

## SOME UNTOWARD REACTIONS TO REPOSITORY THERAPY

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RECENTLY, there has been a surge of interest in the so-called "one-shot" or repository form of treatment of inhalant allergic disease. Although repository therapy has been used by Loveless since 1938 and more recently a large number of cases have been reported by others, there have been only occasional references citing the complications of such therapy.<sup>1-4</sup> One of the most comprehensive has been a collaborative study under the auspices of the Specific Therapy Committee of the American Academy of Allergy.<sup>5</sup> In 1777 ragweed-sensitive patients receiving repository therapy in this study, an incidence of systemic reactions of 6.5 per cent and 6 sterile abscesses were reported. While most allergists agree that reactions to repository treatment decrease as one gains experience in using these materials, it should be brought to the attention of physicians that such reactions do occur with the currently available materials used in preparing allergenic emulsions.

The rationale for the use of repository therapy has been the assumption that an increased antibody titer is produced by the present conventional aqueous treatment methods. That an increased antibody response occurs with repository antigen stimulation via Freund's incomplete adjuvant has been amply demonstrated in the experimental animal.<sup>6-9</sup> It has also been shown that the antibody response in humans is similarly augmented when stimulated by influenza virus vaccine in emulsion form.<sup>10</sup> The response of beneficial allergic antibodies was reasoned to be similar, although current studies in allergic individuals have not confirmed this hypothesis.

During the 1960 grass and ragweed pollen seasons, 64 patients were treated by the repository technique (Table I). Seven patients received one intramuscular injection of 0.30 c.c. grass pollen emulsion (orchard and timothy grasses 50:50); 30 patients received repository ragweed emulsion (giant and dwarf ragweeds 20:80) by two intramuscular injections, each 0.30 c.c. in volume (one injection in each arm), at a 7 week interval. All of these patients received the aqueous pollen extract in an oil medium of filter-sterilized 10 per cent Arlacel A-90 per cent Drakeol 6VR with the oil to aqueous phase ratio of 2. Twenty-seven patients received one intramuscular injection of 0.50 c.c. emulsion in each arm at 30 minute intervals. This emulsion consisted of aqueous ragweed extract

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(giant and dwarf ragweeds) in the same repository base as above, prepared for many investigators by the Committee on Specific Therapy of the American Academy of Allergy.

A total of 55 patients had immediate ( $\frac{1}{2}$  to 12 hours after injection) local reactions of pain and perhaps slight swelling at the repository site, an incidence of 66 per cent (Table I). These were mild and transient, cleared spontaneously in 24 to 48 hours, and were similar to those seen with many types of intramuscular injections. None of these was considered to be significant. In the 27 patients receiving ragweed repository emulsion prepared with materials from the Committee on Specific Therapy, two had immediate systemic allergic reactions. These occurred in two patients who had previously stopped aqueous therapy because of systemic allergic reactions and consisted of urticaria and mild asthma beginning  $2\frac{1}{2}$  hours after treatment, lasting up to two days, and clearing after treatment with epinephrine and antihistamines. These systemic allergic reactions were like those seen with conventional aqueous therapy except for the delay in onset.

Of the 30 patients receiving two separate injections of ragweed allergenic emulsion in 1960, none had allergic reactions, but four had late local reactions. These four all had nodule formation at the site of one or both injections (Table II). A nodule appeared, respectively, 1, 4, 9, or 11 weeks after the last repository injection. The nodules occurring 1 and 11 weeks after the last injection subsided spontaneously.

However, the two patients with nodules appearing 4 and 9 weeks after the last injection developed bilateral cysts, and, in the former patient, both injection sites required surgical drainage. The two patients with cysts will be described in greater detail.

#### CASE REPORTS

1. *F. E.*—A 43-year-old Caucasian male physician had the onset of hay fever at the age of 5 years; his symptoms occurred during the grass season in Europe. In 1950, he moved to New York, and 2 years later he developed hay fever and asthma in the ragweed season. Bass and shrimp ingestion caused urticaria. He first received conventional perennial aqueous treatment in 1952 in New York for a period of 6 years; on moving to Michigan in 1958, he no longer had any symptoms in the grass season and only mild symptoms in the ragweed season.

He was started on conventional perennial aqueous treatment to a mixed weed extract in 1958. He had minimal hay fever symptoms during the ragweed season of 1958, requiring an occasional antihistamine tablet. In the ragweed season of 1959, he had no hay fever symptoms (part of the season was spent in a low ragweed pollen count area). His last aqueous allergenic extract injection was 0.45 c.c. of 1:50 ragweed family on March 7, 1960.

On May 3, 1960, he demonstrated a 3 plus prick reaction to 100,000 (pollen units) ragweed per cubic centimeter. The ophthalmic test was positive at 5500 PU ragweed per cubic centimeter. On May 11, 1960, a prick test to the repository material containing 10,000 PU of ragweed allergen was negative. He received 10,000 PU of ragweed emulsion in a volume of 0.30 c.c. intramuscularly into the left triceps. There was considerable soreness at the injection site for the next few days.

On July 8, 1960, a prick test to the repository material containing 10,000 PU ragweed allergen was again negative, and he received the same dosage in the right triceps. He again

TABLE II. LATE LOCAL IRRITATIVE

| PATIENT | AGE    | DIAGNOSIS | PREVIOUS<br>CONVENTIONAL<br>TREATMENT<br>(LAST AQUEOUS<br>DOSE) | EMULSION DOSE<br>(POLLEN UNITS) | EMULSION<br>VOLUME<br>(c.c.) |
|---------|--------|-----------|-----------------------------------------------------------------|---------------------------------|------------------------------|
| J. B.   | 30 (f) | Hay fever | 4-25-60                                                         | 1. 5000 (lt)                    | 0.30                         |
|         |        |           | 0.35 c.c., 1:50                                                 | 2. 5000 (rt)                    | 0.30                         |
| F. E.   | 43 (m) | Hay fever | 3-7-60                                                          | 1. 10,000 (lt)                  | 0.30                         |
|         |        |           | 0.45 c.c., 1:50                                                 | 2. 10,000 (rt)                  | 0.30                         |
| P. B.   | 32 (m) | Hay fever | 3-1-60                                                          | 1. 5000 (rt)                    | 0.30                         |
|         |        |           | 0.50 c.c., 1:50                                                 | 2. 5000 (lt)                    | 0.30                         |
| L. B.   | 39 (m) | Hay fever | 4-5-60                                                          | 1. 5000 (lt)                    | 0.30                         |
|         |        |           | 0.80 c.c., 1:50                                                 | 2. 5000 (rt)                    | 0.30                         |

TABLE I. SUMMARY OF ALLERGENIC EMULSION THERAPY AND UNTOWARD REACTIONS,  
1960 TO 1962

| YEAR | NUM-<br>BER OF<br>PATIENTS | NUMBER<br>OF IN-<br>JECTIONS | ALLERGEN | TOTAL ALLERGEN<br>DOSE (PU) | ALLERGIC<br>REAC-<br>TIONS | NODULES,<br>AB-<br>SCESSES | LOCAL<br>SORENESS |
|------|----------------------------|------------------------------|----------|-----------------------------|----------------------------|----------------------------|-------------------|
| 1960 | 5                          | 5                            | G        | 1,000-5,000                 | 0                          | 0                          | 2                 |
|      | 57                         | 83                           | W        | 75-20,000                   | 2                          | 6                          | 55                |
|      | 2                          | 4                            | GW       | 10,000-20,000               | 0                          | 0                          | 1                 |
|      | 64                         |                              |          |                             |                            |                            |                   |
| 1961 | 6                          | 12                           | G        | 100-5,000                   | 0                          | 0                          | 4                 |
|      | 111                        | 192                          | W        | 100-5,000                   | 0                          | 0                          | 30                |
|      | 2                          | 3                            | D        | 0.0025-0.0150 mgm           | 0                          | 0                          | 1                 |
|      | 22                         | 66                           | GW       | 250-5,250                   | 0                          | 0                          | 13                |
|      | 2                          | 5                            | WD       | 750-2,750                   | 0                          | 0                          | 0                 |
|      | 4                          | 12                           | GAW      | 183- 367                    | 0                          | 0                          | 1                 |
|      | 1                          | 3                            | DGAW     | 717                         | 0                          | 0                          | 0                 |
|      | 148                        |                              |          |                             |                            |                            |                   |
| 1962 | 13                         | 23                           | G        | 500-10,000                  | 2                          | 0                          | 3                 |
|      | 125                        | 229                          | W        | 100-10,000                  | 5                          | 0                          | 32                |
|      | 46                         | 125                          | GW       | 75-12,500                   | 2                          | 0                          | 24                |
|      | 2                          | 3                            | AW       | 1,000                       | 0                          | 0                          | 0                 |
|      | 4                          | 9                            | DW       | 750-5,000                   | 0                          | 0                          | 1                 |
|      | 26                         | 66                           | GAW      | 167-9,170                   | 0                          | 0                          | 7                 |
|      | 3                          | 8                            | DGW      | 500-12,500                  | 0                          | 0                          | 0                 |
|      | 2                          | 6                            | DAW      | 1,000                       | 0                          | 0                          | 1                 |
|      | 221                        |                              |          |                             |                            |                            |                   |
|      | 433                        | 854                          |          |                             | 11                         | 6                          | 175               |

G = Grass (50 per cent orchard, 50 per cent timothy).

W = Weeds (80 per cent dwarf, 20 per cent giant ragweed).

A = Alternaria.

D = Endo house dust.

Combinations were in equal portions.

noted discomfort at the site of the second injection and took Empirin tablets for the next two nights.

On August 10, 1960, swelling was noted at both injection sites, with more on the right (second injection site). Swelling and discomfort increased until August 17, when the patient gave himself 20 mg. of depo-Medrol intramuscularly. A marked decrease in dis-

## REACTIONS TO REPOSITORY THERAPY

| INTERVAL BETWEEN REPOSITORY INJECTIONS (DAYS) | INTERVAL BETWEEN 2ND INJECTION AND LATE LOCAL (DAYS) | TYPE OF LATE LOCAL REACTION | DURATION OF LATE LOCAL REACTION | RESULT                                      |
|-----------------------------------------------|------------------------------------------------------|-----------------------------|---------------------------------|---------------------------------------------|
| 56                                            | 7                                                    | 2 cm. nodules               | 1 week                          | spontaneous clearing                        |
| 55                                            | 28                                                   | draining abscesses          | 4 months                        | healed after surgical incision and drainage |
| 55                                            | 77 (rt)                                              | 1 cm. nodule                | 1 week                          | spontaneous clearing                        |
| 56                                            | 63 (lt)                                              | cysts                       | 9½ months                       | spontaneous clearing                        |

comfort occurred in the next 24 hours, although the swelling persisted. Approximately 1 week later the swelling and discomfort again increased in spite of analgesics, and the patient started 5 mg. of Prednisolone daily on August 29.

On September 3, 1960, a fluctuant mass approximately 2 by 1½ inches without warmth or erythema was noted on the right upper arm just above the olecranon; the left arm showed a smaller amount of swelling which was not fluctuant. The patient gave himself an injection of 40 mg. of depo-Medrol on that date. On September 7, the mass on the right was 3 by 1¼ inches with "pointing," and the mass on the left arm was 2 by 1½ inches, with hard swelling palpable in the triceps muscle. Prednisolone was given in the dosage of 50 mg. orally and then tapered to 10 mg. a day.

However, the size of the area on the right arm continued to increase, with much turgor and pressure at its superior pole; accordingly, on Sept. 12, 1960, the area was aspirated via an 18 needle, with the removal of 20 c.c. of brown-grey, thick, viscous fluid which partially clotted in 1 hour. Gram stain and methylene blue stain revealed no bacteria—only fibrinous material with cellular debris (apparently white blood cells with homogenous nuclei and a few red blood cells) was seen. The pathology report for this aspirated material read "fragments of amorphous, basophilic debris in which are enmeshed erythrocytes, mononuclear cells, and many eosinophils. Diagnosis: inflammatory infiltrate, predominantly eosinophilic."

The abscess on the right arm again increased in size, and 25 c.c. of grey material was aspirated on Sept. 15, 1960, and 20 c.c. of Varidase solution was injected into the site. After 1½ hours, approximately 8 c.c. of sanguinous, purulent material was aspirated. The following day marked discomfort of the right arm persisted, and the abscess area had again increased in size and inflammation; edema was present near the elbow, and flexion was limited to 90 degrees. Another 15 c.c. of tan sanguinous material was aspirated.

The next day (September 17), spontaneous drainage began from six small sites on the abscess surface (Fig. 1). On September 19, an elliptical area with the sinus orifices was excised and the abscess cavity was curetted. Necrotic, fatty tissue was obtained and the abscess cavity found to be 4 by 11 cm. in the subcutaneous tissue, with a perforation through the fascia and a small abscess in the triceps muscle, a so-called "collar-button" abscess. The cavity was packed with iodoform gauze, which was removed two days later. The pathologic report of this curettage was as follows: "Fibroadipose tissue, consistent with subcutaneum and containing an abundance of densely packed histiocytic cells, as well as many multinucleated giant cells containing lipid vacuoles. These granulomatous foci are infiltrated by large numbers of neutrophils and scattered plasma cells and lymphocytes. In addition, there is a fragment of skin with the dermis and subcutaneous adipose tissue, and there is a suppurative and granulomatous phlegmonous inflammation. This lesion cannot be called an Arthus reaction because of the lack of significant vasculitis. The granulomatous response



Fig. 1.—Abscess at site of repository injection (see text).

may well be secondary to one of the vehicles used in the ragweed emulsion. Diagnosis: skin and subcutaneous suppurative and granulomatous phlegmonous inflammation'' (see Fig. 2).

On October 6, the mass on the left arm became painful and fluctuant. On October 8, incision, drainage and curettage of the abscess in the left upper arm was carried out; a cavity 5 by 3 cm. was found between the deep subcutaneous tissue and the triceps muscle. Thick, yellow material was aspirated, and culture was obtained. The pathologic report of the curettage of the left arm was as follows: "Active chronic granulomatous inflammation. Compatible with tissue reaction to oily injected material as per history. No conclusive evidence of specific chronic infectious granuloma, but with history we would have to consider such a process. Diagnosis: Subcutaneous granuloma related to the injected Drakeol-Arlacel weed antigen 2 months previously'' (see Fig. 3). Cultures obtained at all three aspirations were negative. On October 14, both arms were nontender, both cavities were closed, and there was no drainage or induration. Complete healing took place on Nov. 6, 1960, 88 days after the onset of swelling.

2. *L. B.*—A 39-year-old Caucasian male had the onset of hay fever at the age of 12 years, the symptoms occurred each year during the ragweed season, and there was mild nasal stuffiness perennially. There was occasional tightness of the chest with heavy exertion during the ragweed and grass seasons. Cat dander exposure caused wheezing, mushroom ingestion produced hives, and rice ingestion caused a headache. Immunization was started in 1948, with extracts of ragweed, house dust, and grass pollens, and on April 5, 1960, he received his last aqueous treatment of 0.30 c.c. Endo house dust 1:400, 0.20 c.c. ragweeds 1:50, and 0.30 c.c. grasses 1:50.

On May 3, 1960, he had a negative prick reaction to 5000 PU ragweed emulsion and was given 0.30 c.c. of this emulsion into the left triceps. He then had mild, local soreness in that area for 24 hours. On July 8, 1960, he again had a negative prick reaction to 5000 PU ragweed emulsion and received 0.30 c.c. of this emulsion into the right triceps. Local soreness persisted for several days in that area. Approximately 6 weeks later after the second repository injection (right triceps), he developed soreness and redness in that area to the extent that he could not raise his arm to his head. This occurred while he was painting his home. On October 6, 1960, a 5 by 7 cm. nonfluctuant area was still present, without erythema, heat, or tenderness.

On October 28, the mass on the right had decreased further, but increased again whenever the patient used his arm excessively (e.g., painting). In early October, the left arm (triceps area) became sore and tender, with diffuse swelling. On October 28, the right arm swelling measured 4 by 2½ inches, and the left arm swelling measured 2½ by 2 inches; there was tenderness, but no erythema.

In November, 1960, the swelling in the right arm descended to the area just superior to the elbow and gradually subsided spontaneously. However, by July 7, 1961, there still was a fluctuant, nontender, nonerythematous 3 by 2½ inch mass in the left arm over the triceps area. There was no recrudescence with activity at that time as there had been the entire preceding fall and winter. In January, 1962, there was still a 1 by 1 inch nontender, nonerythematous mass in the same area over the left triceps. This mass gradually subsided spontaneously and was not influenced by activity; by May, 1962, (some 9½ months after the onset of the swelling), this mass had completely subsided.

#### DISCUSSION

In 1961 and 1962, a total of 369 patients were treated by the repository method (Table I). The method of treatment was identical to that of 1960. Again we noted the transient local soreness often associated with intramuscular injections, but the incidence was reduced from 66 per cent in 1960 to 15 per cent. We believe this may be due to improved administration techniques or the use of less irritating emulsions, as described later. The incidence of 2.2 per cent al-

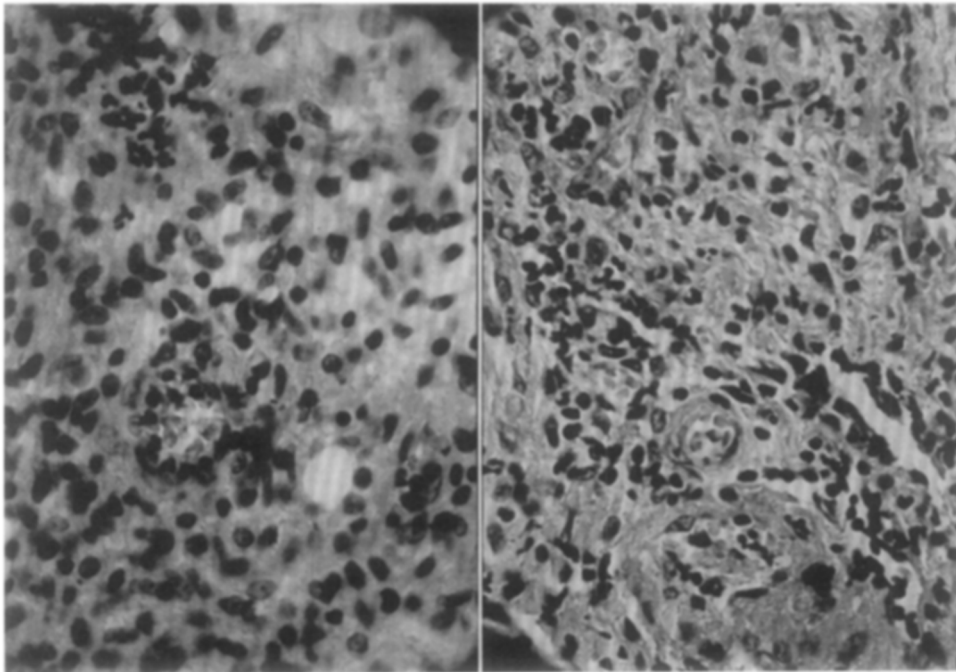


Fig. 2.

Fig. 3.

Fig. 2.—Curretage specimen from abscess of right arm. Note the macrophages and the lipid-induced granuloma.

Fig. 3.—Biopsy of left arm injection site revealing some healing (see text).

lergic reactions in 1960 decreased to 1.3 per cent in 1961 to 1962; the pattern of reactions is similar to those already described. It is interesting that there were no nodule formations, cysts, or abscesses. Because new physicians are trained to prepare and administer emulsion therapy each year and since the methods of preparation have remained the same, we feel that the introduction of preliminary toxicity testing in animals plays a major role in eliminating abscess formation and nodules.

Loveless reported the occurrence of nodules following repository immunization for ragweed allergy<sup>1</sup> during the years 1950 to 1955 and found a decreased incidence in following the patients through 1957. One patient retained a small induration 6 years after a repository injection. She used mineral oil for the emulsion and noted a lower incidence with emulsions containing Delyl or corn oil. However, more overdose reactions and slightly inferior clinical response were noted with the emulsion of Delyl or corn oil. She also noted a lesser number of nodules in 1954 as compared to 1950 and attributed this to the increase in the volume of oil. Brown<sup>3</sup> has reported that large amounts of emulsified house dust extract can produce local reactions in some patients. Others<sup>2, 12, 13, 14</sup> have also reported "sterile cyst" formation with emulsions containing aqueous pollen extracts, house dust extracts, and mold spore extracts (all of these workers administered the emulsions by the subcutaneous route). The same types of nodules and sterile abscesses have been reported<sup>6, 7</sup> with the use of influenza vaccine emulsified in Drakeol-Arlacel; however, these were given intramuscularly.

Several possibilities exist as to the mechanism of development of these sterile abscesses. Since both patients received two injections approximately 7 weeks apart, it might be presumed that these were manifestations of hypersensitivity, with the second injection acting as the challenging dose. The use of an aqueous extract of a material to which the patient is known to be clinically sensitive (ragweed) as well as a foreign substance acting as an adjuvant to enhance the antibody response would also suggest an allergic mechanism. The latent period and increased reaction at the second injection site support this suggestion. Also, the possibility of the patient becoming sensitized to the Arlacel A, the Drakeol, or the combination must be kept in mind. Even though these materials are presumably nonsensitizing, their product might be.

However, there are several factors which militate against the allergic origin of these abscesses. Many allergic patients have received aqueous ragweed extract for many years without the occurrence of such abscesses; in addition, an adjuvant is thought to enhance antibody production to the aqueous antigen and not to the repository vehicle. If sensitization were produced to the emulsion mixture, all or at least many of the other patients receiving varying doses of the same mixture should also have had abscess formation. Both patients received their injections from an emulsion mixture given at the same time to 14 other patients who did not develop the delayed local reaction, except for the two with transient nodules. The pathologic studies of the sections of the surrounding tissues and the abscess cavity (lining and contents) did not show the findings usually seen in an area of hypersensitivity. Thus, no necrotizing vasculitis, no

marked separation of the tissue fibers as seen with edema fluid formation, no thrombosis or fibrinoid necrosis or arteritis as seen in Arthus phenomena, no type of delayed hypersensitivity characterized by a proliferative response about the vessels and infiltration by the mononuclear elements, and no response of the delayed tuberculin-type reaction with the mononuclear forms converting to plasma cells were found. Other allergists have also reported similar cyst-like formations in patients treated with repository therapy for the first time with only one injection; these same patients were then given repository therapy the following year with no reactions.

Another explanation for the abscess formation is the possibility of bacterial contamination during the production of the emulsion base. Although aseptic technique was used in the preparation of the vehicle and the aqueous ragweed extract, and in the mixing and storage of the completed repository preparation, inadvertant contamination cannot be categorically excluded. Sterility tests done throughout production of our emulsions were negative. The "sterile abscess" formation, the negative Gram and methylene blue stains, the negative bacterial cultures, and the absence of reactions in the other patients receiving the same lot of repository extract are, however, overwhelming evidence against bacterial contamination.

It would thus appear that the most likely explanation would be a foreign-body type of irritation, with resultant sterile abscess formation. The following factors are compatible with such a hypothesis: the use of two oily substances for the repository vehicle, a delay of several weeks after the injection before the clinical appearance of the sterile abscess, the clinical course of the abscess and its manner of formation and slow healing following incision and drainage, the failure to respond to steroid medications, the "feel" of the abscess cavity suggestive of "granularity," during probing by the surgeon and the pathologic picture compatible with a nonspecific, foreign-body type of irritation.

The late local nodule and abscess reactions described have been investigated in laboratory animals, by adaptation of toxicity tests described by Berlin.<sup>15</sup> Allergenic emulsions and their components were tested individually by intraperitoneal injection into groups of similar young mice. These were weighed accurately at daily intervals, then killed and the abdominal cavities examined. Weight-gain patterns of test groups were compared with those of a saline control group. Irritating test materials were found to cause a significantly decreased weight gain, and generally produced gross changes of peritonitis. Samples of the allergenic emulsion causing the local reactions described in this paper were tested in mice and compared to emulsions which had caused no such reactions. The animal studies showed a markedly decreased weight-gain pattern only in those animals injected with the ragweed emulsion causing the nodules and abscesses in the patients described. Correspondingly, when this irritating emulsion had its allergenic fraction diluted to dose levels not associated with clinical local reactions, the intraperitoneal mouse toxicity test was also within nonirritative limits. Animal studies have subsequently shown that irritating properties of allergenic emulsions are related to contaminants in the emulsifier, the nature of allergenic extract used, and the concentration

of the allergenic extract.<sup>16</sup> One could infer that the factor or factors causing irritating reactions are the same in humans and mice if these laboratory investigations are applied clinically. We have chosen to so infer, and animal studies with allergenic emulsions to be used in humans are now routinely done. Those emulsions not falling within nonirritating limits are discarded. Since beginning pretreatment toxicity testing in animals, we have treated 369 patients with 762 tested emulsion injections and have noted no local reactions of nodule, cyst, or abscess.

Other causes of delayed local reactions include the incorporation of irritating antigenic materials (e.g., some house dusts) in the repository extract.<sup>3</sup> Delayed inflammatory reactions have been shown to be more common in Negroes and children under 6 years of age.<sup>7, 18</sup> Also the development of delayed sensitivity accompanied by delayed inflammatory reactions (sometimes followed by abscess formation) has been produced in atopic individuals following an injection of an emulsified pollen antigen to which the individual had no spontaneous immediate-type of sensitivity.<sup>19</sup> Indeed, a nonatopic person treated with a repository injection may develop delayed hypersensitivity also.

#### SUMMARY

The types of untoward reactions seen with repository therapy have been divided into three groups. The transient local reactions of pain and swelling are mild and not significant. Allergic overdose reactions are occasionally seen and are similar to those occurring with conventional aqueous hyposensitization treatment, except that they are delayed several hours. Eleven patients of 854 who received repository treatments (1.3 per cent) had such allergic overdose reactions (asthma and/or urticaria), which either subsided spontaneously or responded to oral antihistamines or epinephrine.

The more serious late local reaction is described in four patients, with local abscess formation of the sterile type in two patients. One patient required incision and drainage at both injection sites, and the other patient had a spontaneous regression in 9½ months. The etiology of these late local reactions is discussed, and it is concluded that they represent a type of foreign-body irritative process.

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