

# An unusual form of local reaction to hyposensitization injections

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*Two women, aged 12 and 51, developed an unusual local, chronic, persistent, granulomatous, and suppurative reaction after repeated subcutaneous injections for allergic hyposensitization with polyvalent pollen, food, dust, and bacterial extracts. Histologically, the reactions were consistent with "tuberculoderm" or "foreign body reaction." The onset of local symptoms was seven and two months after injections, respectively. The reactions were confined to sites of subcutaneous inoculation of the antigens and occurred almost simultaneously. There were no constitutional symptoms. Both patients experienced improvement of their allergic symptoms during hyposensitization. No bacterial or fungal microorganism could be found in the antigen solutions or in the cutaneous lesions. Special attention was given to search for acid-fast organisms. Search for particulate matter was also negative. A review of the literature failed to disclose reports of similar reactions to hyposensitization with nonrepository, aqueous antigens. The time of appearance of the lesions and their simultaneous development, as well as the failure to recover viable organisms, suggest that they probably were due to an allergic reaction to an unidentified substance, and the skin lesions may be best described as "allergic granulomas."*

**T**his report describes two instances of the development of unexpected, unpleasant, and disabling reactions following a commonly used procedure. During the course of hyposensitization for allergic bronchial asthma, sinusitis, and uveitis, two women developed chronic suppurative and scarring reactions at the sites of subcutaneous inoculation with multiple antigens:

## Case 1

A 12-year-old white girl, born in Venezuela, was first seen by her physician in December, 1961, for chronic disabling bronchial asthma of "many years' duration." There was no personal or family history of tuberculosis. On Feb. 24, 1962, hyposensitization was begun on a twice-weekly basis with gradually increasing doses of antigens described below. On April 19,

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1962, a tonsillectomy was performed without incident. In May, 1962, the frequency of injections was reduced to weekly or biweekly, since symptoms of asthma were abating. By July, 1962, she was asymptomatic. The last injections were given on Sept. 15, 1962. A total of 26 injections of each of the three types of antigens described below were given over the seven months, the maximum dose being 0.8 c.c. at any one site; the final dose of pollen antigens was 0.6 c.c. of vial "C." On Sept. 22, 1962, a local inflammatory reaction was seen over one deltoid region (site of the pollen antigen injections). Within days, surgical drainage was required; intramuscular penicillin was given. No cultures were made at that time. Within two weeks, all areas of prior subcutaneous injections with all three antigen preparations became inflamed (both deltoids and lateral thighs). Ulcerations and sinus tract formation down to muscle and fascia developed. The edges were erythematous and irregularly undermined. There were no constitutional symptoms.

The patient was referred to our Skin Clinic in November, 1962. The following skin tests (intradermal) were made and were all negative: old tuberculin 1:1,000,000 to 1:1,000; histoplasmin; blastomycin; coccidioidin; phenol (the preservative in the antigen solutions). A chest x-ray, serum protein electrophoresis, and urinalysis were normal. A complete blood count was normal except for 11 per cent eosinophils. Direct smears and guinea pig inoculation for acid-fast bacilli with material from the ulcerated areas were negative. Polariscope studies of the hyposensitizing materials for foreign matter were negative.

Skin biopsies revealed focal areas of nonencapsulated, noncaseating granulomatous inflammatory reactions; there were no vascular changes. The histopathologic impression was foreign body reaction or tuberculoderm.

The patient responded very slowly to a therapeutic regimen of warm compresses, topical Neosporin ointment, and erythromycin systemically. When she was last seen on March 5, 1963, five months after the onset of the reaction, there was nearly complete closure of all ulcerations.

## Case 2

A 51-year-old white woman had a history of "many allergies" and sinusitis for "many years" and recent onset of uveitis. Her family physician initiated hyposensitization therapy, based on the results of intradermal testing with numerous food and environmental antigens, on July 16, 1962, with two to three subcutaneous injections per week of a triple set of antigens described below. This procedure was continued until Sept. 17, 1962, at which time her condition, including the uveitis, was considerably improved. (She had received 10 c.c. of both the autogenous vaccine and Allergenex extract and was on vial "D"—the most concentrated—of the pollens. A maximum of 0.7 c.c. was given of each extract at any time.) At that time, a painful inflammatory reaction developed over the deltoid area which had received the autogenous vaccine. Within two weeks, all the other sites of injections with the three antigen preparations on the arms and thighs became painful, inflamed, and ulcerated. There was a mixture of saucer-shaped, grouped ulcerations, abscesses, and sinus tract formation, with some undermining. Areas undergoing healing left violaceous, atrophic, depressed scars (Figs. 1 and 2).

The patient was referred to our Skin Clinic on Sept. 26, 1963, for treatment of persistent drainage and sinus tract and abscess of one year's duration, which had been unresponsive to local antibacterial care. Bacteriologic and mycologic studies were negative. Tests for acid-fast bacilli, including direct smear, guinea pig inoculation, and culture on Lowenstein-Jensen medium were negative. Intradermal skin tests with old tuberculin 1:100,000 and 1:10,000, trichophyton 1:30, and oidiomycin were negative.

Two biopsies from separate ulcerated areas revealed a mass of epithelioid and scattered histiocytic and giant cells arranged in an ill-defined and irregular manner in the upper corium. The histopathologic diagnosis was "tuberculoid reaction."

The lesions healed very slowly; treatment consisted of compresses with Burow's solution and hexachlorophene soap cleansing. As of January, 1964, sixteen months after onset of the reaction, there were still a few actively draining ulcers, although most had healed with scarring. The patient remains otherwise in good health and without constitutional symptoms.



**Fig. 1**



**Fig. 2**

## **MATERIALS USED FOR HYPOSENSITIZATION**

The materials used for desensitization of these two patients were made by the same laboratory.<sup>1</sup>

### **Autogenous vaccine**

This was prepared from a culture taken from bronchial mucus and grown on tissue agar (veal heart, isotonic saline, whole egg, peptone and agar, all autoclaved). The bacterial growth was then washed with saline, filtered through cotton, and inactivated for one hour at 58° C. Finally, 0.5 c.c. of 5 per cent phenol was added to a 10 c.c. vial containing 5,000 million organisms per cubic centimeter. Spores were looked for and not found.

### **Pollen antigens**

These antigens included weeds, grasses, trees, and molds to which the patients gave positive skin reactions. An extract was made from 10 Gm. of pollen in 500 c.c. of 50 per cent glycerin and 50 per cent water passed through a Seitz filter. This filtrate was the most concentrated (vial "D"). The other three vials were diluted  $\frac{1}{2}$ ,  $\frac{1}{20}$ , and  $\frac{1}{100}$  with the above glycerin-water mixture (vials "C," "B," "A," respectively). Cultures were negative for bacteria and fungi.

### **Foods and dust antigens, "Allergenex"**

The antigens were from dust and foods to which the patients had been found to be sensitive, as determined by scratch tests. They were prepared by extracting 100 Gm. of each allergen with Evans solution (sodium chloride 12.5 Gm., sodium phosphate 3.577 Gm., potassium phosphate 0.907 Gm., and phenol 12.5 c.c., dissolved in 1,000 c.c. of water). These extracts were sterilized by Seitz filtration. Cultures were negative for bacteria and fungi.

*Injection of desensitizing materials in guinea pigs.* Two guinea pigs were given intradermal injections of 0.1 ml. of a mixture of the antigenic materials from Case 2. These intradermal injections were given daily for three days and then twice a week for five weeks. Each site developed a small red papule the size of the initial wheal, which subsided within four to six days after each injection. Sites of previous injections were not reactivated by subsequent injections.

## **COMMENT**

In both of these cases, no microorganism was recovered from the chronic granulomatous draining abscesses and sinuses which could account for the production of the lesions. Cultures for bacteria and fungi with the antigens used in Case 2 were sterile. In a recent report, Owen and co-workers<sup>2</sup> in Texas described 50 cases with granulomatous abscesses developing within three months of the injection of various parenteral medications and vaccines. These patients came from among 1,200 receiving injections at a hospital clinic from July, 1961, to April, 1962. *Mycobacterium fortuitum* was recovered from the wounds of 16 patients who were studied bacteriologically.

A foreign body reaction was suspected in our cases. However, polariscopic

studies for silica, etc., in Case 1 were negative. Furthermore, the antigen solutions used were clear and free from particulate matter grossly and microscopically. The two patients described here received injections during a period of seven months and two months, respectively. In both patients, the local lesions started almost simultaneously (within two weeks) in all areas. The time of onset and the almost simultaneous appearance of all lesions, even those which had not been injected recently, speaks very strongly against an infectious process. Furthermore, no organism was recovered by the methods used.

It would appear much more likely that an allergic process is implicated. Whether the allergen was part of the original antigen preparation, or whether it was a contaminating material such as zirconium or beryllium, has not been established by our studies; it is also possible that the antigens may have contained a substance capable of acting as an adjuvant. We were reluctant (as were the patients) to test them again with the same materials as had been used for the hyposensitization procedures, for fear of reactivating the lesions which had healed or were healing. Patient 2, however, received further hyposensitizing injections during the summer of 1963 from another physician who used similar antigens obtained from a different laboratory; there have been no local reactions or reactivation of existing lesions with use of these new antigen solutions.

Both physicians who first cared for these patients have hyposensitized many other patients without similar untoward reactions, using similarly prepared antigens from the same source. The laboratory which prepares and distributes the allergens has records of three other patients who also had local reactions consisting of inflammation with abscess and ulcer formation. All were sterile on culture. All occurred in the spring and summer of 1962. Over 100 other patients receiving identical mixtures prepared by the same laboratory in that year had no untoward local reactions. Injection of the antigens from Case 2 in guinea pigs intradermally for six weeks failed to cause development of reactions similar to those of the patient.

A review of the literature and personal inquiry of other allergists has failed to reveal similar experiences.

#### REFERENCES

1. Greeley, Horace (Brooklyn): Personal communication.
2. Owen, M., Smith, A., and Coultras, J.: Granulomatous Lesions Occurring at Sites of Injections of Vaccines and Antibiotics, *South. M. J.* **56**: 949, 1963.