The Role of Micro-embolism in the Production of Irreversible Shock*

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MICRO-EMBOLI can be demonstrated in large numbers during shock. The fact that they can block the microvascular system leads one to consider their possible importance in irreversible shock. Embolization of platelet aggregates would seem to be compatible with many pathologic changes which have been reported. Extensive micro-emboli in the lung could account for the right heart failure, pulmonary hypertension and left heart hypotension frequently described in experimental shock. Embolic occlusion of hepatic vessels is compatible with the portal hypertension which develops in treated shock. Sequestration of platelets as emboli may also account for characteristic hypocoagulability of the blood and thrombocytopenia which is reported.

We have made extensive observations of microvascular dynamics during many phases and forms of shock. Cinephotomicrographic technics have made it possible to record, identify, and study activity of individual red and white blood cells and platelet aggregates during both development of and recovery from shock. The formation of platelet micro-emboli has been repeatedly observed. Cinephotomicrographs show that these aggregates break loose and cause mechanical blockage of the circulation at distal points of narrowing. Critical vessels appear to be 10 to 40 microns in diameter.

Materials and Methods

All studies were carried out using a microscope unit (Fig. 1) allowing simultaneous observations and photography. A 16 mm. Cine Special camera was used to record observations made of rabbit bowel, mesentery, liver and lung. Special attention was paid to the occurrence of platelet micro-embolism. Ready identification of the emboli as platelet aggregates was possible [35] when projection magnifications of 50,000 to 100,000 diameters were used.

Observations have been made during shock secondary to hemorrhage, trauma, anaphylaxis, endotoxin and bacteria. The combined effect of fibrinolysin and heparin has been observed.[35] The effects of blood replacement and norepinephrine have been studied.[36]

Observations

Hemorrhage was induced by removing an estimated 30 per cent of the circulating volume. Pressures dropped from a usual

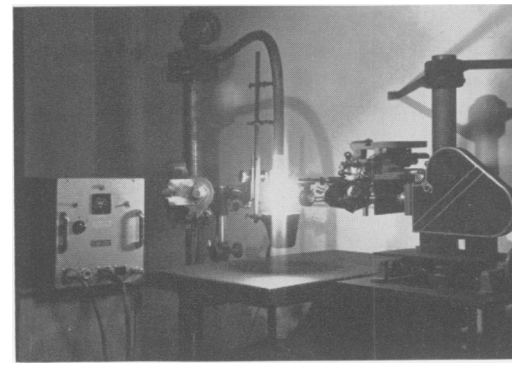

FIG. 1. Horizontal microscope with a *strobe unit* which is synchronized with the 16 mm. motion picture camera.

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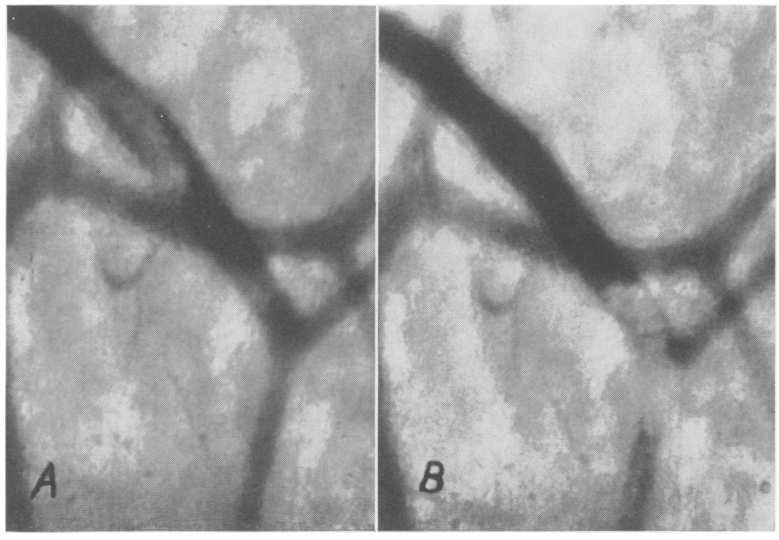

FIG. 2A. Platelet aggregate as it embolizes in a bowel wall vessel. B. Progression of the embolus.

100 mm./Hg mean pressure to 75 mm. pressure.[36] After 15 to 20 minutes we observed the formation and embolization of platelet aggregates through 50 to 100 micron diameter veins in the bowel wall (Fig. 2). A and B show progression of an embolus. These emboli were of such a size and firmness that they were likely to lodge at distal points of narrowing. Whenever blood pressure drops and flow slows there is a separation of blood elements so that like elements stick together, that is, red cells stick to red cells and platelets stick to platelets.[36] Such aggregation occurs in both arterial and venous circulation of the bowel wall. It is most commonly observed, however, on the venous side in the portal drainage. While arterioles become very narrow in all hypotension, veins in the bowel wall narrow very little and perhaps even dilate which would be compatible with an embolic blockage of the portal venous drainage in the liver.

Trauma to the microvascular system can

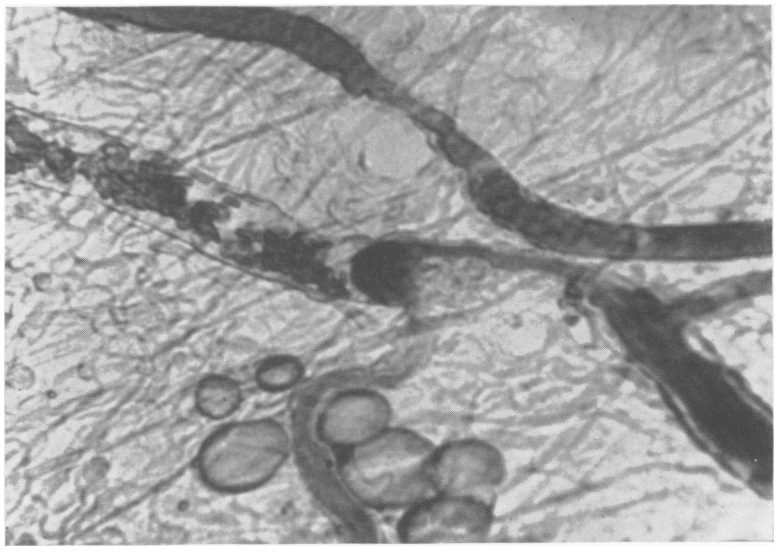

FIG. 3. A point of trauma with blood flowing from right to left and a growing platelet aggregate nearly occluding the inferior branch.

be produced by a micromanipulator. At the point of injury there is an intravascular precipitation of platelet aggregates [37] (Fig. 3) which repeatedly break loose and progress through the vascular system as emboli until they reach a narrow point where they lodge and cause circulatory occlusion.

Anaphylaxis is also associated with the micro-embolization of platelet aggregates 10 to 30 microns in diameter. Such aggregates can be seen within two to ten minutes after injection of foreign protein to which the rabbit has been sensitized. Observations must be made at 200 to 400 magnifications to show platelet emboli as they form in 20 to 50 micron vessels of the bowel wall. It is common for cellular flow to cease completely with veins remaining fully dilated and arteries becoming severely narrowed due to hypotension and constriction.

Norepinephrine, when given following hemorrhagic shock, causes an increase of platelet aggregate embolization. We have observed that platelets tend to precipitate just distal to points of stenosis and in eddy currents. The segmental constriction [35] which occurs when norepinephrine is administered is possibly a factor in platelet aggregation. Total cessation of 10 micron capillary flow is usually observed during norepinephrine administration when given in hypovolemic shock apparently both because platelets embolize and arterioles constrict (Fig. 4).

Our early cinephotomicrographs demonstrating the segmental effect of norepinephrine did not show micro-emboli.[36] These animals were heparinized which may account for this fact.

Coagulase Positive Staphylococci injected into the ears of rabbits cause a continuous embolization of micro platelet aggregates (Fig. 5) usually within 10 to 15 minutes. Veins in the bowel wall become dilated and arterioles become constricted. Small flame-like hemorrhages have been observed in serosal surfaces. Endotoxin injected in the aorta will cause massive precipitation of aggregates.

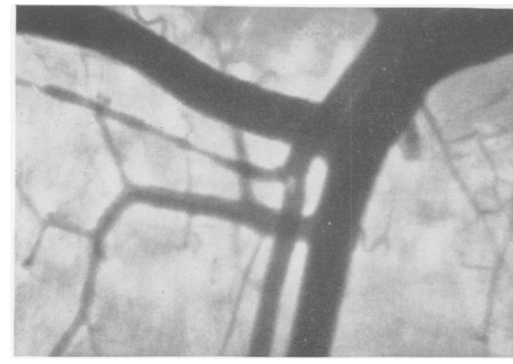

FIG. 4. Norepinephrine causes a segmental constriction as in the arteriole to the left. An embolus is noted at the origin of this branch.

Escherichia Coli bacteria injected in the ear vein will also cause embolization in the bowel wall, as well as a similar narrowing of arterioles and dilatation of veins. The narrowing of arterioles occurs in all shock and may be due to a drop of distending pressure.

Fibrinolysin and Heparin* given prior to the injection of *Staphylococci* or *E. coli* bacteria prevent the occurrence of embolization during an hour immediately following their injection. If a combination of 4,000 units of fibrinolysin and 5.0 mg. of heparin is given a five-pound rabbit following initiation of the emboli they soon

* Supplied by Merck, Sharp & Dohme Research Laboratories.

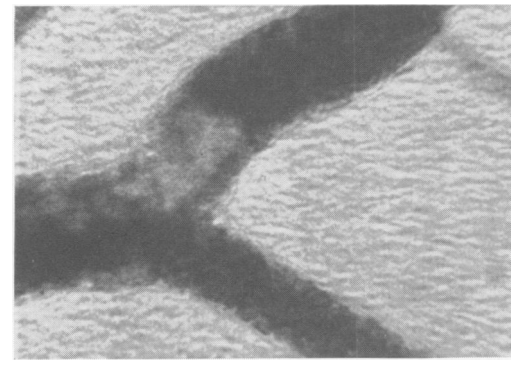

FIG. 5. A platelet embolus in bacterial shock taken with *strobe* illumination.

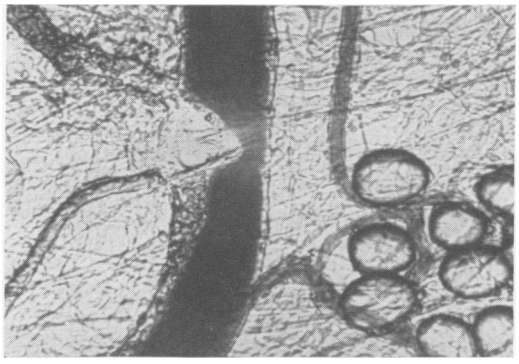

FIG. 6. A vessel narrowed by a micromanipulator with blood flowing past it.

cease forming. Heparin alone does not appear to be as effective as the combination in prevention of embolization.

Blood Replacement following hemorrhagic shock immediately produces a great increase of embolism in the bowel wall. It is possible that stationary emboli are dislodged when heparinized blood is replaced. Previously narrowed vessels regain their normal diameters and pressures. In prolonged shock systemic pressure increases are usually temporary as measured on intra-arterial manometers.

Lodgement of Emboli is difficult to observe. Ready identification of the embolic components as they move rapidly across the field is likewise difficult. A method was devised to make observations easier. By narrowing the blood vessel with a micromanipulator at a point beyond the source of emboli (Fig. 6) one can observe a continuous flow of emboli as they temporarily halt at the point of narrowing. Figure 7 shows a lodged embolus. Cinephotomicrographs clearly show the repetitive nature of this process and show that the embolus is composed of platelets. By cinephotomicrography it is possible to demonstrate emboli as they become lodged in the pulmonary circulation of a frog. One may contemplate the more extensive effect of multiple emboli. Individual recognition of emboli has not been possible in the liver; however, there is slowing and complete cessation of flow depending on the number of emboli involved.

Discussion

Numerous established experimental methods for the production of irreversible shock have been studied by cinephotomicrography. In each instance they are productive of micro-embolism in the rabbit. High magnification films projected at 50,000 and 100,000 magnifications assure one that these emboli are largely of platelet origin although white and red blood cell aggregates must develop.

A review of *shock* literature has been made which suggests that much established experimental data is compatible with and can be explained by platelet microembolism.

Zahn,[45] in 1875, described the formation of white aggregates as they occur with a concentration of blood elements. Bizzozero,[4] in 1882, first considered white thrombi to be composed entirely of platelets. Experimental platelet embolization secondary to trauma has been observed.[22, 27] Within minutes of leg fractures, white embolic masses have been observed in the cheek pouch of the hamster.[3] Similar masses have been observed in ears of rabbits following anaphylaxis.[1] Micro-emboli in the portal circulation could lead to a blockage of blood flow through the liver and portal hypertension. Thrombotic occlusions of the liver have been observed in fixed sections by Hardaway [23] and Crowell [10] and attributed to an early period of hypercoagulability which occurs in shock. Wiggers [44] and others [39, 40, 46] describe the elevation of portal pressures following hemorrhagic shock. This same elevation of pressures has followed endotoxin [34] shock. A cessation of flow has been described in the hepatic micro circulation with a dilatation of the sinusoid.[6, 35] It is reasonable to postulate that this blockage to portal blood flow can hold blood in the portal system. When one considers that the portal system normally

contains one-third the normal circulatory volume a compensatory relative hypovolemia may take place elsewhere. The resultant systemic hypovolemia undoubtedly is a factor in the production of shock. Theoretically, this trapping of blood in the portal system can be eliminated by creating an Eck fistula. Such a preparation has been studied.[16] It was found, however, that animals thus treated had no special protection against shock. Perhaps an increased number of emboli passed through the Eck fistula into the pulmonary capillary systems where the obstruction of circulation is possibly more serious.

The elevation of pulmonary artery pressure following blocking by a major pulmonary embolism is well recognized.[13, 21, 32] Similar elevation has repeatedly been described following traumatic,[30] hemorrhagic,[14, 19] anaphylactic and endotoxin shock.[30] Previously such elevations have been considered secondary to pulmonary vascular constriction.

Pulmonary microvasculature has been observed during death due to anaphylaxis in experimental animals. It has been associated with descriptions of hyalin emboli,[43] clumping of red cells,[7] and construction of the muscular coat [9] in pulmonary vessels.

Multiple micro-emboli in the pulmonary circulation would seem, from our studies, to be common in irreversible shock. The consistent elevation of pulmonary artery pressure and right heart failure in treated shock is compatible with this. Such a blockage of the circulation is compatible with systemic hypotension and, if it is excessive, irreversibility of shock. Much experimental evidence points to this as a major factor in irreversible shock.

Hypocoagulability develops some time after the initiation of hemorrhagic,[42] endotoxin,[28, 31] or anaphylactic shock. This is also associated with the use of norepinephrine.[24] In endotoxin and anaphylactic shock the platelet level has been observed to drop from 350,000 to near 50,000 within five minutes.[11, 33] Thrombocytopenia is associated with the Shwartzman phenomenon [41] in which masses of platelets are found in the skin areas. Plasminogen and fibrinogen levels were found to be depleted in anaphylactic [18] and endotoxin [17] shock; in endotoxin shock this was prevented by pretreatment with heparin.

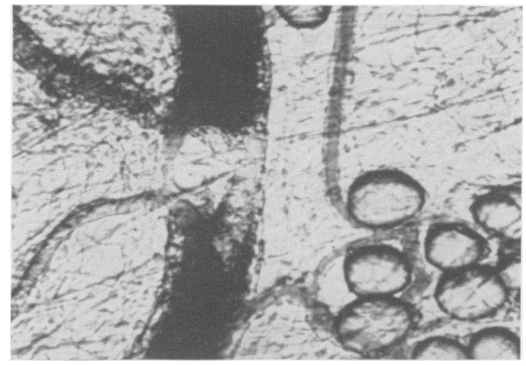

FIG. 7. A platelet embolus which has lodged in the point of narrowing demonstrated in Figure 6.

It would appear that the well established thrombocytopenia and hypocoagulability of blood following various types of shock can be due to sequestration of platelets from the general circulation by means of aggregation and embolization. A similar suspicion was voiced by Lutz in 1951.[29]

We have observed repeatedly that initial platelet emboli may form. Later injections of the shocking agent will not be as effective in forming emboli. It is suspected that with the second injection fewer platelets are left in the circulation so fewer aggregates can form.

A certain resistance to shock has been described in association with multiple sublethal injections of fat emboli,[12] endotoxin and administration of trauma.[2, 15] It is wondered whether a gradual depletion of the platelets creates a temporary thrombocytopenia without critical pulmonary vascular occlusions. Subsequent administration of the shocking agent is then not likely to create a massive precipitation of platelet emboli and vascular obstruction. The finding that few emboli form after sub-lethal

administrations of these substances would be compatible with this.

The concept that anticoagulants may be valuable in the treatment of shock is not new. The inhibition of the local Shwartzman reaction was described in 1953.[8, 20] In 1955, Crowell concluded that heparin could reduce the tendency to clot and death in hemorrhagic shock. More recently, Hardaway has done extensive work describing the value of heparin alone and heparin and fibrinolysin combined in the treatment of endotoxin and hemorrhagic shock.[23, 25, 26] By cinephotomicrography we can show that heparin is effective in bringing about a dissolution of the whole blood clot and that combination heparin and fibrinolysin are most effective in preventing or bringing about the dissolution of the platelet aggregate.[35]

If platelet micro-embolism is a factor in irreversible shock one must consider the possibility that heparin and, possibly, fibrinolysin should be considered in the treatment of shock. Of course, it cannot be used immediately following surgery or where there is likelihood of hemorrhage. When shock is on a non-hemorrhagic basis, however, it may be well to consider anticoagulants to prevent irreversibility. The concept of pulmonary hypertension is also compatible with the use of a temporary veno-arterial pump to assist maintainance of circulation while the acute phase of pulmonary obstruction may be subsiding.

A review of Blalock's [5] work in 1934 might lead one to consider multiple platelet micro-emboli as a cause for the traumatic shock. Release of the emboli on loosening of the tourniquet may flood the circulation with emboli and bring about pulmonary vascular obstruction.

Summary

It has been observed that platelet micro-embolism occurs in animals during many forms of experimental shock. Micro-embolism in the lung may account for pulmonary hypertension, right heart failure and systemic hypotension in treated shock. Embolic occlusion of the hepatic circulation could account for portal hypertension in irreversible shock and damming of blood in the portal system. Hypocoagulability of blood following prolonged shock correlates with depletion of platelets and clotting factors of the blood. Pretreatment with fibrinolysin and heparin will lessen the occurrence of platelet aggregation and may, in certain situations, be important in preventing or treating irreversible shock.

Acknowledgments

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Discussion

Dr. Jacob Fine (Read by Dr. B. E. M. Zetterstrom, Boston). Dr. Simeone and his colleagues find that the pressure gradients in the portal and hepatic veins during hemorrhagic shock give no evidence of obstruction to flow through the liver at any time during or after transfusion. They regard the defect accounting for irreversibility to transfusion as a loss of tone in the small veins everywhere. The data they obtain justify the conclusion that selective pooling in the splanchnic area does not occur.

However, one cannot on that account dismiss the splanchnic area as having no special role in the development of the refractory state. The radiographs in this paper confirm those of Friedman *et al.*, and especially those of Hagberg, who demonstrated by spatial radiography a substantial three-dimensional decrease in the size of the liver during the hypotensive phase. Hagberg found that the shrunken liver gets larger after transfusion, but it does not reach normal size on account of persisting intrahepatic vasoconstriction. This explains the relative portal venous hypertension in shock which Wiggers demonstrated long ago. Vasoconstriction is a generalized phenomenon in shock, but the effects of it in the splanchnic area are of central importance to the course of the shock state, for prolonged severe ischemia of the organs of the splanchnic area caused by unrelenting excessive catechol amine activity, whether there is a normal or deficient blood volume, produces functional damage that threatens survival. We showed this in 1950 when we reported the prevention of irreversibility and death by cross-perfusion of the liver with a donor animal's arterial blood. We can now add to the evidence of the critical importance of this area recently acquired data on the effects of denervation of the abdominal viscera.

The experimental data is derived from 3 series of dogs and 3 series of rabbits (80 animals in all) subjected to denervation of the splanchnic area before inducing shock by one of two methods: 1) surgical removal of the coeliac and superior mesenteric ganglia, and division of all splanchnic nerves below the diaphragm; and 2) infiltration of these nerve structures with nupercain-in-oil. Shock was produced by hemorrhage or by endotoxin given intravenously or intracerebrally. The denervation altered the hemodynamics characteristic of a progressively downward course. In the denervated animal in endotoxic shock the reduced atrial pressure and cardiac output returned after some two hours toward normal, the reduced pH rose toward normal, the increased A-V oxygen difference fell, and urine secretion rose from near zero to a satisfactory level. The denervation also preserved functional integrity of the splanchnic tissues, as indicated by the persistance of the normal endotoxin-detoxifying power of the spleen, a function which is lost in the nondenervated animal. It also prevented the hemorrhagic lesion in the denervated part of the intestine. Finally, the mortality rate, which was over 80 per cent in the nondenervated animals, was converted to an average survival rate of some 70 per cent.

Similar benefit has been observed by injecting xylocaine into the area of the coeliac plexus *during* shock, and preliminary experience with this therapy in desperately ill patients in advanced shock supports the experimental experience. This therapy is more likely to achieve the objective of improving flow through the splanchnic area and, therefore, of the systemic circulation than one can expect from other anti-adrenergic measures, because local denervation selectively inactivates the vasoconstrictors that produce the lethal injury, while drugs such as dibenzyline do not.

Dr. Bengt E. M. Zetterstrom (Boston): Protection of the tissues in the splanchnic area in shock by denervation can be observed directly if one studies the behavior of the exteriorized spleen, half of which has been denervated before shock. Immediately after inducing hemorrhagic shock the nondenervated half of the spleen contracts, and remains contracted so long as the shock continues. When transfusion, given to restore normovolemia, is delayed for some six hours so as to produce irreversibility, this half of the spleen returns to normal size; but, as the pressor response fails after transfusion, and peripheral flow fails, the spleen swells above normal size, and does not respond to intravenous norepinephrine. On the other hand the denervated half of the spleen throughout this entire period of observation remains the same in size, shape and color. This part of the spleen contracts in response to intravenous norepinephrine, indicating preservation of vascular