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Demonstration of an "Anaphylactic Poison".

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That the liver is practically indispensable for the development of anaphylactic shock in the dog has been indicated, principally by Manwaring and his colleagues,[1] Voegtlin and Bernheim,[2] and Simonds and Brandes.[3] Manwaring,[4] in addition, has reported that during anaphylactic shock in the dog, physiologically active substances, called by him "hepatic anaphylatoxins," appear in the circulating blood so that by appropriate cross circulation experiments their presence can be demonstrated by the effects they produce in the recipient animal. A number of considerations led us to suspect that if transportable physiologically active substances are set free during anaphylactic shock in the dog, they might appear in the thoracic duct lymph. Petersen and Levinson[5] have noted the marked increase in the rate of flow of the thoracic duct lymph during shock. That this increase in flow is secondary to the shock phenomena occurring in the liver is indicated by the work of Simonds and Brandes,[6] who reproduced similar effects by mechanical obstruction of the hepatic veins. The points of similarity between the manifestations of anaphylactic shock and mechanical obstruction of the hepatic veins in the dog have been studied in considerable detail by Simonds and Brandes, and warrant the conclusion that a considerable proportion of the increased lymph flow occurring during shock is of hepatic origin. If this is the case, it would seem possible that substances such as the hepatic anaphylatoxins of Manwaring might appear in the lymph.

As one of the most delicate methods of testing for the presence of certain smooth muscle stimulating substances, the isolated surviving strip of guinea pig intestine was used. This method has a number of advantages over cross circulation experiments such as,

[1] Manwaring, W. H., *Johns Hopkins Hosp. Bull.*, 1910, **21**, 275.

[2] Voegtlin, C., and Bernheim, B. M., *J. Pharm. and Exp. Therap.*, 1911, **2**, 507.

[3] Simonds, J. P., and Brandes, W. W., *J. Immunol.*, 1927, **13**, 1.

[4] Manwaring, W. H., Hosepian, V. M., O'Neill, F. I., and Moy, H. B., *J. Immunol.*, 1925, **10**, 575.

[5] Petersen, W. F., and Levinson, S. A., *J. Immunol.*, 1923, **8**, 349.

[6] Simonds, J. P., and Brandes, W. W., *J. Immunol.*, 1927, **13**, 11.

(1) simplicity, (2) opportunity to repeat and check results, (3) the possibility of assaying any physiologically active substance by comparison with known active agents, (4) opportunity to determine the time relations of the appearance of any active substance in relation to the shock, and (5) opportunity to obtain certain data relative to the nature of the active substance.

Dogs were sensitized by the intravenous injection of horse serum, hog serum, or sheep serum. After an interval of 14 to 28 days, they were anesthetized with ether and sodium barbital, the carotid artery cannulated for recording blood pressure, and the thoracic duct cannulated for collecting lymph. The appropriate shocking dose of serum was given intravenously and the lymph collected for varying periods of time thereafter. This was then tested for physiological activity on a strip of guinea pig's intestine suspended in a bath of Tyrode's solution in the usual manner. In approximately 40% of the experiments run to date (22), the lymph collected after shock had a marked ability to stimulate contractions of the guinea pig intestine, both in the case of normal pigs and in pigs immunized by repeated injection of the antigen used. This activity varied in degree so that in some experiments ¼ cc. of lymph when added to the 200 cc. bath used was effective while in other experiments as much as 5 cc. were required. In no instance did normal lymph, even in doses up to 20 cc. have any such effect. It is interesting to note, however, that the intensity of the shock is not necessarily correlated with the presence of the active substance, because it could be demonstrated in the lymph in a few instances of comparatively weak shocks, while it was occasionally absent in fatal shock.

In a number of experiments, after shock was well developed, and in other cases of fatal shock just prior to death, the chest was rapidly opened and blood aspirated from the inferior vena cava just above the diaphragm. In all instances of fatal shock, and occasionally in non-fatal shock, such blood was shown to be active in stimulating the guinea pig intestine, both of normal pigs and of pigs immunized to the antigen used. In no case did normal pre-shock blood have any such effect, and in only one instance did the femoral vein blood obtained after shock have any activity.

The nature of the active substance appearing in the lymph and in the inferior vena cava blood during anaphylactic shock is at present under investigation.