

STUDIES IN BACTERIAL ALLERGY*

VII. BRONCHIAL DESENSITIZATION AND RESENSITIZATION IN PASSIVELY SENSITIZED GUINEA PIGS

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THE experiments presented here are additions to a series of observations¹⁻³ on different aspects of the broad problem of desensitization with bacterial haptens. The last report³ was concerned largely with the role of specific hapten aerosols in local desensitization of bronchi. The problem of local re-sensitization following desensitization is introduced here, together with additional data on local desensitization.

METHODS

Guinea pigs were the experimental animals. Pneumococcal polysaccharides types VI and VIII were used and are referred to as challenging and desensitizing haptens. Types VI and VIII refined antipneumococcal rabbit sera were used as the heterologous, passively sensitizing antibodies.

Passive sensitization was produced by intra-abdominal injections of varying amounts of antiserum.

Challenging and desensitizing concentrations of the polysaccharide haptens varied from 0.1 to 5.0 mg. per milliliter. The haptens were nebulized into a small glass box large enough to contain three small guinea pigs without crowding. The aerosol chamber was not quite airtight. The aerosol fog was kept dense enough to ooze visibly from the loose seams. A DeVilbiss No. 40 nebulizer, connected with a source of compressed air bubbled through water, provided the fog.

Local desensitization was assumed to be present when the guinea pigs were no longer affected by relatively prolonged exposures (eight to ten minutes) to the aerosol fog which previously had caused unequivocal dyspnea.

When testing for local sensitization, the animals were removed from the fog promptly at the onset of unequivocal dyspnea. Failure to do so resulted in three undesirable effects in preliminary experiments: (1) a much higher incidence of anaphylactic death; (2) partial desensitization from the more prolonged hapten exposure; (3) partial desensitization from the progressively more severe reactions which developed when left in the fog.

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TABLE I. EXPERIMENT I. (A) MULTIPLE PASSIVE SENSITIZATION TO AEROSOLS
(B) SPECIFIC REACTIONS TO AND DESENSITIZATION

EA	I.A.* SENS. DOSE ANTISERUM (ML.)		AEROSOL CHALLENGE POLYSAC. (MG./ML.)	EXPOSURE TIME (MIN.)	REACTION	AEROSOL DESENS. POLYSAC. (MG./ML.)	EXPOSURE TIME (MIN.)	AEROSOL RECHAL- LENCE POLYSAC. (MG./ML.)	EXPOSURE TIME (MIN.)	RE- ACTION
	Type VI	Type VIII	Type VI					Type VI		
	0.5	0.5	3.0	1	Moderate	0.3	30	3.0	8½	None
	0.5	0.5	3.0	1½	Moderate	0.3	30	3.0	8½	None
	0.5	0.5	3.0	1	Severe	0.3	30	3.0	8½	None
	0.5	0.5	3.0	1	Severe	0.3	30	3.0	9	None
	0.5	0.5	3.0	1½	A.D.†					
			3.0		A.D.†					
			Type VIII					Type VIII		
	0.5	0.5	3.0	2	Slight to Moderate	0.3	45	3.0	8	None
	0.5	0.5	3.0	2	Moderate	0.3	45	3.0	8	None
	0.5	0.5	3.0	1½	Moderate	0.3	30	3.0	8	None
	0.5	0.5	3.0	1	Moderate	0.3	30	3.0	8	None

I.A.—Intra-abdominal.
A.D.—Anaphylactic death.
Animals 9 and 10. No reaction when rechallenged for eight minutes with Type VI (3.0 mg. per milliliter).

Sensitized animals were considered to be locally insensitive when, on first postsensitization exposure, they showed no dyspnea after being in the hapten aerosol for eight to ten minutes.

The animals were observed for several minutes after removal from the fog. The degree of dyspnea recorded in the tables was the maximum observed in this postaerosol period.

Positive reactions were graded *slight dyspnea* when the respiratory volume per breath increased definitely and unequivocally, usually with some slowing of respiration. Dyspnea was graded *severe* when asphyxia seemed imminent. *Slight-moderate*, *moderate*, and *moderately severe* were used to describe intermediate degrees of dyspnea. *A. D.* describes the typical anaphylactic death which occurred in a few animals. These terms were described in detail previously.³

The term *bronchial resensitization* is used when locally desensitized pigs react to subsequent challenges with specific hapten aerosols. Spontaneous resensitization, as used here, means local resensitization which occurs without the use of additional sensitizing antiserum.

Experiment I (Table I).—

Purposes: a. To sensitize passively against two types of pneumococcal polysaccharides by simultaneous intra-abdominal injections of antiserum.

b. To demonstrate the specificity of the hapten reactions by challenging and then desensitizing with one type without preventing reactions and subsequent desensitization to an aerosol of the other type.

TYPE VI AND TYPE VIII PNEUMOCOCCAL POLYSACCHARIDES AND TO ACACIA;
 TH TYPE VI AND TYPE VIII POLYSACCHARIDES

ALLENGE WITH POSITE OLYSAC. (MG./ML.)	EX- POSURE TIME (MIN.)	REACTION	AEROSOL DESENS. POLYSAC. (MG./ ML.)	EX- POSURE TIME (MIN.)	AEROSOL RECHAL- LENCE POLYSAC. (MG./ ML.)	EX- POSURE TIME (MIN.)	RE- ACTION	I.A.* SENS. DOSE ANTI- ACACIA SERUM (ML.)	AEROSOL CHAL- LENCE ACACIA (PER CENT)	EX- POSURE TIME (MIN.)	REAC TION
<i>type VIII</i>			<i>Type VIII</i>								
3.0	2	Moderate	0.3	30	3.0	8	None	0.75	3	10	Sligh to mod erate
3.0	8	Slight	0.3	30	3.0	8	None	0.75	3	10	Slight
3.0	8	Slight	0.3	30	3.0	8	None	0.75	3	10	Slight
3.0	5½	Very slight	0.3	30	3.0	8	None	0.75	3	10	None
<i>Type VI</i>			<i>Type VI</i>								
3.0	3	Moderate	0.3	28	3.0	7½	None	0.75	3	10	Very slig Slig
3.0	3½	Moderate	0.3	28	3.0	7½	None	0.75	3	10	Slig
3.0	1	Moderate to severe	0.3	80	3.0	8	Slight†	0.75	3	10	Non
3.0	1	Moderate to severe	0.3	80	3.0	8	Slight†	0.75	3	10	Non

c. To sensitize the same animals passively with antiacacia serum after they had been desensitized with both types of pneumococcal haptens.

This experiment was prompted by previous unsuccessful efforts to produce multiple sensitization.³ It was assumed that those failures were due to the unfortunate selection of ineffectual antigen-antibody systems.

Preliminary studies showed that antisera given at intervals of two hours intra-abdominally resulted in specific concurrent local sensitization to acacia and to type VI and type VIII pneumococcal polysaccharides. This local sensitization could be demonstrated more regularly to the polysaccharides than to acacia.

Method: Ten guinea pigs were sensitized passively with 0.5 ml. each of type VI and type VIII antiserum intra-abdominally.

Six of these were challenged first with type VI hapten aerosol. The four which survived were desensitized with type VI hapten. They were then challenged and subsequently desensitized with type VIII hapten. The remaining four animals were challenged and then desensitized with type VIII hapten first. They then were challenged and desensitized with type VI hapten.

The same eight survivors were then sensitized passively with antiacacia rabbit serum intra-abdominally. They were challenged the next day with 3 per cent acacia aerosol.

Results: Two of the animals challenged with strong (3 mg. per cubic milliliter) type VI polysaccharide aerosol died promptly in anaphylactic shock.

The four which were challenged and then desensitized first with type VI hapten aerosol reacted later when challenged with the type VIII aerosol and were subsequently desensitized specifically by it.

The four animals challenged and desensitized first with type VIII subsequently reacted to and were desensitized by type VI hapten aerosol.

Four of the eight animals sensitized with antiacacia serum reacted definitely to the aerosol challenge. Desensitization of these was not attempted, since it had been accomplished many times previously in acacia-sensitive animals. The reaction of another was, perhaps, equivocal. The other three showed no reaction. This percentage of reactions to acacia aerosol is comparable to that of other animals sensitized with the same batch of antiacacia rabbit serum.

Conclusions: 1. Specific local passive sensitization to multiple aerosol haptens and antigens can be conferred by suitable antisera.

2. Local desensitization may be produced by aerosols specifically, one at a time.

Experiment II (Table II).—

Purpose: To see if intra-abdominal hapten injections will desensitize locally against aerosols of haptens.

Method: Three groups of animals were used. The first three animals were sensitized with 0.15 c.c. of type VIII antiserum. They were challenged with type VIII hapten aerosol (1.0 mg. per milliliter) to demonstrate sensitization. They were then given three desensitizing injections of 0.5, 1.0, and 1.5 mg. of type VIII polysaccharide intra-abdominally in one day.

The day after desensitization they were challenged with three times (3.0 mg. per milliliter) the initial reacting concentration of hapten aerosol.

The second group of three animals was sensitized with an arbitrarily larger dose, 0.5 c.c., of type VIII antiserum. They were challenged with type VIII aerosol hapten (1.0 mg. per milliliter) to demonstrate sensitization. They were desensitized by the same method and dose as the first group. They were challenged the day after desensitization with five times (5.0 mg. per milliliter) the initial reacting concentration of polysaccharide aerosol.

The third group of four animals was sensitized with 0.25 ml. of type VI antiserum. They reacted to the initial challenge with 1.0 mg. per milliliter hapten aerosol.

They were desensitized with three larger doses of polysaccharide intra-abdominally, 0.5, 1.5, and 2.5 mg. in one day. The next day they were challenged with three times the initial reacting concentration of hapten aerosol.

Results: Two of three animals in both of the first two (type VIII) groups and all four of those in the third (type VI) group were completely desensitized locally. The intensity of the reaction was significantly reduced in the two animals (Nos. 3 and 4) which were not completely desensitized.

In eight other animals (not in the table) in which the initial reaction to aerosol challenge was slight, desensitization by the intra-abdominal polysaccharide was complete.

Conclusions: Desensitization with haptens given intra-abdominally may prevent reactions to specific hapten aerosols. Larger doses of hapten intra-abdominally probably would have provided complete protection in pigs 3 and 4.

Experiment III (Table III).—

TABLE III. EXPERIMENT III. FAILURE TO ELICIT REVERSE PASSIVE SENSITIZATION REACTIONS WITH AEROSOL ANTISERUM BUT ANAPHYLAXIS FOLLOWED INTRAVENOUS ANTISERUM

GUINEA PIG	I. V. SENS. DOSE TYPE VI POLYSAC. (MG.)	AEROSOL TYPE VI 1:5 ANTISERUM EXPOSURE TIME (MIN.)	REACTION	I. V. CHALLENGE TYPE VI CONC. ANTISERUM (ML.)	REACTION
1	2.0	10	None	2.0	Severe
2	2.0	10	None	2.0	Severe
3	2.0	10	None	2.0	A. D.
4	2.0	10	None	2.0	Severe
5	2.0	10	None	2.0	A. D.
6	1.0	8	None	2.0	Moderate
7	1.0	8	None	2.0	Moderate
8	1.0	8	None	1.0	Moderate
9	1.0	8	None	1.0	Moderate

16- to 24-Hour
Interval

Purpose: To attempt to produce reversed passive allergic bronchial reactions with an intravenous hapten as the sensitizer and specific antipneumococcal rabbit serum as the aerosol antibody.

Method: Nine pigs were sensitized intravenously with 1.0 or 2.0 mg. of type VI pneumococcal polysaccharide. They were challenged one hour later with an aerosol of type VI antipneumococcal rabbit serum. After a negative aerosol challenge, they were given antipneumococcal type VI antiserum intravenously to test for systemic reversed passive sensitization.

Results: There were no reactions to the antiserum aerosol. All the animals had anaphylactic shock when challenged intravenously with the antiserum.

Two of three animals similarly treated with type VIII polysaccharide and antiserum had equivocal reactions to the antiserum aerosol.

A number of other animals similarly treated, with other antigen-antibody systems, failed to react to the antiserum fog.

Conclusions: Definite reversed, passive, anaphylactic reactions to nebulized antiserum were not produced, although anaphylaxis followed intravenous injections of the same antiserum.

Experiment IV (Table IV).—

Purposes: To resensitize bronchi passively after they have been desensitized locally.

Method: Preliminary experiments showed that guinea pigs could be sensitized with 0.05, 0.1, and 0.15 ml. of antipneumococcal rabbit serum intra-abdominally.

Six guinea pigs (1 to 6 in table) were sensitized, three with type VI and three with type VIII antiserum. Sensitization was confirmed by positive reactions to a relatively weak concentration (1.0 mg. per milliliter) of the hapten aerosol. They were then desensitized by an aerosol of one-tenth (0.1 mg.

TABLE V. EXPERIMENT V. LARGE DOSES OF SENSITIZING ANTISERUM MAY PRODUCE SPONTANEOUS RESENSITIZATION (A) SEVEN AND (B) TWO DAYS AFTER LOCAL DESENSITIZATION BY SPECIFIC HAPTEN AEROSOL

GUINEA PIG	I. A. SENS. DOSE TYPE VI ANTI-SERUM (ML.)	CHALLENGE TYPE VI POLYSAC. (MG./ML.)	EX-POSURE TIME (MIN.)	REACTION	DESENS. TYPE VI POLYSAC. AEROSOL			CHALLENGE TO CON-FIRM DESENS. CONC. POLYSAC. AEROSOL (MG./ML.)	EX-POSURE TIME (MIN.)	RE-ACTION	CHALLENGE TYPE VI POLYSAC. (MG./ML.)	EX-POSURE TIME (MIN.)	REACTION	
					(MG./ML.)	TIME IN MIN.	TYPE VI POLYSAC. AEROSOL							
														A*
1	5.0	1.0	1/2	Moderate	1.0	84	Interval 16-to 24-Hour	3.0	8	None	Interval 7-Day	3.0	7 1/2	Sl. mod.
2	5.0	1.0	1	Severe	1.0	84		3.0	8	None		3.0	4	Moderate
3	5.0	2.0	1/2	Moderate	0.5	120		3.0	8	None		2.0	8	Sl. mod.
4	5.0	2.0	1/2	Mod. Sev.	0.5	120		3.0	8	None		2.0	8	None§
Controls														
5	5.0	NINE-DAY INTERVAL										3.0	2	Severe
6	5.0											3.0	2	Moderate
B†														
7	5.0	2.0	1	Mod. Sev.	0.5	60	Interval 16-to 24-Hour	3.0	8	None	Interval 2-Day	3.0	5	Mod. sev.
8	5.0	2.0	2	Severe	0.5	60		3.0	8	None		3.0	8	Slight
9	5.0	2.0	1	Mod. Sev.	0.5	60		3.0	8	None		3.0	7 1/2	Moderate
10	5.0	2.0	8	Slight	0.5	60		3.0	8	None		3.0	7 1/2	Slight
11	5.0	2.0	1/2	Moderate	0.5	120		3.0	8	None		2.0	8	None§
12	5.0	2.0	1/2	Severe	0.5	120		3.0	8	None		2.0	8	None§
13	5.0	2.0	1/2	A. D.				3.0	8	None				
Controls‡														
14	None	2.0	10	None	0.5	60	Interval 1-to 2-Hour	3.0	8	None	Interval 2-Day	3.0	8	None
15	None	2.0	10	None	0.5	60		3.0	8	None		3.0	8	None
16	None	2.0	10	None	0.5	60		3.0	8	None		3.0	8	None
17	None	2.0	10	None	0.5	60		3.0	8	None		3.0	8	None

*No effort was made to desensitize any of these pigs after initial desensitization.
†Pigs 7 to 12 were rechallenged on the fourth, fifth, and sixth days; Nos. 7 to 10 reacted to each challenge while Nos. 11 and 12 did not react to either challenge.
‡Pigs 14 to 17 were negative controls. They, too, were exposed to 3.0 mg. per milliliter of polysaccharide on the fourth, fifth, and sixth days. They did not react.
§Failure to become resensitized spontaneously.

per milliliter) of the reacting concentration of the hapten. Desensitization was confirmed by a negative aerosol challenge with thirty times (3.0 mg. per milliliter) the desensitizing concentration of hapten. After desensitization the initial intra-abdominal sensitizing dose of antiserum was repeated.

Two other pigs (7 and 8) were given initial sensitizing doses of 0.05 ml. of antiserum. They had no or equivocal reactions to the first (strong, 3.0 mg. per milliliter) aerosol hapten challenge. They were then given an additional 0.1 c.c. of antiserum intra-abdominally. They were rechallenged the next day with the strong aerosol concentration which initially had failed to elicit significant reactions.

Results: None of the pigs reacted to the desensitizing concentration (0.1 mg. per milliliter) of the hapten. Five of the six animals which had been desensitized locally by the weak hapten aerosol were resensitized by repeating the initial sensitizing dose of antiserum. The one which was not resensitized was one of the two which received the smallest resensitizing dose of antiserum. The other two, which had been sensitized very slightly or not at all by the first small dose of antiserum, became sensitized when additional sensitizing doses of antiserum were given.

Conclusions: 1. Locally desensitized guinea pigs can be resensitized usually by repeating the initial intra-abdominal dose of sensitizing antiserum.

2. Guinea pigs which do not become sensitized locally by small intra-abdominal doses of antiserum may become sensitive if subsequent larger sensitizing doses are given.

3. Local desensitization may be effected by subreacting concentrations of the hapten aerosol. This desensitization may be effective against thirty multiples of the desensitizing concentration of the hapten.

Experiment V (Table V).—

Purpose: To determine whether spontaneous local resensitization will occur after local desensitization in guinea pigs previously sensitized with very large doses of antiserum.

In earlier experiments,³ using small sensitizing doses of 0.65 ml. of antiserum or less, local desensitization persisted nine to eleven days (about as long as passive sensitization lasted) and spontaneous resensitization was not observed.

Method and results: Thirteen guinea pigs were sensitized with 5.0 ml. type VI antiserum. The next day eleven of them reacted when challenged with type VI pneumococcal polysaccharide aerosol. The ten survivors were desensitized promptly with 1.0 or 0.5 mg. per milliliter hapten aerosol. Desensitization was confirmed by failure to react when challenged with a stronger (3.0 mg. per milliliter) aerosol. Seven days (Nos. 1 to 4) and two days (Nos. 7 to 12) later they were rechallenged with type VI polysaccharide aerosol. Seven of the ten pigs reacted.

Two pigs (Nos. 5 and 6) were not desensitized. They were used as positive controls and were challenged with type VI polysaccharide on the ninth day. They reacted promptly.

Four pigs (Nos. 14 to 17) were not sensitized. They were negative controls. They did not react to any of the aerosol challenges.

Conclusions: 1. Guinea pigs passively sensitized with large amounts of antiserum may remain sensitized for at least nine days.

2. Seven of ten such animals had become spontaneously resensitized locally when challenged seven or two days after effective local desensitization by an aerosol of specific hapten. Three did not become resensitized.

3. This is in contrast to the persistence of local desensitization for at least nine days when small doses of sensitizing antiserum were used.³

4. Some unrecognized factor other than the administration of ± 30 multiples of a normally sensitizing dose of antiserum is necessary to produce spontaneous resensitization at will.

DISCUSSION

It was stated earlier³ that: "It would have emphasized the specificity of the desensitization if some guinea pigs had been sensitized to antigens or haptens and had then been desensitized, specifically against one, without prevention of the aerosol reaction to the other." Experiment I provides this emphasis of the specificity of the aerosol desensitization. In addition, it shows that guinea pigs may be passively sensitized so they will react locally and specifically to aerosols of three, and presumably more, haptens or antigens. The earlier unsuccessful attempts³ are not completely explained. Partial explanations lie in: (1) the unfortunate selection of the type II pneumococcal antibody-polysaccharide system, which would not sensitize;³ (2) the fact that passive local sensitization of the bronchi is much less consistently demonstrated by aerosols, both in degree and incidence, than is systemic sensitization by intravenous challenge. This is true of the six antigen-antibody systems used so far in this laboratory.

It has been shown³ that aerosol desensitization is local, that is, subsequent intravenous haptens will cause prompt anaphylaxis. Experiment II shows that the converse of this is not true. In other words, the bronchi of guinea pigs desensitized by intra-abdominal injections of the hapten did not react to the postdesensitization aerosol hapten challenge. It is assumed that these pigs were systemically desensitized, since earlier experiments² had shown that smaller doses of hapten would protect against intravenous challenge with the polysaccharide.

A ready explanation of the broader effectiveness of intra-abdominal versus aerosol desensitization seems to lie in the great differences in the amounts of hapten used in the two procedures. Intra-abdominal desensitization required 3 to 4.5 mg. of the hapten, whereas in local desensitization by aerosol only about 350 gamma of hapten is inhaled per hour (using Feinberg's⁴ estimates of antigen inhaled by aerosol). No method has been devised yet for estimating how much inhaled antigen gets into the circulation.

The importance of the quantity of hapten used in intra-abdominal desensitization against local reactions to aerosols is suggested by these observa-

tions: (1) All four animals receiving the larger desensitizing doses, in Experiment II, were completely protected. (2) The smaller desensitizing doses protected only two of three animals in each of the first two groups.

It is of interest that all eight of the animals, mentioned but not tabulated in Experiment II, which reacted only slightly to the initial aerosol challenge were completely desensitized by the smaller intra-abdominal doses of hapten.

No effort has been made to explain the unsuccessful attempts to elicit dyspnea in the reverse passive aerosol anaphylaxis experiment (III). It is probable that too little antiserum is absorbed by aerosol⁴ to mediate a reaction. It is not likely that massive sensitizing doses of hapten would be successful.

Passing attention should be given to the observation in Experiment IV that very weak nonreacting concentrations of hapten aerosol desensitized completely against thirty multiples of the desensitizing concentration. This is more impressive than the fifteen to twenty multiples previously reported.³

In the preceding article³ it was shown that local desensitization lasted nine to eleven days, under the conditions of those experiments. Herxheimer⁵ reported that actively sensitized guinea pigs desensitized by an aerosol of a whole antigen became resensitized spontaneously in a few days. It seemed proper to attempt to reconcile these two seemingly contradictory conclusions. Examination of the earlier data³ suggested that the observed failure to become resensitized might be due to amounts of circulating antibody insufficient to induce spontaneous local resensitization after local desensitization. Experiments IV and V were designed to test this hypothesis.

The results of Experiment IV supported this hypothesis in three ways: (1) animals which were not sensitized by the initial small sensitizing dose became sensitive when additional sensitizing antiserum was given; (2) most of the locally desensitized animals were resensitized when the original sensitizing dose was repeated; (3) the desensitized animal which did not become resensitized was one of two which received the smallest sensitizing and resensitizing doses of antiserum.

The results in Experiment V give additional support to the hypothesis. In the earlier experiments,³ in which local desensitization was lasting, the sensitizing doses of antiserum were small, roughly, 3.5 to 4.5 multiples of the nearly minimal effective sensitizing dose of 0.15 c.c. used in Experiment IV. When 33.3 multiples (5.0 c.c.) of this small (0.15 c.c.) sensitizing dose were used in Experiment V, spontaneous resensitization occurred. It seems reasonable to assume that the large (5.0 ml.) sensitizing dose of antiserum supplied enough excess circulating antibody (a) to neutralize the small amount of desensitizing hapten locally and subsequently (b) to resensitize the bronchi.

Antibody production in actively sensitized guinea pigs continues long enough to maintain active sensitization for several months.^{6, 7} The assumption seems reasonable, therefore, that there was enough excess antibody to explain the spontaneous resensitization in Herxheimer's⁵ actively sensitized animals. It should take very little to replace the antibody neutralized by the ± 350 gamma per hour of haptens inhaled in desensitization.

The problem of spontaneous resensitization is not as simple as the preceding discussion would lead one to believe. Other unrecognized factors are undoubtedly concerned. This opinion is derived from two attempts to titrate, roughly, the smallest amounts of type VIII and type VI antisera which would produce spontaneous resensitization. The results with type VIII were so at variance with those with type VI antiserum that further study is needed to resolve the differences.

Spontaneous resensitization has received scant attention in the recent literature. It is obviously important in any consideration of the duration of desensitization. It seems likely that a quantitative relationship between sensitizing antibody and desensitizing hapten or antigen will be shown to be the crux of the problem. Such a relationship already has been reported in reverse passive anaphylaxis resensitization.⁸

No hypothesis is offered to explain the marked variations observed in: (1) the incidence, intensity, and time of onset of the reactions to specific aerosols; (2) the desensitizing time; (3) the concentration of effective challenging doses; (4) the amounts of sensitizing antiserum necessary to produce spontaneous resensitization; and (5) the efficiency of different antigen-antibody systems. This is in striking contrast to the relatively uniform reactions to intravenous challenges obtained in similarly sensitized animals.

SUMMARY AND CONCLUSIONS

These additional studies of bacterial haptens in local desensitization of passively sensitized guinea pigs permit the following conclusions:

1. Suitable antisera can confer multiple passive sensitization to guinea pigs so they will react to and be desensitized specifically by aerosols of each hapten, one at a time.

2. Specific bronchial desensitization may be induced by intra-abdominal injections, as well as by the previously reported aerosols of haptens.

3. Attempts to elicit reverse passive anaphylactic reactions to nebulized antiserum were unsuccessful, although anaphylaxis followed intravenous injections of the same antiserum.

4. Locally desensitized bronchi can be resensitized, usually, by repeating the intra-abdominal dose of sensitizing antiserum.

5. Subsequent larger intra-abdominal doses of antiserum may sensitize when earlier smaller doses do not.

6. Local desensitization of bronchi may be effected by subreacting concentrations of hapten aerosol. This desensitization may be effective against thirty multiples of the desensitizing concentration of haptens.

7. Spontaneous local resensitization was observed two days and seven days after effective local desensitization in some, but not all, animals sensitized passively with large amounts of antiserum.

8. The problem of resensitization has received scant attention in the past. It needs more study.

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