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CONTENTS

The Lungs in Anaphylaxis and in Conditions Simulating Anaphylaxis. By Howard T. Karsner, M.D.	33
Specimens Presented January 12, 1911.	39
The Cellular Basis of the Determination of Sex. By Thomas H. Montgomery, Jr., Ph.D.	45
Malaria. By William Pepper, M.D.	50
Observations on Natural and Experimental Yaws. By Henry J. Nichols, M.D.	50
Piroplasma (the Development of Piroplasma Parvum; the Cause of East Coast Fever in South Africa.) By K. F. Meyer, M.D.	52
The Chemotherapy of Ehrlich, with Special Reference to the Trypanosome Infections. By B. T. Terry, M.D.	54
Specimens Presented February 9, 1911.	63
A Scientific Study of the Deterioration of Poultry during Marketing. By M. E. Pennington, Ph.D.	66
A Preliminary Note upon the Enzymes and the Leukoocytes in Acute Leukemia. By Warfield T. Longcope, M.D., and J. V. Cooke, M.D.	72
Some Effects of Underfeeding on the Growth of the Brain. By Henry H. Donaldson.	74
Specimens Presented March 9, 1911.	70
A Study of Case Histories and Autopsy Protocols with Special Reference to the Renal Findings. By J. H. Austin, M.D., and O. H. Perry Pepper, M.D.	78

THE LUNGS IN ANAPHYLAXIS AND IN CONDITIONS SIMULATING ANAPHYLAXIS.

BY HOWARD T. KARSNER, M.D.

(From the State Serotherapeutic Institute, Vienna, Prof. Dr. R. Kraus, Director, and from the Laboratory of Pathology, University of Pennsylvania, Philadelphia, Pa.)

THE purpose of this paper is to aid in the identification of anaphylaxis as a distinct biological entity. Since the early work on true anaphylaxis by Richet, Arthus, von Pirquet, Otto, Rosenau and Anderson, and others, various attempts have been made to produce by a single injection of some substance the same effect

that is produced by the repeated injection, with suitable time intervals, of a protein, particularly an animal protein. Of the substances used in the attempts to produce an artificial anaphylaxis in guinea-pigs, fresh ox serum (toxic for guinea-pigs), Witte's peptone, and various hematoxic substances such as ricin, abrin, solanin hydrochlorate, hirudin, sodium oleate, and some others have been employed. Symptomatically and to a certain extent physiologically, the effects of the administration of these substances resemble those of true anaphylaxis. There is much question, however, as to whether or not the similarity is so close biologically; and it was with the idea of throwing some light on the differences between true anaphylaxis and these conditions which in many ways simulate it that the present anatomical study was undertaken.

The pathological anatomy of anaphylaxis was first studied by Gay and Southard,¹ who declared the lesions to be: Vascular dilatation and hemorrhages, both gross and minute, especially in the abdominal viscera; fatty degeneration in voluntary muscle fiber, heart muscle fiber, and nerve fiber. Rosenau and Anderson² ascribe the vascular dilatation to shock as a general condition, not necessarily anaphylactic, and state that the "macroscopic congestions and hemorrhages were frequently absent in guinea-pigs poisoned by a second injection of horse serum given into the brain." They were "unable to confirm Gay and Southard's findings in regard to the fatty changes." Auer and Lewis³ have pointed out what they consider "the most characteristic sign of immediate anaphylaxis in the guinea-pig." They describe the lungs as being distended so as to apply themselves closely to the chest wall. The organ is pallid or bluish, light in weight, buoyant in water, and of spongy consistence. Occasionally fine points of hemorrhage are seen. The trachea and bronchi are dry, but often show a marked congestion of the mucosa. Observations of Kraus confirm this, and my own studies further support it. The slight exception I find is that the hemorrhages are very infrequent and that the reddening of the trachea and bronchi is by no means constant.

My studies have been made with guinea-pigs weighing about 250 grams. The second injections of horse serum and the primary and only injections of other substances were made into the jugular vein. The histological preparations in all cases were made from tissues fixed in Zenker's fluid and stained with hematoxylin and eosin and with the Mallory connective-tissue stain.

In order to make clear the entire series of experiments an outline is appended.

¹ Journal of Medical Research, 1907, xvi, 143.

² Archives of Internal Medicine, June, 1909, iii.

³ Journal of Experimental Medicine, 1910, xii, No. 2.

- I. Experiments with anaphylactic guinea-pigs (horse serum).
- II. Experiments with peptone injections.
- III. Experiments with toxic serum (ox serum).
- IV. Experiments with immune serum.
 1. Hemolytic amboceptor.
 2. Precipitating amboceptor.
- V. Experiments with hemotoxic agents:
 1. Ricin.
 2. Abrin.
 3. Solanin hydrochlorate.
 4. Sodium oleate.

I. In the work with the anaphylactic guinea-pigs sensitization was accomplished by the subcutaneous injection of 0.05 c.c. normal horse serum. Secondary fatal doses of 0.5 c.c., 1 c.c., 1.5 c.c., 3 c.c., were given in the jugular vein. Rapid death ensued with the usual symptoms of anaphylaxis, *i. e.*, more or less general convulsive movement, cyanosis, respiratory effort, and final cessation of respiration with the heart still beating. Autopsy showed the heart to be slightly or not at all dilated and when opened free from clots. The lungs grossly in all cases were markedly distended, pallid, light in weight, spongy in consistence, but in no instance showed any gross hemorrhage or well-marked congestion of the bronchi. Histologically, the bronchi were found to be constricted in all the lungs and showed marked folding of the mucosa. The arteries also showed well-marked constriction. The large veins were slightly distended and showed the presence in some instances of masses of conglutinated blood corpuscles. In one pig there was found well-marked fading of the red corpuscles. In some of the capillaries that were not emptied by the marked alveolar distention an occasional occluding mass of conglutinated corpuscles was found, but this was by no means a frequent occurrence. A noticeable feature was the presence of a moderately marked perivascular edema occupying both the perivascular lymph spaces and the loose connective tissue in their neighborhood. The edematous fluid showed small amounts of fibrin with the Mallory connective-tissue stain. The alveoli were distended and showed frequent rupture into one another; the walls were markedly thinned and the alveolar spaces empty, except in the case of the pig which received 3 c.c. horse serum. In one section from this pig a small area showed filling of the alveoli with red blood corpuscles—an area of microscopic hemorrhage. In so far as the alveoli were considered, the lungs showed the typical picture of vesicular emphysema.

II. Several guinea-pigs were given injections of Witte's peptone, 10 per cent. in 0.85 per cent. sodium chloride solution. The doses were 3 c.c. and 3.5 c.c. of this solution. The symptoms were

typical of anaphylaxis. The autopsies showed well-marked distention of the lungs, a condition very closely resembling that of the true anaphylactic lungs except that small macroscopic hemorrhages were more frequently observed. The heart was slightly dilated and free from clots. Histologically the picture simulated that of anaphylaxis very closely with the exception that the bronchial and arterial constriction were not so marked. The perivascular edema was about the same and the same degree of conglutination of red blood corpuscles in both capillaries and veins was observed. No microscopic hemorrhages could be found, so it is believed that the areas which grossly were supposed to represent hemorrhage corresponded to small foci of relative atelectasis observed microscopically, in which the capillaries were much distended with blood.

III. Three guinea-pigs were injected respectively with 0.5 c.c., 1 c.c., and 2 c.c. fresh ox serum. Death ensued very rapidly with symptoms like those of anaphylaxis. The autopsies showed small, intensely congested lungs with frequent punctate areas of hemorrhage and a markedly dilated heart which contained small clots of blood. The cardiac dilatation affected the right side more than the left. Histologically, the lungs showed moderate constriction of the bronchi, but the arteries were practically normal in caliber. The veins, however, were markedly distended and showed fairly large masses and meshes of fibrin. Perivascular edema was present in about the same degree as in the anaphylactic lungs. The alveoli in some places were markedly distended and ruptured, but for the most part were of normal size or collapsed, showed thick congested walls and well-marked capillary occlusion with hyaline conglutinated red blood corpuscles. The alveolar spaces in many places showed marked edema and hemorrhage.

IV. Two types of amboceptor were used in the experiment, the first the serum of a rabbit immunized against sheep's corpuscles so that the serum in a dilution of 1 to 2400 dissolved 1 c.c., 5 per cent. corpuscle suspension, the second a precipitin obtained by immunizing a rabbit against horse serum, the resulting serum producing a precipitate when acting on horse serum of a dilution of 1 to 1,000,000. The intravenous injection of 5 c.c. of such a precipitating serum produced only slight respiratory disturbance in the guinea-pig followed by complete recovery. The intravenous injection of 0.5 c.c., 1 c.c., 2 c.c., 3 c.c. of the hemolytic amboceptor (1 to 2400) was fatal, with symptoms closely simulating true anaphylaxis. Hemolytic amboceptor of less strength (1 to 800) produced no more effect than normal rabbit serum. Of the guinea-pigs injected with the stronger hemolysin, all died with symptoms of anaphylaxis. At autopsy, the lungs were found to be moderately distended and showed intense congestion, pinpoint hemorrhages, and easily demonstrable edema. The heart

was dilated and filled with dense black clot. Histologically, the bronchi and arteries showed very moderate constriction. The veins were considerably distended and filled with red blood corpuscles, hyaline masses of serum, fibrin threads, and in some instances showed conglutination of the corpuscles. The perivascular spaces were markedly edematous, and in many places showed extensive hemorrhage with fibrin formation. The alveoli showed well-marked distention and rupture of their walls. The walls showed moderate congestion and conglutination of the corpuscles. The alveolar spaces in some few places showed hemorrhage, but the most noticeable feature of these slides was the extensive edema present in the alveoli.

V. Of the hematotoxic agents used, the effects of ricin and abrin were so closely alike that a combined description seems justified. The ricin was given in doses of 0.001, 0.002, 0.003, 0.01, 0.02 gram, the abrin in doses of 0.001, 0.004, 0.01, 0.02 gram. The pigs died in all cases at periods varying from ten to twenty-four hours. Grossly the lungs were moderately distended, occasionally showing small areas of atelectasis. The organs were deeply congested and showed numerous points of hemorrhage. The pleura in several of the animals showed a moderate amount of clear, limpid yellow fluid. The heart was dilated and filled with dark red clot. Histologically the lungs showed moderate constriction of bronchi and arteries and marked distention of veins and many of the capillaries. All the vessels showed conglutination of the corpuscles which in the capillaries appeared to have caused occlusion. Well-marked perivascular edema was present. The alveoli showed moderate distention, edema, and in some places hemorrhage.

Solanin hydrochlorate was given in doses of 0.002, 0.004, and 0.005 gram. Death was rapid with symptoms of anaphylaxis. At autopsy the lungs were found to be slightly distended, and in one case distinctly collapsed, with a few areas of distention. Slight pulmonary congestion was present. The heart was still beating and showed the presence of fine clots. Histologically there was moderate constriction of arteries and bronchi; the veins were distended with red blood corpuscles, hyaline serum, fibrin, and showed moderate conglutination; the capillaries also showed occluding masses of conglutinated corpuscles. The perivascular spaces showed moderate edema, sometimes richly fibrinous. The alveoli showed fairly well marked distention alternating with areas of collapse. Slight edema and less noticeable hemorrhage were seen in the alveolar spaces.

Sodium oleate was used in doses of 0.05, 0.1, and 0.2 gram. Death ensued very quickly with symptoms of anaphylaxis. The lungs showed distention, marked congestion, numerous hemorrhagic points, and distinct edema. The heart was markedly dilated and filled with clots. Histologically the lungs showed

distinct but not very marked constriction of the bronchi and arteries and well-marked distention of veins and capillaries. There was very marked conglutination of corpuscles in the larger veins and in the capillaries. The perivascular spaces were moderately edematous. The alveoli showed considerable distention and slight rupture of the walls. The alveolar spaces were markedly edematous, almost as much as in the lungs after hemolytic amboceptor injections, and in several places hemorrhage had occurred into the alveoli.

The similarity between the lung, heart, and blood conditions after the injection of abrin, ricin, and sodium oleate, and after the injection of fresh (toxic) ox serum is very close, and suggests that the action of ox serum is of a nature similar to the action of these hemotoxic agents.

As a result of these studies it seems fair to conclude:

1. That the lung picture in the horse serum anaphylaxis of guinea-pigs is quite distinctive, the most noticeable features being bronchial constriction and marked distention and rupture of alveoli.

2. That the pictures presented by the various agents suggested to produce artificial anaphylaxis are quite different from those of true anaphylaxis except in the case of peptone injections, where the similarity is so close that only non-essentials serve to distinguish it.

3. The effect on the lungs of hemolytic amboceptor is characterized, especially by marked edema; that of toxic ox serum by hemorrhage; and that of the hemotoxic agents mentioned is closely similar to that of fresh ox serum.

4. Conglutination (fusion) of erythrocytes is common to all the processes studied, but is more marked in the non-anaphylactic than in the truly anaphylactic conditions.

In conclusion, I wish to thank Prof. Dr. R. Kraus at whose suggestion this study was undertaken, for facilities used in the earlier parts of the work.

DISCUSSION.

DR. R. M. PEARCE: The very interesting paper of Dr. Karsner presents two points for discussion. The first is in connection with the negative results which were obtained by the injection of serum characterized as a "precipitating" serum. One of the theories concerning anaphylaxis which has recently attracted considerable attention is that which assumes that the phenomena resulting from the injection of a toxic dose are due to the precipitation of proteins within the cell. I do not now recollect which system Dr. Karsner used in preparing his precipitin, but if it was

directed against the protein elements of the guinea-pig, his observations would detract from the importance of the theory which assumes that the reaction of anaphylaxis depends upon the precipitation of such protein elements.

The other point is in regard to the results obtained with the injection of peptone as contrasted with the true anaphylactic reaction. Both of these phenomena are characterized by a sudden drop in blood pressure. This may be seen best, perhaps, in the dog, as has been shown by Eisenbrey and myself, but is more or less characteristic of the reaction in the rabbit and guinea-pig as well. This sudden drop of blood pressure in the dog, essentially a condition of shock, is perhaps the equivalent of the respiratory disturbances in the guinea-pig. It is of great interest in this connection to note that Auer and Lewis refer the latter to the effect on the smooth muscle of the bronchioles. In the dog, Eisenbrey and myself believe the action to be on the smooth muscle of the bloodvessels of the peripheral circulation, especially in the splanchnic area. The reactions differ, it is true, in that the effect on the bronchial muscles is a contraction, while in the dog the vessel muscle is paralyzed, but this selective action in either instance indicates that the anaphylactic reaction is in some way associated with an effect on the function of smooth muscle or of the nerves controlling such nerves. Detailed observations carried out in the thorough manner which characterizes Dr. Karsner's work, must be continued in the hope of eventually reaching a solution of this most interesting biological phenomenon.

December 22, 1910.

SPECIMENS PRESENTED JANUARY 12, 1911.

DR. SIDNEY J. REPLIER:

Specimen Showing the Simultaneous Occurrence of Carcinoma and Sarcoma of the Breast.

M. W., white, female, aged sixty-four years, operated on by Dr. Wm. L. Rodman at the Presbyterian Hospital. No history of injury obtainable. Tumor had been present for three or four years but had begun to grow rapidly in the last few months. On palpation several rounded masses could be felt, one of which seemed cystic and was discolored a reddish brown.

Pathological examination shows the breast to be almost entirely composed of new growth. The area under the discolored spot is a cyst the size of a hen's egg containing a dark red fluid. The tumor mass appears to be made up of distinct lobules differing in gross