Proceedings
of the
Society
for
Experimental Biology and Medicine

VOL. 73 APRIL, 1950 No. 4

SECTION MEETINGS

CLEVELAND	
Western Reserve University	December 9, 1949 February 10, 1950 March 10, 1950
ILLINOIS	
Chicago Medical School	March 21, 1950
SOUTHERN	
Louisiana State University	March 16, 1950

Penicillin in the Treatment of Peritonitis Due to Liver Autolysis in Dogs. (17734)

F. JOHN LEWIS AND OWEN H. WANGENSTEEN.

From the Department of Surgery, University of Minnesota Medical School, Minneapolis, Minn.

Since the observation of Mann(1) that small pieces of dogs' liver left free within the peritoneal cavity would cause death within 16 hours was confirmed and extended by Mason and Davidson(2), interest in this phenomenon has generally centered about explanations of the lethal outcome. Debate has arisen on the question of whether anaerobic bacteria normally present in the dogs' liver play a decisive or merely a secondary role in producing the fatal toxemia of this condition. It is thought that the experiments to be described will help to answer this question and also demonstrate a successful treatment for what has previously been described as a uniformly fatal condition.

Experiments of Mason and Davidson were repeated by Wangensteen and Waldron(3) and by Haden and Orr(4) with similar results. Ellis and Dragstedt(5) first suggested the importance of bacteria normally present in the dogs' liver in producing a fatal infection in the dead liver. They called attention to the earlier work of Wolbach and Saiki(6) who had described an anaerobic, spore-forming, gas-producing bacillus found in normal dogs' liver. They supported their thesis by confirming the presence of this bacillus in dogs' liver and by showing that liver sterilized by autoclaving, or sterile liver taken from fetal dogs produced no toxic effects in the peritoneal cavity of dogs. Disagreement arose when Andrews and Hrdina(7) reported that

1. Mann, F. C., as cited by Mason and Davidson.
2. Mason, E. C., and Davidson, E. C., *J. Lab. and Clin. Med.*, 1925, v10, 622.
3. Wangensteen, O. H., and Waldron, G. W., *Arch. Surg.*, 1928, v17, 430.
4. Haden, R. L., and Orr, T. G., *J. Exp. Med.*, 1928, v48, 639.
5. Ellis, J. C., and Dragstedt, L. R., *Arch. Surg.*, 1930, v20, 8.
6. Wolbach, S. B., and Saiki, T., *J. Med. Res.*, 1909, v21, 267.
7. Andrews, E., and Hrdina, L., *S. G. O.*, 1931, v52, 61.

the toxic reaction of autolytic peritonitis could be provoked by the implantation of finely ground sterile liver; they described the toxic agent as probably an albumose arising from liver autolysis. They felt that the bacterial invasion was of secondary importance, probably produced by an increased permeability of the bowel, allowing bacteria to pass through and then infect the material lying within the peritoneal cavity. Trusler, Reeves and Martin(8) who, after careful bacteriological studies, came to disagree with Andrews and Hrdina, found that fresh ground liver sterilized by autoclaving would not cause death when injected intraperitoneally unless it was contaminated.

Methods and results. The 25 healthy, dewormed dogs used in these experiments were divided into 3 groups. The animals in Groups I and II were subjected to the intraperitoneal autolysis of segments of their own liver. The dogs in Group I had penicillin treatment and those in Group II did not; otherwise their treatment was similar. Under intravenous pentobarbital anesthesia and using aseptic precautions, the abdomen was opened and the quadrate lobe of the liver, weighing from 4.5 g to 34.0 g and averaging 17.6 g, was removed and dropped into the free peritoneal cavity. Bleeding from the liver was controlled with mattress sutures. Among the animals of Group I penicillin treatment was begun from 1 to 4 hours postoperatively, when each dog received an intramuscular injection of 300,000 units of penicillin G in oil and wax.* This dose of penicillin was repeated daily for a total of 4 to 11 injections in the dogs that recovered. Of the dogs in the penicillin-treated group only 3 of the 12 died while all of the 5 control animals died within 3½ days or less following surgery. With one exception, the penicillin-treated animals which died all survived longer than any of the control animals. At autopsy there was a characteristic picture of peritoneal injection, brownish serosanguinous fluid and gas in the peritoneal cavity, and frequently a spongy pale remnant of the free liver segment still in the peritoneal cavity. Microscopic sections of the necrotic free segments of liver showed many rod-shaped bacteria. None of the survivors had any evidence of peritonitis at autopsy. In several of them necrotic remnants of liver were found encapsulated by omentum.

The dogs in Group III were exposed to the intraperitoneal autolysis of fresh segments of human liver from 11.0 g to 44.0 g and averaging 30.8 g in weight. Specimens of human liver were obtained aseptically from recently dead cadavers with no intra-abdominal disease and placed in the peritoneal cavity of dogs through a wound made aseptically under intravenous pentobarbital anesthesia. Only 2 of the 7 non-penicillin-treated dogs exposed to human liver autolysis died. Neither of the animals dying of human liver autolysis showed the large amount of serosanguinous intraperitoneal fluid characteristic of canine liver autolysis.

Discussion. The short survival of the control animals with devitalized canine liver is the typical result of this experiment. There has been only one dog described in the literature(9) who has survived more than 5 days after a small, free, non-autoclaved segment of adult dog liver has been placed in the peritoneal cavity. This regularly fatal outcome has followed even when attempts have been made to treat the dogs by gas gangrene antitoxin(10), by correcting their anhydremia(11), or by abdominal drainage(11).

The results of these experiments argue strongly for the importance of bacteria in the mechanism of death due to intraperitoneal canine liver autolysis and seem to support the theory of Ellis and Dragstedt(5) that infection originating in the devitalized liver is the cause of death. In the recent brief report of Markowitz, Rappaport, and Scott(12), it

* Provided by E. R. Squibb and Sons, New York City.

8. Trusler, H. M., Reeves, J. R., and Martin, H. E., *Arch. Surg.*, 1935, v30, 371.

9. Trusler, H. M., and Martin, H. E., *Surg.*, 1937, v1, 243.

10. Boyce, F. F., and McFetridge, E. M., *Arch. Surg.*, 1937, v34, 977.

11. Mason, E. C., and Lemon, C. W., *S. G. O.*, 1932, v55, 427.

12. Markowitz, J., Rappaport, A., and Scott, A. C., PROC. SOC. EXP. BIOL. AND MED., 1949, v70, 305.

is stated that dogs with totally ligated hepatic arteries usually survived when given massive doses of penicillin, whereas the control animals usually died. These findings also emphasize the importance of bacteria in causing death due to liver autolysis in dogs.

To our knowledge the relatively benign effect of placing segments of human liver in the peritoneal cavity of dogs has not been previously described. The fact that devitalized human liver is less toxic than devitalized dog liver may be due to the absence in the human liver of the anaerobic, spore-forming, gas-producing organism found normally in dogs' liver. No such organism was found in the human liver specimens used in this experiment, though *Aerobacter aerogenes* and *staphylococci* were found. Shann and Fradkin(13) describe a patient who recovered following sequestration of a large fragment of liver and review the literature describing several other cases of recovery following liver sequestration secondary to biliary tract surgery or abdominal trauma. These clinical findings seem to be in agreement with our observation as to the relative non-toxicity of the devitalized human liver as compared with dog liver.

Conclusions. 1. Treatment with penicillin in oil reduces the fatality of peritonitis due to canine liver autolysis in dogs. 2. Autolysis of devitalized human liver in dogs is less fatal than autolysis of canine liver in dogs.

13. Shann, H., and Fradkin, W. Z., *J. A. M. A.*, 1933, v101, 829.

Received December 22, 1949. P.S.E.B.M., 1950, v73.

Hormonal Mechanisms in Nervous Mechanism of Gastric Acid Secretion in Humans.* (17735)

GEORGE B. JERZY GLASS AND STEWART WOLF. (Introduced by D. P. Barr.)

From the Department of Medicine, Cornell University Medical College, and New York Hospital, New York City.

It has been shown that the so-called chemically induced secretion of gastric acid occurring in response to the ingestion of food depends upon the elaboration of an histamine-like hormone, which has been named gastrin(1-8). Moreover, the pyloric end of the stomach has been identified as the source of this hormone(1-8), although hydrochloric acid secreting parietal cells are known to be generally distributed throughout the whole stomach(9). Recently several workers have adduced evidence that the secretion of gastric acid in response to vagal impulses also requires the mediation of histamine (9-12) or the histamine-like hormone gastrin(13-15). As a by-

* Aided by grants from the Commonwealth Fund and the Estate of Lester N. Hofheimer.

1. Edkins, J. S., *Proc. Roy. Soc.*, 1905, v76, 376; *J. Physiol.*, 1906, v34, 133.

2. Edkins, J. S., and Tweeny, M., *J. Physiol.*, 1909, v38, 263.

3. Komarov, S. A., PROC. SOC. EXP. BIOL. AND MED., 1938, v38, 514.

4. Gregory, R. A., and Ivy, A. C., *Quart. J. Exp. Physiol.*, 1941, v31, 111.

5. Komarov, S. A., *Rev. Canad. Biol.*, 1943, v1, 380.

6. Harper, A. A., *J. Physiol.*, 1946, v105, 31P.

7. Friedman, M. H. F., and King, E. N., *Fed. Proceed.*, 1947, v6, 107.

8. Grossman, M. I., Robertson, C. R., and Ivy, A. C., *Am. J. Physiol.*, 1948, v153, 1.

9. Babkin, B. P., Secretory mechanism of the digestive glands, P. Hoeber, New York, 1944.

10. Babkin, B. P., Schacheter, M., and Nisse, Ruth, *Clinics*, 1944, v3, 494.

11. MacIntosh, F. C., *Quart. J. Exp. Physiol.*, 1938, v28, 87.

12. Code, C. F., Hallenbeck, G. A., and Gregory, R. A., *Am. J. Physiol.*, 1947, v151, 593.

13. Uvnas, B., *Acta Physiol. Scandinav.*, 1942, v4, Suppl. 13, 1-86.

14. Kahlson, G., *Brit. Med. J.*, 1948, v4590, 1091.

15. Thomas, J. E., *Gastroenterology*, 1949, v12, 545.