THE RELATION BETWEEN ANTIANAPHYLAXIS AND ANTIBODY BALANCE*

I. The Rôle of Excess of Circulating Antibody in Hypersensitiveness

By MARION C. MORRIS, Ph.D.

(*From the Department of Bacteriology and Immunology, Washington University School of Medicine, St. Louis*)

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At the present time the most widely accepted view concerning the mechanism of hypersensitiveness is that symptoms occur when antigen combines with fixed but not with circulating antibody, and that an excess of circulating antibody reduces the hypersensitive response of the sensitized animal by preventing access of antigen to sensitized tissues, or by causing it to reach the cells so slowly and gradually that no explosive reaction occurs.

The most direct evidence supporting such a view may be found in the work of Weil (1) who injected additional antibody into the circulation of guinea pigs already passively sensitized, and then tested the animals with antigen. He reported that such animals are actually protected against several lethal doses of antigen. Analogous observations have been made more recently by Dale and Kellaway (2) who found that the uterus of a sensitized guinea pig suspended in a bath to which antibody has been added will not contract when antigen is introduced, presumably because the latter is intercepted by the antibody in solution as it is intercepted in the living animal by circulating antibody before it can reach the sensitized cells. On the other hand, the work of Friedberger (3) indicated that such protection as was occasionally noted following the introduction of additional immune serum into sensitized animals was very slight and was not due directly to the antibody content of the antiserum but rather to traces of antigen remaining in it. Similarly, the work of von Fennyvessy and Freund (4) failed to offer any evidence of the protective effect of an excess of circulating antibody against anaphylactic shock.

Notwithstanding this meager amount of confirming evidence to support Weil's concept of the rôle of circulating antibody in anaphylaxis, his contributions have

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been largely responsible for the view that anaphylaxis is a purely cellular reaction, and that resistance to shock in a sensitized animal depends upon the presence of humoral antibodies. By analogy, Weil (5) applied this same concept to explain the mechanism of resistance to infection, also. Because of the confusion arising from such a view, the precise relation of the states of anaphylaxis, antianaphylaxis, and immunity to each other and to antibody balance is still somewhat unsettled. Before attempting to determine the relation of these various states to each other, it seemed essential to reinvestigate the rôle of circulating antibody in the hypersensitive animal.

Method

Guinea pigs of a uniform weight were passively sensitized by intraperitoneal injection of 0.5 cc. of rabbit antiserum. Following an incubation period of approximately 24 hours, the sensitized animals were divided into three groups. In the first, the lethal dose of antigen was determined by intravenous injection. In the second group of animals, an excess of antibody was given intravenously 20 to 60 minutes preceding the intravenous injection of antigen; while in the last group, which served as a control, rabbit or guinea pig serum containing none of the specific antibody was introduced intravenously prior to injection of antigen. All intravenous injections were made by way of the jugular vein.

The antigens used for producing the antisera in rabbits were: (*a*) crystalline egg albumin; (*b*) horse serum; and (*c*) heat-killed virulent Friedländer's bacillus Type B. The same antigens were used for demonstrating hypersensitiveness in passively sensitized guinea pigs, with the exception that the type-specific polysaccharide of Friedländer's bacillus prepared according to the method of Heidelberger, Goebel, and Avery (6) was used to induce shock, instead of bacteria themselves.

The antisera used were: (*a*) pooled anti-crystalline egg albumin rabbit serum with a precipitin titer of 1:700,000; (*b*) pooled anti-horse rabbit serum with a precipitin titer of 1:10,000–1:20,000; (*c*) pooled anti-Friedländer rabbit serum which agglutinated Friedländer's bacillus in a dilution of 1:20–1:40. The undiluted antiserum precipitated the specific carbohydrate diluted 1:1,000,000.

Effect of Excess of Antibody on Hypersensitiveness to Egg Albumin

In order to determine whether protection against anaphylaxis is readily demonstrable when excess of antibody is present in the circulation, preliminary experiments were undertaken using the egg albumin anti-egg albumin system. In experiments made for orientation, such protection was not easily demonstrated. On the contrary, as may be seen from Table I, animals having an excess of circulating antibody appeared to exhibit an enhanced sensitivity as shown by the fact that they succumbed with symptoms of typical anaphylaxis upon

injection of less than 1 M.L.D. of antigen. These results suggest that excess of circulating antibody, far from protecting against the shock, may actually increase the susceptibility of the animals.[1]

Unfortunately both the antialbumin and anti-horse sera were found to be toxic when introduced intravenously into the guinea pigs, so

TABLE I

The Effect of Excess of Circulating Antibody upon the Anaphylactic Response of Guinea Pigs Passively Sensitized with Anti-Egg Albumin Rabbit Serum

Guinea pig	Weight	Anti-egg rabbit serum (i.p.)	Interval	Additional anti-egg rabbit serum (i.v.)	Rabbit serum (anti-horse) (control) (i.v.)	Interval	Egg albumin antigen (i. v.)	No. of M.L.D. of antigen	Symptoms	Result
	gm.	*cc.*	*hrs.*	*cc.*	*cc.*	*min.*	*cc.*			
8-35	190	0.5	24				0.1	1	++++*	D*
8-42	175	"	"				0.1	1	++++	D
8-40	190	"	"				0.05	1/2	+++	S
8-45	205	"	"	1.5		55	0.05	1/2	++++	D
8-44	205	"	"	1.5		20	0.025	1/4	++++	D
8-43	212	"	"	1.5		20	0.0125	1/8	++++	D
8-48	180	"	"	1.5		20	0.00625	1/16	−	S
6-54	195	"	"		1.0	20	0.05	1/2	++++	D
4-00	187	"	"		1.0	20	0.025	1/4	−	S

* In this as well as in all subsequent tables, the symbols have the following meanings:

++++, intense symptoms; immediate death.
+++, intense symptoms; survived.
++, moderate but definite symptoms.
+, very mild symptoms.
−, no symptoms.
S, survival.
D, anaphylactic death.

that all of the animals died an hour or more after intravenous injection of these antisera. While these toxic reactions could not be confused with the immediate and typical reactions characteristic of anaphylaxis they were, nevertheless, a disturbing element in the interpretation of

[1] It must be noted, however, that one of two controls tested with less than 1 M.L.D. of antigen also died.

TABLE II

The Effect of Excess of Circulating Antibody upon the Anaphylactic Response of Guinea Pigs Passively Sensitized with Anti-Friedländer Type B Rabbit Serum 1

Guinea pig	Weight	Anti-Friedländer Type B rabbit serum (i.p.)	Interval	Additional anti-Friedländer Type B rabbit serum (i.v.)	Rabbit serum (anti-horse) (control) (i.v.)	Interval	Friedländer Type B specific carbohydrate (i.v.)		No. of M.L.D. of carbohydrate	Symptoms	Result
	gm.	*cc.*	*hrs.*	*cc.*	*cc.*	*min.*	*cc.*				
7-97	217	0.5	24			20				++	S
8-93	235	"	"			"	0.4	1:10,000	1	++++	D
8-69	215	"	"			"				++++	D
8-81	212	"	"			"				−	S
7-96	215	"	"			"				+++	S
7-91	224	"	"			"	0.2	1:10,000	1/2	−	S
8-91	240	"	"			"				++++	D
8-90	252	"	"			"				+++	S
8-94	222	"	"			"	0.1	1:10,000	1/4	++	S
3-33	232	"	"	2		"	0.2	1:1000	5	++++	D
7-85	216	"	"			"				−	S
3-32	215	"	"	2		"	0.8	1:10,000	2	++++	D
3-42	212	"	"			"				++++	D
7-83	217	"	"			"				−	S
3-36	217	"	"	2		"	0.4	1:10,000	1	++	S
7-11	251	"	"			"				++++	D
7-03	232	"	"	2		"	0.2	1:10,000	1/2	−	S
7-50	243	"	"			"				++	S
7-13	235	"	"			"				+	S
7-08	242*	"	"	2		"	0.1	1:10,000	1/4	−	S
8-92	240*	"	"			"				+	S
7-18	229	"	"	2		"	0.2	1:40,000	1/8	+	S
7-07	231	"	"	2		"	0.1	1:40,000	1/16	−	S

* Two different lots of Friedländer antiserum used for intravenous injection, one in each of these two animals.

TABLE II—*Concluded*

Guinea pig	Weight	Anti-Friedländer Type B rabbit serum (i.p.)	Interval	Additional anti-Friedländer Type B rabbit serum (i.v.)	Rabbit serum (anti-horse) (control) (i.v)	Interval	Friedländer Type B specific carbohydrate (i.v.)		No. of M.L.D. of carbohydrate	Symptoms	Result
	gm.	*cc.*	*hrs.*	*cc.*	*cc.*	*min.*	*cc.*				
3-20	232	0.5	24		2	20	0.4	1:1000	10	++++	D
3-35	241	"	"			"				−	S
3-38	228	"	"		2	"	0.2	1:1000	5	++++	D
7-84	216	"	"			"				−	S
3-49	215†	"	"		2	"	0.8	1:10,000	2	++++	D
3-52	227†	"	"			"				++++	D
7-86	222	"	"			"				−	S
3-48	233†	"	"		2	"	0.4	1:10,000	1	++++	D
3-47	232†	"	"			"				++++	D
7-61	250	"	"			"				+	S
7-64	250	"	"		2	"	0.2	1:10,000	1/2	−	S
7-49	237	"	"			"				++++	D
7-46	241	"	"		2	"	0.1	1:10,000	1/4	−	S

† Different lot of anti-horse rabbit serum used for intravenous injection of these four animals.

results. Because of this serum toxicity, too, the number of animals surviving for the final test was so small that the only conclusion drawn was that excess of circulating antibody does not appear to exert a protective effect.

Effect of Excess of Antibody on Hypersensitiveness to Friedländer's Bacillus Type B

With the hope of eliminating the difficulties attendant upon the use of toxic antisera, another series of experiments was undertaken in which anti-Friedländer Type B rabbit serum and the corresponding haptene were employed. This antiserum proved to be nontoxic when injected intravenously. As may be seen from Table II, 0.4 cc. of a 1:10,000 dilution of carbohydrate appears to represent 1 M.L.D. of antigen for guinea pigs passively sensitized with 0.5 cc. of this antiserum. From the table it appears that a slight degree of protection may be af-

forded occasionally merely by preliminary introduction of foreign serum (containing none of the specific antibody) as is shown by the fact that one sensitized guinea pig injected with anti-horse serum as control 20 minutes before inoculation of the specific carbohydrate survived 5 M.L.D. of antigen. It is also evident from the table that additional specific antibody introduced intravenously into similarly sensitized animals 20 minutes before the antigen has no very appreciable effect either in enhancing sensitivity or in affording any significant protection.

While it seemed evident from this and the preceding experiment that excess of antibody in the circulation affords no protection against anaphylaxis, it still remained undetermined whether circulating antibody enhances sensitivity as suggested by the first experiment (Table I). That such an increase in sensitivity actually does occur became clear from the experiments which follow.

Effect of Excess of Antibody on Hypersensitiveness to Horse Serum

In this set of experiments, the horse–anti-horse system was used, two lots of rabbit anti-horse serum being available. The first antiserum tested proved to be toxic when injected intravenously, but sufficient data were obtained from experiments with this antiserum to illustrate several important points concerning the effect of an excess of antibody on passive hypersensitiveness to horse serum. These results were controlled by intravenous inoculation of some of the passively sensitized animals with normal guinea pig, normal rabbit, or antialbumin instead of anti-horse rabbit serum previous to injection of the antigen (horse serum) (Table III).

From Table III it appears that 0.1 cc. of horse serum represents 1 M.L.D. of antigen for these passively sensitized animals. It is clear that here, as in the preceding experiment (Table II), foreign serum introduced parenterally into a sensitized animal tends to reduce its reactivity. Apparently, this reduction in reactivity is roughly related to the amount of foreign serum introduced, since large amounts of serum protect against greater quantities of antigen. It is interesting that even homologous normal serum (guinea pig) shows a protective effect which, however, is rather slight, in comparison with the protection afforded by rabbit serum. Kellaway and Cowell (7) have made a similar observation and have shown that the loss and return of reactivity in sensitized guinea pigs treated with normal guinea pig

TABLE III

The Effect of Excess of Circulating Antibody upon the Anaphylactic Response of Guinea Pigs Passively Sensitized with Anti-Horse Rabbit Serum 1

Guinea pig	Weight	Anti-horse rabbit serum (i.p.)	Interval	Additional anti-horse rabbit serum (i.v.)	Serum (control) (i.v.)			Interval	Horse serum antigen (i.v.)	No. of M.L.D. of antigen	Symptoms	Result
					Pooled normal guinea pig	Pooled normal rabbit	Anti-albumin rabbit					
	gm.	*cc.*	*hrs.*	*cc.*	*cc.*	*cc.*	*cc.*	*min.*	*cc.*			
6-59	217	0.5	24						0.2	2	++++	D
6-64	233	"	"						0.1	1	++++	D
6-65	190	"	"						0.05	1/2	−	S
6-66	212	"	"								−	S
8-11	185	"	"	2				60	0.2	2	++++	D
8-19	185	"	"	1–2				60			++++	D
8-26	195	"	"	1–1.5				60	0.05	1/2	++++	D
8-32	175	"	"	1				60			++++	D
8-51	220	"	"	1				20	0.025	1/4	++++	D
6-88	220	"	"	1				20	0.0125	1/8	−	S
8-39	187	"	"		5			60	0.4	4	++++	D
8-57	207	"	"		5			60	0.2	2	−	S
8-33	215	"	"		3			60	0.1	1	++	S
8-41	195	"	"		2			60	0.1	1	++++	D
6-61	207	"	"			5		60	0.8	8	+++	S
6-62	215	"	"			4		60	0.6	6	+++	S
8-16	200	"	"			2		60	0.4	4	++++	D
8-18	185	"	"			2		60	0.2	2	−	S
8-20	200	"	"			1		60	0.2	2	++++	D
8-37	200	"	"			1		60	0.1	1	−	S
8-47	225	"	"				1.5	20	0.05	1/2	−	S
8-49	210	"	"				1.5	20	0.05	1/2	+++	S

serum may be correlated with a similar loss and return of reactivity of the smooth muscle.

In contrast with these control experiments, it will be seen that sensi-

TABLE IV

The Effect of Excess of Circulating Antibody upon the Anaphylactic Response of Guinea Pigs Passively Sensitized with Anti-Horse Serum 3

Guinea pig	Weight	Anti-horse rabbit serum (i.p.)	Interval	Additional anti-horse rabbit serum (i.v.)	Rabbit serum (control) (i.v.)		Interval	Horse serum antigen (i.v.)	No. of M.L.D. of antigen	Symptoms	Result
					Anti-Friedländer Type B	Anti-egg					
	gm.	*cc.*	*hrs.*	*cc.*	*cc.*	*cc.*	*min.*	*cc.*			
8-70	225	0.5	24				20	0.5	5	++++	D
3-27	252	"	"				"			−	S
8-73	220	"	"				"	0.1	1	++++	D
3-05	227	"	"				"			++++	D*
8-87	201	"	"				"			−	S
8-71	225	"	"				"	0.05	1/2	−	S
3-02	194	"	"				"			++++	D
3-23	237†	"	"				"			−	S
3-24	225†	"	"	2			"	0.2	2	++++	D
3-22	220†	"	"				"			++++	D
3-03	245	"	"				"			++	S
7-89	222	"	"	2			"	0.1	1	++++	D
7-11	224	"	"				"			++++	D
3-21	203†	"	"				"			++++	D
3-28	222†	"	"	2			"	0.05	1/2	++++	D
3-30	225†	"	"				"			++++	D
7-82	200	"	"				"			+++	S
7-63	250	"	"				"			+++	S
7-75	226	"	"	2			"	0.025	1/4	−	S
7-80	216	"	"				"			−	S
8-74	208	"	"	1			"			++++	D
8-72	206	"	"	1			"			+++	S
3-29	230†	"	"				"			−	S
8-84	227	"	"	2			"	0.0125	1/8	+++	S
8-83	212	"	"				"			++++	D
8-79	212	"	"				"			++++	D

* Death after ½ hour.

† Different lot of anti-horse rabbit serum used for intravenous injection in these animals.

TABLE IV—*Concluded*

Guinea pig	Weight	Anti-horse rabbit serum (i.p.)	Interval	Additional anti-horse rabbit serum (i.v.)	Rabbit serum (control) (i.v.)		Interval	Horse serum antigen (i.v.)	No. of M.L.D. of antigen	Symptoms	Result
					Anti-Friedländer Type B	Anti-egg					
	gm.	*cc.*	*hrs.*	*cc.*	*cc.*	*cc.*	*min.*	*cc.*			
8-77	212	0.5	24	2			20	0.00625	1/16	−	S
7-60	212	"	"				"			++++	D
7-87	212	"	"		2		"	0.8	8	++++	D
7-19	255	"	"				"			−	S
7-65	222	"	"		2		"	0.4	4	++++	D
3-26	200	"	"				"			++++	D
7-01	233	"	"				"			−	S
7-70	216	"	"		2		"	0.2	2	++	S
7-69	185	"	"				"			++++	D
3-37	208	"	"		2		"	0.1	1	−	S
3-23	208	"	"				"			++++	D
3-39	206	"	"				"			+	S
7-98	224	"	"			2	"	0.1	1	+	S
8-88	204	"	"				"			++++	D
8-85	221	"	"			2	"	0.05	1/2	+	S
8-78	212	"	"				"			+++	S
8-75	187	"	"			1	"	0.05	1/2	++++	D
7-99	230	"	"				"			−	S
3-01	209	"	"				"			−	S
3-04	207	"	"			2	"	0.025	1/4	−	S
3-07	232	"	"				"			+	S
3-40	232	"	"			2	"	0.0125	1/8	+	S
3-25	207	"	"				"			−	S

tized animals which had received additional specific antibody previous to introduction of antigen, failed to tolerate even 2 M.L.D. of antigen. Furthermore, two animals died when injected with 0.05 cc. and one when injected with 0.025 cc. of horse serum, that is, 1/2 and 1/4 M.L.D.

respectively. The important point here, then, is that rabbit and even guinea pig serum containing no specific antibody, when introduced intravenously into sensitized guinea pigs before testing with antigen, reduces reactivity while the introduction of rabbit serum containing the specific antibody does not reduce but rather tends to enhance sensitivity. These results are in agreement with those reported earlier with antialbumin serum (Table I).

Further corroboration was obtained with a second anti-horse rabbit serum which was not toxic for guinea pigs. The results were controlled by determining the effect of intravenous inoculation of anti-Friedländer or anti-egg rabbit serum upon the hypersensitive response of guinea pigs passively sensitized with 0.5 cc. of this anti-horse serum. The interval between injection of these antisera and the horse serum antigen was 20 minutes (Table IV).

Here again, it may be seen that the mere introduction of foreign serum may reduce slightly the reactivity of the sensitized animal. Hence, the protection afforded by antibody-containing serum (if it occurs at all) should be attributed to its action as a foreign protein rather than to its antibody-content. It is more significant, however, that several of the animals given an excess of antibody-containing serum died when tested with less than 1 M.L.D. of antigen. Thus, three died after introduction of 1/2 M.L.D., one after 1/4 M.L.D., and two after 1/8 M.L.D., while only one animal out of nine died when tested with less than 1 M.L.D. of antigen after being given an excess of other than specific antiserum. The enhancement of sensitivity observed in the present experiments would indicate that similar, though less extensive, findings in previous experiments were not accidental. These findings are particularly significant because foreign serum containing none of the specific antibody tends to reduce the reactivity of sensitized animals when injected in comparable amounts. As a consequence, the actual increase in sensitivity conferred by an excess of antibody might have been even greater than that recorded here were it not for the fact that a nonspecific foreign protein reaction which tends to decrease the animal's reactivity was occurring at the same time.

The summary of the results of experiments in guinea pigs passively sensitized with both lots of anti-horse serum is presented in Table V.

This table indicates in a graphic manner the essential features of these experiments. Guinea pigs passively sensitized with anti-horse rabbit serum and injected with additional antibody show a definitely greater sensitivity than animals similarly sensitized, but given an additional inoculation of other rabbit sera containing none of the specific antibody. This increase in sensitivity is demonstrable in two ways: (*a*) Death occurs in some animals upon injection of amounts of antigen

TABLE V

Composite Results of Passive Sensitization of Guinea Pigs with 0.5 Cc. of Anti-Horse Rabbit Serum, Showing Effect of Subsequent Introduction of Excess of Antibody into the Circulation

		No. of M.L.D. of horse serum				
		2	1	1/2	1/4	1/8
Without injection of additional antiserum	No. of animals tested		4	5		
	No. of deaths		3	1		
	Percentage of deaths		75%	20%		
With injection of additional anti-horse rabbit serum previous to testing with antigen	No. of animals tested	5	3	5	6	6
	No. of deaths	4	2	5	2	2
	Percentage of deaths	80%	66%	100%	33%	33%
With injection of rabbit serum (control) previous to testing with antigen	No. of animals tested	5	6	5	4	2
	No. of deaths	2	2	1	0	0
	Percentage of deaths	40%	33%	20%	0%	0%

M.L.D. of antigen = 0.1 cc.

less than 1 M.L.D., and (*b*) when tested with 1 or 2 M.L.D. of antigen the mortality rate among animals receiving excess of antibody is considerably higher than among those which received other rabbit sera.

DISCUSSION

The preceding experiments were undertaken because of the prevalent view that the presence of an excess of antibody in the circulation is responsible for the refractoriness to anaphylaxis manifested by some hypersensitive animals. This concept is based largely on the work of Weil (1) quoted previously and on other experiments of his (8) in

which he showed that guinea pigs actively sensitized with large amounts of antigen became hypersensitive more slowly and required larger amounts of antigen for induction of fatal shock than guinea pigs sensitized with small amounts of antigen. This he attributed to the fact that the former animals had more circulating antibody than the latter. Even if this quantitative difference in the amount of antibody formed in these two groups of animals does occur, which in the light of immunological experience is rather doubtful, it is not necessarily the only explanation of the greater refractoriness of animals sensitized with large amounts of antigen, as will be shown later.

This concept, however, has led even such an authority as Wells (9) to state that "this term [antianaphylaxis] should logically be applied only to a resistance due to antibodies." From the experiments recorded in this paper, however, it would appear that an excess of antibody in the circulation does not establish a state of antianaphylaxis. On the other hand, some protection against anaphylactic shock may be induced nonspecifically merely by the introduction of serum whether containing the specific antibody or not. This is in agreement with numerous reports in the literature concerning the capacity of a wide variety of unrelated substances to render sensitized animals refractory to anaphylaxis (hypertonic salt, alkalis, mineral waters, saponin, lipoids, foreign sera, narcotics, hirudin, etc. (10, 11)). In the light of our results, then, it is extremely likely that the occasional instances of protection noted in our experiments in sensitized animals inoculated with additional antibody, as well as a similar though more extensive protection reported by Weil, are attributable to the nonspecific effect of the serum injected. It is also possible that traces of antigen remaining in the antiserum which was injected intravenously into the already hypersensitive animal may have caused some degree of specific desensitization. It may be pertinent to point out here that persistence of antigen in animals undergoing active sensitization is also a very likely explanation of Weil's failure to establish as high a degree of reactivity in animals sensitized with large amounts of antigen, as contrasted with those inoculated with smaller quantities. Antibody may be demonstrated in the circulation of animals undergoing active sensitization often before all of the antigen

has been eliminated, and hence ideal conditions for specific desensitization are present. It is natural that larger amounts of antigen persist longer than smaller quantities and this fact, not the greater amount of circulating antibody, may account for Weil's results. That the same fundamental mechanism may underly specifically or nonspecifically induced antianaphylaxis will be elaborated upon in a subsequent publication.

While the present experiments have shown that circulating antibody is not responsible for a state of antianaphylaxis they have indicated in addition, that frequently those animals which have received an excess of antibody react to smaller quantities of antigen than animals which have not received an injection of additional antibody. It should be emphasized that in these experiments a period of only 20 minutes was allowed to elapse between the intravenous injections of additional antiserum and of antigen into the hypersensitive animals (although in some instances the interval was 1 hour). In any event, the interval was shorter than that which has usually been acknowledged to be the minimum incubation period for the development of passive hypersensitiveness in the guinea pig, during which time it is claimed the antibody becomes fixed in the cell. These experiments, then, suggest the possibility that anaphylaxis is determined by both circulating and fixed antibody, and that circulating antibody, far from being a protective mechanism for the hypersensitive cell, actually increases the degree of sensitivity.

This view of the rôle of circulating antibody receives considerable support from the work of Kellett (12) who showed that it is possible to induce anaphylaxis in guinea pigs by injecting antiserum 45 minutes after the specific antigen. Indeed, the recent work of Zinsser and Enders (13) has shown that some guinea pigs may be thrown into fatal shock when an interval as little as 1½ minutes intervenes between the injections of antigen and antiserum, and that this phenomenon may be demonstrated regardless of whether the antigen or antiserum is the first to be injected. It is admitted (14–16) that circulating antibody may be responsible in some part for the anaphylactic reactivity of dogs, mice, and rabbits, and hence not unlikely it should play a part in the reactivity of guinea pigs.

The failure of some of the sensitized animals in the present experiments to manifest an increased reactivity when given additional

antibody may possibly be attributed to individual variation in the animals, to the nonspecific effects induced by introduction of additional antiserum, or to traces of antigen remaining in the antiserum.

The experiments reported here tend to invalidate the idea that anaphylaxis is due to fixed antibody alone, and that refractoriness to anaphylaxis is due to circulating antibody. The precise mechanism of antianaphylaxis and its relation to anaphylaxis and to immunity (resistance to infection) will be discussed in a subsequent publication.

CONCLUSIONS

1. Sensitized guinea pigs injected with normal rabbit or guinea pig serum previous to intravenous inoculation of antigen may be protected against a few lethal doses of antigen. The protection is greater with foreign than with homologous serum and appears to be related roughly to the amount of serum introduced.

2. Sensitized guinea pigs injected with antibody-containing serum preliminary to intravenous injection of antigen, show no greater refractoriness to anaphylaxis than do those injected with normal serum.

3. Moreover, in many instances, the injection of an excess of antibody into the circulation of sensitized guinea pigs, leads to an increased susceptibility of these animals to anaphylaxis.

4. These results indicate that an excess of circulating antibody is not responsible for a state of antianaphylaxis, but on the contrary, may contribute toward the anaphylactic reaction itself.

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