

Active specific local and systemic desensitization by aerosols of antigen

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These are thought to be the first examples of (a) active specific systemic desensitization and (b) sustained local but not systemic desensitization by aerosols of antigen. Twelve guinea pigs, actively sensitized by aerosols, had mild anaphylactic reactions to weak aerosols of antigen 10 days later. Repeated aerosol exposures to progressively stronger concentrations of antigen for 5 days induced local desensitization, i.e., complete tolerance for aerosols of concentrated antigen. Six of these pigs, Group I, were exposed to aerosols of concentrated antigen three hours daily for four weeks, except on weekends. There were no reactions to the aerosols, showing that local desensitization persisted. Intravenous injections of anaphylactic doses of antigen elicited no reactions in five pigs. The sixth pig had a mild, transient (1+) anaphylactic reaction. This was interpreted as virtually complete active systemic desensitization by aerosols of antigen. The other six pigs, the Group II controls, were challenged with concentrated antigen aerosols once a week for four weeks. None of them reacted, signifying that local desensitization was maintained. Intravenous injections of antigen elicited anaphylactic reactions in all six controls. This was interpreted as maintenance of local desensitization without producing systemic desensitization. Possible clinical application of these observations is discussed.

Active systemic and local desensitization of guinea pigs follows several parenteral injections of small, nonreacting doses of antigen.¹ Passive desensitization follows the parenteral injection of specific antisera.² Local bronchial desensitization follows repeated exposures to aerosols of specific antigens.³ Intravenous injections of antigen, so far, have elicited severe or fatal anaphylactic reactions in sensitized guinea pigs, even after they have developed complete tolerance for antigen by aerosols.⁶ In other words, until now, aerosol desensitization has been local but not systemic.

Active sensitization by exposures to aerosols of antigen has been confirmed recently.⁴ This suggested that prolonged exposures to antigen by aerosol might induce systemic desensitization. The following experiment shows that

From the Allergy Research Laboratory, University of Virginia School of Medicine.
Supported by a grant from the Knoll Pharmaceutical Company, Orange, N. J.
Received for publication Dec. 28, 1967.

this was indeed the case. In addition, it demonstrated that local *but not* systemic desensitization may be maintained by weekly brief exposures to aerosols of antigen.

METHOD

Details of the preparation of antigen, active sensitization and local desensitization by aerosols, and the aerosol equipment have been described.^{2, 5} The experiment was done in four stages.

1. Sensitization (Table I)

Twelve random-bred guinea pigs were exposed to aerosols of a 1:20 saline dilution of egg white (EW) one hour daily for 4 days. Ten days later they were challenged with aerosols of 1:1,000 and 1:100 EW. All 12 had anaphylactic reactions to the 1:1,000 or 1:100 EW aerosol dilutions within less than 10 minutes on two successive days.

2. Local desensitization (Table II)

On day 16, they were exposed to aerosols of 0.05 mg. per milliliter of crystalline egg albumin (CEA), morning and afternoon. Nine did not react. The other 3 reacted weakly (1+), within 11 to 33 minutes, to the first but not to the second aerosol exposure. The next day all of them were challenged with the 0.5 mg. per milliliter CEA concentration. None of them reacted.

On day 20, they were challenged with 0.05 and 0.5 mg. per milliliter CEA concentrations. None of them reacted. Six reacted (1+) to the 5.0 mg. per milliliter concentration within 4 to 6 minutes. The other 6 did not react. None reacted to the second hour of 5.0 mg. per milliliter aerosol challenge that day.

On day 21, none of them reacted to the 0.05 or the 0.5 mg. per milliliter CEA concentrations. All 12 pigs reacted (1+) to the first but not to the second aerosol exposure to the 5.0 mg. per milliliter CEA.

Table I. *Active sensitization*

No. days	Aerosol exposures			No. guinea pigs
	Antigen	Duration (min.)	Reaction*	
1-4	1:20 EW	60	0	12
14	1:1,000 EW	4-8½	1+	5
	1:100 EW	1½-4	1+	6
	1:100 EW	2	2+	1
15	1:1,000 EW	2-9½	1+	11
	1:100 EW	7	1+	1
Totals	1:20 EW	2,880		12
	1:100 EW	240		12
	1:1,000 EW	360		12

*Reaction code: 1+ = mild dyspnea, scratching nose, urination, or defecation (recovery in 5 to 10 minutes); 2+ = moderately severe dyspnea, obvious distress, response to sensory stimuli, ruffled hair, crouching (recovery in 10 to 20 minutes); 3+ = severe dyspnea, convulsions, lying on side, near fatal (slow recovery); and AD = anaphylactic death within 3 to 15 minutes.

On day 22, there were no reactions to the 5.0 mg. per milliliter CEA aerosol. This means that they were desensitized locally.

At this point they were divided into two groups, 6 pigs in each group. The 6 in Group I were desensitized systemically by repeated prolonged daily CEA aerosols. Group II, the controls, were challenged briefly with CEA aerosols once a week.

3. Group I: Systemic desensitization by aerosol (Table III, A)

Beginning on day 23, these 6 pigs were exposed to 5.0 mg. per milliliter CEA aerosol 3 hours daily, 5 days each week, for 4 weeks, a total of 60 hours for each pig. There were no reactions after day 21.

On day 51, each pig was challenged intravenously with 0.2 mg. CEA, which usually elicits fatal or near-fatal reactions in sensitized guinea pigs. Five of the pigs did not react. The sixth pig had a mild, transient anaphylactic (1+) reaction. The obvious conclusion is that they were desensitized systemically.

4. Group II: Controls (Table III, B)

The 6 locally desensitized controls were exposed to 0.05, 0.5, and 5.0 mg. per milliliter CEA aerosols, 10 minutes each, once a week for 5 weeks. None of them reacted, indicating that these weekly exposures maintained local desensitization. The total time in each concentration of CEA aerosol was about 60 minutes. This was less than one daily exposure of the pigs in Group I.

On day 51, the 6 control pigs were challenged intravenously with 0.2 mg.

Table II. *Local desensitization by aerosols*

No. days	Aerosol exposures			No. guinea pigs
	Antigen CEA (mg./ml.)	Duration (min.)	Reaction	
16	0.05	11-33	1+	3
	0.05*	60	0	9
		60	0	12
17	0.5	60	0	12
20	0.05	60	0	12
	0.5	60	0	12
	5.0	4-6	1+	6
	5.0	60	0	6
	5.0	60	0	12
21	0.05	60	0	12
	0.5	60	0	12
	5.0	19-57	1+	12
	5.0	60	0	12
22	0.5	60	0	12
	5.0	60	0	12†
Total	0.05 × 4	± 200	1+	3
	0.5 × 3	240	0	12
	5.0 × 3	+ 220	0	10

*Second challenge with 0.05 mg. per milliliter.

†Local desensitization: no reaction to two exposures on two consecutive days.

Table III. *Systemic desensitization by aerosols*

No. days	Aerosol exposures			No. guinea pigs
	Antigen* CEA (mg./ml.)	Duration (min.)	Reaction*	
Desensitization data				
A. Group I				
23-24	5.0	180 daily	0	6
27-31	5.0	180 daily	0	6
34-38	5.0	180 daily	0	6
41-45	5.0	180 daily	0	6
48-51	5.0	180 daily	0	6
Totals	5.0	22,680	0	6
Local desensitization maintained				
51	0.2		0	5
	0.2		1+	1
Local densitization maintained				
B. Group II (controls)				
23-24	0.05	10	0	6
	0.5	10	0	6
	5.0	10	0	6
31	5.0	10	0	6
38	5.0	10	0	6
45	5.0	10	0	6
51	5.0	10	0	6
Totals	0.05	60	0	6
	0.5	60	0	6
	5.0	60	0	6
Intravenous antigen				
51	0.2		2+	3
			3+	1
			AD	2

*See footnotes, Table I and II.

CEA. All had anaphylactic reactions. Three were moderately severe (2+), 1 was nearly fatal (3+), and 2 were fatal (AD). In other words, they were still desensitized locally, but not systemically.

DISCUSSION

This demonstration of active systemic desensitization by aerosols of antigen necessitates a revision of the previous dictum that "aerosol desensitization is local but not systemic."⁶ The revised facts are that transient local *but not* systemic desensitization by aerosols is easy and requires little time—a few hours in a few days. By contrast, local *and* systemic desensitization by aerosols is arduous and time-consuming, requiring many hours for several weeks.

No effort was made to determine (a) the minimum number of aerosol hours required for systemic desensitization, (b) when sensitizing or precipitating antibodies first appeared during the sensitizing or desensitizing periods, or (c) whether serum from these guinea pigs would mediate specific passive sensitization or desensitization. Attempts to answer those questions are in process.

Possible clinical applications of these observations are obvious. Effective specific aerosol treatment of hay fever and asthma has been reported.⁷ The time required to develop local tolerance for CEA (4 to 5 days) is comparable to that reported in pollen cases. Topical application of CEA by aerosol once a week maintained effective tolerance for concentrations of antigen far in excess of those inhaled during pollen seasons. This observation was an unexpected "bonus" from the original plan of the experiment.

Relief from pollen hay fever and asthma has been obtained by several brief daily inhalations of pollen extracts, usually within 4 days. Relief was maintained by a few whiffs of the extract daily from a hand nebulizer at home.⁷ No simpler method for controlling seasonal pollinosis has been suggested. Controlled confirmation and refinements of these observations are long overdue. A review of the literature summarized in the seven references will show that this is not a simple problem.

The difficulties encountered in reducing reagin titers by parenteral injections of pollen extracts make it unlikely that inhaled antigen will reduce reagins effectively. It is well known, however, that relief may be obtained by allergen injections while reagin titers are still high.

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