to treat the patient by adding diphenhydramine (1 mg/10 U of insulin) directly to the syringe used for insulin injection.

No reactions have been observed since the addition of diphenhydramine to the insulin syringe. The patient is now well controlled with daily intramuscular injections of 50 U of U 100 pork NPH insulin and 5 mg of diphenhydramine.

Case 2. Systemic reaction

M. R., a 30-yr-old black woman, was admitted to the hospital with diabetic ketoacidosis. She presented with a 30-lb weight loss in spite of a good appetite, increasing fatigue and



FIG. 4. A 24-hr specimen. Advanced degranulation of leukocytes (L) is observed in the perivascular space. E, Endothelial cell; P, pericyte. ($\times 6,500$.)

weakness, polydipsia and polyuria, and a progressive coma of 12-hr duration. Physical findings and laboratory data were consistent with diabetic ketoacidosis. The blood sugar was 650 mg/100 ml, serum acetone was positive at a 1:8 dilution, urine glycosuria and ketonuria were present, and the electrolytes were as follows: Na, 150; K, 3.9; Cl, 116; HCO_3 , 7.

The patient responded to standard therapy and was discharged 1 wk after admission on a 1,200-calorie ADA diet and 60 U of U 100 NPH insulin daily.

Five days after discharge she experienced generalized pruritus followed shortly by generalized urticaria and angioedema of her face, hands, and feet. This reaction occurred 30 min after an insulin injection. Because of the reaction the patient was seen in consultation by the allergy service.

Skin testing was performed to a battery of insulin preparations (kindly supplied by Eli Lilly and Company, Indianapolis, Ind). She exhibited classical wheal-and-flare reactions 15 min after intradermal injection of all preparations of insulin used for testing. The test results are summarized in Table IV.

Because the endocrinology consultant felt that insulin therapy was necessary for this patient, desensitization was performed using U 100 regular pork insulin. Initial doses were given intradermally and later subcutaneously beginning with 10^{-3} units. Progressively increasing doses were given every 15 min with constant physician observation and anaphylactic and hypoglycemic precautions available. The patient experienced no difficulty during the procedure until a dose of 5 U was reached. At this time she experienced generalized urticaria.

TABLE IV. Skin test reactivity to insulin before and after successful desensitization

Dosage 0.02 cc ID	0.0001 U/cc	0.001 U/cc	0.01 U/cc	0.1 U/cc	1 U/cc	10 U/cc	100 U/cc
<i>April 2, 1975 (before desensitization):</i>							
Beef-pork SP, lente	←	Neg*	1+	1+	2+	3+	4+
Beef SP, lente	←	Neg	1+	1+	3+	3+	4+
Human	←			Neg	1+	3+	—†
Pork SP, lente	←	Neg	1+	1+	2+	3+	4+
<i>April 9, 1975 (after desensitization):</i>							
Beef-pork SP, lente	←			Neg	1+	2+	3+
Beef SP, lente	←			Neg	1+	1+	2+
Human	←			Neg	1+	2+	—†
Pork SP, lente	←			Neg	1+	2+	3+

*Scale:

Neg: No erythema and/or induration.

1+: Induration < 1 cm without pseudopods or erythema.

2+: Induration > 1 cm without pseudopods; erythema < 2 cm.

3+: Induration > 1 cm without pseudopods; erythema > 2 cm.

4+: Induration > 1 cm with pseudopods; erythema > 3 cm.

†Not available.

The patient was given diphenhydramine 100 mg and Periactin 4 mg orally and the desensitization was reinstituted with a dose of 0.1 U of insulin. She continued to have minor evanescent bouts of mild urticaria for the next 48 hr. These, however, did not require further antihistamine therapy. She was discharged on the seventh hospital day on 30 U of pork U 100 NPH insulin and a 1,200-calorie diabetic diet. Her diabetes was under good control. She has continued to do well.

Repeat skin testing 2 wk after desensitization demonstrated a prominent decrease in cutaneous reactivity (Table IV).

COMMENT

Case 1 is representative of a patient with unusually severe local reactions to insulin injections. As mentioned previously, the etiology of these responses is poorly understood. Considerable work has been done in an attempt to better elucidate the mechanisms involved. Federlin¹³ has studied these reactions extensively with a variety of immunologic techniques. Histologic studies in 3 of his 14 patients with delayed reactions revealed varying degrees of perivascular round cell infiltration with eosinophils and histiocytic components and mast cell degranulation. These findings were felt to be due to a combination of humoral mechanisms and a delayed hypersensitivity reaction (Gell and Coombs type IV). The reaction in our patient differed histologically and suggests a dual type I and type III response.

The time sequence, i.e., onset rather early with progressive worsening for 12-24 hr also suggests an immediate, probable IgE-mediated response, followed by a secondary Arthus reaction. An early, classical IgE reaction followed by a "late IgE response"¹⁸ was also considered a possibility on the basis of the gross clinical picture. However, the histology was more representative of a leukoclastic angiitis or Arthus reaction.

Case II represents a more dramatic systemic reaction. These reactions have been reported in previous studies,¹⁹ and have been shown to be mediated by antibodies of the IgE class.²⁰ The antibody is directed against the insulin

TABLE V. Summary of clinical data on patients with systemic reactions

Pt. No.*	Age	Sex	Allergic manifestation	Preceding local reaction	Gap in therapy	Duration of diabetes (yr)	Injections prior to reaction
1	26	F	Urticaria	Yes	Yes	10	5
2	71	F	Urticaria, angioedema	Yes	Yes	12	8
3	24	M	Urticaria, angioedema	Yes	Yes	3	—†
4	48	F	Urticaria, angioedema	Yes	Yes	7	6
5	60	M	Urticaria, angioedema	Yes	Yes	10	3
6	37	F	Urticaria, angioedema	Yes	Yes	5	6
7	32	F	Urticaria	Yes	Yes	15	10
8	54	M	Urticaria	Yes	Yes	3	2
9	65	M	Urticaria	Yes	Yes	25	—†
10	72	M	Urticaria	No	Yes	4	7
11	76	M	Urticaria	Yes	Yes	9	6
12	51	M	Urticaria	Yes	Yes	8	3
13	37	M	Urticaria, angioedema	Yes	Yes	2	10
14	64	M	Urticaria, angioedema	Yes	Yes	6	4
15	52	F	Urticaria, angioedema	Yes	No	8	14
16	72	M	Urticaria	Yes	Yes	6	10
17	54	F	Urticaria	Yes	Yes	8	8
18	57	F	Urticaria, hoarseness	Yes	Yes	12	1
19	25	F	Anaphylactic shock	Yes	Yes	11	90
20	39	F	Urticaria, angioedema	No	No	1 mo	30

*Patients 1-15, Northwestern University Medical School; Patients 16-20, University of Tennessee Center for the Health Sciences.

†Not available.

molecule per se and not against its protein contaminants.²⁰ All of these patients reported to date demonstrate immediate skin test reactivity to a variety of insulins, often including extracted human insulin. It is felt that the acid-alcohol extraction process used in the commercial preparation of insulin is responsible for its allergenicity.¹⁴ Interestingly, Case 2 had no interruption of therapy or local reactions, both of which usually precede the generalized reaction.¹⁹

Approximately 40% of patients being treated with insulin will exhibit positive immediate skin test reactivity to the insulin being used for therapy. The reason some patients with evidence of IgE antibodies against insulin do not experience systemic reactions is unknown, but may be due to the presence of IgG "blocking antibodies." There are case reports of insulin resistance (due to IgG antibodies against insulin) alternating or occurring simultaneously with insulin allergy.²¹

Table V summarizes data on five cases of systemic reactions to insulin we have seen at our institution plus 15 cases recently published from another institution.¹⁹ Pertinent points to be emphasized are the wide age spectrum, frequent preceding local reactions, and the fact that insulin therapy had often been intermittent, the reaction occurring within a few days after the resumption of treatment.

Treatment for the local reactions can be difficult. If these are not too severe, continued insulin administration may result in a "spontaneous" resolution. A switch to one of the newly developed chromatographically purified preparations (monospecific single peak or single component) may alleviate the reaction entirely.²² If there is no improvement, injecting the insulin intramuscularly with an antihistamine (e.g., diphenhydramine) may be tried, as was successfully done

in our case. It should be noted, however, that it is possible that the addition of Benadryl to the syringe containing insulin might in some way alter the biologic activity of the insulin by changing the pH of the solution. Although this did not appear to be the case in our patient the possibility of this occurrence cannot be excluded in future cases.

The systemic reactions demand more rigorous treatment. If the patient cannot be managed easily with diet and oral hypoglycemic agents alone and has not received insulin in 24 hr it is probably best to proceed immediately with skin testing with both pure beef and pure pork crystalline insulin preparations. The least allergenic preparation as determined by skin test reactivity should be used for desensitization. Desensitization is then carried out with anaphylactic and hypoglycemic precautions at a rate depending upon the urgency of the clinical setting. Representative schedules have been published.^{14, 19}

An alternative method of desensitization has been successfully employed when insulin has not been discontinued for over 24 hr after a reaction.¹⁹ In this instance the initial desensitizing dose should be lowered to one third of the dose causing the reaction. Subsequent doses can be increased 5 U per injection at daily or twice daily intervals. If insulin has not been administered within 24 hr this form of desensitization should not be attempted since large amounts of unbound IgE-anti-insulin will be available for antigen-antibody combination.

It should also be noted that the risk of desensitization should be carefully weighed against the need for continued insulin therapy. The procedure should be performed only in patients who cannot be adequately controlled without insulin. Also it should be stressed again that adequate precautions against both anaphylactic and hypoglycemic reactions should be taken.

The mechanism of protection involved in desensitization is probably initial antibody neutralization or "occult anaphylaxis." Later increased production of IgG blocking anti-insulin antibodies may also afford protection.

Lieberman and associates¹⁴ and Mattson, Patterson, and Roberts¹⁹ have demonstrated a decrease in both serum titers of IgE insulin antibodies and skin test reactivity during desensitization. This was evident in our Patient 2 (Table V). An increasing level of IgG-anti-insulin antibodies²¹ and decreasing Prausnitz-Küstner titers²³ have also been noted during desensitization. It should be emphasized that, even though reactions continue to occur during the desensitization process, appropriate supportive treatment, e.g., antihistamines, and perseverance in insulin therapy will usually result in cessation of the reaction. It should also be stressed that, once desensitization has been accomplished, insulin must be continued regularly to avoid a recurrence of symptoms.

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