ACTIVE AND PASSIVE IMMUNITY TO PNEUMOCOCCUS INFECTION INDUCED IN RABBITS BY IMMUNIZATION WITH R PNEUMOCOCCI.

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In a previous publication (1) the fact was established that rabbits, immunized with degraded, avirulent, non-type-specific pneumococci —so called R strains derived from any one of the three types—acquire a considerable degree of resistance against subsequent infection with virulent Type III pneumococci. Active resistance was demonstrable under these conditions in spite of the fact that the sera of the immunized rabbits contained no type-specific antibodies capable of agglutinating Type III S cells, or of precipitating the soluble specific substance derived from Type III cultures, or of conferring passive protection on mice against Type III infection. It was suggested (1) that this form of active immunity, effective in the absence of demonstrable type-specific antibodies and unrelated to the variety of pneumococcus used for immunization, differed in principle from type-specific immunity. The previous experiments were restricted to the study of the active resistance to Pneumococcus Type III. However, it seemed possible that this form of immunity—induced by immunization with R cells—might be effective against infection with other virulent types of pneumococcus. Consequently, additional studies have been carried on to determine whether the apparently non-type-specific resistance thus induced is as effective against Type I and Type II as against Type III. The results are recorded in this communication. In view of the differences which appear to exist between the form of active immunity stimulated in rabbits by type-specific S organisms and intimately associated with type-specific antibodies, and active resistance induced by prolonged immunization with R cells, further investigation into the nature and mechanism of the latter type of immunity is in progress.

In addition, the work has been extended to include passive immunity in order to determine whether the blood of rabbits immunized with R pneumococci, is capable of conferring protection upon normal animals of the same or of different species. The results of experiments on passive immunity are also included in this report.

Methods.

Antigens.—An R strain originally derived from Type II S culture (designated R_2), an R strain similarly derived from Type I S culture (designated R_1), and a Type III S strain were employed for the immunization of all rabbits used in the experiments on active immunity. Only the R_2 strain was used for immunization in the tests for passive immunity.

Vaccines were prepared from 12 to 14 hour plain broth cultures. The organisms, removed from the broth by centrifugation, were resuspended in physiological salt solution in such proportion that 0.5 cc. of the suspension was equivalent in bacterial content to 1 cc. of original culture, and heat-killed at 56° for 30 minutes.

Technique of Immunization.—The method of immunization, described by Cole and Moore (2), consisted of a total of 18 intravenous injections; 0.5 cc. doses of vaccine were given daily for 6 days followed by a week of rest until the procedure was repeated 3 times. As a rule, the animals were tested 9 to 14 days after the last dose.

Protection Tests.—12 to 14 hour blood broth cultures of virulent pneumococci of Types I, II, and III were used in all tests for active and passive immunity. Type I cultures possessed a maximum virulence for rabbits of 0.000001 cc.; Type II were usually fatal in 0.000001 cc. and always in 0.00001 cc. amounts; Type III killed regularly at 0.0001 cc. In most of the experiments, in order to follow the degree of the bacteremia, blood cultures were taken at frequent intervals during the course of infection as previously described (3).

Rabbits tested for increased resistance to Type I infection had previously been treated as follows: 1 had been immunized with R pneumococci derived from Type I S strain, 15 with R pneumococci derived from Type II S strain, and 3 with Type III S pneumococci. Their sera were tested for the presence of agglutinins for R organisms and for the S forms of the three specific types. In no instance were type-specific agglutinins demonstrable; there were, however, agglutinins for R cells present in titres of 1:640 to 1:1280. Antibody response was similar regardless of organisms used for immunization. That rabbit avirulent strains of Type III stimulate in rabbits antibody formation of the same character as that elicited by R cells has been previously described (4). The infecting dose of Type I pneumococcus, in every instance, represented 10,000 to 100,000 lethal doses. By keeping the test strain at a maximum virulence for rabbits of 0.000001 cc., 0.01 cc., or 0.1 cc. of such culture constituted the dosage of organisms employed.

In each experiment, in addition to the immunized rabbits, normal animals receiving the minimal lethal dose and others the test dose served as controls of the virulence of the culture.

TABLE I.

Active Immunity against Infection with Pneumococcus Type I in Rabbits Immunized with R Strains. (Three Rabbits Immunized with S_{III} Are Also Included.)

Number of rabbits	Immunized with	Infected with Pneumococcus Type III	Route of infection	Number died	Number survived
		cc.			
1	R_I	0.01	Intravenous	0	1
3	S_{III}	0.1	"	1*	0
		0.01	"	0	2
8	R_3	0.1	"	1†	5
		0.01	"	0	2
4	R_3	0.1	Intraperitoneal	1‡	0
		0.01	"	0	3
6	R_2	0.1	Intradermal	0	2
		0.01	"	0	4
Total 22				3	19
9	Normal controls	0.000001	Intravenous	6	0
		0.000001	Intraperitoneal	1	0
		0.000001	Intradermal	2	0
Total				9	0

* Animal died 8 days after infection.

† Animal died 5 days after infection.

‡ Animal died 7 days after infection. Controls receiving test dose of culture died within 36 hours.

Active Immunity.

Rabbits were tested for resistance to infection by the injection of organisms intravenously, intraperitoneally, and intradermally (Table I). Blood cultures were taken at frequent intervals in order to observe the duration and degree of the bacteremia.

Rabbits Infected Intravenously.—Of 12 rabbits infected intravenously, 5 of which received 0.01 cc., and 7 0.1 cc. each of virulent Type I culture, 10 survived. The 2 which finally succumbed, lived 5 and 8 days respectively, whereas normal rabbits receiving the same dose died in 24 to 48 hours. As evidence of the duration of the immunity, 2 of the rabbits in this group were tested 4½ months after the last immunizing dose and found to be resistant. As demonstrated by blood cultures, organisms persisted in the circulation for 3 to 6 days, increasing and decreasing in number irregularly until their final disappearance. Even in the two fatal instances, the animals possessed some degree of partial immunity as revealed by the fact that both lived several days longer than the controls, that neither suffered an overwhelming septicemia, and that at autopsy each showed evidence of attempted localization in the form of pleurisy and pericarditis. A bacteremia characterized by an irregular course was previously shown to occur when R immunized rabbits were infected with a rabbit virulent strain of Type III pneumococcus (1). This form of bacteremia appears to be characteristic of the benign blood infection occurring when rabbits, immunized with R cells, are infected intravenously with any of the specific types of pneumococcus and suggests a similarity in the mechanism of recovery in each instance.

Rabbits Infected Intraperitoneally.—Four rabbits, immunized with R_2 organisms, were infected intraperitoneally; 1 received 0.1 cc. and 3 received 0.01 cc. of Type I pneumococci. The latter 3 animals survived; the one injected with 0.1 cc. lived 7 days. In the 3 animals which survived, only a few bacteria were transiently present in the blood stream. The duration of cocci in the peritoneal cavity was not determined.

Rabbits Infected Intradermally.—Type I organisms in doses of 0.01 cc. and 0.1 cc. were introduced intradermally into 6 rabbits which had previously been immunized with R_2 cells. All 6 animals survived. The local lesion developed rapidly; in 24 to 48 hours it appeared fulminating, usually reddish purple, edematous, spreading ventrally in a well defined and elevated band and forming a boggy pouch of edema over the more dependent portions of the abdominal wall. Areas of ecchymosis were commonly present. Normal rabbits reacted with a similar lesion, although succumbing to the infection. Furthermore, blood cultures revealed a striking difference in the course of the infection in normal and immunized animals. The blood stream of immune rabbits either remained sterile or contained only a few organisms transiently present. In sharp contrast, normal rabbits developed, within a few hours, a blood infection which increased rapidly in severity until death ensued from an overwhelming septicemia. Recently Goodner (5) has reported results obtained following intradermal injection of Type I pneumococci. The lesion which he describes as occurring in normal rabbits is identical with the inflammatory reaction encountered in the animals used in these experiments. Results which have been obtained following the intradermal inoculation of pneumococci into normal, type-specifically immune, and R immunized rabbits will be reported later in a separate communication.

In addition to the rabbits immunized with R organisms and tested for resistance to infection with Type I, 3 rabbits which had received similar preliminary injections were infected intravenously with virulent Type II pneumococci. They survived 10,000 lethal doses. The character of the blood infection and the process of recovery were similar in all respects to those already observed in the case of infection with Types I and III.

From the results of these experiments with Type I and Type II pneumococci, and from those reported (1) using Type III, it may be concluded that adequate immunization of rabbits with R pneumococci stimulates the development of active immunity which is effective against any of the fixed types. A consideration of these results and their possible significance will be presented in the discussion.

Passive Immunity.

In the course of an analysis of the immunity induced by repeated injections of R pneumococci, experiments have been carried out to determine whether this form of resistance is passively transferable. Whole citrated blood and serum of rabbits which have acquired resistance through immunization with R cells have been passively transferred to normal rabbits and also to mice. The R strain used for immunization was derived from Type II S culture. The infecting organisms were virulent S strains of Type I or Type III. These precautions were taken in order to minimize the possible participation of type-specific antibodies. The blood for transfusion was drawn 9 to 14 days after the last immunizing dose.

In the first experiments the procedure was to transfer whole blood or its constituents from resistant to normal rabbits and 24 hours later to inject the recipients with virulent pneumococci. An example of the results obtained following the passive transference of whole citrated blood, plasma, cells, and serum is given in Table II.

A description of this experiment will serve as an illustration of the method employed and the results obtained.

From the ear vein of an R immunized rabbit 20 cc. of blood was allowed to drop into a tube containing 0.5 cc. of a saturated solution of sodium citrate. This made in final dilution approximately a 2 per cent sodium citrate solution. Immediately upon obtaining the desired amount, the blood was injected by means of a syringe into the ear vein of a normal rabbit. In making transfusions from rabbit to

rabbit no precaution was taken with regard to blood grouping. Sometimes immediately after the operation the recipient would show evidence of shock, characterized by clonic and tonic muscular spasms. Complete recovery usually occurred in 3 to 4 minutes. In one instance death ensued and in 2 other animals permanent paralysis of the hind limbs resulted. 20 cc. of blood similarly collected in citrate were separated by centrifugation into plasma and cells. An equal amount without citrate was allowed to clot and the serum collected. Sterile

TABLE II.

Passive Protection of Rabbits against Pneumococcus Infection by Transfusion of Blood, Plasma, Cells, and Serum of Rabbits Immunized with R Pneumococci.

1. Protocol of Course of Bacteremia in Anti-R Donor and Recipients.

Time of blood culture	Number of colonies per unit of blood								
	Anti-R donor	Anti-R recipients				Normal donor	Normal recipients		Control 0.0001 cc. Type III
		Whole blood	Plasma	Serum	Cells		Whole blood	Serum	
2 hrs.	1	42	86	93	113	∞	20	1000	
6 hrs.	13	5	0	40	13	∞	2	816	
10 hrs.	1	9	15	62	142	∞	23	∞	
20 hrs.	58	15	7	12	518	D	148	∞	
24 hrs.	142	1	2	38	∞		272	D	
30 hrs.	32	0	29	116	∞		522		
48 hrs.	1	1	1	25	∞		∞		
72 hrs.	0	1	1	3	∞		D		D
96 hrs.	4	0	12	14	D				
5 days	0	0	1	8					
6 days	0	0	8	1					
9 days	0	0	0	0					
11 days	0[s]	0[s]	0[s]	0[s]					

0.1 cc. of rabbit virulent strain of Type III used as infecting dose.
D indicates death of the animal.
S indicates survival of the animal.
Numerals represent number of colonies per unit of blood.

precautions were observed throughout the procedure. 20 cc. of whole blood, or its equivalent in plasma, cells, or serum were then injected intravenously into normal rabbits. 24 hours later these rabbits were infected intravenously with 0.1 cc. of a rabbit virulent strain of Type III. Normal rabbits which had received comparable amounts of whole blood or serum from other normals were similarly infected. Other normal rabbits without preliminary treatment were infected with the maximal test dose and the minimal lethal amount of culture.

From Table II it may be seen that whole blood, plasma, and serum from resistant rabbits afforded protection against 1000 lethal doses of Type III pneumococcus, whereas blood cells alone were inadequate. Controls receiving normal blood or serum were unprotected. Tabulation of the number of organisms in the blood cultures reveals the fact that the resistant rabbits continued to have pneumococci in varying numbers in the blood stream from 3 to 6 days before permanent sterility was attained. Rabbits receiving normal blood, on the other hand, although possessing a slight initial capacity to reduce the number of circulating bacteria were unable to cope with the subsequent rapid increase, and died of an overwhelming septicemia.

Repetitions of protection experiments of this character using virulent Type I pneumococci instead of Type III gave results equally definite, indicating that, as in the case of active immunity, passive protection of rabbits is not limited as to type of infecting pneumococcus.

From these experiments it is established that resistance induced in rabbits by immunization with R pneumococci can be passively transferred to normal rabbits. In titering the amount of blood necessary to confer passive protection it was found that 15 to 20 cc. were necessary against doses of culture as high as those constantly employed, *i.e.* 1000 lethal doses of Type III or 10,000 to 100,000 of Type I. This quantity of blood was regularly used in all subsequent experiments. In Table III the total number of transfusions and the results are recorded. It may be seen that, with the amount of blood transfused and the dosage of culture kept constant, the time elapsing between transfusion and injection of organisms has been varied from 1 hour to 21 days. Of 5 rabbits infected within 5 hours of the time of transfusion 4 died and 1 survived. Twenty-three animals were infected 1 to 7 days after transfusion and of these 18 recovered. One rabbit infected 14 days after transfusion, survived, and of 5 in which an interval of 3 weeks elapsed, 3 recovered.

With the use of 8 to 10 cc. of serum, an amount comparable to that contained in 15 to 20 cc. of whole blood, protection was demonstrable but the results were somewhat less striking. In Table III the results of protection tests by the use of serum are presented. Of 5 rabbits infected 1 to 5 hours after serum administration, 4 survived. With an interval of 1 to 7 days, out of 9 animals tested, 4 survived; in 3 in-

TABLE III.

Passive Protection of Rabbits against Pneumococcus Infection by Transfusion of Blood and Serum of Rabbits Immunized with R Pneumococci.

2. Summary of Results of Passive Protection Tests in Rabbits.

Rabbit No.	Amount of blood	Time interval	Infection with	Result
	cc.			
1	20	1 hr.	0.1 cc. Type I	D 6 days
2	20	2 hrs.	0.1 " " "	S
3	16	4 "	0.5 " " III	D 4 days
4	15	4 "	0.5 " " "	" 4 "
5	15	5 "	0.5 " " "	" 4 "
6	20	24 "	0.1 " " I	" 4 "
7	15	24 "	0.1 " " "	S
8	20	24 "	0.5 " " III	"
9	20	24 "	0.2 " " "	"
10	20	24 "	0.2 " " "	"
11	20	3 days	0.1 " " I	"
12	20	3 "	0.1 " " "	"
13	20	3 "	0.1 " " "	D 4 days
14	20	3 "	0.01 " " "	S
15	20	3 "	0.01 " " "	"
16	20	3 "	0.5 " " III	"
17	15	4 "	0.1 " " I	D 4 days
18	15	4 "	0.1 " " "	S
19	15	4 "	0.01 " " "	"
20	20	7 "	0.01 " " "	"
21	20	7 "	0.01 " " "	"
22	20	7 "	0.1 " " "	"
23	20	7 "	0.1 " " "	D 4 days
24	17	7 "	0.1 " " "	S
25	15	7 "	0.4 " " III	"
26	15	7 "	0.5 " " "	"
27	15	7 "	0.5 " " "	D 8 days
28	20	7 "	0.1 " " "	S
29	20	14 "	0.01 " " I	"
30	20	21 "	0.01 " " "	"
31	20	21 "	0.01 " " "	"
32	20	21 "	0.01 " " "	"
33	15	21 "	0.01 " " "	"
34	20	21 "	0.01 " " "	"

D indicates death of the animal.
S indicates survival of the animal.

TABLE III—*Concluded.*

Rabbit No.	Amount of serum	Time interval	Infection with	Result
	cc.			
35	10	1 hr.	0.1 cc. Type I	S
36	10	1 "	0.1 " " "	"
37	10	2 hrs.	0.1 " " "	"
38	10	4 "	0.5 " " III	D 7 days
39	10	4 "	0.5 " " "	S
40	10	24 "	0.1 " " I	D 10 days
41	10	24 "	0.5 " " III	" 3 "
42	8	24 "	0.5 " " "	" 7 "
43	10	24 "	0.1 " " I	S
44	12	3 days	0.1 " " III	"
45	8	7 "	0.4 " " "	"
46	8	7 "	0.5 " " "	D 7 days
47	10	7 "	0.01 " " I	" 2 "
48	10	7 "	0.01 " " "	S
49	10	14 "	0.1 " " "	D 4 days
50	10	21 "	0.1 " " "	" 4 "
51	10	21 "	0.1 " " "	" 2 "

stances where the time interval was longer than 7 days, none of the animals recovered.

In all of the experiments controls were used consisting of rabbits which received quantities of normal whole bood or serum equal to the amount of immune blood or serum transferred. Altogether 20 control rabbits were transfused with normal whole blood and 10 received injections of normal serum. They all died of pneumococcus septicemia.

Differences in the effectiveness of passive protection depending on the time elapsing between administration of serum or blood and the injection of the infecting organism may be noted in Table III. In those instances where serum was employed, protection appeared to be most effective, if only a few hours elapsed before the injection of organisms. On the other hand, when whole blood was transfused, protection was less striking when the interval was short than when the animals were permitted to rest 24 hours or longer before infection. The duration of the protection conferred by whole blood is evidenced by animals which survived pneumococcus infection 3 weeks after transfusion.

No definite conclusions can be drawn at the present time from the results concerning the time intervals employed in passive protection tests. The significant fact is that the circulating blood of rabbits immunized with R pneumococci possesses active prinicples which, when transferred to normal rabbits, confer upon the recipients protection against infection with virulent pneumococci.

TABLE IV.

Comparison of Passive Protection of Mice and Rabbits by Serum of Rabbits Immunized with R_2 Pneumococci.

Anti-R rabbit serum		Amount of culture Type I	Results	
			Rabbits	Mice
cc.		*cc.*		
10	*Interval of 2 hrs.	0.1	D 24 hrs.	
10		0.01	S	
10		0.01	S	
10		0.01	S	
0.5		0.00001		D 24 hrs.
0.5		0.00001		D 24 hrs.
0.5		0.000001		D 36 hrs.
0.5		0.000001		D 36 hrs.
0.5		0.000001		D 40 hrs.
		Controls		
None		0.000001	D 60 hrs.	D 24 hrs.
None		0.000001		D 24 hrs.
None		0.000001		D 30 hrs.

D indicates death and figures the number of hours before death of animal.

* 2 hours following intraperitoneal injection of serum all animals were infected intraperitoneally with virulent culture in amounts indicated.

In contrast to the effective protection of rabbits just described, attempts to protect mice by the use of the same sera have been entirely negative. From Table IV it may be seen that serum which protected rabbits against 0.01 cc. did not protect mice against even 0.000001 cc. of culture. This was true in spite of the fact that the mice received a much larger amount of serum per unit of body weight than did the rabbits. Repeated attempts to protect mice with resistant rabbit's serum have failed regardless of whether the infecting organisms were

introduced simultaneously with serum or after intervals of 2, 6, 12, or 24 hours. The whole citrated blood of rabbits has been similarly tested and found to be without effect in mice.

It may be concluded, then, that the serum or whole blood of rabbits immunized by repeated injections of R pneumococci, although able to afford protection to normal animals of the same species, is incapable, under comparable conditions, of conferring protection upon animals of a foreign species—*i.e.* mice. These results are in striking contrast to those obtained with antipneumococcus sera which possess a high content of type-specific antibodies.

DISCUSSION.

The experiments recorded in the present communication demonstrate that a considerable degree of active immunity against Type I and Type II pneumococci may be stimulated in rabbits by repeated injections of R pneumococci. This form of resistance, elicited by R organisms which are devoid of type specificity, is effective in the absence of demonstrable *type-specific* agglutinins, precipitins, and antibodies passively protective for mice. In a preceding paper (1) it was reported that rabbits similarly treated are resistant to virulent Type III organisms; the present results with Types I and II establish the fact that immunity induced in rabbits by R strains is sufficiently broad to be effective against infection with each of the three specific types of pneumococcus. The Type III infections as previously pointed out, were characterized by a bacteremia which ran a polonged course during which the number of circulating bacteria varied from time to time but eventually disappeared. The Types I and II infections encountered in the present experiments behave similarly. These facts are suggestive that in this form of immunity the mode of recovery from infection involves the same mechanism, or different mechanisms acting in a similar manner, against each type of pneumococcus. Furthermore, these results strongly imply that resistance under these conditions is dependent either upon other factors than those concerned in type-specific immunity, or upon the same factors operative in a different manner.

Although the majority of previous investigators have found that active immunity against pneumococcus infection is type-specific, the ex-

perimental conditions, either as to the species of animal or the method of immunization employed, have differed from those reported in this paper. Cecil and Blake (6) observed that in monkeys vaccination with living cultures of Type I conferred a certain amount of cross-immunity, the degree of effectiveness being subject to variation. The immunizing dose in their experiments consisted of *one* subcutaneous injection of either 0.001 cc. of virulent or 1 to 2 cc. of avirulent organisms. Wright (7) found that *one* preliminary intravenous injection of S pneumococci produced active immunity in rabbits effective only against homologous organisms. Barach (8) employing mice gave *one* intraperitoneal injection of S organisms and obtained strict type-specific immunity.

In the experiments here reported the active resistance which was stimulated by immunization with R pneumococci and which was found to be effective against all the fixed types, was obtained by a more prolonged series of injections. The process of immunization comprised 18 intravenous injections carried out over a period of 6 weeks according to the method described by Cole and Moore (2). Although the degree of immunization necessary to incite non-type-specific immunity has not been determined, it has been found that one injection of from 5 cc. to 25 cc. of R culture is insufficient.

The purpose of these experiments has been an attempt to understand the factors underlying the resistance. Since this form of cross-immunity can be induced by pneumococci devoid of type-specific properties, it seems highly probable that a mechanism of a different order from that involved in type-specific resistance is implicated. Work is in progress at the present to define more clearly the points of similarity and difference between these two forms of acquired resistance.

Having determined the presence of active immunity in rabbits previously treated with R cells, consideration has been given to passive immunity. Since one of the chief characteristics of type-specific immunity is the passive protection afforded animals of any species by an immune serum of the homologous type a study of the possibility of passively transferring this non-specific resistance has been carried out. It was found that whole blood or serum of R immunized rabbits protected normal rabbits against infection with virulent Type I and

Type III pneumococci.* As a rule, blood in 15 to 20 cc. amounts was found to afford a more solid resistance against a given infecting dose than the equivalent amount of serum.

Under the experimental conditions described the most striking results have been obtained when an interval of time elapsed between the transfusion and the injection of organisms. The exact significance of these relations has not as yet been sufficiently studied to justify final conclusions. However, it can be stated at the present time, that the immunity elicited by repeated injections of R pneumococci in rabbits can be passively transferred by the circulating blood to normal rabbits. This is evidence that there is present in the circulation of resistant rabbits either protective substances in an active state or something which stimulates the mechanism of resistance in the transfused animal.

Attempts to confer passive protection on mice under similar conditions have been uniformly negative. This failure is in sharp contrast to the positive results always obtained in mice with type-specific sera, and is further evidence of a difference in the mechanism involved in each instance.

SUMMARY.

1. Rabbits, vaccinated by repeated intravenous injections of suspensions of heat-killed R pneumococci, acquire a marked degree of active immunity to infection with the virulent S forms of Pneumococcus Types I and II. Previously (1) it was shown that the immunization of rabbits with R cells induces active resistance to Type III infection. This immunity is effective when the infecting organisms are injected either intravenously, intraperitoneally, or intradermally.

2. Whole citrated blood or serum of rabbits immunized with R pneumococci, under the experimental conditions described, is capable of passively protecting normal rabbits against Type I and Type III infection. Whole blood appears to be more effective than an equivalent amount of serum.

3. Passive protection of mice by the use of whole blood or serum of

* Resistance to Type II was not tested by reason of the fact that an R strain originally derived from Type II S culture was used for immunization. It seemed desirable to minimize the possible participation of type-specific substances.

the immune rabbits has been entirely ineffectual. This is in striking contrast to the results obtained with type-specific immune serum.

4. This form of acquired resistance to pneumococcus infection, elicited by R organisms which are devoid of type specificity, and exemplified in animals whose sera possess no demonstrable type-specific antibodies, has many characteristics strongly suggesting that the underlying mechanism differs from that concerned in type-specific immunity.

CONCLUSION.

A broad immunity against infection with virulent S pneumococci (Types I, II, and III) can be induced in rabbits by vaccination with the degraded R strains of pneumococcus. This form of active resistance is effective in the absence of demonstrable type-specific antibodies, and may be passively transferred to normal rabbits by the blood of the immunized animal.

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