THE PRODUCTION AND SIGNIFICANCE OF CUTANEOUS ALLERGY TO PNEUMOCOCCUS PROTEIN.

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PLATE 4.

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The type of hypersensitiveness represented by the much studied tuberculin allergy has been observed to occur in a number of non-tuberculous infections. Studies of the altered skin response to soluble derivatives or to intact organisms have been made in infections due to *Bacillus typhosus*, *Bacillus abortus bovinus*, *Bacillus mallei*, *Spirochæta pallida*, *Sporotrichum*, and *Trichophyton;* and there are indications that the same phenomenon may occur in other infections. At any rate it may be said that allergy to derivatives of microorganisms is not an uncommon accompaniment of infection. In a consideration of infection from the point of view of allergy, one of the questions which arises is the relation of the tuberculin type of allergy to anaphylaxis. The experiments of Krause and the recent work of Zinsser (1) indicate that this type of altered reactivity is quite independent of anaphylaxis. They are distinct phenomena which may or may not coexist during an infection. A second question which has long been under investigation and discussion is whether actual infection is necessary for the production of the tuberculin type of allergy. Students of tuberculosis have until lately regarded actual infection as a necessary prerequisite of tuberculin and other similar allergies, although foci produced by the injection of killed cultures have sometimes been found to be accompanied by a temporary skin allergy. The studies of Zinsser (1), McJunkin (2), Petroff (3), Lange (4), and Eberson (5) have in the last few years cast doubt on the belief that actual infection is necessary. The experiments reported in this paper add additional evidence in support of the idea that an allergy of the tu-

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berculin type may be produced in the absence of infection. A third question relates to the rôle that allergy plays in the immunity mechanism.

While opinion has favored the view that tuberculin allergy is an important factor in tuberculosis immunity, the evidence is not complete, and with regard to the rôle of this kind of allergy in the immunity mechanisms of other types of infection, there has been little more than analogy to support the hypothesis that its presence indicates resistance to infection by the homologous organism.

In a separate paper (6) experiments dealing with the effects of anaphylaxis to pneumococcus protein upon resistance to pneumococcus infection have been reported. The present paper deals with the effects, or rather, as will be shown, the nearly complete absence of effects upon resistance to pneumococcus infection of an allergy produced with soluble derivatives. The organism used in the present study has been the same strain of Pneumococcus Type I, with virulence enhanced by repeated passage through guinea pigs, that was described in the preceding paper. The pneumococcus protein was prepared in the same way. The animals used were guinea pigs weighing at the beginning of each experiment 200 to 250 gm.

In attempting by several methods to render guinea pigs allergic to pneumococcus protein it was found that repeated intracutaneous injections (0.02 to 0.05 cc.) of a solution containing 10 mg. of nitrogen per 100 cc. yielded the most satisfactory results. About two-thirds of the animals so treated developed during the 3rd, 4th, or 5th week after the first injection a distinct cutaneous allergy. The cutaneous reaction produced in this way develops after a latent period of 8 to 16 hours; it consists of a firm bright red nodular elevation varying, when 0.02 cc. has been injected, from 6 to 15 mm. in diameter (Fig. 1). It persists 2 or 3 days and then recedes without breaking down. It is, therefore, in its appearance and course, similar to a mild tuberculin reaction. We have not succeeded either by the uterus strip method or by intravenous injection of the intact animal in demonstrating anaphylaxis in these allergic animals. This is in agreement with Zinsser's (1) observations on the independence of tuberculin allergy and tuberculoprotein anaphylaxis. When the intraperitoneal or the intravenous method of administering the pneu-

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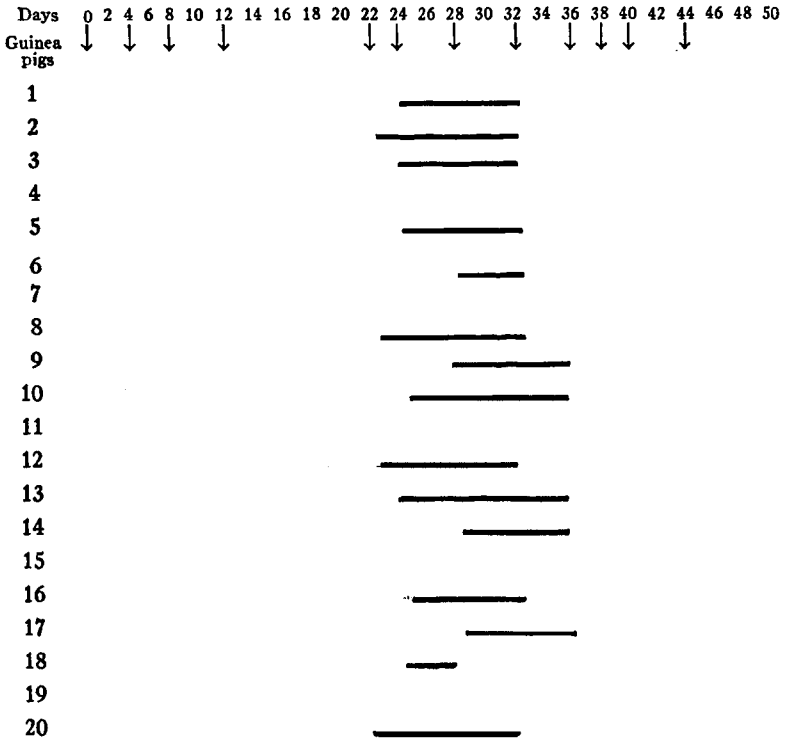
mococcus protein was used a large proportion of the animals died between the 10th and 20th days. Presumably such deaths were due to an immunological process since there was no gross pathology, and post mortem cultures were sterile. Rosenow (7) has recorded similar deaths in using pneumococcus autolysates for sensitization.



TEXT-FIG. 1. Time of appearance and duration of skin allergy in a group of guinea pigs given repeated intracutaneous injections of pneumococcus protein. The lines indicate the periods during which allergy was demonstrable. The arrows indicate the days on which injections were given in amounts of 0.02 to 0.05 cc. Five of the animals in this experiment failed to develop a skin reaction. The others showed variations in intensity and duration of the allergy.

Text-fig. 1 records an experiment of this type. It is seen that the skin allergy is manifest during the 4th and 5th weeks after the first injection. Guinea pigs as purchased from dealers show important individual variations in their susceptibility to this type of allergy. Some fail to develop it; others show only slight reaction for 3 or 4

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TABLE I.

Immunity of Allergic Guinea Pigs to Pneumococcus Infection.

		Guinea pig No.	Weight.	Amount of 18 hr. culture (intraperitoneally).	Result.	Autopsy.	Cultures from peritoneum.	Cultures from heart's blood.
			gm.	*cc.*				
Group I.	Animals with skin allergy to pneumococcus protein.	159	297	0.1	Died 36 hrs.	Typical.	Pneumococcus.	Pneumococcus.
		141	387	0.01	" 36 "	"	"	"
		142	315	0.001	" 36 "	"	"	"
		143	338	0.0002	" 36 "	"	"	"
		157	344	0.0001	Survived.			
		152	308	0.00002	Died 36 hrs.	"	"	"
		136	314	0.00001	" 56 "	"	"	"
		144	325	0.000002	Survived.			
		145	346	0.000001	Died 36 hrs.	"	"	"
" II.	Injected animals which failed to develop skin allergy.	138	246	0.1	" 20 "	"	"	"
		155	345	0.001	" 44 "	"	"	"
		147	308	0.0002	" 36 "	"	"	"
		150	341	0.0001	" 36 "	"	"	"
		149	314	0.00002	" 36 "	"	"	"
		151	352	0.00001	Survived.			
		153	316	0.000002	Died 36 hrs.	"	"	"
		156	307	0.000001	" 56 "	"	"	"
" III.	Controls.	160	388	0.01	" 20 "	"	"	"
		161	280	0.001	" 36 "	"	"	"
		162	280	0.0001	" 36 "	"	"	"
		163	342	0.00001	" 56 "	"	"	"
		164	336	0.000002	" 56 "	"	"	"
		165	337	0.000001	" 56 "	"	"	"

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days; others have intense reactions during a period of 10 days or more. As is indicated in Text-fig. 1, continuance of the intracutaneous injections after the skin allergy has developed results in a desensitization, so to speak. The skin response is no longer demonstrable.

If the resistance to the homologous pneumococcus is titrated in a group of guinea pigs rendered allergic in this way, it is found that their susceptibility to infection differs little or not at all from that of normal controls. The same absence of any measurable alteration in resistance is found in the animals which have been injected but have failed to develop skin allergy. Table I illustrates such a titration. We have also found that the animals which have passed through the phase when skin allergy is demonstrable and become desensitized are likewise neither more nor less resistant than normal controls to infection with the homologous organism.

The animals in Groups I and II (Table I) received preparatory intracutaneous injections of pneumococcus protein at intervals of 2 or 3 days. After 6 weeks it was found that some animals had developed skin allergy (Group I) and others had not (Group II). The resistance of these two groups to pneumococcus infection was then tested by intraperitoneal injection of the amounts shown. At the same time normal controls (Group III) were injected with graded amounts. From the table it is seen that there is very little evidence that the animals with skin allergy to the pneumococcus protein had acquired an increased resistance. Two of these animals survived larger amounts of culture than sufficed to kill other animals. But since survivals of this kind not infrequently occur in normal animals injected with graded doses we feel disposed to attribute them more to individual variations in natural susceptibility than to actively produced immunity. From our results, however, the possibility that an occasional animal acquired some immunity synchronously with the acquisition of skin allergy cannot be completely excluded. But if such be the case, it is very irregular in occurrence and slight in degree.

While our results fail to bring out any evidence in favor of the idea that allergy to pneumococcus protein is a factor in pneumococcus immunity, there is no valid reason to think that the same relation exists

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between allergy and immunity in other types of infection. As was stated at the beginning of this paper, there is sufficient evidence to convince most students of tuberculosis that in the mechanism of resistance to tubercle bacillus infection allergy plays a significant and perhaps predominant rôle. And so with other types of infection allergy may or may not be immunologically important. Each type of infection presents a special case; and only experimental analysis, it would seem, can determine whether allergy is important or unimportant in the immunity mechanism of an infection. No generalization on the basis of results with the tubercle bacillus or the pneumococcus is justified.

CONCLUSIONS.

1. Intracutaneous injection of guinea pigs with an alkaline extract of pneumococcus produces in about two-thirds of the animals an allergy with a skin reaction similar to the allergic skin response of tuberculosis.

2. Continuance of the intracutaneous injections after the appearance of allergy results in its disappearance. The skin ceases to react.

3. Neither the animals manifesting skin allergy nor those which fail to develop it show any significant alteration in susceptibility to pneumococcus infection by intraperitoneal inoculation. Similarly, animals desensitized by continuing the intracutaneous injections after the appearance of allergy show an unaltered susceptibility.

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EXPLANATION OF PLATE 4.

FIG. 1. Skin reaction produced by the intracutaneous injection of 0.02 cc. of pneumococcus protein (N_2 = 10 mg. per 100 cc.) 24 days after the first of a series of intracutaneous injections.

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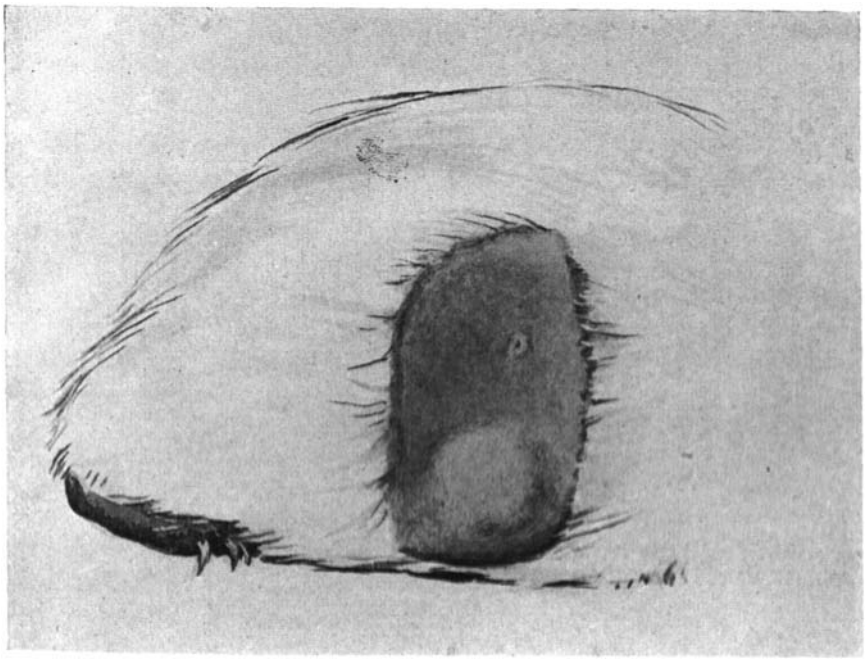

(Mackenzie and Woo: Cutaneous allergy and pneumococcus protein.)

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