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Shock in Bile Peritonitis.*

VIRGIL H. MOON AND DAVID R. MORGAN.

From the Department of Pathology, Jefferson Medical College, Philadelphia.

The toxicity of bile and its salts has long been recognized. Either whole bile or the cholic salts produce severe systemic intoxication when injected, and produce intense local irritation of the tissues at the site of injection. (See Horrall[1] for review of literature.)

Horrall and Carlson[2] found that intraperitoneal injection of sterile bile produced severe illness characterized by vomiting, diarrhea, oliguria, albuminuria, bradycardia, low blood pressure and death in coma within 24 hours. They described edema, congestion and petechial hemorrhages of the lungs, brain, gastrointestinal mucosa, and marked congestion of the liver and kidneys as postmortem findings following bile peritonitis. These physiologic and pathologic features are characteristic of shock, whether occurring clinically or experimentally.[3] Similar disturbances followed intravenous or subcutaneous injections of bile. A small amount injected rapidly caused death promptly, while larger amounts given slowly caused severe illness followed by death from infection. Sublethal doses rendered dogs *especially susceptible to pneumonia.*

We have shown that edema of lungs is a characteristic feature of shock and predisposes to infection. Terminal pneumonia regularly developed following sublethal shock resulting from bile or from other agents.[4] This confirmed our observations[5] on terminal pneumonia following sublethal shock in man. The results of Horrall and Carlson were published before attention had been called to the pathology of shock[6] and to pneumonia as a sequella.

Shock has been studied by narcotizing an animal with barbital or similar drug, and recording blood pressure and pulse rate kymographically through an arterial cannula. Shock is then induced by severe tissue abuse such as trauma to the muscles. This method is open to serious objections. Variations in blood pressure and

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1 Horrall, O. H., *Phys. Rev.*, 1931, **11**, 122.

2 Horrall, O. H., and Carlson, A. J., *Am. J. Physiol.*, 1928, **85**, 591.

3 Moon, V. H., *Ann. Int. Med.*, 1935, **8**, 1633.

4 Moon, V. H., and Morgan, D. R., PROC. SOC. EXP. BIOL. AND MED., 1936, **33**, 560; *Arch. Path.*, 1936, **21**, 565.

5 Moon, V. H., *Am. J. Path.*, 1933, **9**, 899.

6 Moon, V. H., and Kennedy, P. J., *Arch. Path.*, 1932, **14**, 360.

pulse rate often result from other conditions. Deep narcosis with barbiturates causes low blood pressure and other shock-like manifestations. Hemorrhage occurs incident to the trauma. Sublethal degrees of shock cannot be studied, since the animal cannot be kept in a condition suitable for subsequent observations. The recorded phenomena may be due to the narcotic, the trauma, the associated hemorrhage, or to a combination of these indeterminate factors.

These objections were obviated by producing shock without trauma and without narcosis, using variations in hemo-concentration as a physiologic criterion. Both lethal and sublethal degrees of shock can be produced and observations made on subsequent days. The accuracy of these was confirmed by the presence of the gross and microscopic features distinctive of shock.

Our results following injections of bile were like those of Horrall and Carlson except in one particular: their postmortem data included congestion of the spleen. We found the spleen firm, dry and relatively anemic following injections of bile and following shock otherwise produced.

A dog weighing 9 kg. was given intravenous injections of 7.5, 5.0, 7.5, 15 and 15 cc. of sterile normal dog bile at intervals of 2 hours. He became acutely weak and ill, showed muscular tremors, vomited, and the urine was scanty and deeply bile tinged. Twenty-four hours later the red cell count had risen from 6,100,000 to 8,000,000, indicating hemo-concentration of about 30%. The illness did not progress and the hemo-concentration three days later had declined to 15%. The dog was then killed and examined. The lungs were congested and somewhat edematous. There were petechiae in the pleura, and congestion of the liver and kidneys. There was no excess of fluid in the serous cavities. The spleen was firm, dry and anemic.

A dog weighing 9.3 kg. received intravenous injections of sterile dog bile, 40, 40, 50 and 60 cc. at intervals of 24 hours. Signs of illness and hemo-concentration were as described. He died 6 days following the first injection. The postmortem findings were as in the previous experiments except that the congestion and edema were more marked (Fig. B) and involved also the gastro-intestinal mucosa.

Sterile bile diluted with saline solution was injected into the peritoneal cavity, 5 cc. per kg. of weight. The dog promptly became ill as following intravenous injections of bile. In 3 hours the red cell count rose from 5,530,000 to 7,290,000; in 8 hours the count was 8,720,000, indicating hemo-concentration of about 57%.

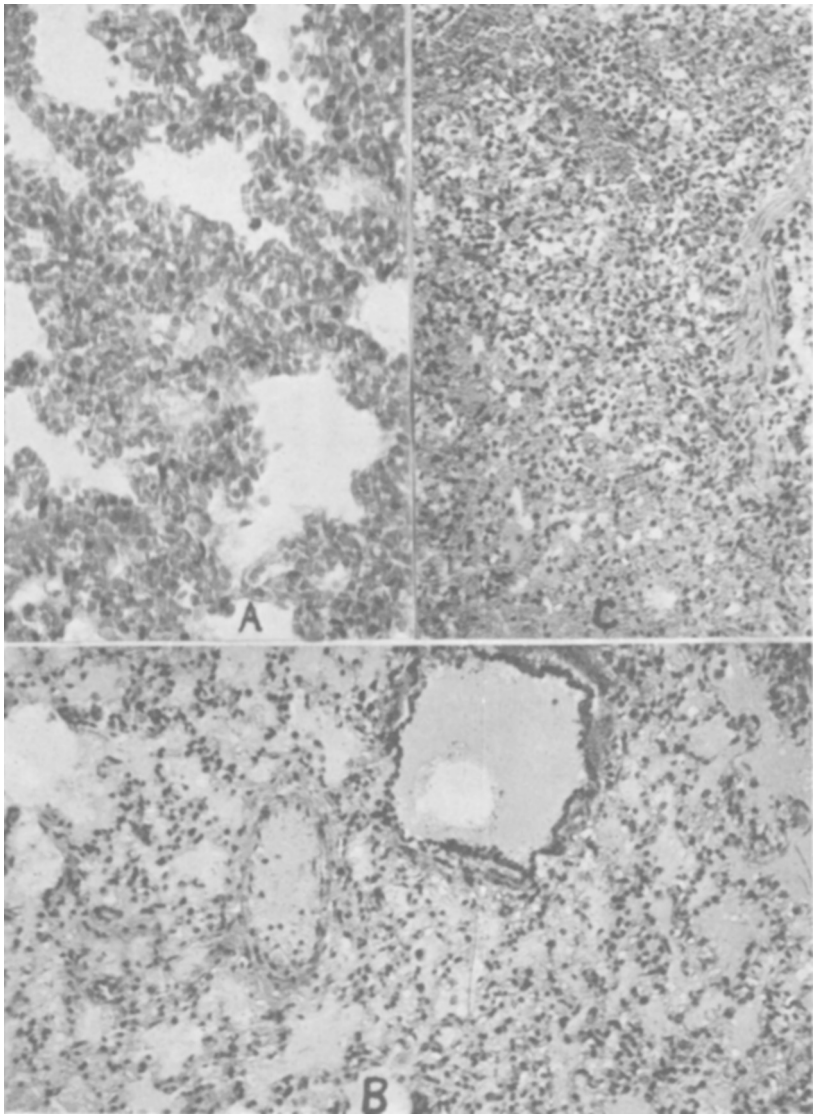

FIG. A.

Lung following death from bile peritonitis. Marked engorgement of the capillaries and slight edema are shown. x 1000.

FIG. B.

Pulmonary congestion and marked edema in shock with delayed death following repeated intravenous injections of bile. Such lungs are prepared for the development of pneumonia. x 200.

FIG. C.

Incipient pneumonia in congested edematous lung in sublethal shock. x 200.

He died the following night. The pleural, pericardial and peritoneal surfaces were deeply congested and contained blood-tinged fluid: 25 cc. in either pleural sac, 10 cc. in the pericardium and 100 cc. in the peritoneum. The lungs were heavy and intensely congested. The vessels along the mesenteric attachment were greatly engorged and prominent. The mucosae of the stomach and intestines were deeply congested and resembled purple velvet. There was marked congestion of the liver, pancreas and kidneys. The spleen was firm, contracted and dry. Microscopic examination showed marked capillary and venous engorgment, moderate edema and capillary hemorrhage in the lungs (Fig. A) and gastro-intestinal mucosa; marked congestion, parenchymatous degeneration and necrosis of the liver; marked congestion, capillary hemorrhages and parenchymatous degeneration of the kidneys, and moderate congestion of the pancreas and adrenals.

Two other dogs were similarly treated with exactly similar results. A fourth dog weighing 8.5 kg. received 25 cc. of bile intraperitoneally. This animal showed moderate illness and hemo-concentration, but he recovered.

Four dogs received 10% solution of sodium glycocholate intravenously. A dose of 1 gm. per kg. of body weight caused immediate death in one. Another received 8 doses of 0.4 gm. per kg. of body weight at daily intervals. This produced progressive illness and hemo-concentration, 35%, ending in death on the eighth day. Another received 10 injections of 0.4 gm. per kg. with intervals of 1 or 2 days, during 25 days. Moderate illness and hemo-concentration progressed to death 4 days following the last injection. The fourth dog died of acute shock 3½ hours following an intravenous injection of 0.4 gm. per kg. The postmortem findings in each case were those characteristic of shock. But following prolonged sublethal shock there was marked pulmonary edema and terminal pneumonia (Fig. C).

Recently Harkins *et al.*[7] made experiments on bile peritonitis with results similar to those described. In a series of 12 dogs the results were uniform and were recognized as shock. Hemo-concentration, low blood pressure, decreased blood chlorides and increased non-protein nitrogen were noted. They stated that the peritoneal cavities contained quantities of fluid resembling blood plasma, but did not state whether other congestive, edematous and hemorrhagic features were present. Such postmortem features are of especial significance when shock is under consideration. They interpreted

[7] Harkins, H. H., Harmon, P. H., Hudson, J., and Andrews, E., PROC. SOC. EXP. BIOL. AND MED., 1935, **32**, 691.

bile peritonitis as causing death by shock, but emphasized the local loss of fluid as the shock-producing factor.

Our studies indicate that shock results from atony and dilatation of the capillaries and venules in visceral areas. Their permeability is increased, allowing leakage of plasma into the tissue spaces. This results in hemo-concentration and tissue edema, and leads to circulatory failure. The capillaries and venules are visibly engorged and packed with corpuscles. That the fluid in the tissue spaces and cavities results from leakage of plasma was shown by intravenous injections of trypan blue during shock. The viscera and the serous fluids became distinctly blue.

In shock loss of fluid occurs by vomiting and diarrhea, by edema and serous effusions, and by local loss of blood and fluid at the site of the injury when such injury has occurred. But no local loss of blood or fluid occurs when shock is produced by intravenous injections of bile or its salts, various drugs and poisons, histamine, peptone, bacterial products or by anaphylaxis. Any local loss of blood and/or fluid as in extensive trauma or burns, is a factor, but it is not the only factor. Its importance is proportional to the amount of blood and fluid lost.

Conclusions. Intraperitoneal or intravenous injections of bile or of sodium glycocholate produce the shock syndrome characteristically in dogs. This is accompanied by hemo-concentration as in shock otherwise produced. Sublethal degrees of shock follow sublethal doses of the agents mentioned. These may recover or may result in pulmonary edema, pneumonia and subsequent death. The postmortem findings are the same as those following shock otherwise produced. These are: marked capillary and venous engorgement of the lungs, serosa, gastro-intestinal mucosa, liver and kidneys; edema of lungs, gastro-intestinal mucosa, and serous effusions; anemia of the splenic substance. The evidence indicates that bile or its salts cause acute injury to the walls of capillaries and venules. This results in atony and increased permeability, whereby a disparity develops between blood volume and volume-capacity of the vascular system. Such a disparity manifests itself in the shock syndrome.