Review and Abstracts

New Forms of Insulin and Their Use in the Treatment of Diabetes

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Major attempts have been made in recent years to purify insulins in order to reduce their antigenicity.[1-3] On the assumption that antigenicity is due to the "a" and "b" components of crude insulin, attention has been focused on elimination of these large-molecular-weight contaminants. This approach has led to the production of purified insulins including "single peak" (SP) and "single component" (SC) insulins by the Eli Lilly Company[1,3] and "monocomponent" (MC) insulins by the Novo Company.[2]

SP insulin is the "c" component of crude insulin. It contains insulin plus some related peptides of similar molecular weight, such as monodesamido insulin and arginyl insulin. SC and MC insulins are prepared by further purification using anion-exchange chromatography, achieving purity greater than 99 per cent. These insulins have very low or negligible antigenicity in animals,[2] and it was hoped that similar results would be found in man, with a reduction in the immunologically mediated complications associated with insulin treatment.

Purification of insulins occasions marked production losses, with serious implications because of low worldwide insulin reserves. Furthermore, it assumes that the insulin molecule itself is nonantigenic. Extensive experience has been attained over the last five years with these new insulins; thus it is time to reappraise their antigenicity and efficacy.

ANTIGENICITY OF INSULIN

Although early studies led to optimism,[4,5] there is now little doubt that the purified insulins are antigenic.[3,6-9] Antigenicity can be demonstrated in patients previously established on conventional insulins (group I) or in patients treated only with purified insulins (group II). Our experience with MC porcine insulin in two groups of patients is summarized in table 1. In 18 patients from group I, insulin antibodies remained detectable in all and there was no significant fall in the mean level. After a follow-up period of 20.8 months, insulin antibodies were detectable in 10 of 14 patients in group II, and the mean level was 46 per cent of that in a population receiving conventional insulins. This difference was significant at the 5 per cent level. These results are in agreement with those reported for SC porcine insulin.[3] Other investigations have reported a fall in insulin antibodies in patients transferred from conventional to purified insulins.[5,9]

These results support the conclusion that porcine insulins purified by ion-exchange chromatography are less antigenic than conventional insulins in diabetics who have not received any other insulin previously. However, caution is necessary in any generalization from these results. Conflicting results are common, even from the same investigators.[8] As porcine insulin is less antigenic than bovine insulin,[10] the results obtained cannot be extrapolated directly to that of a mixture containing bovine and porcine insulins. Furthermore, when the antigenicity of various insulin preparations are compared, care must be taken to standardize the physical state of the insulin. Both the duration of action and the pH of the preparations have been reported to be important determinants of antigenicity.[11] Differences in the types and species of insulins used before the change to purified insulin may account for the discrepancies reported for group I

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patients in different series.

It is uncertain whether antigenicity should be attributed to the insulin molecule itself or to inadequate purification. Although undoubtedly these insulins have been purified to a considerable extent, impurities can still be demonstrated.[7,12] Specific antibodies against proinsulin have been reported in patients treated exclusively with MC insulins.[7,8] In contrast to previous reports,[4,13] specific antibodies directed against the "a" and "b" components can be demonstrated in both group I and group II patients during treatment with MC insulins (table 1). The presence of these impurities in antigenically significant quantities precludes the possibility that insulin antigenicity can be attributed confidently to the insulin molecule itself. A more highly purified insulin is necessary to resolve this question. While it may not be possible to eliminate these contaminants completely from any insulin preparation, the minimal requirement for purity will be that which does not cause antibody formation against the large-molecular-weight components. The lower level of antibodies against "a" and "b" components in group II patients, in comparison with diabetics receiving conventional insulins, suggests that these contaminants have been reduced significantly. The removal of "a" component is more complete in MC insulins as there was also a reduction of anti-"a" antibody level in group I patients after the change in therapy.

Determination of the cause of insulin antigenicity is complicated further by the formation of insulin dimers, desamido insulin, and other degradation products during storage of insulin.[7,14] Although the antigenicity of these products is low in animals,[2,4] this has not been established in man with certainty. Indeed, desamido insulin has been assumed by some investigators to be a major source of antigenicity.[3] As it is impossible to inject insulin as soon as it is produced, it may be crucial to develop techniques to prevent the formation of dimers and degradation products during storage.[3]

EFFICACY OF PURIFIED INSULINS

Insulin Dosage

There is no agreement as to the effect of insulin purification on insulin dosage.[3,5-9] Results in table 1 indicate that there is not a significant fall in insulin requirement after a change to purified insulins. Even in the group II patients in whom MC porcine insulins have induced a lower mean insulin antibody level, the requirement is not significantly less than that of a control population on conventional insulins. Similar results have been demonstrated for SC and SP insulins.[3,6] Although other investigators have demonstrated a fall in insulin requirement, the decline was gradual and modest.[5,9] Certainly, early fears of frequent hypoglycemia following a change to purified insulins have not materialized. This lack of a dramatic response is not surprising, as insulin antibodies are not major determinants of insulin dosage in the major-

TABLE 1

Insulin requirement and antibodies to insulin and high-molecular-weight components in patients treated with MC and conventional insulins

	Period of follow-up	Insulin antibody	"a" Component antibody	"b" Component antibody	Insulin requirement
	Months	Nanomolar	Micrograms per liter		Units/day
Group I					
Diabetics changed from conventional to MC insulin (n=18)					
(a) before change	—	0.50 ± 0.13	6.65 ± 1.02	11.55 ± 3.03	79 ± 9
(b) after change	19.2 ± 1.0	0.47 ± 0.12*	3.86 ± 0.80†	9.54 ± 2.09*	69 ± 10*
Group II					
Diabetics treated only with MC insulin (n=14)	20.8 ± 1.2	0.23 ± 0.07§	1.67 ± 0.61‡	3.80 ± 1.64†	66 ± 10*

Groups I (b) and II were compared with group I (a) on Student's *t*-test.
*Not significant.
†$p < 0.025$.
‡$p < 0.005$.
§$p < 0.05$.

ity of insulin-sensitive diabetic patients. It has not been possible to demonstrate a good correlation between insulin dosage and insulin antibodies.[15,16]

The efficacy of purified insulins in the treatment of insulin resistance has not been established.[3,7,9] Systematic investigation of a large number of patients is difficult, as insulin resistance is not a common complication of diabetes. Sporadic case reports have appeared claiming dramatic resolution of insulin resistance following the introduction of purified insulin, but evidence for a direct effect of the purified insulin is not convincing.[17,18] Many patients were receiving highly antigenic bovine insulin during the development of insulin resistance. In some cases insulin requirement had begun to decline before commencing purified insulin of porcine origin. In others, clinical improvement could have been attributed to simultaneous corticosteroid therapy. These considerations, together with the spontaneously variable course of insulin resistance, make it difficult to assess the efficacy of purified insulins in reducing insulin resistance. We have treated five patients wtih a mean insulin requirement of 266 ± 70 U. daily and insulin antibodies of 1.70 ± 0.47 μM for 5.0 ± 2.3 months with MC insulin, following which the insulin requirement and insulin antibody level were 312 ± 120 U. and 1.51 ± 0.48 μM, respectively. Similar disappointing results have been reported for SP and SC insulins.[3,6] The periods of treatment in these studies were relatively short and do not exclude the possibility that more prolonged therapy would have resulted in a favorable response. In patients with a high initial level of insulin antibodies, corticosteroid treatment has proved to be effective in suppressing the levels of insulin antibodies, with a concomitant fall in insulin requirement.

The differing results obtained wtih purified insulins in insulin resistance cannot be resolved at the moment. It is possible that purified porcine insulins are more successful in patients who have been treated with bovine insulin previously. Furthermore, patient selection may be extremely important. It is now certain that insulin resistance is not a single disease entity. In insulin resistance due to anti-insulin receptor antibodies[19] or to abnormally fast degradation of insulin[20] even a nonimmunogenic insulin cannot be expected to be effective.

Perhaps purified insulins will be effective in reducing the incidence and severity of insulin resistance. However, insulin resistance is not a common complication of diabetes, and it is rare when porcine insulin alone has been used in therapy. Deckert[21] was not able to find a single case of insulin resistance in 3,000 diabetics treated only with porcine insulin. The role of purified insulins in the prevention of insulin resistance will need to be studied separately for bovine and porcine insulin over a prolonged period.

Stability of Diabetes

The effect of any treatment regime on the stability of diabetes is difficult to determine because of the problem of assessing stability objectively. After purified insulins became available there were many reports of improvement in diabetes control.[5] On the other hand, there were reports of increased risks of hypoglycemia.[22] When quality of control was assessed objectively by calculation of the M factor[7] or measurement of the Regulation Index,[23] purified insulins did not improve the quality of control. In recent years, Dixon et al.[24] have proposed that insulin antibodies exert a stabilizing effect on the control of diabetes by acting as a buffer to prevent major fluctuations in free circulating insulin levels. If this can be substantiated, a nonimmunogenic insulin would result in a population of diabetics with highly unstable diabetes. In other studies,[25-28] neither the levels nor the binding characteristics of insulin antibodies could be correlated with the degree of diabetic control. While the latter studies do not increase the probability that purified insulins will be beneficial in the treatment of labile diabetes, they certainly do not add to the fear that their use will increase the incidence of instability.

Insulin Allergy

Evidence has accumulated that all types of purified insulin reduce the incidence of local pain and swelling at the site of insulin injection.[3,6,7] Unexpectedly, lipoatrophy at the site of injection disappears gradually, especially if purified insulins are injected into the atrophic areas.[3,29] In our experience, lipohypertrophy does not respond to this treatment. It has been inferred that local symptoms are mediated by immunologic mechanisms;[29] however, supporting evidence is lacking. Improvement occurs without a decline in circulating IgG insulin antibodies. We have studied 11 patients with severe local reactions and found that the IgG and IgE antibodies against insulin and the large-molecular-weight contaminants were not increased above that expected in insulin-dependent diabetics. These studies do not exclude the possibility that local manifestations can be mediated by abnormal tissue antibodies, nor do they detract from the value of purified insulins in these conditions. However, the observed improvement in local phenomena during treatment with purified insulins

cannot be ascribed to immunologic mechanisms until further evidence is available. The purification process could have removed substances with a direct action on the skin. Although the efficacy of purified insulins in the treatment of cutaneous reactions is well established, some diabetics do not respond.

In systemic insulin allergy, the response to purified insulins is more variable. Systemic allergy has resolved after a change to purified insulin. Other diabetics have developed systemic allergy while on purified insulin and then responded to conventional insulin. Using a solid-phase technique, we have demonstrated IgE antibodies against insulin or "b" component in only one of five patients with systemic allergy during insulin therapy. Using a similar technique, Mattson et al.[30] have identified IgE insulin antibodies in eight of 12 diabetic subjects with systemic insulin allergy. It is likely that the responsible allergen is not always insulin itself; thus, purified insulins cannot be expected to be effective in all patients.

Diabetic Complications

Experiments on rabbits have shown that injection of "a" and "b" components, but not purified insulin, leads to deposition of electron-dense material in renal glomeruli.[31] However, accumulation of electron-dense material can be induced by the preservative in commercial insulin preparations or even appear as part of the normal aging process in rabbits. Extrapolation to man must be treated with caution.

Complications of diabetes occur in some patients never treated with insulin. Immunologic factors cannot be implicated in these circumstances. Although definitive conclusions cannot be reached for another 10 to 15 years, it appears unlikely at this stage that purified insulins will prevent diabetic complications.

Natural History of Diabetes

Although Anderson[23] has suggested that treatment of juvenile diabetics with purified insulins may prolong a transient remission period, there is no conclusive evidence that these insulins modify the natural history of diabetes in man. In vitro, insulin antibodies do not affect insulin and glucagon secretion from human fetal islets.[32,33]

CONCLUSION

The purified insulins are the treatment of choice for severe or disfiguring local reactions at the site of insulin injection. They should be used in the treatment of insulin resistance mediated by elevated levels of insulin antibodies. Although a favorable response cannot be predicted with certainty, in some patients insulin requirement will be reduced, particularly if corticosteroids are given simultaneously. Purified insulins are indicated in the treatment of systemic insulin allergy. However, conventional insulins should be used if the allergy develops during treatment with a purified insulin. In most diabetic patients purified insulins do not alter insulin requirement or the quality of diabetic control; thus they cannot be justified routinely for all insulin-dependent diabetics. Purified insulins should be used for diabetics who have an increased risk of resistance, including those in whom interrupted insulin therapy has been used or in the presence of liver diseases, such as hemochromatosis. Purified insulins do not have any significant effect on the natural history of diabetes or its complications. It appears that insulin antibodies are deleterious only in a small number of patients with antibody-induced insulin resistance.

Even if a completely nonimmunogenic insulin can be produced in the future, it is unlikely that dramatic therapeutic benefits will result. Any potential benefit must be balanced against production losses of insulin during purification. In the preparation of SC insulin, only 40 per cent of the insulin is recovered.[3] This loss may not be justifiable with an increasing diabetic population requiring treatment, in the presence of limited insulin reserves throughout the world. As it is not possible to treat all diabetics with purified porcine insulin, a mixture of porcine and bovine insulins will be necessary. SC bovine insulin has already been shown to be highly antigenic.[3] Thus, a mixture of purified porcine and bovine insulin may not be superior to conventional insulins, a further point against large-scale purification. In addition, the antigenicity of desamido insulin and the insulin dimer is unresolved. If these insulin products are antigenic, then purification alone will not be adequate to produce a nonimmunogenic insulin.

Other new insulins are appearing on the scene. Des-PheB1 insulin is a structurally altered insulin that binds less avidly to guinea-pig anti-insulin antibody.[34] Similar insulin derivatives may overcome some of the immunlogically mediated problems without eliminating antigenicity completely.

Finally, bacterially synthesized human insulin is a possibility in 1977—this may be the solution to insulin supply for the future.

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ABSTRACTS

(All are verbatim summaries)

Tantillo, J.J.; Karam, J.H.; Burrill, K.C.; Jones, M.A.; Grodsky, G.M.; and Forsham, P.H. (Metabolic Res. Unit and Dept. of Med., Univ. of Cal., San Francisco): IMMUNOGENICITY OF "SINGLE PEAK" BEEF-PORK INSULIN IN DIABETIC SUBJECTS. Diabetes *23*:276, 1974.

Highly purified insulins of the "single-component" or "monocomponent" varieties have been previously reported to be non-immunogenic. Since mass production of insulins with a high degree of purity is not convenient, a "single-peak" insulin with large molecular weight substances removed, has been developed in U-100 concentration. To evaluate its immunogenicity, three groups of diabetic subjects were studied. Seven patients previously untreated with insulin were given single-peak beef-pork insulin

for forty-five to 435 days; in undiluted sera, insulin-I^{-131} binding reached a mean of 18 per cent (range, 2 to 46 per cent). In comparison, fifteen diabetics treated with standard USP beef-pork insulin for ninety days or more showed a mean insulin-I^{-131} binding of 15 per cent (range, 3.5 to 38 per cent). Six patients who had received USP insulin were treated with the single-peak preparation. Five of these had a mean insulin-I^{-131} binding of 16 per cent (range, 2 to 38 per cent) before single-peak therapy and a mean binding of 27 per cent (range, 6 to 44 per cent) after treatment with single-peak insulin for 105 to 230 days. The sixth patient had severe chronic insulin resistance and required up to 400 U. per day of USP insulin; treatment with single-peak insulin for five weeks produced no fall in antibody titer, and insulin requirements remained high: an initial response to only 50 U. per day of fish (bonito) insulin demonstrated that resistance was due to immunogenicity. U-100 single-peak beef-pork insulin reduces lipoatrophy but does not appear to offer obvious immunologic advantages over standard USP insulin.

Yue, D.K.; and Turtle, J.R. (Dept. of Med., Univ. of Sydney, and the Royal Prince Alfred Hosp., Sydney, N.S.W., Australia): ANTIGENICITY OF "MONOCOMPONENT" PORK INSULIN IN DIABETIC SUBJECTS. Diabetes *24*:625, 1975.

"Single-peak," "single-component," and "monocomponent" insulins have been produced in an attempt to eliminate insulin antigenicity. Recently "single-peak insulin" has been shown to be antigenic. From animal experiments and preliminary human studies it has been claimed that monocomponent (MC) insulin is nonantigenic or only negligibly so. In this study the antigenicity of MC insulin was determined in two groups of diabetic patients. In group 1, seven patients treated with insulin for the first time were given MC insulin for seven to fifteen months. Four of the seven patients developed significant IgG insulin antibodies after four to ten months. In one patient the IgG insulin antibody concentration was high (8.51 mU./ml.). In two patients IgG proinsulin-specific antibodies were detected. In group 2, fourteen patients with unstable diabetes, insulin allergy, or resistance were changed from conventional to MC insulin. Treatment with MC insulin did not decrease insulin requirement or improve diabetic control when assayed by the M factor. After seven to eleven months of therapy there was no significant fall in insulin antibodies except in two patients in whom corticosteroids had been administered simultaneously. These results differ significantly from those previously reported and could be interpreted as suggesting that insulin itself is antigenic. When the purity of the MC insulin was determined, significant contaminants coulc be demonstrated in all of ten separate batches of MC insulin. Gel chromatography, polyacrylamide gel electrophoresis, and proinsulin radioimmunoassay were used to identify the presence of nonconvertible insulin dimer, proinsulin and monodesamido insulin in antigenically significant concentrations.

The generation of IgG insulin antibodies in MC-insulin-treated patients cannot be interpreted as a true indication that insulin itself is antigenic. The problem of insulin antigenicity has not been resolved and will not be until a highly purified insulin is available. Unfortunately, the MC insulins do not meet these requirements.

Andreani, D.; Iavicoli, M.; Tamburrans, G.; and Menzingir, G. (Cattedra di Medicina Constituzionale ed Endocrinologia del Universita degli studi di Roma, Italy): COMPARATIVE TRIALS WITH MONOCOMPONENT (MC) AND MONOSPECIES (MS) PORK INSULINS IN THE TREATMENT OF DIABETES MELLITUS. INFLUENCE ON ANTIBODY LEVELS, ON INSULIN REQUIREMENT AND SOME COMPLICATIONS. Horm. Metab. Res. 6:447, 1974.

Levels of anti-insulin antibodies (AAI) in serum, and insulin requirement have been studied for two years in six groups of diabetics treated with different kinds of insulin.

The patients in the first three groups had never been treated with insulin; group 1 was treated with Monocomponent (MC) insulins, group 2 with Monospecies pork (MS) insulins and group 3 with commercial insulins.

In group 1 there was a negligible and transitory rise, in group 2 there was a moderate rise and in group 3 there was a marked increase of AAI.

The patients in groups 4, 5, 6 had been treated for at least one year with commercial insulins; group 4 was switched over to MC insulins, group 5 to MS insulins; group 6 was studied for control purposes.

At the beginning of the study AAI levels were comparable in these latter groups: thereafter in group 4 there was a striking reduction of AAI, in group 5 there was a relevant, but less marked reduction. In group 4 there was also a significant reduction of insulin requirement.

A marked improvement in lipodystrophy and allergic phenomena was observed in some patients in group 4.

Two further patients with a severe resistance to insulin, a very high binding capacity for MS and MC insulin, and a moderate or very high binding capacity for human insulin did not improve with MC insulins.

Kawazu, S.; Kanazawa, Y.; Kajinuma, H.; Miki, E.; Kuzuya, T.; and Kosaka, K. (Third Dept. of Intern. Med., Faculty of Med., Univ. of Tokyo, Hango, Tokyo, and Dept. of Med., Jichi Med. Sch., Minami-kawachimachi, Tochigi-ken, Japan): DEMONSTRATION OF ANTI-"A-COMPONENT" ANTIBODY—A POSSIBLE MEANS TO DIFFERENTIATE PATIENTS WITH AUTO-ANTIBODIES TO ENDOGENOUS INSULIN FROM INSULIN-TREATED PATIENTS. Diabetologia *11*:169, 1975.

The presence of anti-"a-component" antibody was examined in sera of 4 groups of patients with or without anti-insulin antibody, using ^{125}I-a-component and the polyethylene glycol precipitation method. ^{125}I-a-component cross-reacted with insulin antibody. This cross-reactivity was abolished after preincubation of these sera with monocomponent insulin. The specific anti-"a-component" antibody could be estimated in this procedure. After preincubation with monocomponent insulin, significant binding of ^{125}I-a-component was demonstrated in sera of most patients treated with ordinary commercial insulin, but not in sera of 2 hypoglycemic patients suspected of an insulin autoimmune syndrome. Some cases treated with commercial insulin for less than one year and all cases treated with monocomponent insulin for 7-10 months did not have significant anti-"a-component" antibody. The test for the presence of anti-"a-component" antibody is not definitive but if positive it differentiates "auto-antibodies" from the antibodies produced by injections of commercial insulin.

Logie, A.W.; and Stowers, J.M. (Diabetic Clinic, Aberdeen Royal

Infirmary, Scotland): HAZARDS OF MONOCOMPONENT INSULINS. Br. Med. J. *1*:879-80, 1976.

Conventional insulins are being replaced by the new monocomponent insulins (Actrapid MC, Semitard, and Monotard), which are claimed to be more beneficial. The following report, however, shows that dosage requirements in individual patients may be much smaller than with standard insulins, and thus more warning of the changeover should be given.

Flier, Jeffrey S.; Kahn, C. Ronald; Roth, Jesse; and Bar, Robert S. (Diabetes Branch, NIAMDD, NIH, Bethesda, Md.): ANTIBODIES THAT IMPAIR INSULIN RECEPTOR BINDING IN AN UNUSUAL DIABETIC SYNDROME WITH SEVERE INSULIN RESISTANCE. Science *190*:63, 1975.

Six patients with a unique form of diabetes associated with extreme insulin resistance have markedly reduced insulin binding to specific receptors on their circulating monocytes. When normal insulin receptors were exposed to serum or immunoglobulin fractions from three of these patients in vitro the specific binding defect was reproduced.

Andersen, O. Ortved (Steno Memorial Hosp., Gentofte, Denmark): THE IMMUNOGENIC PROPERTIES OF HIGHLY PURIFIED INSULIN PREPARATIONS: THE CLINICAL IMPORTANCE OF INSULIN-BINDING ANTIBODIES. Acta Endocrinol. (Copenhagen) *78*:723, 1975.

Twenty-four diabetic patients were treated with porcine protamine-insulin (NPH-insulin) containing 7-13 mmol proinsulin per mol insulin and 27 diabetic patients were treated with porcine protamine-insulin (HP-insulin) containing 0.36 mmol proinsulin per mol insulin. 75% of the patients treated with NPH-insulin and 15% of the patients treated with HP-insulin formed detectable insulin-binding antibodies. The difference in the antibody titre in the two groups was significant. As a group, patients treated with HP-insulin did not have a significant rise in the plasma insulin-binding capacity when compared to pretreatment values. When comparing patients with antibodies and patients without detectable anti-bodies no difference in the degree of regulation could be demonstrated between the two groups. Young patients with antibodies had a higher insulin requirement per kg per day than patients without detectable antibodies.

Among patients in remission those without detectable antibodies had a longer remission period than those with antibodies. Apart from the difference in antibody formation and hence a different distribution in the groups compared, the patients treated with NPH-insulin and HP-insulin did not differ with regard to the degree of regulation, the insulin requirement or the duration of the remission period.

Dixon, K.; Exon, P.D.; and Malins, J.M. (Dept. of Clin. Chem., and The Diabetic Clinic, The General Hosp., Birmingham, England): INSULIN ANTIBODIES AND THE CONTROL OF DIABETES. Q. J. Med. *44*:543, 1975.

Seventy-two insulin-treated diabetic patients were classified on the basis of a clinical evaluation of their control of diabetes. There were 39 stable patients, 23 unstable patients and 10 patients of intermediate degree of control. Four insulin resistant patients were also studied. Serum insulin antibodies were measured in each patient and the concept of insulin buffering by its antibody was developed.

Must unstable patients had low concentrations of insulin antibody. Twenty-four of the 39 stable patients had a significant concentration of insulin antibody and 15 patients had low levels of antibody. The insulin resistant patients had high levels of antibody. All unstable patients had low antibody buffering and all insulin resistant patients had high antibody buffering. Although many stable patients had buffering antibodies others lacking antibody required a low insulin dose and their stability of diabetic control was attributed to residual pancreatic function.

Teuscher, A. (Medizinische Universitätsklinik, Inselspital, Bern, Switzerland): TREATMENT OF INSULIN LIPOATROPHY WITH MONOCOMPONENT INSULIN. Diabetologia *10*:211, 1974.

A female diabetic with severe insulin-induced hpoatrophy was successfully treated with a monocomponent (MC) Lente preparation. This patient was studied for over 6 years and, during periods of treatment with various insulins of different purity, a variety of reactions was observed in the adipose tissue. Evidence is presented that lipoatrophy may be caused by insulin impurities. Lipoatrophy occurring after treatment with recrystallized, mixed species Lente insulin was substantially reduced after treatment with 10 times recrystallized porcine Lente, but recurred on 4 times recrystallized beef Lente, also in areas where beef Lente was not injected. Beef insulin impurities seem more prone to produce lipoatrophy than pork insulin impurities. It is suggested that MC-insulin is the treatment of choice for this condition.

Mattson, James R.; Patterson, Roy; and Roberts, Mary (Sect. of Allergy-Immunol. Dept. of Med., Northwestern Univ. McGaw Med. Centr., Chicago, Ill.): INSULIN THERAPY IN PATIENTS WITH SYSTEMIC INSULIN ALLERGY. Arch. Intern. Med. *135*:818, 1975.

Insulin was administered to 12 of 15 patients with systemic insulin hypersensitivity. Eight patients with a history of a systemic reaction to insulin but not receiving current therapy were skin-tested and desensitized. Four receiving insulin had temporary dose reduction followed by slow increase to therapeutic levels. No noticeable reactions recurred in any of them.

Levels of IgE antibodies against insulin were determined in 12. Substantial elevations were found in eight. These levels declined rapidly in three desensitized patients who were studied in contrast to the slower decline in three patients who were not desensitized.

Insulin can be cautiously administered if necessary to patients with prior systemic insulin hypersensitivity. Evidence that IgE antibodies are against the insulin molecule in at least some patients indicates the need for a desensitization regimen.
