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Acrolein and Shock. Possible Relationship of Lipoid Breakdown Products to Shock Associated with Burns.*

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The causative factor in shock associated with burns is still questionable. Many theories have been proposed and more than 20 substances have been listed as having a part in its production. Yet no one substance has been demonstrated in the blood or tissues of patients suffering from this condition to prove definitely that it is the cause.

Many investigators who adhere to the toxic theory assume that breakdown products of *proteins* are responsible for the peripheral circulatory failure and capillary damage which are perhaps the most important factors in producing the condition of shock. This concept may be true but the possibility that similar breakdown products of body fats may play an equally important role should not be entirely disregarded.

It is well known that when fats or other glycerol esters are heated directly, a certain amount of the glycerol portion of the radical is changed to acrolein, a very toxic substance. Since fats are normally present in all tissues of the body, it appears likely that acrolein may be produced when tissue is subjected to burns, especially if the burn extends to the subcutaneous fat.

In order to test the validity of this assumption, experiments were undertaken to demonstrate first, whether acrolein itself might produce the picture of shock in animals; and second, whether the causative agent in shock produced by burns might be identified as, or linked with, acrolein or its breakdown products. This paper is a preliminary report of the first part of these studies.

Laboratory Procedure. Employing 10 dogs (wt. 4-8 kg), 2 cats (wt. 3.5-3.7 kg), and one rabbit (wt. 2.7 kg), the following procedure was used: acrolein† diluted in normal salt solution to a concentration of 1:10 was injected in one or another manner; subcutaneously, intraperitoneally or intravenously in single or divided dosage. Total dosage of acrolein ranged from 0.1-0.5 ml (One animal received 2.33 ml in divided doses). In addition 3 control animals (dogs) were run with ether anesthesia alone, 2 of them for comparable periods of 4 to 5 hours. The third was maintained under anesthesia for 18 hours.

Careful kymographic records of blood pressure levels by means of a cannula in the carotid artery, as well as pulse rate and respiration were kept. Hematocrit readings were taken at frequent intervals for evidence of fluid shift with associated hemoconcentration. The femoral vein was used for injections and for removal of blood samples. Ether anesthesia was maintained through a tracheal cannula. All animals were examined pathologically at autopsy and their tissues studied microscopically.

Results. All the reactions were acute, the animals surviving from one to 5 hours, an average of 3 hours after the initial injection of acrolein. Hematocrit readings consistently showed some degree of hemoconcentration even in the brief period of these acute experiments, with a maximum increase of 12% of cells. All animals clinically presented the classical picture of shock with hemoconcentration, a falling blood pressure and terminal pulmonary edema. Pulse and respiration rates were less regularly altered. Pathologic examination both grossly and microscopically showed confirmatory evidence of shock, with intense pulmonary edema, and visceral con-

* Acknowledgment is hereby expressed to the members of the Departments of Pathology, Pharmacology, Physiology, Chemistry, Bacteriology and Immunology for their interest, encouragement and cooperation.

† The acrolein used was obtained from the Eastman Kodak Company.

gestion even to the point of capillary hemorrhage, especially in the mucosa of the stomach and duodenum. The spleen less regularly presented the classical picture of constriction and pallor, due we believe to the acute nature of the experiments. One animal injected subcutaneously (0.37 ml) showed almost complete hemolysis. The 3 control animals with ether anesthesia alone showed an average hemoconcentration of less than 5%. Pathologically, their tissues were normal.

Summary and Conclusions. Acrolein injected into experimental animals by any of several routes produces a condition identical in its clinical and pathological manifestations to that generally accepted as "shock." By using the intravenous route and relatively large doses in certain animals, it is believed that this picture is the direct result of capillary damage by acrolein or lipoid breakdown products, rather than the result of the liberation of "H" substance or other tissue breakdown protein substances. Studies concerning the development of antibodies to acrolein in the serum of burned animals and individuals are in progress.

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Action of Bacterial Toxins on Tumors. IV. Distribution of Tumor-Hemorrhage Agents Among Bacterial Species.*

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In a survey[1] ranging over 28 genera and nearly 100 strains of bacteria it was found that bacterial substances capable of inducing hemorrhage in implanted tumors were restricted to gram-negative species. A close correlation between the occurrence of hemorrhage-producing agents and the toxic somatic O antigens of gram-negative bacteria was adduced. Further investigations demonstrated a close parallelism between the lethal and the tumor-hemorrhage properties of purified bacterial products[2] and a parallel inhibition of both of these actions by sulfonamide drugs.[3]

Since the O antigens of gram-negative bacteria (and the chemically similar Vi antigens) have been identified in several recent studies with the essential immunizing constituents of antibacterial vaccines, it was considered of interest to explore further, in both pathogenic and non-pathogenic bacteria, the distribution of toxins inducing the type of vascular damage which we believe to be characteristic of the O and Vi antigens. The present study is an extension of the original survey, and includes the testing for tumor-hemorrhage activity of an additional 30 gram-negative and 7 gram-positive species.

Methods. The hemorrhage activity of concentrated bacterial cultures was tested on white male Rockland mice bearing 7-day-old implants of Mouse Sarcoma 180. In preparing mice for assay, a 2-3 mm cube of tumor tissue was implanted subcutaneously near the axilla and allowed to grow for 7 days, by which time it had become well vascularized and had developed into a spherical mass about 1 cm in diameter. The material to be assayed was administered intraperitoneally. The bacteria were killed by addition of a small quantity of toluene-chloroform mixture. This treatment is unlikely to inactivate the O antigen.[4] Where necessary the volume was reduced by pervap-

* We wish to express our gratitude to Prof. C. B. Van Niel, who supplied most of the cultures used in this survey.

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