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of patients with rheumatoid arthritis. Gold therapy, however, is complicated and is usually reserved for those patients who have not responded to conservative measures and chloroquine. Currently the aqueous preparation of sodium aurothiomalate is given intramuscularly at weekly intervals. The first two doses are usually 10 mg. and 25 mg. and the course is continued with 50-mg. injections, to a total of one gram. If improvement has occurred, the gold may be continued at increasing intervals up to monthly injections. The well-known toxic effects of gold, bone marrow depression, exfoliative dermatitis and nephropathy, necessitate regular leukocyte counts, platelet estimations, urinalysis and questioning of the patient concerning rashes.

Combinations of Salicylates, Tranquillizers, Vitamins, Steroids and Phenylbutazone

Poor medicine.

Propoxyphene Hydrochloride (Darvon)

With or without other drugs probably has little usefulness as an antirheumatic agent.

CASE REPORTS

Allergy to Insulin

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THIS communication concerns a 50-year-old man with diabetes mellitus who became "allergic" to all available forms of insulin. This problem is of considerable importance because an increase in the incidence of insulin allergy may occur in the future in view of the fact that more diabetics may develop sensitivity to insulin while changing their medication from insulin to oral hypoglycemic agents, and back to insulin again. The purpose of this presentation is to discuss the treatment of insulin allergy.

H.C., a 50-year-old man with mature-onset diabetes, had previously been under my care for diabetes mellitus. I saw him on August 13, 1962, when his treatment was changed from chlorpropamide to insulin.

His diabetic history began in July 1955, when he was 43 years of age; at that time sugar was found in his urine on an insurance examination. Treatment through dietary restriction was not followed faithfully enough to lower the blood sugar, and he was admitted to hospital for further therapy on October 2, 1955.

There was no family history of diabetes or of allergy. He had had an appendectomy, and in 1943 a duodenal ulcer. He had passed a ureteral calculus in 1944 and another in 1954.

A significant feature of his personal history was an allergy to alcohol; drinking of any type of alcoholic beverage produced a swelling about the lips and eyes. Many years before, he had one episode of a generalized dermatitis which apparently developed from a plastic wrist-watch strap. He also had headaches after the application of after-shave lotions; these had not recurred when the lotions were discontinued. There was no other history of specific respiratory or food allergy.

Immediately before his first admission to hospital in July 1955, a glucose tolerance test gave the following results: fasting 154, 1 hr. 276, 2 hr. 297, 2½ hr. 345, and 3 hr. 262 mg. %.

First Hospital Admission

In hospital he was treated with diet and NPH insulin. His weight was reduced from 180 to 174 lb. Prior to leaving the hospital the fasting blood sugar was 107 mg. %, and 2 hr. p.c. lunch was 134 mg. % (these values were obtained by the Folin-Wu method; all other blood sugars reported in this communication were obtained by the Sömögyi method).

His regimen on leaving the hospital was a diet of 1825 calories, normal fat (American Diabetic Association No. 7) and NPH insulin 20 units each morning. At this time it was noted that the site of each injection showed a painful red area of induration with a mild itching sensation. This reaction was not due to contamination of the syringe, since the patient rinsed his syringe with water after using, and sterilized it by boiling. On November 9, 1955, because of the local reaction produced, NPH insulin was changed to globin insulin 10 units each morning; a decrease in the local subcutaneous reaction followed this change. On May 22, 1956, the dose of insulin had been reduced to five units of globin daily, and the patient felt that he could do without insulin altogether, relying on diet alone to control the diabetes.

Following this change of program, the patient's weight and blood sugar began a slow but steady increase, chiefly the result of inadequate dietary control. On July 4, 1957, he was given tolbutamide 0.5 g. four times a day. He continued on this drug until September 24, 1959, when a change was made to chlorpropamide 500 mg. daily. On May 4, 1960, this was reduced to chlorpropamide 250 mg. daily, but later increased again to 500 mg. daily. On August 13, 1962, he was reexamined. At this time he had been taking chlorpropamide 500 mg. daily. His weight had increased to 190 lb., and his fasting blood sugar was 143 mg. %. His blood pressure, previously normal, was 160/100 mm. Hg. Although a proper diet would have been adequate to control his diabetes, the diet had not been followed, and protamine zinc insulin was substituted for the oral medication.

On August 23, 1962, 10 days later, he developed a severe allergic reaction with giant hives, itching of the skin and marked swelling about the lips and eyes. He had fainted in the bathroom on arising that morning, and he was again admitted to hospital.

Second Hospital Admission

On examination it was noted that his voice was hoarse. In addition to the skin reaction, there was some reddening of the mucosa of the mouth and pharynx. The optic fundi showed Grade 1 arteriolosclerosis. His blood pressure was 165/105 mm. Hg, the rhythm was regular and the rate was 90 per minute. There were no murmurs. His physical examination was otherwise within normal limits. The temperature was elevated to 100° daily until the rash subsided.

The laboratory findings were as follows: hemoglobin 14.6 g., leukocyte count 9600 per c.mm. with a differential of polymorphonuclear leukocytes 76, stab forms 4, lypmhocytes 19 and monocytes 1. The sedimentation rate was 18 mm. per hour (Westergren). The fasting blood sugar on August 25 was 178 mg. %. The urine was negative for sugar, with a trace of acetone; the microscopic examination was negative.

Insulin therapy was discontinued and the patient was given one injection of 5 min. adrenaline, methapyrilene hydrochloride (Histadyl) 1 c.c. intramuscularly twice daily, trimeprazine (Panectyl) 5 mg. four times daily, and a long-acting form of chlorpheniramine (Chlortripolon Repetabs) one tablet every eight hours.

Two days after admission, when most of the allergic signs had disappeared and while he was still receiving antihistamines, 10 units of lente insulin were administered to the patient. This suspension of zinc insulin crystals in acetate-buffer solution is considered less likely to provoke allergic reactions than the modified insulins (protamine, NPH or globin). In a few hours the giant hives and edema of the face and eyelids had returned. Once more withdrawal of insulin, with administration of adrenaline and antihistamines, was effective in controlling the reaction. The use of adrenocorticotrophic hormone (ACTH) was considered, but rejected because the anti-insulin effect of ACTH might aggravate the diabetes.

The administration of insulin was not absolutely necessary in the management of this patient; his diabetes was stabilized on an 825-calorie diet and chlorpropamide 500 mg. daily. The fasting blood sugar on August 27, 1962 was 92 mg. % and 2 hours after lunch it was 144 mg. %. The patient was able to leave the hospital on this program.

In an attempt to find a type of insulin that could be used, the patient was skin-tested with all the insulin products locally available and a number of special varieties provided by the Connaught Medical Research Laboratories, Toronto. In Canada, insulin manufactured by the Connaught Laboratories is made from mixed beef and pork pancreas. Insulin from either pork or beef pancreas is also available on request. In skin-testing this patient the skin was cleansed with ether, 1/10 c.c. of each type of insulin was injected intradermally and the skin reactions were noted at frequent intervals. The following types of insulin were used: Toronto insulin, P-Z, NPH, globin, lente, P-Z (pork), P-Z (beef), Toronto (pork) and sulfated insulin (sulfated insulin is an experimental product and the manufacturer, Connaught Laboratories, has not yet reported on its use).

An injection of sterile water intradermally produced no reaction. The other test sites showed a typically positive allergic reaction to all forms of insulin injected, with a wheal measuring three-quarters of an inch to one inch in diameter, some pseudopods, and a surrounding red flare. These responses appeared in a few minutes.

From these skin tests it was concluded that the patient's allergy was to the insulin molecule itself, or possibly to a protein closely associated with the insulin molecule. Insulin would appear to have acted as an antigen in the production of the allergic state.

Progress Note

On February 4, 1963, five and one-half months later, the patient was again examined. He had been taking chlorpropamide 500 mg. and, unfortunately, an uncontrolled caloric intake. His weight had risen to 189 lb. His blood sugars were: fasting, 139 mg. % and 2 hours p.c. lunch, 173 mg. %. The patient was reluctant to embark on any program which involved the use of insulin, and a more rigorous attention to diet was promised.

In an attempt to isolate the allergen, the patient was subjected to further skin tests on February 5, 1963.

Since alcohol is used in the extraction of insulin from pancreas, it was considered remotely possible that an antigen may have been carried to the insulin molecule by alcohol. Intradermal skin tests were performed with the various grains, etc. used in making alcoholic beverages. The tests were all negative.

To rule out the possible presence of antigens in the diluents used in insulin vials, skin tests were done by the same method. Diluents used in the packaging of Toronto, NPH and lente insulins were found to produce no reaction on skin testing. There were some positive reactions to grain and meat products. Table I lists the skin tests which were carried out and the reaction obtained.

TREATMENT OF INSULIN ALLERGY

Allergy to insulin may be abated in several different ways: (1) by spontaneous (auto-) desensi-

TABLE I.—RESULTS OF SKIN TESTS

Solution	*Reaction*
Water	Negative
Toronto insulin	4 plus
P-Z insulin	4 plus
NPH insulin	4 plus
Globin insulin	4 plus
Lente insulin	4 plus
P-Z (beef) insulin	4 plus
P-Z (pork) insulin	4 plus
Toronto (pork) insulin	4 plus
Sulfated (pork) insulin	4 plus
Diluent (Toronto)	Negative
Diluent (NPH)	Negative
Diluent (lente)	Negative
Wheat	3 plus
Rye	2 plus
Corn	2 plus
Barley	3 plus
Oats	3 plus
Rice	3 plus
Orris root	3 plus
Rice powder	2 plus
Hops	3 plus
Malt	2 plus
Beef	3 plus
Lamb	3 plus
Pork	3 plus

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tization to insulin, (2) by avoiding its use through reduction of dietary intake, with or without oral hypoglycemic agents, (3) by change of type of insulin on the basis of skin-testing, (4) by a desensitization program with repeated small doses of insulin and (5) by the use of ACTH or cortisone concurrently.

Spontaneous desensitization to local allergic reactions is frequent in diabetics using insulin, and often no additional treatment is needed. Oral antihistamines may help in reducing the severity of the local reaction.

In non-ketogenic diabetes, reduction of diet, with or without the addition of oral hypoglycemic agents, may be sufficient to control the diabetes.

Where dietary treatment is not sufficient, substitution of a different type of insulin may allow the allergen to be avoided. Where the patient is allergic to protamine, lente or globin insulin can be tried. Similarly, insulin made from beef or pork pancreas can be used in patients sensitive to the protein of one of these animals.

Where these methods fail and the need for insulin is urgent, a desensitization program, as in allergy to horse serum, can be used.

In 1938, before modern antihistaminics were available, Corcoran[2] reported desensitization in a diabetic patient whose disease was complicated by infection and allergy to insulin. Desensitization was accomplished in one day, starting with 0.2 unit of insulin intradermally, increasing the dose every 20 minutes, and later changing to larger subcutaneous and intravenous doses of insulin. Thus, although desensitization of these individuals is feasible, as in any other allergic type of reaction, there is no standard method.

In 1958 Poliakoff[3] used ACTH and antihistamines in a similar situation. His patient had been treated with insulin but had discontinued it for several months because of local hives. A generalized urticaria began a few days after insulin was administered again on the advice of his physician. This patient was seriously ill with diabetic ketosis and required large doses of insulin. In the treatment of the allergy, intravenous diphenhydramine (Benadryl) in a 100-mg. dose and ACTH in a 20-unit dose were administered whenever the dermatitis showed signs of recurring. The anti-insulin effect of ACTH was accepted as a calculated risk and was allowed for by increasing the insulin dosage; a total of 1700 units was administered in the first two days. Spontaneous desensitization occurred, and the patient's diabetes was subsequently controlled by crystalline beef insulin and dietary restriction.

This type of management would appear to be the treatment of choice of a severe diabetic who is allergic to insulin, perhaps combined with a multiple-dose desensitization. Corticotrophin zinc is preferable to other forms of ACTH because it is less liable to produce additional allergic reactions due to its own protein.

DISCUSSION

The patient described in this report appears to be a diabetic with an allergic diathesis who developed allergy to all forms of insulin. It would appear that the allergy was to the insulin molecule itself, or possibly to a protein closely associated with the insulin molecule. The animal source of the insulin may be of some importance. Fortunately, his disease could be treated at this time without using insulin. However, its administration may be necessary at some time in the future.

Insulin allergy is commonly seen in diabetics newly started on insulin. This is usually a local response and disappears in a few weeks. Repeated daily injections of insulin desensitize the patient to this foreign protein. Less commonly, generalized allergic reactions occur, with urticaria, edema of the face, and rarely other symptoms, such as respiratory difficulty, thrombocytopenic purpura, or anaphylactic shock. Local reactions to insulin injection may sometimes be due to the alcohol used in syringe sterilization; this can be eliminated by boiling the syringe instead.

Allergy to insulin itself may be due to: (1) sensitivity to the insulin molecule itself, as is suspected in the patient reported herein; (2) sensitivity to one or more of the proteins of the animal from which the insulin is extracted (beef or pork, etc.); (3) impurities not removed in the preparation of the insulin; or (4) added substances of protein nature such as protamine or globin. Modified insulins in the last group are the most likely to give allergic reactions.

Joslin *et al.*[1] stated that the majority of diabetics with generalized allergic reactions have been taking insulin previously, have discontinued it for a variable length of time, and then have started using it again. The allergic signs followed thereupon, after a latent period of from five to 15 days. My patient followed this pattern.

CONCLUSION

A man with diabetes who was allergic to all available forms of insulin has been described. In the future, the incidence of allergy to insulin may increase because of the frequent intermittent use of insulin and oral hypoglycemic agents.

In severe insulin allergy a multiple-dose desensitization program, in which the allergy is controlled by adrenaline, ACTH and antihistamines, is recommended.

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