

LOCAL ORGAN HYPERSENSITIVITY TO AUTOGENOUS ANTIGENS

I. EXPERIMENTAL PRODUCTION OF A PNEUMONITIS*†

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THE subject of autoantigenicity has, in the last fifteen years, assumed an increasing importance. Autoantibodies have been found in various human diseases. Animal experimentation has given weight to the concept of sensitization to one's own tissues.¹⁻³¹ The experimentally produced lesions were usually obtained in animals generally sensitized with organ or tissue extracts to which bacteria or other foreign antigens were added as adjuvants. The mechanisms involved were modified Arthus phenomena⁹ and, presumably, the reaction of induced autoantibodies with the homologous organ.¹⁸⁻³¹

The purpose of the experiments reported here has been to study the autoantigenicity of: (a) a partly hydrolyzed autogenous substance (hydrolyzed autoserum); (b) normal body components (skin and liver extracts) placed in an abnormal environment within the same organism; and (c) an excretory product (urine) also placed in an abnormal environment.

A technique of local organ hypersensitivity was applied to the rabbit's lung; the production of an allergic pneumonitis was the criterion used to determine the antigenicity of the various autogenous products tested. No foreign antigens were added.

MATERIALS AND METHOD

Materials:

All experiments were performed on young adult rabbits weighing approximately 2,000 grams. Most of the rabbits used were albinos.

Three different autogenous allergens were employed.

(A) *Hydrolyzed Autoserum*.—The blood was obtained from the ear vein of the rabbit. After separation of the serum, hydrolysis was achieved in the following manner: 4 c.c. of serum were diluted with 8 c.c. of distilled water and 0.6 c.c. of 10 per cent sulfuric acid were added. This mixture was heated for one hour at 80° C. in a water bath. As a result of this treatment, a mixture of the normal proteins and the products of their partial hydrolysis (proteoses, large polypeptides) was obtained. The solution was neutralized to pH 7 with sodium hydroxide and then filtered through a Berkefeld filter. Sterile vials were filled with the solution to be used immediately, or stored in the ice box at 5° C. for further use on the same rabbit.

(B) *Autogenous Urine*.—The rabbit's urine was obtained aseptically from the bladder by puncture after laparotomy under general ether anesthesia and was injected slowly to the same rabbit, usually while the animal was still under anesthesia.

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†Preliminary reports of this work have appeared. ³²⁻³¹

(C) *Saline Extract of One Organ Used to Sensitize Another Organ.*—A piece of tissue was resected, rapidly washed in saline to eliminate the excess of blood, cut into small pieces, ground in a mortar with physiologic saline and sand, then blended for 2 to 4 minutes in a Waring blender and centrifuged. The supernatant material was used immediately after filtration through Berkefeld or Seitz filters. Two extracts were prepared in this way; a skin extract prepared from the same rabbit on which the experiment was made and a liver extract prepared from another rabbit.

A parallel series of experiments was run in which exogenous antigens (horse, bovine, and human serum) were used, with the purpose of comparing the antigenic power of endogenous and exogenous material.

Method:

The lung was sensitized by a single transthoracic injection of a small amount of antigen, using a 22-gauge needle, length one inch, introduced in the fifth or sixth intercostal space, at about the level of the posterior axillary line, avoiding any unnecessary trauma. The needle was inserted until contact with the lung tissue was felt, then advanced one more millimeter and the antigen was injected slowly.

After an interval of 2 to 9 weeks, the shock injection was given intravenously. The amount of antigen used for the shock injection was always larger than the amount used for the sensitizing injection. The amount of antigen injected and the time interval in the various experiments are shown in the tables.

After the shock injection, the animals were studied for signs of shock. In order to follow the evolution of the lesion the animals were killed, by injection of air unto the ear vein, at intervals of 1, 24, 48, 72, and 96 hours after the shock injection. Immediately after death a gross examination of the lungs, heart, liver, spleen, kidneys, peritoneum, and pleura was performed. Histological studies of the lungs were made for all the sensitized animals and most of their controls. The usual hematoxylin and eosin method of staining was used. In a number of instances, elastic and connective tissue stains were employed. Histological studies of other organs, especially the liver, were performed in certain cases.

Controls:

(A) In one series of controls, only the sensitizing injection was made, the animals being killed at different time intervals thereafter.

(B) In another series, only the intravenous injection of the antigen was made, the animals being killed at various time intervals after this injection. In a few cases, an injection of saline was made into the lung, followed after a suitable time interval by an intravenous injection of hydrolyzed autoserum.

(C) Another group of controls was used to demonstrate that the localization of the lesion in the rabbit's lung was not due to a special property of this organ. Experiments were performed in which the sensitizing injection was given in the eye, subconjunctivally or into the vitreous humor, or intracerebrally. The shock injection was given intravenously, as it had been for the animals sensitized in the lung. The animals were killed at various time intervals thereafter.

The details of the experimental procedure are shown in the tables. Animals sensitized in the lung with autogenous antigens are included in Table I; the various controls made with autogenous antigens are included in Table II; the animals sensitized in the lung with exogenous antigens and their controls are included in Table III.

TABLE I. EXPERIMENTAL (AUTOGENOUS ANTIGENS)
SITE OF SENSITIZING INJECTIONS: RIGHT LUNG

AUTO-ANTI-GEN USED	NO. OF ANIMALS	EXPERIMENTAL PROCEDURE	TIME AFTER LAST INJECTION WHEN ANIMAL WAS KILLED	RESULTS*
Hydrolyzed auto-serum	19	Sensitizing injection: 0.5-1 c.c.	2 rabbits: 10-20 min.	1 rabbit: lesions, R lung ### 1 rabbit: lesions, R lung #
		Time interval: 3-9 weeks	14 rabbits: 1-3 days	5 rabbits: lesions, R lung ### lesions, L lung # in 2 rabbits
		Second injection: 2 c.c. intravenously		5 rabbits: lesions, R lung ## lesions, L lung # in 1 rabbit
			1 rabbit: 10 days	2 rabbits: Lesions, R lung # 2 rabbits: no lesions
			1 rabbit: 20 days	Ascitic fluid in pleural cavity. No lesions in the lung
Auto-urine	3	Sensitizing injection: 1/2 c.c.	20 min.	No lesions
		Time interval: 18 days		No lesions
		Second injection: 1-2 c.c. intravenously		No lesions
Rabbit liver	10	Sensitizing injection: 1/2-1 c.c.	1-3 days	1 rabbit: lesions, R lung ## 1 rabbit: lesions, R lung # Some lesions, L lung
		Time interval: 3-9 weeks		1 rabbit: lesions, R lung ### Some lesions, L lung
Auto-skin	2	Sensitizing injection: 0.5 c.c.	2 days	1 rabbit: lesions, R lung ## 1 rabbit: lesions, R lung #
		Time interval: 15 days		
		Second injection: 1 1/2 c.c. intravenously		

*The results are based on the gross examination of the various organs. The organs examined are listed in the section "Material and Methods." Where no reference is made to the organ, there were either no lesions or lesions due to parasites, or caused by the air injection.

The lesions are classified as follows:

- (a) No lesions (including those animals with only parasitic or caused by the air injection).
- (b) #: one or a few small patches, or histologic lesion only.
- (c) ##: one large patch (i.e., part of a lobe) or many large patches throughout the lung.
- (d) ###: whole lung or one lobe.

TABLE II. CONTROL EXPERIMENTS (AUTOGENOUS ANTIGENS)

AUTO-ANTI-GEN USED	SITE OF SENSITIZING INJECTION	NO. OF ANIMALS	EXPERIMENTAL PROCEDURE	TIME AFTER LAST INJECTION WHEN ANIMAL WAS KILLED	RESULTS
Hydrolyzed auto-serum	Lung	8	Sensitizing injection: 0.5-2 c.c.	1 rabbit: 20 min.	Slight edema, localized at site of injection
				1 rabbit: 3 days	Small area of hepatisation, sharply localized at site of injection
			No second shock injection	2 rabbits: 10 days	Very small and no reaction at site of injection
				2 rabbits: 20 days	No lesions
				1 rabbit: 40 days	No lesions
				1 rabbit: 60 days	No lesions
		2	Injection of 0.5 c.c. saline in R. lung Time interval: 5 weeks Second injection: 2 c.c. Hydrolyzed auto-serum, intravenously	2 days	No lesions
Hydrolyzed auto-serum	Right eye (subconjunctivally)	2	Sensitizing injection: $\frac{1}{2}$ -1 c.c. Time interval: 2 weeks Second injection: $\frac{1}{2}$ c.c. intravenously	2 days	Congestion of conjunctival vessels of right eye; beginning 2 hours after shock injection, lasting 24 hours Normal lungs
Hydrolyzed auto-serum	Right eye (vitreous humor)	2	Sensitizing injection: 0.1 c.c. Time interval: 4 weeks Second injection: 1 rabbit 2 c.c. intravenously 1 rabbit 5 c.c. subcutaneously	2 days	
					Retinal edema and rise in ocular tension (right eye)
					No lesions, no change in ocular tension
					Normal lungs
Hydrolyzed auto-serum	Brain	2	Sensitizing injection: 0.2 c.c. Time interval: 18 days Second injection: 2 c.c. intravenously	36 hours	Bilateral edema of brain
					Normal lungs
Hydrolyzed auto-serum	Brain	2	Sensitizing injection: 0.2 c.c. No second shock injection	20 days	No lesions
Auto-urine	Lung (Right)	2	Sensitizing injection: $\frac{1}{2}$ c.c. No second shock injection	7 days	No lesions
				18 days	No lesions
Auto-urine	No sensitizing injection	2	Intravenous injection only: 2 c.c.	20 min.	No lesions

TABLE II—CONT'D

AUTO-ANTI-GEN USED	SITE OF SENSITIZING INJECTION	NO. OF ANI-MALS	EXPERIMENTAL PROCEDURE	TIME AFTER LAST INJECTION WHEN ANIMAL WAS KILLED	RESULTS
Auto-urine	Eye (left) (subconjunctivally)	2	Sensitizing injection: $\frac{1}{4}$ c.c. Time interval: 20 days Second injection: 2 c.c. intravenously	2 days	Congestion of conjunctival vessels of right eye, beginning 1 hour after shock injection, lasting 24-36 hours Normal lungs
Rabbit liver	Lung (Right)	5	Sensitizing injection: $\frac{1}{2}$ -1 c.c. No second shock injection	18 days 5 weeks	No lesions
Rabbit liver	No sensitizing injection	6	Intravenous injection: $1\frac{1}{2}$ to 3 c.c.	1 to 3 days	No lesions

RESULTS

1. *Control animals which had received only the intrapulmonary sensitizing injection.*—The sensitizing injection into the lung was followed by a focal congestive and edematous lesion which disappeared within from 10 to 15 days. Lungs studied from 2 to 6 weeks after this injection showed no gross or microscopic lesions.

2. *Control animals which had received only the intravenous injection.*—No reaction was elicited by the intravenous injection alone.

3. *Previously sensitized animals which, after a suitable time interval, had received an intravenous injection of the same antigen* showed a lesion in the sensitized organ, namely the right lung.

No lesions were found in other organs, except in a few cases (9/44) where similar lesions occurred in the other lung; these were as a rule much less severe than in the sensitized lung.

There was no evidence of shock following the intravenous injection. The pulmonary lesions appeared during the first hour. They were still present in animals killed 96 hours after the shock injection. Three animals killed on the eleventh, twentieth, and fortieth day showed no pulmonary lesions.

There were variations in the severity of the lesions in different animals even when the same antigen was used. A certain number of sensitized animals did not react at all to the shock injection. Of 44 animals, 11 showed no lesions,* 8 showed lesions classified as one plus, 11 showed lesions classified as 2 plus, and 14 showed lesions classified as 3 plus.

The severity of the lesions was not appreciably influenced when the time interval between the two injections was varied between 2 and 10 weeks, nor when the doses used at the two injections were varied within the limits used in these experiments.

*This number included the 3 rabbits killed at the eleventh, twentieth, and fortieth day.

TABLE III. EXOGENOUS ANTIGENS

ANTIGEN	SITE OF SENSITIZING INJECTION	NO. OF ANIMALS	EXPERIMENTAL PROCEDURE	TIME AFTER LAST INJECTION WHEN ANIMAL KILLED	RESULTS
Human serum	Lung (Right)	2	Sensitizing injection: $\frac{3}{4}$ c.c. Time interval: 2 weeks Second injection: 2 abd. c.c. intravenously	30 min.	1 rabbit: lesions, R lung ## 1 rabbit: lesions, R lung ### Also L lung #
Ox serum	Lung (Right)	2	Sensitizing injection: $\frac{3}{4}$ c.c. Time interval: 2 weeks Second injection: 3 c.c. intravenously	1 day	1 rabbit: no lesions 1 rabbit: lesions of both lungs, more marked in R lung ### than in left ##
Horse serum	Lung (Right)	6	Sensitizing injection: $\frac{1}{2}$ c.c. Time interval: 3 weeks Second injection: 2 c.c. intravenously	20 min. to 4 days	3 rabbits: lesions, R lung ### 1 rabbit: lesions, R lung ## (very slight reaction L lung) 1 rabbit: lesions, R lung # 1 rabbit: no lesions
Horse serum	Lung (Right)	3	Sensitizing injection: $\frac{1}{2}$ -2 c.c. No second shock injection	4 days 12 days 14 days	No lesions No lesions No lesions
Ox serum	Brain	1	Sensitizing injection: 0.6 c.c. Time interval: 4 weeks Second injection: 2 c.c. intravenously	10 hours	Bilateral edema of brain Normal lungs
Horse serum	Brain	1	Sensitizing injection: 0.15 c.c. Time interval: 4 weeks Second injection: 2 c.c. intravenously	36 hours	Bilateral edema of brain Normal lungs
Horse serum	Brain	1	Sensitizing injection: 0.2 c.c. No second shock injection	4 weeks	No lesion
Ox serum	Eye (Right) (subconjunctivally)	3	Sensitizing injection: $\frac{1}{4}$ -1 c.c. Time interval: 20 days Second injection: 2 c.c. intravenously	3 days	Violent congestion of conjunctival vessels of R eye In 1 rabbit slight congestion, L eye The lesions began to appear after 3 hours, lasted 2 days Normal lungs
Horse serum	Eye (Right) (subconjunctivally)	3	Sensitizing injection: $\frac{1}{4}$ -1 c.c. Time interval: 20 days Second injection: 2 c.c. intravenously	2 days	Congestion of conjunctival vessels of R eye Slight congestion of conjunctival vessels of L eye The lesions began to appear after 2 hours, lasted 24 hours Normal lungs

As a rule the lesions observed in dark-haired rabbits were somewhat more severe than those observed in albino rabbits.

The lesions obtained with exogenous antigens were identical to those obtained with endogenous antigens.

4. *Control animals in which the sensitizing injection was given subconjunctivally, in the vitreous humor, or in the brain* developed lesions in the respective organs (conjunctivitis, retinal edema, brain edema) after the shock injection. No pulmonary lesions were found in these animals.

PATHOLOGY

Gross Pathology:

The distribution of the lesions in the affected lung varied. In severe cases, the entire lung or one or several lobes were involved in the reaction. Less severe reactions involved part of a lobe or were disseminated in foci throughout one lobe or the whole lung.

In animals killed during the first hour (Fig. 1), the affected areas showed congestion and edema with an increase in lung volume. In animals killed after the first 24 hours (Fig. 2), the affected areas appeared as dark, dull red patches, with sharp borders, often surrounded by small emphysematous zones; their consistency was firm and some fluid could be expressed on pressure. The involved parts were heavier than the rest of the lung when floated in water.

The control animals, including those which were sensitized in another organ (eye, brain) (Fig. 3), did not have lesions in the lungs, except occasional pinpoint red foci probably due to the air injection used to kill them.

Microscopic Pathology (Figs 4-8):

The lesions were located mainly in the blood vessels and alveoli. The differences in the pathological picture in different animals seem to be related to: (a) various degrees of severity of the vascular injury, and (b) differences in the age of the lesion; in general, the alveolar reaction preceded the visible arteriolar changes and the congestive and edematous features preceded the cellular infiltration.

Arteries.—Both the larger (muscular) and the smaller arterioles were involved.

Endothelium and lumen.—The endothelial reaction was characterized by swelling, desquamation, proliferation, and sometimes necrosis of the endothelial cells. It was seldom observed in animals killed during the first hour after the shock injection, was at a maximum in those killed at 24 and 48 hours, and decreased somewhat in the 72 and 96 hours' group. The lumen had often decreased in size, partly because of the endothelial proliferation and partly because of the increased thickness of the rest of the arterial wall. When blood was present, the number of leukocytes was increased and they were marginating.

Intima and media.—In the larger arterioles and especially in association with the more severe reactions of the endothelium, the intima was thickened. At

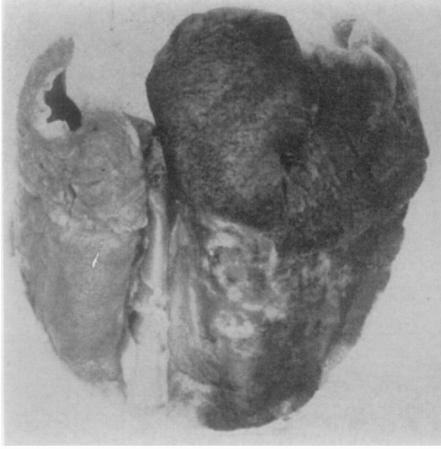


Fig. 1.

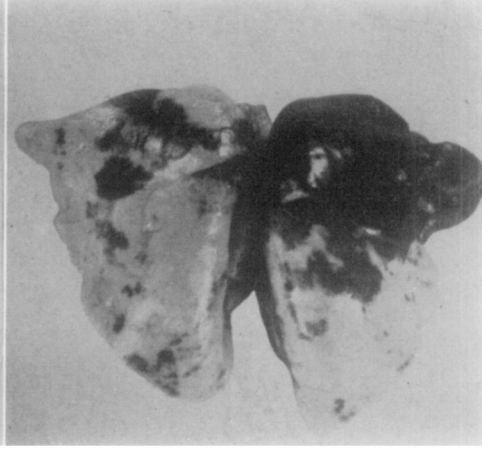


Fig. 2.

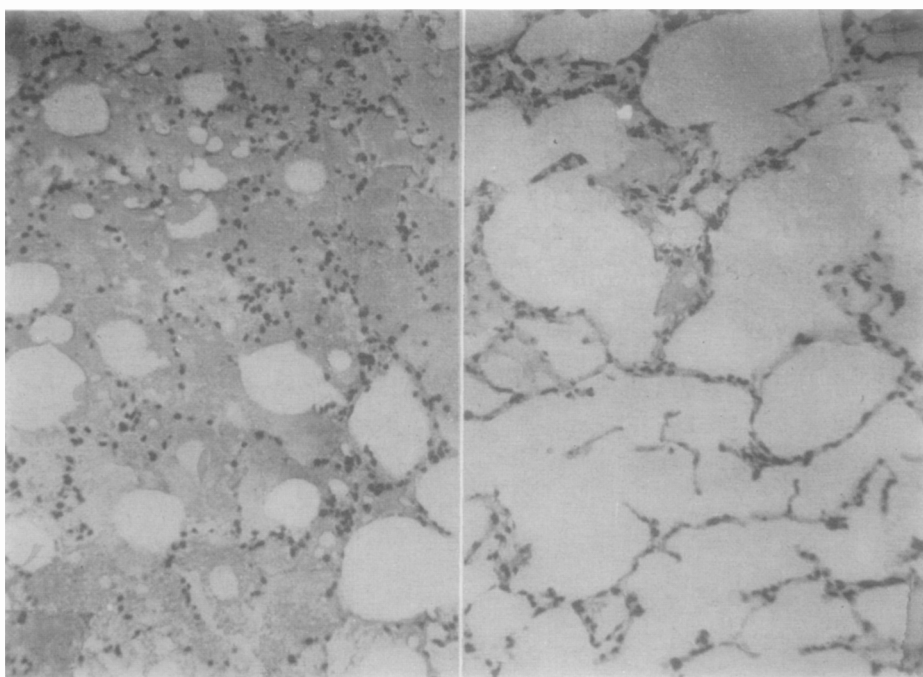
Fig. 1.—Lung sensitization. Lung reaction classified ###. Allergen: hydrolyzed auto-serum. Sensitizing injection: 0.5 c.c. Time interval: 6 weeks. Shock injection: 1 c.c. Rabbit killed within one hour after shock injection.

Fig. 2.—Lung sensitization. Right lung reaction classified ###; left lung #. Allergen: hydrolyzed auto-serum. Sensitizing injection: 0.5 c.c. Time interval: 6 weeks. Shock injection: 2 c.c. Rabbit killed 48 hours after shock injection.



Fig. 3.—Left. Brain sensitization. Allergen: hydrolyzed auto-serum. Sensitizing injection: 0.2 c.c. Time interval: 18 days. Shock injection: 2 c.c. Rabbit killed 36 hours after shock injection. Brain edema. The lungs were normal.

Right. Control animal received only sensitizing injection of same antigen. No shock injection. Killed 20 days later. Normal brain. The lungs were normal.



Right lung.

Left lung.

Fig. 4.—Lung sensitization. Allergen: hydrolyzed autoserum. Sensitizing injection: 0.5 c.c. Time interval: 6 weeks. Shock injection: 2 c.c. Rabbit killed 48 hours after shock injection. Alveolar edema of right lung. Slight reaction of the opposite lung.

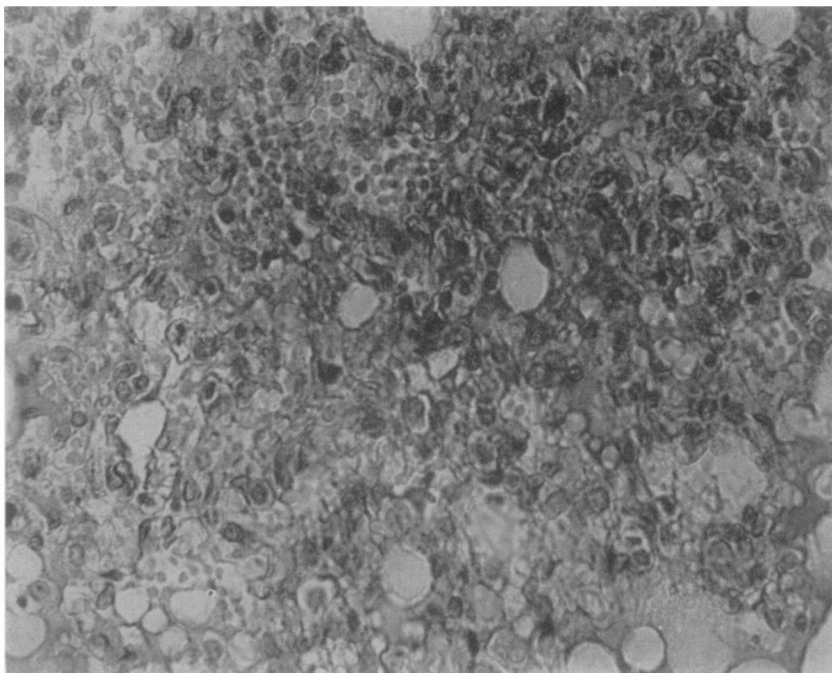


Fig. 5.—Lung sensitization. Allergen: homologous liver. Sensitizing injection: 0.5 c.c. Time interval: 6 weeks. Shock injection: 2 c.c. Rabbit killed 24 hours after shock injection. Alveolar edema, exudation of fibrin and red blood cells, infiltration by isolated large mononuclear cells (phagocytic), atelectasis, and destruction of alveolar pattern.

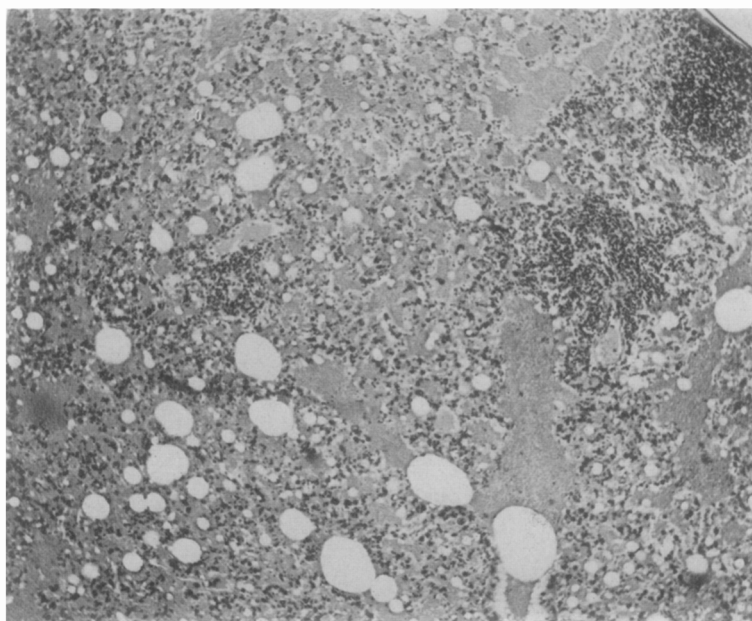


Fig. 6.—Lung sensitization. Allergen: homologous liver. Sensitizing injection: 1 c.c. Time interval: 25 days. Shock injection: 2 c.c. Rabbit killed 72 hours after shock injection. Alveolar edema, areas of necrosis of alveolar septa, and focal periarteriolar infiltration of eosinophiles.

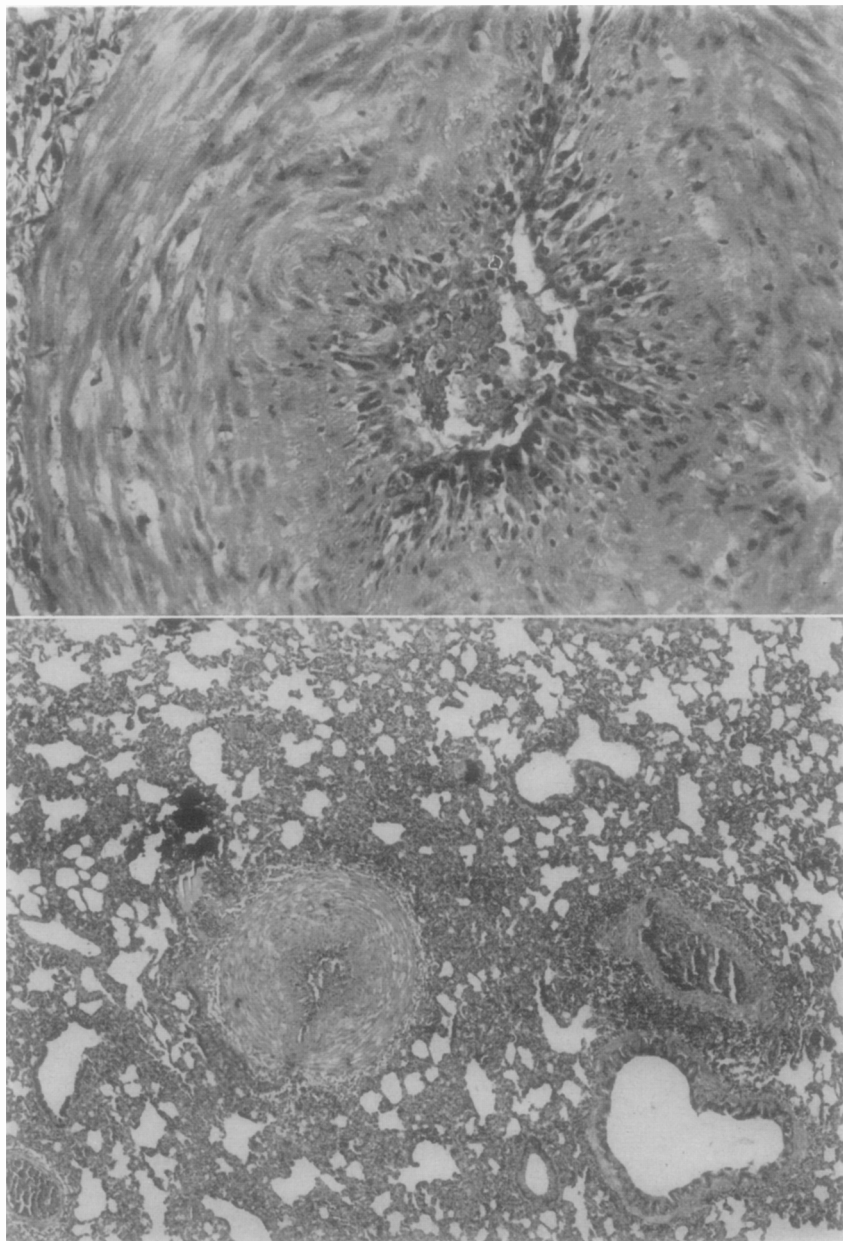


Fig. 7.

Fig. 7.—Lung sensitization. Allergen: autogenous skin. Sensitizing injection: 1.5 c.c. Rabbit killed 48 hours after shock injection. Shock injection: 0.5 c.c. Time interval: 16 days. Dense infiltration of eosinophiles and small and large mononuclears around artery and vein.

Fig. 7, A.

Fig. 7, A.—Artery of Fig. 7. High power. Endothelial proliferation, swelling, and desquamation.

24 hours it had a lacunar appearance, together with an infiltration by occasional eosinophilic cells*; after 48 hours, it often had a fibrinoid appearance. The media was the site of an edema which was maximum at 24 to 48 hours and decreased after 48 hours; in the more severe reactions this was associated with partial destruction of the media. In the smaller arterioles, especially after 48 hours, hyalinization and necrosis of the media, together with infiltration by eosinophilic cells and mononuclears, were noted in some cases.

Adventitia and periarterial region.—The earliest change, seen within the first hour, was an exudate of serum in the periadventitia and adjacent alveoli. Animals killed at 24 hours showed an extensive periarterial edema containing a variable number of cells. Animals killed after 48 hours showed in general a less extensive edema and a greater number of cells; the cellular infiltration consisted mainly of eosinophilic cells and small round cells; one or the other of these types of cells predominated in different animals; large mononuclear cells were often present and occasionally a few polymorphonuclears were to be seen.

Veins.—The veins were in general less frequently involved than the arteries. When they were, they showed the same endothelial reaction and perivascular edema and infiltration as in the arteries. During the first 48 hours marked congestion was noted. In some animals venous thrombi were seen. In a few cases there was a necrosis of the wall of the vein with infiltration by mononuclear and polymorphonuclear cells.

The perivascular lymphatics sometimes showed an increase in their lymphocyte content.

Alveoli.—The main pathological features were a thickening of the alveolar septa, alveolar edema, and atelectasis.

The thickened alveolar septa showed congestion (which was most marked during the first 24 hours), capillary thrombi in some animals, and proliferation and desquamation of septal cells.

The alveolar edema appeared as early as the first hour and decreased somewhat after 48 hours. It was variable in composition. In some instances there was a massive edema, composed of serum, which left the alveolar structure relatively intact; in other animals there was an edema composed of serum, red blood cells, and fibrin, often destroying the alveolar pattern. As a rule there was little cellular infiltration; when present, it consisted of isolated large mononuclear cells. In the later days, however, foci of eosinophilic cells from a periarteriolar infiltration extended into the adjacent alveoli and an increasing number of alveolar macrophages were found. In a few instances in which the edema was absent, an interstitial infiltration of mononuclear cells occurred.

Bronchi.—Serum and red blood cells were present in the lumen of many bronchi. When a vessel in the wall of a bronchus or bronchiole was the site of a marked perivascular infiltration, the invading cells often infiltrated the wall of the bronchus, but the bronchial epithelium remained intact.

*These cells had a bilobed nucleus and large eosinophilic granules and by comparison with other granulocytes appeared to be true eosinophiles.

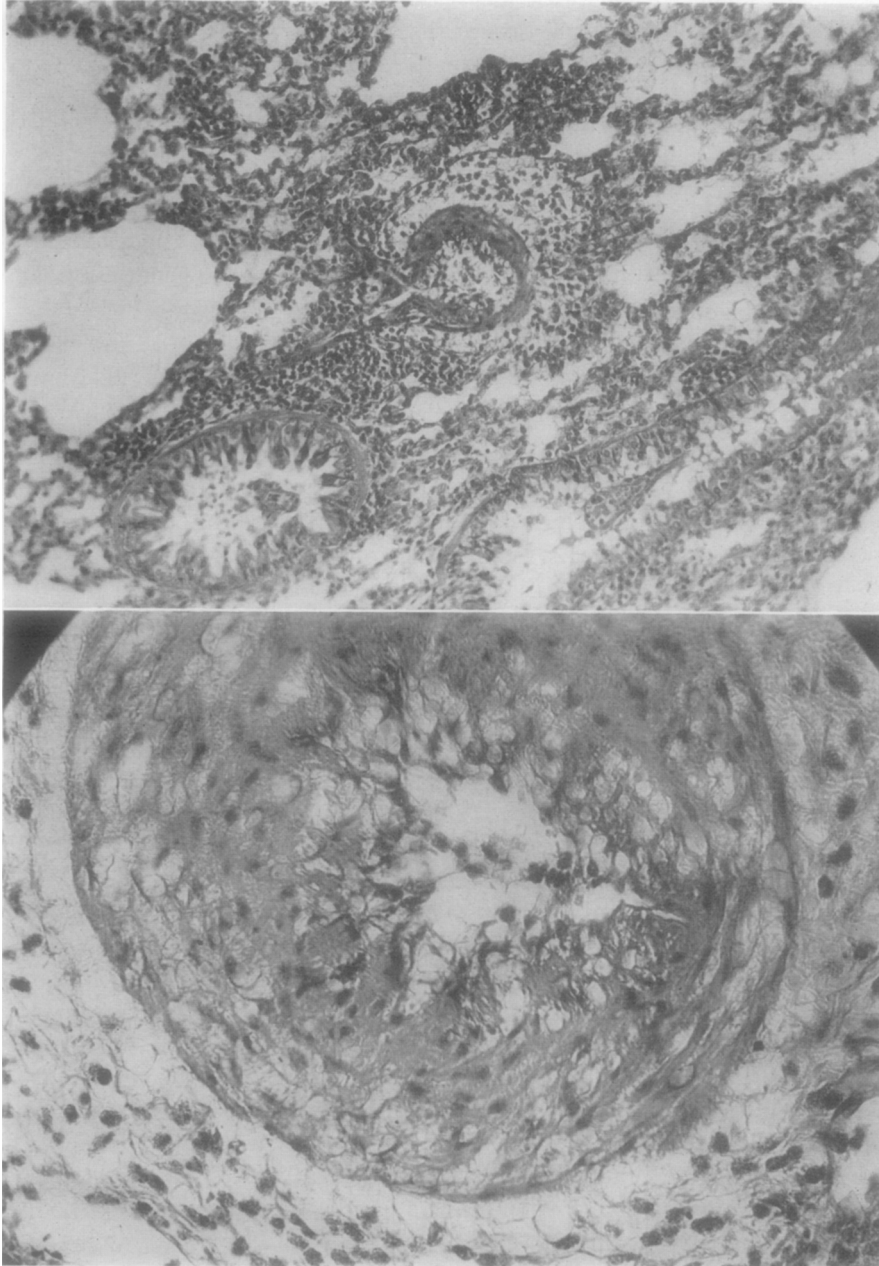


Fig. 8.

Fig. 8, A.

Fig. 8.—Lung sensitization. Allergen: homologous liver. Sensitizing injection: 0.5 c.c. Time interval: 6 weeks. Shock injection: 2 c.c. Rabbit killed 24 hours after shock injection. Endothelial swelling, proliferation, and desquamation; lacunar appearance of intima; moderate edema of media; perivascular infiltration of eosinophils. High power.

Fig. 8, A.—Same rabbit as shown in Fig. 8. Endothelial reaction and perivascular infiltration in a swollen arteriole.

Pleura.—In some animals there was an exudative reaction of the pleura with serum, red blood cells, and often fibrin. There was little cellular infiltration. The lymphocyte content of the pleural lymphatics was often increased.

Controls:

The various types of controls showed, in general, normal lungs. The following features were however present in some of them: Atelectasis, with a thickening of the alveolar septa, without changes in their structure, was seen very frequently and was probably an artefact of fixation. In a few cases, there was slight alveolar congestion and patches of alveolar edema. In the arteries, slight desquamation of the endothelium was found at times, as well as thickening of the wall which appeared to be an artefact and could not be confused with the swelling due to endarterial edema in the experimental animals. Occasionally, alveolar macrophages, old pleural thickening, and lesions due to parasites were found.

COMMENT

The experiments herein reported indicate the development of specific pulmonary lesions in the rabbit by the use of the above described autogenous antigens. In an animal which had previously received a local injection of a given antigen, the reintroduction of the same antigen in intravenous injection after a suitable time interval, resulted in a lesion at the site of the primary local injection. Neither the intravenous nor the local injection alone caused such lesions. This is regarded as an anaphylactic reaction in the organ due to a locally induced hypersensitivity.

The pneumonitis obtained represents an allergic vascular reaction of the lung involving relatively large vessels as well as arterioles, venules, and alveolar capillaries. The lesions resemble those obtained in the rabbit's lung with other methods of sensitization and with exogenous antigens by Gregory and Rich,³⁵ Fried,^{36, 37} Cannon, Walsh, and Marshall³⁸ and Herbut and Kinsey,³⁹ although they do not show the transitory alveolar infiltration with granulocytes described by the latter three authors. They also resemble in many respects the lesions observed in early stages of rheumatic pneumonia by Epstein and Greenspan⁴⁰ and, in certain respects, those observed by Harkavy⁴¹ in eosinophilic pneumonitis.

The immunological features of the locally sensitized organ have been studied in the eye and with foreign antigens by Seegal and Seegal,⁴²⁻⁴⁴ Seegal, Seegal, and Khorazo,⁴⁵ and Thompson, Gallardo, and Khorazo.⁴⁶ Thompson, Gallardo, and Khorazo showed that there was primarily a local formation of antibodies in the corneal stroma and that circulating antibodies appeared only secondarily. There is no reason to believe that the sequence of events is different when the lung is the sensitized organ, or when an endogenous, rather than an exogenous, antigen is used. Local organ hypersensitivity may therefore be interpreted as corresponding to a local formation of fixed tissue antibodies in the sensitized organ (local immunity).

Lesions in the contralateral organ were observed in some animals sensitized in the lung and in some animals sensitized in the eye. There is no satisfactory explanation of the mechanism of this phenomenon. One may suppose that some

of the antigen injected in one lung or in one eye may have reached the contralateral organ by retrograde lymphatic flow in concentration sufficient to sensitize. This is, however, purely hypothetical.

The experiments showed that hydrolyzed autoserum, homologous liver, autogenous skin, and autogenous urine are capable of producing an allergic pneumonitis in the animal which served as their source of origin or in an animal of the same species. We are planning to continue these studies and investigate the specificity of the autogenous material used.

The first allergen was obtained by a partial hydrolysis of autogenous serum. It may be inferred that the autosensitizing power was due to a change in specificity caused by hydrolysis. It has not yet been ascertained at which stages of hydrolysis the material acquires and then loses its autosensitizing power. It is known that changes in the specificity of proteins can be brought about by denaturation (MacPherson and Heidelberger⁴⁷), mild hydrolysis (Landsteiner⁴⁸) or even hydrolysis to proteoses (Stull and Hampton⁴⁹). It may be recalled in this respect that Uwazumi⁵⁰ found that when rabbit serum is heated to 80° C., it acquires both a different specificity and the power to elicit the formation of autoantibodies.

The sensitization of the lung with saline extracts of other organs (skin, liver) shows that a normal body constituent can sensitize an organ in the same animal or an animal of the same species when placed in an abnormal environment. The role of autolysis in enhancing the autoantigenicity in this case is difficult to evaluate.

The allergens present in autogenous urine may have consisted of proteins in amounts too minute to be detected by the usual methods, or of other simpler substances which could play the rôle of haptens, capable of combining with the local tissue proteins of the sensitized organ. Being excretory products, they behaved as foreign allergens when they were reintroduced in the organism and placed in an abnormal environment.

These experiments may have certain clinical implications. The results obtained with hydrolyzed autoserum indicate that denaturation and partial hydrolysis of autogenous proteins may give rise to autogenous antigens. This further suggests that autolysis could play the same role in man. The experiments with homologous liver and autogenous skin suggest that cellular destruction or necrosis in man can also give rise to autogenous antigens.

In other experimental work,^{9, 18-31} the autoantigens used to produce lesions had been activated by the addition of foreign antigens, usually bacterias. While these experiments give a possible explanation for the presence of autogenous antigens in various infectious diseases, they do not give one applicable to those diseases in which there is no evidence of an infectious process. Autolysis and cellular destruction due to various causes such as nonbacterial toxic agents, metabolic and vascular diseases, as well as infectious agents, may now be conceived as possible sources of autogenous antigens in man.

Indeed, there is some clinical evidence to show that the presence of autoantigens is not limited to diseases in which infectious agents play a role. Autoantibodies against liver have been found not only in infectious hepatitis, but also

in toxic hepatitis, acute yellow atrophy, obstructive jaundice, and other diseases (Eaton, Murphy, and Hanford,⁵¹ Bjørneboe and Krog⁵²). It has been possible to desensitize certain patients who showed allergic phenomena following several applications of radium by repeated exposures to small doses of radium; these patients were then able to sustain the large doses without reaction. Hypothesis based on the role of autogenous antigens have been advanced for such diseases as multiple sclerosis (Rivers, Sprunt, and Berry¹⁹) and peptic ulcer (Jahiel⁵³) in which there is, at the present time, no evidence of an infectious process. In glomerulonephritis and rheumatic fever the multiplicity of the lesions or symptoms leads one to suspect that more than one antigen or mechanism is operating.

This hypothesis may find an application in the field of tumors. Hodgkin's disease in which there is often a considerable tissue destruction, sometimes shows pathological features which suggest an allergic process, such as the presence of eosinophiles, periarterial phenomena in the spleen, and in certain cases, amyloid degeneration (Feldman⁵⁴). It would be interesting to find out if autoantigens are liberated and what role they could play in the evolution of the disease.

In connection with the excretory product, urine, used in our experiments, it may be recalled that other abnormally reabsorbed excretory products, such as menstrual blood (Jahiel,⁵⁵ Salen⁵⁶) have been found to cause certain allergic manifestations in women. In the case of the menstrual allergies, it was possible to desensitize patients with their own menstrual discharge.

SUMMARY

1. An allergic pneumonitis was obtained in the rabbit by using various autogenous materials as allergens.

2. The autogenous allergens used were: (1) partly hydrolyzed autogenous serum; (2) saline extracts of autogenous skin and homologous liver; and (3) an excretory product, autogenous urine. A complementary study was done with exogenous allergens.

3. A local sensitization of the lung was achieved by a single intrapulmonary injection of the allergen under investigation. After a suitable time interval, the shock injection of the same allergen was given intravenously and an allergic pneumonitis developed in the sensitized lung.

4. The pneumonitis was characterized by alveolar lesions (congestion, edema) and vascular lesions (endothelial reaction, endarterial, and periarterial edema, periarterial infiltration with eosinophilic cells and small and large mononuclears).

5. The immunological mechanism involved, the factors granting antigenicity to the autogenous substance used in these experiments and the possible events capable of leading to the release of similar allergens in man are discussed.

6. These experiments suggest that partial hydrolysis of autogenous proteins, tissue destruction and liberation of endocellular material, and reabsorption of an excretory product can, under certain conditions, give rise to autogenous allergens and provoke pathological changes in a previously sensitized tissue.

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