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SHOCK AND CIRCULATORY HOMEOSTASIS

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Fifth Conference on Shock and Circulatory Homeostasis

THE JOSIAH MACY, JR. FOUNDATION CONFERENCE PROGRAM

DURING THE PAST FIFTEEN years the Josiah Macy, Jr. Foundation has organized more than twenty conference groups, each group meeting for at least two days annually over a period of five or more years. Each meeting is limited to twenty-five participants (members and guests), selected to represent a multidiscipline approach to some urgent problem in the field of medicine and health. The goal of this conference program is the promotion of communication, the exchange of ideas, and the stimulation of creativity among the participants. The purpose of the publication of the transactions of the meetings is to share, as far as possible, the conference process with a larger audience than could participate personally in the discussions.

These conferences provide an opportunity for informal give and take among the participants. To further this purpose the number of presentations planned for each day is generally restricted to one or two. The member, or guest, selected to give such a presentation is requested not to "read a paper," but rather to highlight, in an informal manner, some of the more interesting aspects of his or her research, with the expectation that there will be frequent interruptions by participants in the form of questions, criticism, or comment. Such interruptions during the course of a presentation are encouraged and form an essential part of the "group interchange."

The conference program has always been viewed by the Foundation as an experiment in communication in which there is room for improvement and need for frequent reappraisal. Sufficient experience has already been gained to justify the conclusion that this type of conference is an effective way of improving understanding among scientists in medicine and allied disciplines, of broadening perspectives, of changing attitudes and of overcoming prejudices. The further conclusion has been reached, as the result of this experiment, that the major obstructions to understanding among scientists lie in the resistance of human attitudes to change, rather than in difficulties of technical comprehension. Less extensive experience with non-scientists has indicated that the effectiveness of this type of conference is not limited to groups of scientists, but will function in any group meeting where more effective

communication is the primary goal. It is also clear that the same conference technique, with minor changes, is readily adapted to small international conferences.

The style of publication of the Transactions has aroused considerable interest and some criticism. The criticism has been directed primarily to editorial permissiveness which has allowed in the final text, in some instances, too many questions, remarks, or comments which, although perhaps useful during a heated discussion, seem out of context and interrupt the sequence of thought in the printed volume. A few have objected to the principle of publishing in this style and would prefer a depersonalized summary without interruptions.

The Foundation Staff and the Scientific Editors of these volumes welcome criticism and hope to profit thereby in increasing the usefulness of the Transactions to scientists and students of science in this country and abroad.

FRANK FREMONT-SMITH, M.D.
Medical Director

EPHRAIM SHORR

June 1, 1897 - January 6, 1956

Ephraim Shorr brought to the Chairmanship of the five Conferences on Shock and Circulatory Homeostasis a unique cluster of talents. His rich capacity for original and creative ideas was well disciplined by long experience with the experimental method. The range of his competence in scientific research extended from the intricate biochemical processes within living cells to the integrative functions of organs and systems which maintain the intactness of the organism as a whole.

Above all Ephraim Shorr was a great physician. He was unsparing of himself in responding to the needs of his patients and their families. His diagnostic skill and clinical judgment were outstanding. As a teacher and friend he was receptive to new ideas, kindly in criticism, and generous with encouragement. He was unswerving in his devotion to scientific and human ideals.

We who have shared the privilege of close association with Ephraim Shorr mourn our irreparable loss in his untimely death. We will always cherish the gift of his friendship and rejoice that he has lived.

FRANK FREMONT-SMITH

HEPATIC BLOOD FLOW IN EXPERIMENTAL SHOCK

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THE HEPATIC CIRCULATION undoubtedly plays an important role in the circulatory adjustments that develop in the body following hemorrhage or trauma. There is too little direct or reliable evidence available to permit more than a tentative hypothesis regarding the character and mechanisms of the changes that occur in the splanchnic vascular bed. The information yielded by morphologic and physiologic study often appears to be in conflict, and successive or continuing shifts in the pattern of response complicate the picture. In consequence, interpretation must be guarded and generalizations accepted with caution. At this conference my task, as I understand it, is simply to present the problem, to note some of its complex features, and to raise questions that seem important for further investigation. In initiating the discussion, I should like to avoid the term "shock" and all of the confusion that term involves, but I know quite well that it is not altogether possible. I shall deal with the problem of adjustments in the splanchnic bed which are precipitated by blood loss and a fall in the total blood volume. Whether these considerations are also germane to the shock that follows trauma, burns, fever, and so forth, is uncertain, but it seems possible that to some extent they may apply. Here at once we enter an area regarding which there is little or no evidence; more is needed, and a trustworthy survey must wait upon further investigation.

The size of the splanchnic bed and the volume of blood lying within it and flowing through it each minute give a seemingly sound *a priori* basis for the belief that it is important in systemic hemodynamic adjustments. Measurements of splanchnic blood flow following hemorrhage in dogs indicate that the blood flow diminishes, but no more than would be expected on the basis of the associated fall in arterial pressure alone (1,2,3). Does this mean that vasoconstriction does not develop at all or that the various components of this complex bed are affected

differently with no net change in calculated resistance? Do hepatic arterial inflow, mesenteric arterial inflow, and splenic inflow behave similarly? I have no answers to these questions. I hope that someone among you will.

Further observations of the behavior of the splanchnic circulation suggest that vasodilation develops spontaneously within an hour or more after a single hemorrhage, and that it occurs in the absence of a notable restoration or arterial pressure or cardiac output. This "spontaneous recovery," if "recovery" it is, must be associated with compensatory adjustments elsewhere in the body so that a further fall in blood pressure is prevented. Where do these adjustments take place? Does this response imply that protracted reduction in hepatic blood supply gives rise to local alterations that induce vasodilation? Within what parts of the splanchnic vasculature is this response most marked or is it a generalized phenomenon? What is its mechanism, neural or humoral?

When hemorrhage is repeated at frequent intervals so as to prevent any effective restoration of the blood pressure level, the splanchnic blood flow continues to be depressed at least to the same extent as the perfusing pressure. In what manner, then, is the "spontaneous recovery," just alluded to, that follows a single bleeding, interfered with? Is there a shift in the splanchnic hemodynamic adjustment in more protracted hypotensive states? Do all parts of the splanchnic vascular bed behave similarly in this response? Is there, indeed, vasoconstriction in some sections and vasodilation in others?

Measurements of splanchnic blood volume following hemorrhage indicate that the amount of circulating blood held within the splanchnic blood vessels decreases. In this manner a considerable volume of blood is transferred from the splanchnic reservoir to the systemic circuit as a kind of "autotransfusion." This phenomenon is observed in both intact and splenectomized animals, and it seems probable that movement of blood from the spleen may also contribute to the shift. How is this transfer brought about? Does vasoconstriction result in an active reduction in splanchnic vascular capacity, or is a fall in distending pressure which results from the decrement in perfusing pressure and perhaps also from arteriolar vasoconstriction sufficient to account for the change? If this effect depends upon vasomotor adjustments, how is it mediated?

Much has been said about the possibility of "pooling" in the splanchnic bed as a factor conducive to the development of "irreversible" shock, but clear-cut evidence that it actually occurs as a primary event seems so far to have eluded us. The splanchnic blood volume seems to

be greatly reduced after hours of sustained hypotension. It may be argued that a greater proportion of the total blood volume is confined to the splanchnic bed, but accurate data on the distribution of blood in different parts of the body at different stages in the progression to irreversibility are not yet, to my knowledge, available.

In this brief introduction I have been content to point to a number of unanswered questions regarding the role of the splanchnic circulation in the circulatory adjustments to hemorrhage or other causes of arterial hypotension. I do hope that answers to many of them will emerge from the discussion to follow.

Zweifach: Are you considering the visceral mass as one organ system?

Bradley: I think of the splanchnic bed as that system of vessels which lies between the aorta and the hepatic vein, and this includes the vasculature of the spleen, the gastrointestinal tract, the pancreas, the portal venous system, and the hepatic artery and its drainage system.

Zweifach: Do you believe that all of these visceral structures necessarily undergo changes in the same direction or to the same degree?

Bradley: No, there is no *a priori* reason to suppose that all the components of this system should behave similarly. Indeed, there is much evidence that they do not, but it seems to be fragmentary in character and not as yet satisfactorily integrated.

Zweifach: I believe that our direct microcirculatory studies have provided pertinent information in this regard. In the omentum, the circulation becomes highly ischemic following simple hemorrhage sufficient to lower the blood pressure of the anesthetized dog to from 40 to 50 mm. Hg. Observations on the mesentery of the small intestine permit us to record the flow in the large veins and arteries which feed the bowel proper. Both the arteries (from 150 to 250 μ) and the veins (from 200 to 400 μ) undergo extreme constriction to less than one-third of the original caliber. The return of blood from the bowel through the large veins is slowed to such an extent that the blood is moving only sluggishly and intermittently. One of our criteria of shock has been the degree of hypotension which was necessary to interfere with the venous return of blood from the bowel by way of these large veins. Irreversible hemorrhagic shock, a state which progressively becomes refractory to blood replacement, does not develop unless the blood pressure is lowered sufficiently to interfere with the venous return of blood flow from the bowel.

Observations on the surface of the small intestine (especially in small animals such as the rat) indicate a sluggish, ischemic circulation during the initial phase of the hypotensive episode and venous and capillary stagnation during the terminal stage. We have no direct

observational evidence concerning the circulation in the liver proper although several studies in this regard have been reported (4,5). Your calculations indicate certain discrepancies in over-all splanchnic blood flow, evidence for which cannot be provided in the bowel proper, its mesenteric appendages, and probably not in the liver.

Remington: Are you making a distinction between the circulation in the bowel and the mesentery?

Zweifach: I am drawing a distinction between the capillary circulation in the various mesenteries proper and the flow through the large veins and arteries which enter and leave the bowel by way of the mesentery. Observations of these large blood vessels should reflect accurately disturbances in blood flow through the intestines.

Horvath: Is the reduction here greater than that in any other area?

Zweifach: With the onset of hypotension (65 mm. Hg or less) following hemorrhage, the flow through the small blood vessels of the skin and skeletal muscle almost ceases. This is accompanied by extensive vasoconstriction of the arteries, arterioles, and veins in these tissues. At this stage, there is only a moderate narrowing of the arteries and veins in the mesentery, with the slowing in blood flow roughly parallel to the degree of hypotension. When the blood pressure falls below critical levels (in the anesthetized dog below from 35 to 40 mm. Hg), marked vasoconstriction of the mesenteric arteries and veins develops, with little or no unidirectional flow in the veins.

Bradley: You seem to be contradicting yourself. First you seem to say that the blood flow falls in proportion to the decrease in blood pressure, and then you speak of vasoconstriction. Is that not contradictory?

Zweifach: Why am I contradicting myself? I say when an animal is bled, the blood pressure falls.

Remington: It would seem that the term *vasoconstriction* should be reserved for a greater diameter decrease than would accompany, through passive recoil, the reduction in pressure.

Zweifach: I am using the term *vasoconstriction* to indicate a narrowing of the vessel under observation, with no implication concerning the factors responsible for its narrowing.

Fremont-Smith: Certainly the vessel has contracted to get a reduced diameter.

Horvath: The important part is how much blood is going through the vessel. In my own observations using iodinated albumen and radioactive chrome, the distribution of circulating fluid is no different in an animal in hemorrhagic shock than in the normal state. We find as a rule

that there is about 28 per cent of the total circulating blood volume in the splanchnic bed in both groups.

Baez: May I ask at what time during the hemorrhagic experiment these measurements were taken?

Horvath: About an hour after they have been maintained at an arterial blood pressure of 40 mm. Hg. So it is really a true, severe state of shock. The difference between the volume of circulating blood and the volume of apparent disturbance in the flow, which can be determined by the visual observations, may be great.

Remington: What do you mean by the volume of the circulating blood?

Horvath: The volume of blood in the total circulation is reduced by a significant fraction by continued bleeding. The volume removed is greater than that replaced, for instance, by movement of fluid from the intravascular spaces.

Baez: I believe the difficulty arises because we are speaking of two different things, namely, arterial or arteriolar vasoconstriction versus blood flow, which were recorded by different observers in separate experiments and most likely at different times. Visible and measurable narrowing of the arteries and large arterioles occurs during hemorrhagic hypotension, as Dr. Zweifach described, either as an active process caused by neurogenic or humoral influences or as a passive adjustment to a decrease in the head of pressure. This adjustment, however, would not necessarily be reflected in blood flow measurements made in the portal or hepatic veins. A rapid and massive passage of interstitial fluid into the vascular compartment occurs when the hydrostatic head of pressure decreases and the muscular metarterioles and precapillary sphincters are actively closed. This could account, at least in part, for the unchanged blood flow measured in the portal and hepatic veins.

Dr. Bradley, did I understand you correctly, that the blood flow in the splanchnic viscera increases again after a period of reduced flow following hemorrhage?

Bradley: No, I said the blood flow seemed to return toward normal, that is, toward the control levels.

Baez: When does this occur?

Bradley: Perhaps I can answer this question more clearly by presenting data collected in our laboratory by Dr. Heinemann, Dr. Smythe, and Dr. Marks (1). In Figure 1, values for estimated hepatic blood flow (EHBF) measured by the bromsulphalein method and expressed in terms of the control values are plotted against time for eight dogs studied before and following blood loss amounting to approximately 2 per cent of the body weight. Blood flow fell sharply after hemorrhage,

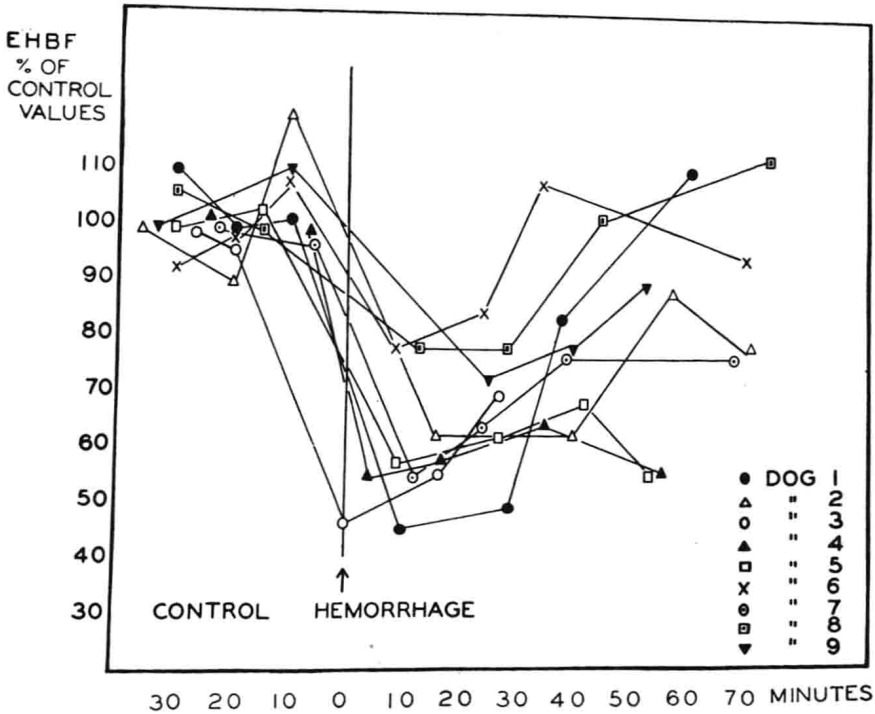

FIGURE 1. Effect of hemorrhage on estimated hepatic blood flow in dogs. Reprinted, by permission, from Heinemann, H. O., Smythe, C. M., and Marks, P. A.: Effect of hemorrhage on estimated hepatic blood flow and renal blood flow in dogs. *Am. J. Physiol.* 174, *352 (1953)*.

and then returned within one hour to or toward the control level in the absence of restoration of blood pressure or cardiac output.

Horvath: There is no question that after a single massive hemorrhage, the estimated splanchnic blood flow does tend to return to normal. I think there have been several other reports besides theirs that showed the same thing (6).

Zweifach: Doesn't the same type of readjustment develop in most other areas of the body, although possibly to a different degree?

Horvath: This occurs, if I am not mistaken, despite the fact the cardiac output is still low.

Bradley: Yes.

Dobson: How can this occur all over the body and the cardiac output still remain low? If the cardiac output does stay low while the splanchnic circulation returns toward normal with time after hemorrhage, then some tissue or tissues elsewhere in the body must be getting less and less blood flow with time after the hemorrhage.

Bradley: That is true. In the experiment shown in Figure 2, from a study by Reynell *et al* (3), it may be seen that the fall in blood pressure and cardiac output (measured by the direct Fick method) after hemorrhage persisted until the time when "recovery" in EHBF was evident. Thus, vasodilation apparently develops within the splanchnic bed, presumably accompanied by more pronounced vasoconstriction elsewhere in the body.

Selkurt: Because of the uncertainty of the bromsulphalein method, we made measurements with the bristle flow meter developed by Dr. Brecher and Dr. Praglin (7) in our department. The meter is inserted directly into the portal vein of dogs. For the hepatic artery flow, flow measurement was made by a carotid-hepatic artery shunt, because the flow meter head was too large to insert directly into the artery.

We employed the hemorrhagic shock procedure previously used in

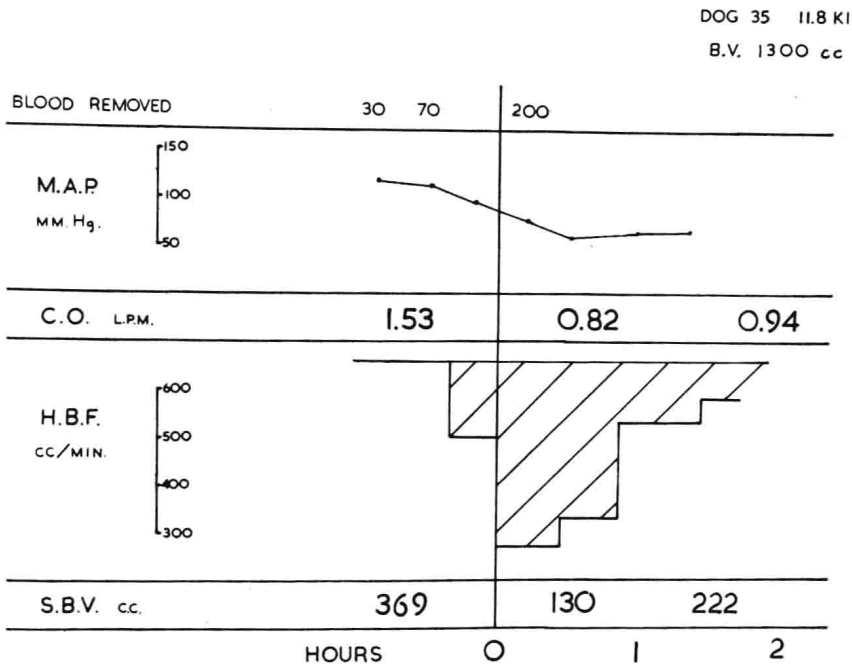

FIGURE 2. Changes in mean arterial pressure (M.A.P.), cardiac output (C.O.), estimated hepatic blood flow (H.B.F.), and splanchnic blood volume (S.B.V.) after acute blood loss. The major hemorrhage was produced at time 0; the first 100 ml. of blood were removed for analytical purposes. Reprinted, by permission, from Reynell, P. C., Marks, P. A., Chidsey, C., and Bradley, S. E.: Changes in splanchnic blood volume and splanchnic blood flow in dogs after haemorrhage. *Clin. Sc.* 14, *407 (1955).*

our laboratory. Figure 3 shows a representative experiment with arterial blood pressure at the top; immediately below this the bleeding volume is given as per cent of body weight; then the portal vein flow and hepatic artery flow are given; next are the pressures in the portal vein and hepatic artery in mm. Hg; and at the bottom is a calculation of resistance in these vascular beds by the A-V pressure difference over flow (P/F ratio).

Resistance increases in the hepatic artery immediately with hemorrhage, but it subsides later. It increases with further bleeding in the 40-mm. Hg period. The mesenteric resistance does not appear to be significantly increased with initial hemorrhage but does so later when the animal is bled down to 40 mm. Hg arterial blood pressure.

An interesting thing about these experiments was that upon transfusion of blood there was in every instance a marked hyperemia of the portal vein flow, as is evidenced by the very marked overshooting of

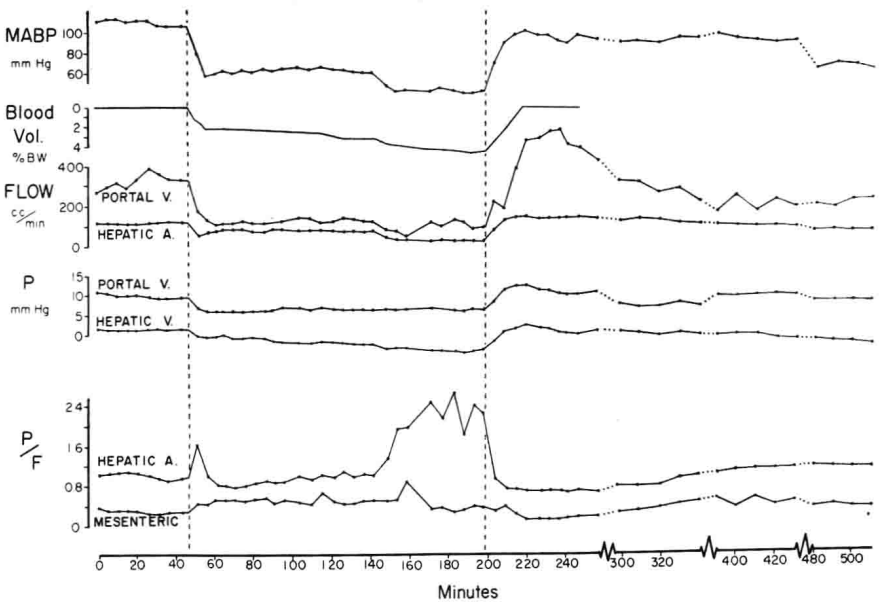

FIGURE 3. Splanchnic hemodynamics during hemorrhagic shock. MABP denotes mean arterial blood pressure.

$$\text{P/F (hepatic artery)} = \frac{\text{MABP - Hepatic V. Press. (mm. Hg)}}{\text{Hepatic A. Flow (ml./min.)}}$$

$$\text{P/F (mesenteric)} = \frac{\text{MABP - Portal V. Press. (mm. Hg)}}{\text{Portal V. Flow (ml./min.)}}$$

Dotted segments in figure to right represent condensed portions of the experiment. Vertical dashed lines denote the beginning of hemorrhage and time of restoration of blood.