Medical Progress

Progress in Disseminated Intravascular Coagulation

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THE PAST FEW YEARS have brought many new developments in the field of disseminated intravascular coagulation. To the practitioner of medicine, many of these may seem to represent advances that are of interest but not of importance since they appear to be related more to experimental or research medicine than to clinical medicine. However, with the concomitant advances in therapy, the possibility of prevention of morbidity and mortality in certain human diseases becomes more likely. In fact, the major recent effort in disseminated intravascular coagulation has been the attempt to control the clotting in these diseases at a clinical level. The results have been variable. During this period of rapid change, it seems worthwhile to take a circumspect look at the field, with the object in mind of examining the lessons learned from some of these clinical trials and attempting to evaluate what the experimental observations may imply for the future of clinical medicine. Another object of this review is to bring together those diseases in which disseminated intravascular clotting has recently been demonstrated to play a role.

In order to put the problem in its proper context, certain general principles must be understood.

Nature of the Problem

An Intermediary Mechanism of Disease

Disseminated intravascular coagulation is an intermediary mechanism of disease.[1] Behind every clotting episode lies an etiologic factor that triggers the clotting. The major categories of etiologic factors causing intravascular coagulation are: (1) intravascular hemolysis, (2) release of tissue thromboplastin, (3) bacterial endotoxin, (4) proteolytic enzymes, (5) particulate or colloidal matter, (6) anoxia and anoxemia, (7) endothelial damage and (8) ingestion of certain lipid substances.

Each disease process has its own unique clinical and pathologic changes in addition to those associated with intravascular clotting. It is obvious that the best prevention and treatment of intravascular coagulation lies in the prevention and treatment of the underlying disease.

Definition

Disseminated intravascular coagulation encompasses more than the simple formation of a thrombus. It is a biologic process involving many chemical substances and physiologic responses. It begins with the entry of a procoagulant material or activity into the circulating blood; it progresses to the stage of platelet aggregation and fibrin formation which may or may not result in thrombosis of capillaries, arterioles and venules of various organs; it is associated with activation of the fibrinolytic enzyme system with dissolution of fibrin and fibrinogen and the release of fibrin-split products into the plasma; and it is not complete until the hemostatic mechanism and vasomoter apparatus have returned to normal and the last significant amount of fibrin-split product has been cleared from the blood.

In some patients activation of the fibrinolytic system is minimal and intravascular clotting is the major problem, whereas in other patients the fi-

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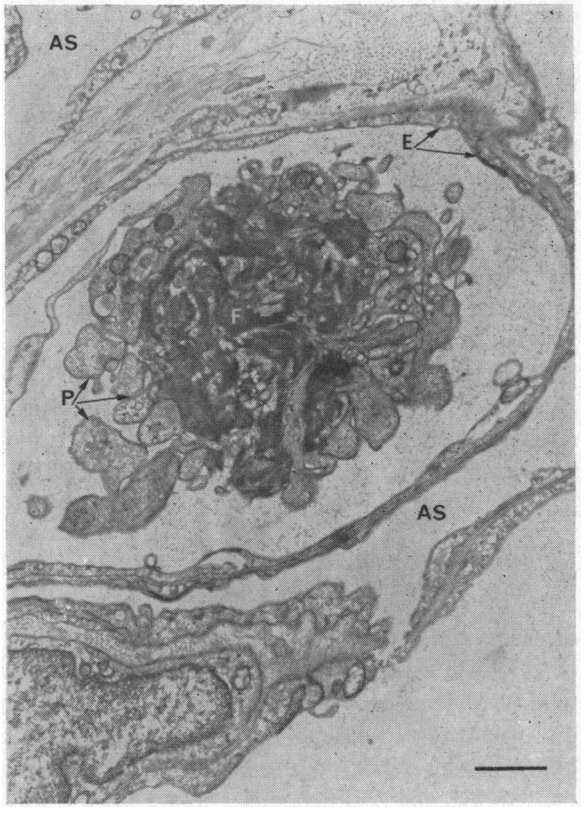


Figure 1.—Endotoxin shock. A pulmonary capillary contains a mass of fibrin and platelets, some of which are undergoing viscous metamorphosis. Electron micrograph. × 16,000. AS=Alveolar space. E=Capillary endothelium. P=Platelets. F=Fibrin.

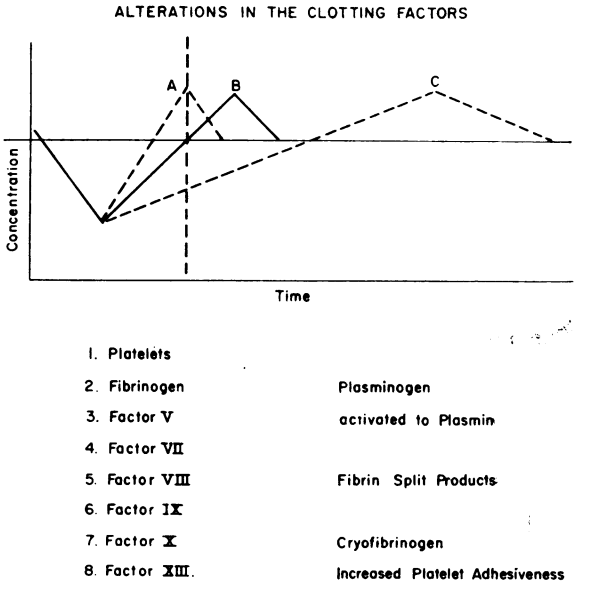


Chart 1.—Schematic representation of the effect of a single large intravascular clotting episode on the hemostatic mechanism. The top horizontal line represents 100 percent concentration or levels of all Factors. All Factors fall proportionately immediately. Following this they recover and rise to above normal values. The rate of return and overshoot is dependent on the rate of regeneration of each individual Factor. Line A represents Factor VIII; Line B = Fibrinogen; Line C = Platelets.

The hypothetical vertical line (dash) shows that a single determination of these Factors at this time may yield a high level of Factor VIII, a normal level of fibrinogen and a low platelet count.

brinolytic system is rapidly and massively activated so that fibrinolysis overshadows the initiating clotting process.

It should be emphasized that disseminated intravascular coagulation may be quite extensive or severe without the development of occlusive thrombi. Considerable clotting may occur and not be visible by light microscopy. In some instances this is due to lysis of thrombi. In others it is because the fibrin is submicroscopic and can be detected only in electron microscopy. An example is endotoxin shock in monkeys, in which no thrombi appear in the light microscope but fibrin strands are visible by electron microscopy.[2]

Diagnosis

Evidence of disseminated intravascular coagulation comes from four sources: (1) pathologic examination, (2) examination of the hemostatic mechanism, (3) the clinical manifestations and (4) the response of the hemostatic mechanism to a therapeutic trial of heparin.

Pathologic Evidence

In the majority of these diseases, tissue examination reveals platelet or fibrin thrombi, or both, in the arterioles, capillaries or venules of many viscera. If these microscopic thrombi are of sufficient duration they are associated with hemorrhage or ischemic necrosis of the organ involved. The organs most frequently involved are the kidney, brain, pituitary, lungs, liver, adrenal glands and mucosa of the gastrointestinal tract (Figure 1).

The severity of involvement of an organ is variable from one disease to another and from one patient to another with the same disease. The spectrum of damage is exemplified by the kidney, in which there may be evidence of (1) no disease, (2) "lower nephron nephrosis" or acute focal tubular necrosis, or (3) bilateral renal cortical necrosis. The brain may exhibit (1) no changes, (2) capillary platelet thrombi, (3) capillary fibrin thrombi, (4) perivascular ring hemorrhages, or (5) focal infarcts. The pituitary may show (1) no change, (2) capillary fibrin thrombi, (3) focal hemorrhage, or (4) extensive infarct necrosis. In

patients who survive the acute process the necrotic lesion evolves into a collagenous scar. The liver may reveal (1) no anatomic change, (2) sinusoidal platelet or fibrin thrombi, (3) hemorrhage, (4) focal necrosis of liver cells, or (5) extensive infarction. The adrenals may exhibit (1) no anatomic alteration, (2) platelet and fibrin thrombi in the sinusoids, (3) focal hemorrhage or necrosis, or (4) diffuse hemorrhagic necrosis. Involvement of the gastrointestinal tract is extremely variable. The mucosa is predominantly involved and this may include the mucosa from the esophagus to the colon. Gross observations include no change, petechiae, ecchymoses, small focal ulcers, large multiple ulcers to pseudomembranous enterocolitis. The lung may show no change, platelet and fibrin thrombi, or focal alveolar hemorrhage.

The presence of microscopic thrombi in multiple organs constitutes proof of the reaction although it does not indicate the duration or severity of the clotting episode.

The Hemostatic Mechanism

Intravascular coagulation produces a characteristic sequence of changes in components of the hemostatic mechanism. Initially, there is a decrease in platelets, circulating fibrinogen, prothrombin complex, Factors V, VII, VIII, and X (Chart 1). This depletion is due to the fact that these substances are used up in the process of coagulation and to the activation of plasminogen with the formation of active fibrinolysin which further diminishes the concentration of fibrinogen and certain other factors by enzymatic degradation. Intravascular clotting and fibrinolysin activation usually occur simultaneously. Although, in disease states, activation of the fibrinolytic system is almost always preceded by intravascular coagulation, there are some diseases in which intravascular coagulation predominates and fibrinolysin activation is minimal or slow. In other conditions fibrinolysin activation is rapid and maximal and may overshadow the initial activation of the clotting mechanism.

The initial period of depletion of clotting factors is followed by a recovery period, and this is characterized by elevation of these components above normal. During this rebound the abnormally high levels of any one factor may vary from 100 percent to 200 percent of the normal concentration. Subsequently, with the recovery of the patient, the values return to normal. The time at which the peak of overproduction of any one factor is reached is dependent upon its half-life and rate of synthesis. The half-life of platelets is much longer than that of Factor VIII, and the peak of overproduction of platelets is a matter of days while that of Factor VIII is a matter of hours. The duration of the stimulus to clotting and fibrinolysin activation also determines the rate of recovery, the latter being considerably slower when the stimulus acts over a long period of time and more rapid when it is of short duration.

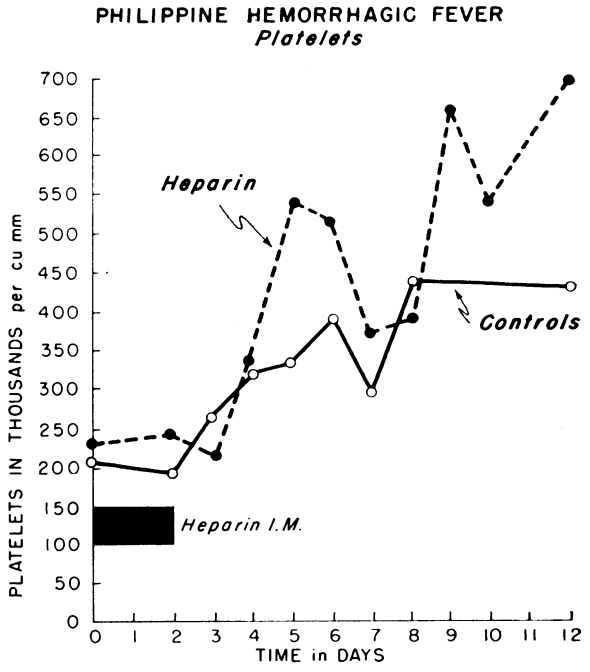
Other changes in the hemostatic mechanism include the appearance of increased platelet adhesiveness, increased amounts of cryofibrinogen and antithrombin, and initial depletion of fibrin stabilizing factor (Factor XIII).

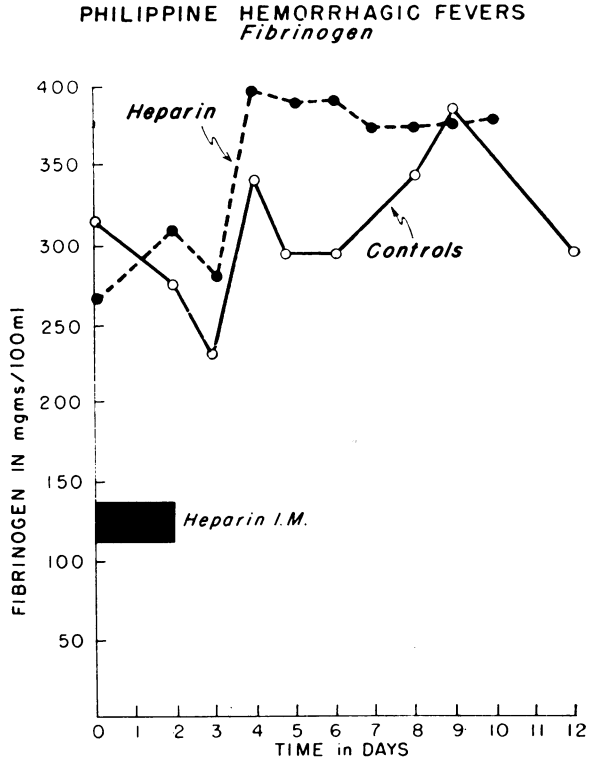
Clinical Manifestations

In spite of the varied clinical picture in these diseases, which one would expect from the variety of etiologic agents, certain clinical events occur with great frequency in patients with severe acute disseminated intravascular coagulation.[3] These are hypotension (shock), a bleeding tendency, oliguria or anuria, convulsions and coma, nausea and vomiting, diarrhea, abdominal pain, back pain, dyspnea, and cyanosis. Such a constellation of clinical signs and symptoms regardless of the etiologic agent or the presence of other signs and symptoms, particularly when they occur almost simultaneously, is presumptive evidence of disseminated intravascular coagulation.

The hypotension may be mild or severe, transient or irreversible. The hemorrhagic diathesis may consist only of the appearance of a few petechiae on the skin or mucous membranes, or it may show any degree of severity up to the development of totally incoagulable blood with massive internal or external hemorrhages. The same variability may be observed in renal function. There may be transient oliguria, anuria for several days followed by diuresis, or irreversible anuria and death in uremia.

The variations in tissue reaction, hemostatic mechanisms, and clinical manifestations are due to variations in the rate, amount and localization of intravascular coagulation. These can be ascribed to the following: (1) differences in the potency of the clot-promoting agent; (2) differences in quantity of the agent; (3) difference in portal of entry of the agent; (4) differences in the condition of the vascular bed at the time clotting takes place;





Charts 2 and 3.—Response of platelets and fibrinogen to heparin trial in Philippine Hemorrhagic Fever. (Twenty patients in each group.)

and (5) rate and extent of activation of the fibrinolytic system.

It is also important to note that multiple mechanisms may operate to trigger clotting in any one disease. The process may become a vicious cycle particularly with the development of shock which, in itself, can be responsible for causing a certain amount of intravascular coagulation.

Response to a Therapeutic Trial of Heparin

The response to heparin may be clinically apparent in those diseases in which patients exhibit a hemorrhagic diathesis. Not infrequently, heparinization stops the oozing from the gums, the gastrointestinal tract or the uterus.

The administration of heparin to patients with disseminated intravascular coagulation usually results in a return toward normal levels of all the factors of the coagulation mechanism. As in the cases with a spontaneous recovery, the different factors return at different rates. For the most part the response is rather slow, with fibrinogen and platelets returning to almost normal values within three to five days (Charts 2 and 3). Of course, the beginning of the trend back may be observable within the first 24 hours. This response to heparin indicates two things: (1) that intravascular coagulation is occurring in the patient and (2) that the intravascular clotting is associated with the release of thrombin or thromboplastin into the circulation (since heparin is both antithrombic and antithromboplastic).

A word of caution concerning the interpretation of such data is necessary. The spontaneous recovery of a patient is accompanied by a spontaneous recovery of the hemostatic mechanism after a single massive episode of disseminated intravascular coagulation. Thus, to ascertain the effectiveness of heparin the rate of recovery of the hemostatic mechanism after its use in any single patient must be compared with either the rate of recovery in other similar patients without heparin, or with the trial of other therapeutic agents in the same patient which have failed.

With these few general principles in mind, we shall turn to those diseases in which the occurrence of disseminated intravascular coagulation has recently been discovered. Although disseminated intravascular coagulation is ubiquitous and knows no categorical limitations, it may be useful

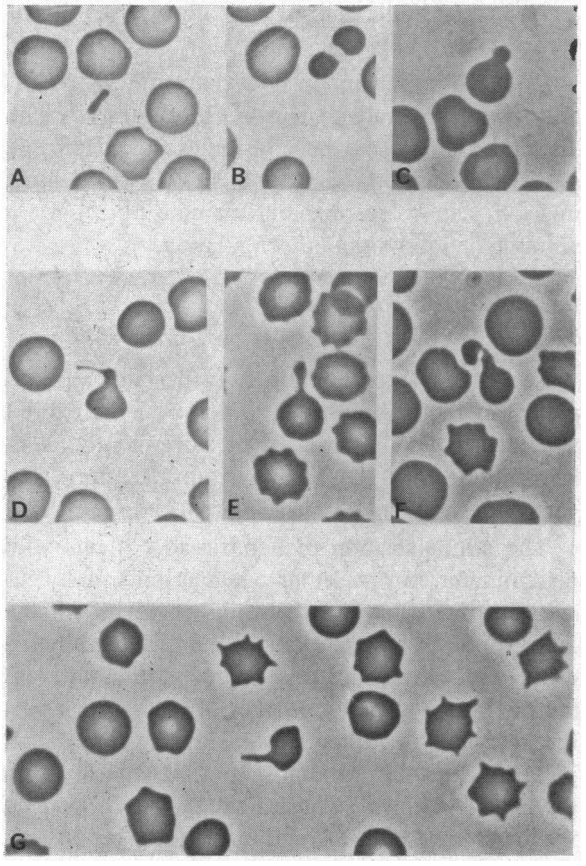


Figure 2.—Films of peripheral blood. Phase contrast microscope. Wright's stain. A, Elongated red cell fragment. B, Red cell cut in half with dense cytoplasm. C, Red cell with "bud" from surface and dense cytoplasm. D, E, F, and G, Various types of elongated "tails" on red blood cells. These present a similar appearance to the distorted cells in the lung and spleen observed by electron microscopy. The "crenated" cells were more numerous in the terminal phases of the experiments.

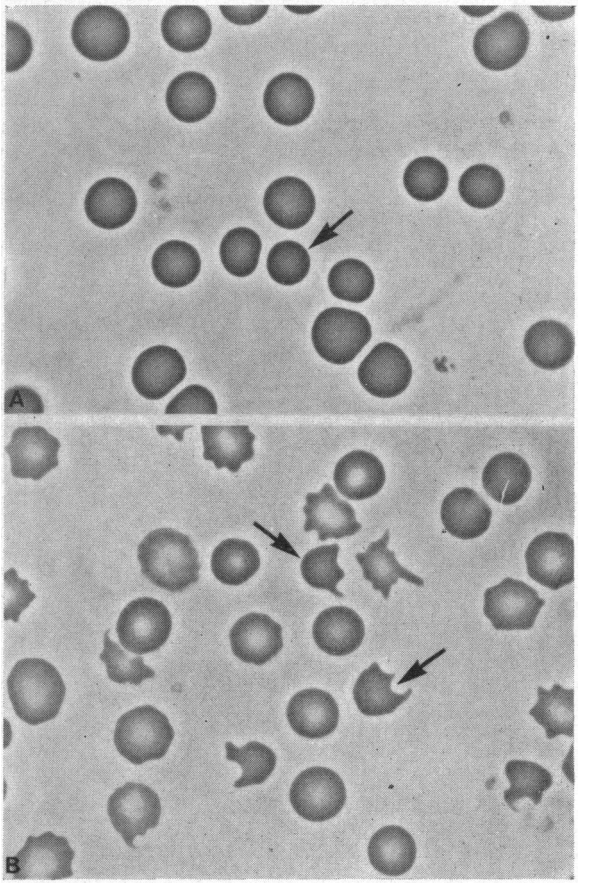


Figure 3.—Films of peripheral blood. Phase contrast microscope. Wright's stain. A, The small densely stained cells (arrows) are microspherocytes. B, The arrows indicate ("helmet cells") typical of microangiopathic hemolytic anemia.

to consider them with respect to the medical specialty to which they are related.

Internal Medicine

Microangiopathic Hemolytic Anemia

The term *microangiopathic hemolytic anemia* was introduced by Brain, Dacie and Hourihane[4] as a label for hemolysis of a type found in association with thrombotic thrombocytopenic purpura, the "hemolytic-uremic" syndrome, polyarteritis nodosa, some cases of malignant hypertension and in certain patients with carcinomatosis. Disseminated intravascular coagulation occurs in all these diseases.[1]

The simplest and most rapid means of recognizing hemolysis of this type lies in the examination of the blood film. Characteristically, the red blood cells are altered to a variety of bizarre but readily recognized shapes.[5] Among these are "helmet cells," "burr cells," crenated cells, schistocytes (cell fragments) and microspherocytes (Figures 2 and 3. These structural alterations are also accompanied by an increased osmotic and mechanical fragility. They may be accompanied by rises in the reticulocyte count, plasma hemoglobin, increased indirect plasma bilirubin and hemosiderinuria, depending on the severity and rate of the hemolysis.

In the past, these alterations in the red cell have been attributed to azotemia which frequently, but by no means always, accompanies these diseases. However, there is now ample clinical and experimental evidence to show that they are caused by disseminated intravascular coagulation. This was first suggested by Brain and coworkers (1962) who noted that the most pronounced structural alterations of the red cells occurred in patients

with necrosis and fibrin deposition in arterioles and capillaries. Further evidence came from their experimental studies with bacterial endotoxin.[6,7] Using doses of endotoxin which elicit the generalized Shwartzman reaction, they observed changes in the red cells characteristic of "microangiopathic hemolysis." They also infused thrombin into the circulation and produced the same effect. This is as direct a means of producing disseminated intravascular coagulation as is now available. Curiously, with thrombin, the effect was minimal, but when epsilon aminocaproic acid (EACA) was added to prevent lysis of thrombi, the hemolytic effect was greatly enhanced. An extract (arvin) derived from the venom of Malaysian pit viper which induces intravascular clotting had the same effect on the red cell.

The formation of hemoglobin-containing fragments suggested that the membrane of red cells had sustained localized damage and then had resealed. Such damage must have been mediated by an agent with physical dimensions that were small relative to the size of a red cell — and fine fibrin strands possess the necessary physical characteristics.

To test this idea under direct observation *in vitro*, a simple circuit was constructed around which blood could be pumped while a fibrin thrombus was in the process of formation.[8] Coagulation was initiated by introducing small amounts of thrombin or snake venom into the circuit. By controlling the rate of build-up of thrombus, the pressure to which the blood was exposed was maintained within physiological limits. The passage of blood through these fibrin clots resulted in hemoglobinemia and red cell fragmentation (Bull 1968). Microscopic examination of this process revealed many individual red cells attached to or folded over single fibrin strands. Red cells in various stages of hemolysis could be seen in the heavy fibrin columns. The investigators concluded that fragmentation occurs when a rapidly moving red cell encounters a thin fibrin strand. The red cell becomes attached to or folded about the strand. Such a cell is subjected to buffeting from unattached red cells and hence to forces which may tear the membrane. If the tear takes place along the line of the fold at the site of membrane apposition, two hemoglobin-containing fragments may form with loss of little, if any, hemoglobin. Tears at other sites of the membrane will result in partial loss of hemoglobin and the formation of irregularly shaped fragments.

One need not consider that *in vivo* the fibrin strands are stationary as in the *in vitro* experiments of Bull and Brain (1968). It is worth emphasizing that one of the characteristic features of disseminated intravascular coagulation is that the fibrin is forming in a moving stream of blood. As a modification of Brain's concept, it may well be that the fibrin forms in larger vessels and traps red cells within it, and the trauma which fragments the cells comes when the moving mass suddenly impinges against smaller vessels such as arterioles, capillaries, or (on the venous side) against the small vessels of the pulmonary circulation. The red cells would be squeezed out of such a loose fibrin mesh at the time of impact.

Brain[9] recently described his experience with the use of heparin in patients with "microangiopathic hemolysis." Four patients were infants with the "hemolytic-uremic" syndrome and three were young women with pre-eclamptic toxemia of pregnancy or shock and a hemorrhagic diathesis. Not only did the clotting mechanism return toward normal, but the hemolysis was stopped as evidenced by a drop in the plasma hemoglobin and a disappearance of the fragmented red blood cells.

We have recently[10] made some observations on the mechanism of hemolysis in experimental catecholamine shock which may be related to certain diseases of man. The continuous infusion of epinephrine in high doses into monkeys and rabbits caused shock, disseminated intravascular coagulation and hemolysis. The hemolysis was characterized by an elevation of plasma hemoglobin, an increase in osmotic fragility, and changes in the shapes of red blood cells. The structural alterations in the red cells in the circulating blood included "helmet" cells, crenation, schistocytes and microspherocytosis. The spherocytosis was correlated with an increased osmotic fragility. *In vitro* studies demonstrated that the hemolysis was not due to release of hemolytic substance into the plasma, nor to a direct action of epinephrine on the red cell.

Blockade of the alpha-adrenergic receptor sites by Dibenzyline®* (phenoxybenzamine hydrochloride) completely prevented the hemolysis, as well as the intravascular coagulation. It was concluded that the hemolysis was mediated by the stimulation

*Supplied through the courtesy of Smith, Kline & French Laboratories, Philadelphia.

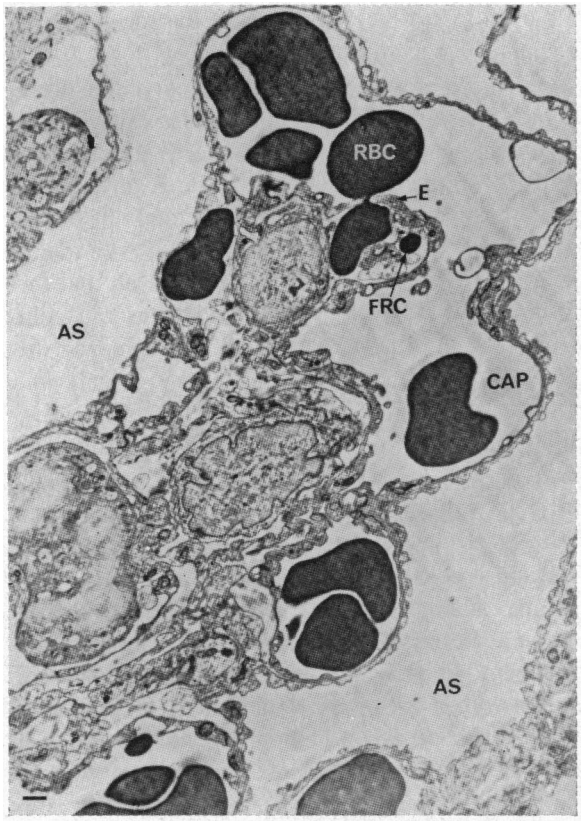


Figure 4.—Rabbit lung. A red blood cell is seen traversing a small gap in the endothelium. The mechanical stress producing such a distorted cell may be responsible for some of the red cell fragmentation caused by epinephrine infusion. × 5,300. RBC=Red blood cell. E=Endothelium. FRC=Fragmented red cell. CAP=Capillary lumen. AS=Alveolar space.

of the alpha-adrenergic receptor sites in small vessels.

In general, the severity of hemolysis correlated with the amount of intravascular clotting. Pretreatment of the animals with heparin greatly reduced the amount of hemolysis, but did not completely prevent it. This suggests that some other mechanism besides intravascular coagulation is in action.

Electron microscopy of the tissues of these animals revealed another mechanism. Red blood cells were found traversing small gaps in the endothelium of the capillaries of the lung and sinusoids of the spleen (Figure 4). Passage through the capillary walls produced distortion of the cells with large cytoplasmic extensions and fragmented cell membranes. These changes were of more than a temporary nature since they were found in red cells in the circulating blood both by light and electron microscopy. It seems likely that the mechanical distortion produced by this "pinching" process is in part responsible for cell membrane damage, spherocytosis and ultimately some hemolysis. The hemolysis produced by epinephrine infusion resembles that which occurs in the "microangiopathic hemolytic anemia" syndrome and is ultimately due to (1) disseminated intravascular coagulation, (2) distortion and fragmentation of red cells in their passage through gaps in the capillary epithelium and (3) the acquired spherocytosis.

From the clinical standpoint, this phenomenon has great interest because it is now possible to detect the occurrence of disseminated intravascular coagulation by the simple expedient of making a blood smear. The observation of the characteristic structural alterations of the red blood cells is strong presumptive evidence of intravascular clotting.

From the standpoint of the etiology and pathogenesis of certain diseases this mechanism of hemolysis is of great interest. For example, in the past we had categorized thrombotic thrombocytopenic purpura as a disease with intravascular coagulation caused by some unknown hemolytic process.[1] However, with the demonstration that disseminated intravascular coagulation can cause hemolysis, the problem of which is cause and which effect must now be explored. The problem can be easily resolved, at least in part, by the simple administration of heparin to these patients with a measurement of the amount of alteration in the rate of hemolysis.

Renal Disease

A recent promising report by Kincaid-Smith[11] from Australia serves to focus attention on the role of intravascular clotting in the pathogenesis of certain types of kidney disease. Kincaid-Smith has treated six patients with oliguric renal failure shown histologically to be due to glomerulonephritis or obstructive lesions in arterioles and glomeruli with infusion of heparin, which was given in addition to steroids and immunosuppressive drugs. The rapid improvement in urine output which followed heparin infusion in five of the six patients, and deterioration in renal function when heparin was stopped in three patients, suggested that the heparin had some direct effect on the renal lesion. Steroids or cytotoxic drugs were given before heparin in some patients and after heparin in others, and no obvious improvement was noted at the time of giving these drugs.

To what extent anticoagulation will prove useful

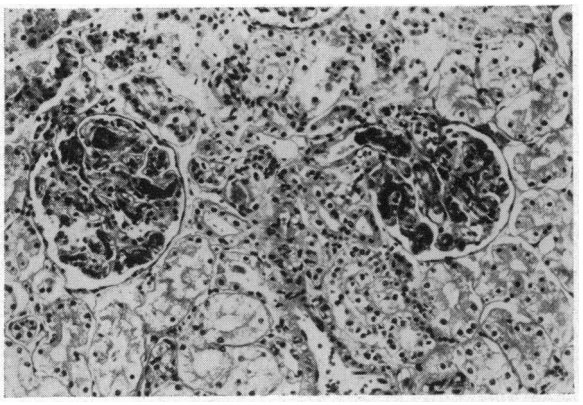


Figure 5.—Glomerular capillary thrombi secondary to acute, massive disseminated intravascular coagulation. Hematoxylin and eosin stain. × 160.

in the management of glomerulonephritis, or other renal diseases, will require testing in many more patients. However, in the meantime it may be worthwhile to consider the various known ways in which fibrin is deposited in the kidney as a background to this clinical consideration.

Thrombosis of the microcirculation. The sudden formation of glomerular capillary thrombi with obstruction to the flow of blood in the renal cortex is perhaps the most extreme form of renal fibrin deposition (Figure 5). This is the basic mechanism of the production of bilateral renal cortical necrosis with total renal insufficiency in man and can be reproduced experimentally by intravenous infusion of thromboplastin,[12] thrombin,[13] or the appropriate doses of bacterial endotoxin.[14] The studies of Muller-Berghaus[15,16] indicate that relatively large amounts of fibrin can be deposited in the kidney by this mechanism; amounts equivalent to 56 percent of the circulating fibrinogen. In the experimental animals, the glomerular capillary thrombi induced by bacterial endotoxin can be prevented by intravenous infusion of heparin.[17]

Several recent studies dealing with the pathogenesis and prevention of the experimental generalized Shwartzman reaction raise the possibility that agents other than heparin may be useful in preventing this form of ischemic renal damage.

Muller-Berghaus was able to prevent the glomerular-capillary thrombosis caused by bacterial endotoxin in pregnant rats by blockade of the alpha-adrenergic receptor sites by Dibenamine® and Dibenzyline® (phenoxybenzamine). These experiments indicate that endotoxin-induced glomerular thrombi are localized in the kidney by

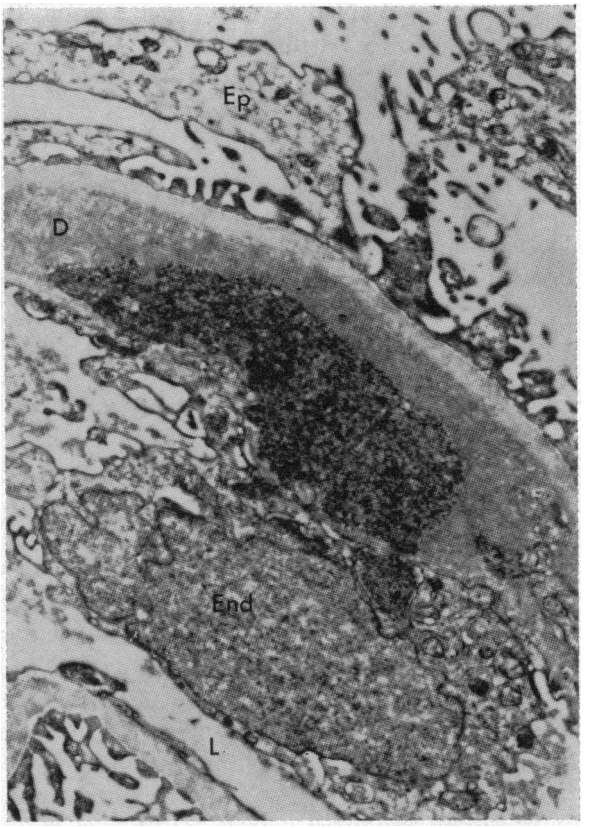


Figure 6.—Toxemia of pregnancy. Renal glomerulus. The basement membrane is normal in thickness. A granular deposit of fibrin is present on the luminal side. The endothelial cell is lifted off the basement membrane and appears to be phagocytizing some of the granular deposit. The epithelial cells are essentially normal. × 12,000. D=Deposit of granular fibrinogen. Ep=Epithelium. End=Endothelial cell nucleus. L=Capillary lumen. (Electron micrograph courtesy of Dr. W. Mautner of the Mt. Sinai Hospital, New York.)

stimulation of the alpha-adrenergic receptor sites. Whether or not alpha-adrenergic blockade for this purpose would be feasible in man remains to be demonstrated.

Evans and Mustard[18] prevented the renal capillary thrombi caused by bacterial endotoxin by use of anti-inflammatory agents including phenylbutazone, sulfinpyrazone and sodium salicylate. They gave these agents intravenously for four hours before the first injection of endotoxin and throughout the experiment. The doses used were: 400 mg per kg per day of sodium salicylate; 200 mg per kg per day of sulfinpyrazone and 150 mg per kg per day of phenylbutazone. In addition to their other actions, all of these agents prevent platelet aggregation *in vitro* and, since platelets are an essential requirement for the evolution of the Shwartzman reaction,[19] the investigators in-

terpreted the results as an effect primarily on the platelets *in vivo*.[20] Whether or not lower doses or other routes of administration of these agents would be effective in animals or man remains to be explored.

Renal glomerular filtration. Another mechanism by which fibrin is deposited in the kidney is through the action of glomerular filtration. The human disease which illustrates this best is pre-eclamptic toxemia of pregnancy.[21] In this disease, there is a stimulus to intravascular coagulation which is mild in nature and chronic in duration. It produces an increased platelet adhesiveness[22] and an increased amount of cryofibrinogen in the circulating blood.[23] The fibrin deposits in the glomeruli have quite a different appearance by electron microscopy from the long strands with cross-striations with a periodicity of approximately 200 Angstrom units which occur in occlusive thrombi. The deposits of chronic intravascular coagulation are granular in structure and lie as irregular amorphous masses against the basement membrane on the luminal side (Figure 6). In all likelihood, these deposits represent an incompletely polymerized form of fibrin, possibly a complex of fibrinogen and fibrin monomer which has been accumulated on the basement membrane by the filtering action of the glomerulus. The endothelial cells attempt to phagocytize this material and, in doing so, swell up and lift away from the basement membrane causing a narrowing of the capillary lumen. It is conceivable that these alterations are responsible for the albuminuria and diminished glomerular filtration rate which are characteristic of pre-eclamptic toxemia. This mechanism is also operative in other disease states, most notably in disseminated lupus erythematosus. Also, we have observed this mechanism in animal experiments on Aleutian disease of mink.[24] The glomerular fibrin deposits in all these conditions are very much alike and chronic intravascular coagulation has been shown to accompany them. Taking toxemia as the example, these deposits appear to be resolvable since no permanent renal damage occurs following delivery of the patient.

Endothelial cell basement membrane damage. Another mechanism for the deposition of fibrin in the kidney appears when the endothelial cells and basement membrane of capillaries are damaged. This mechanism is found in glomerulonephritis. Although the deposition of fibrin under these conditions may be intravascular, it is also extravascular and is best thought of as a leakage of plasma from the vessels with clotting of fibrin after exposure to the extravascular environment.

One of the most interesting examples of damage of this type comes from experimental work — that is, nephrotoxic serum nephritis, or "Masugi nephritis." In essence it was this experimental model which led Kincaid-Smith to her clinical studies with anticoagulants in glomerulonephritis.

The basic inflammatory agent in Masugi nephritis is probably the antigen antibody complex formed in the glomerulus. The fact that fibrin plays a role in the process was shown by the studies of Silfverskiold,[25] Kleinerman,[26] Halpern,[27] and Vassalli and McCluskey.[28] Using derivatives of heparin or coumadin or both, they were able decidedly to alter the course of the disease. Halpern treated rabbits with heparin and found that the mortality rate in nephrotoxic serum nephritis was reduced from 12 in 18 to 1 in 17. Neither epithelial crescent foundation nor scarring of glomeruli, which were present in untreated controls, could be demonstrated by light microscopy in heparin treated animals. By the same token blood urea nitrogen levels were greatly diminished in the heparin treated group.

Although the primary and major effect of heparin is antithrombin, Halpern pointed out that heparin also acts against complement. Since the primary inciting agent for the inflammatory reaction is antigen antibody complex, he raised a question as to whether heparin acted to prevent the combination of antigen antibody complex with complement, thus preventing the inflammatory response. The study of Vassalli and McCluskey[28] indicated that it is most likely the anticoagulant activity of heparin rather than its anticomplementary effect which is responsible. They anticoagulated their test animals with warfarin and obtained a result very similar to that of Halpern. Thus, since the action of warfarin is to reduce the amount of circulating prothrombin complex, without affecting complement, the deposition of fibrin is incriminated. They also showed that, even though the kidneys of the treated animals exhibited a minimal inflammatory response, gamma globulin (interpreted as antibody) was found by immunofluorescence in the glomerular basement membrane. It would seem that anticoagulation did not act by preventing deposition of antigen antibody complex, but rather by preventing the deposition of fibrin. Whether the beneficial results are due to

the prevention of fibrin formation within the microcirculation or outside the circulation (that is, the glomerular capsular space and tubules) is a subject for future investigation.

Mural deposition of fibrin in arteries and arterioles. Fibrin is deposited in the walls of arterioles and arteries as well as in the glomerular capillaries in malignant hypertension. It may be deposited acutely or over a long period. It is formed in the vessels that show the characteristic concentric, lamellated hyperplasia of the smooth muscle, sometimes referred to as the "onion peel" appearance. This fact has escaped the attention of most pathologists because it cannot be seen by light microscopy with the conventional histologic stains, but has been clearly demonstrated by use of the immunofluorescent technique of Coons by Gitlin et al[29] and Fennell et al.[30] These vessels are the hallmark of a rapidly rising blood pressure and this probably represents a leakage of plasma fibrinogen into the interstices of the hyperplastic smooth muscle cells.

This process may be seen in its acute form in the lesion which in the past has been referred to as "fibrinoid necrosis" of the arterial wall. This lesion can be easily detected by ordinary histologic techniques and is often considered a diagnostic criterion for malignant hypertension. It is not a mysteriously derived unknown substance, but simply represents acute damage to the vessel wall with clotting of fibrin following the escape of plasma into the arterial wall.

Lendrum[31] has shown that in patients with malignant hypertension, small focal deposits of fibrin may be found in glomerular capillaries.

Renal deposition of fibrin has been detected in several types of experimentally induced malignant hypertension. Masson and coworkers[32] produced massive glomerular capillary thrombosis by inducing malignant hypertension with angiotensin. Skelton made similar observations with hypertension produced by anabolic steroids.[33] More recently intravascular as well as intramural clotting has been demonstrated in hypertension induced by unilateral nephrectomy, sodium chloride and desoxycorticosterone administration.[34] The malignant hypertension was accompanied by fibrin deposition in subendothelial and intramural location in the mesenteric, pancreatic and renal arteries. Fibrin was also found in the glomeruli in the capillary lumens and the mesangial interstices. In addition to the intravascular clotting, a hemolytic anemia which exhibited the red cell changes characteristic of microangiopathic hemolysis developed in these animals.

Intravascular clotting and microangiopathic hemolysis have been demonstrated in malignant hypertension in man as well.[31,35]

The most likely explanation for the fibrin within the muscular walls of arteries and arterioles is that the increased intraluminal pressure caused by the hypertension distends the vessels and separates endothelial walls and disrupts basement membranes, allowing plasma and red blood cells to escape from the circulation. The exposure of the fibrinogen in the plasma to the tissue thromboplastin of the extravascular environment then causes conversion to fibrin. At the same time the exposure of the basement membrane on the luminal side triggers the clotting mechanism by attracting platelets and activating Hageman factor, resulting in mural and intravascular occlusive thrombi. We have observed the phenomenon in an experimental model of eclampsia.[36]

In summary, fibrin is deposited in the kidney by a variety of mechanisms. Knowledge of these mechanisms is essential to a rational approach to therapy. It is doubtful that anticoagulant therapy will prove useful in all instances, but it is clearly useful in some and needs considerable experimental and clinical exploration. It is also important to be aware of the fact that agents other than those directed against the clotting mechanism such as phenoxybenzamine (Dibenzyline®) may be useful in preventing the deposition of fibrin in the kidney.

Liver Disease

Hemorrhage is a frequent complication of both acute and chronic hepatic disease. On occasion it is a fatal complication. Upper gastrointestinal tract hemorrhage may be due to mechanical rupture of esophageal varices or to erosion of a blood vessel at the base of a mucosal ulcer in the stomach or duodenum. Some patients have a hemorrhagic diathesis with petechiae and ecchymosis of the skin, particularly at points of trauma.

It has long been recognized that many patients with liver disease have a defect in their blood coagulation mechanism. In the past this has been largely attributed to two causes: (1) diminished synthesis of certain components of the hemostatic mechanism and (2) a rapid, easy activation of the fibrinolytic enzyme system. Recent studies have

demonstrated that disseminated intravascular coagulation must be added to this list.

It may be useful to bear in mind the function of the normal liver. The liver plays an essential role in hemostasis and thrombosis. There are two basic reasons for this: (1) the liver cells synthesize, and release into the blood stream, fibrinogen, prothrombin, Factor V, Factor X and Factor IX, and (2) the Kupfer cells (phagocytic reticuloendothelial cells) rapidly remove substances from the circulating blood which trigger the clotting mechanism, namely thromboplastin[37] and colloidal and particulate matter. It has also been claimed that they remove fibrinolysin activator from the circulation.[38]

The role of the liver in the removal of procoagulant substances from the circulation is well illustrated by the recent studies of Deykin et al.[39] Intravenous injection of serum into rabbits resulted in a hypercoagulable state characterized by a shortening of the whole blood clotting time and in the formation of a thrombus in an isolated segment of vein. The procoagulant activity of the serum was dependent on the presence of activated Factors IX and XI in the serum. The thrombotic response was rapidly dissipated in the intact animal. The infusion of serum into the portal vein was less efficient in producing thrombosis and the thrombotic response disappeared more rapidly. When the hepatic circulation was occluded the thrombotic response was prolonged. The importance of the hepatic clearance mechanism was emphasized by the observation that when the circulation to the liver was occluded the rabbits routinely died within 15 minutes. The lethal effect could be prevented by the administration of heparin, indicating that it was caused by disseminated intravascular coagulation. During perfusion of serum through the isolated rabbit liver *in situ,* Factors IX and XI activities were reduced to low levels and the thrombogenic activity of the serum was similarly depressed.

The role of the reticuloendothelial system and of hepatocellular damage in liver disease in man is dependent on the type of damage. In acute hepatocellular change, as in acute yellow atrophy, the major problem is reduced synthesis of fibrinogen and prothrombin complex. However, in cirrhosis, although there may be some reduced synthesis, the major problem is "blockade" of the reticuloendothelial system. "Blockade" of the reticuloendothelial system implies a diminished uptake of particulate matter from the circulating blood. It occurs in a variety of circumstances and can be induced temporarily by exposure of the blood stream to bacterial endotoxin, particulate matter, cortisone and certain fatty acids. In cirrhosis it is probably due to an overload of the Kupfer cells with lipid substances[40] and to the diversion of blood away from the liver through the collateral shunts that develop.

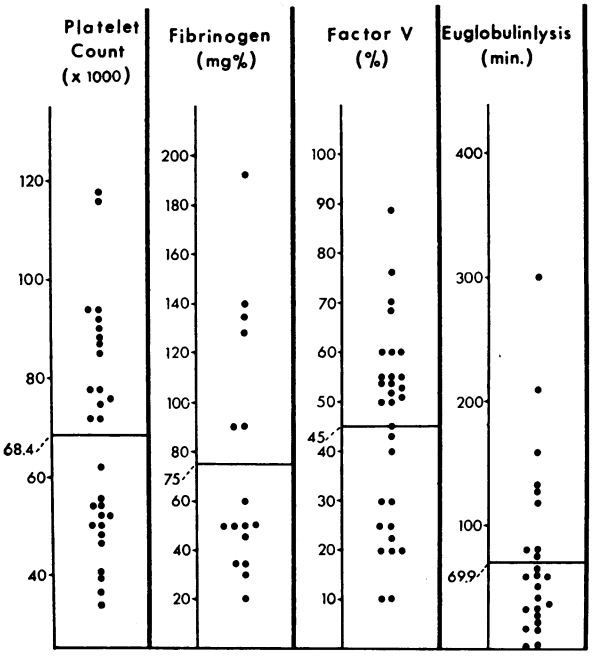


Chart 4.—The low levels of circulating platelets, fibrinogen, Factor V and the evidence of an activated fibrinolytic system are indicative of disseminated intravascular coagulation in these patients. (Courtesy of Dr. M. Horder[42] of the Department of Medicine, Justus-Liebig University, Giessen, Germany.)

The first evidence that cirrhosis may be accompanied by disseminated intravascular coagulation came from the study of Johansson.[41] He observed a patient with cirrhosis, a bleeding tendency and a rapidly enlarging tender spleen. Clotting studies revealed the changes characteristic of intravascular coagulation. When heparin was administered to the patient, all the clotting factors returned to normal levels.

A study of Hörder[42] puts this observation on solid ground. Thirty patients with cirrhosis and portal hypertension had a decided reduction in platelet count, in fibrinogen and in Factor V. The great majority also had an increased fibrinolytic activity (Chart 4). In addition, he gave heparin to one of the patients, with a return to normal of all clotting indices (Chart 5).

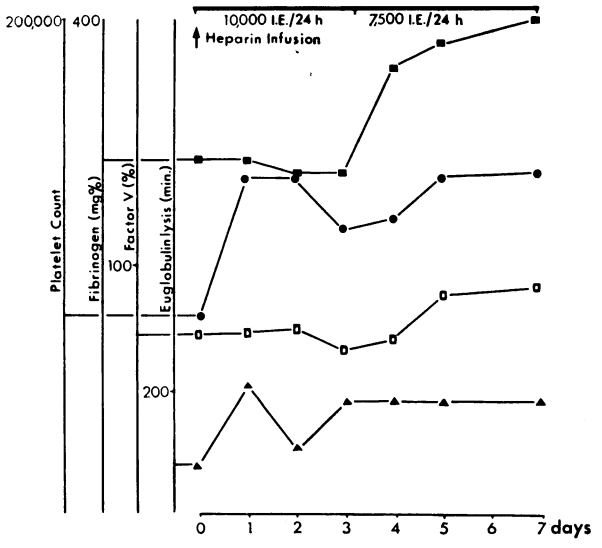


Chart 5. — Heparin administration in cirrhosis of the liver with portal hypertension. (Courtesy of Dr. M. Horder[42] of the Department of Medicine, Justus-Liebig University, Giessen, Germany.)

Of major interest is the question of where the intravascular clotting occurs in cirrhosis. Pathologic studies have revealed that it is primarily in the portal circulation, but in some cases also in the pulmonary circulation. In 64 of 126 cases (51 percent) of postnecrotic cirrhosis, Hou and McFadzean[43] found fresh mural thrombi composed of platelets and fibrin or old fibrin plaques which were the sequelae of previous thrombi. These recent and old thrombi varied from 1 mm to 12 mm in diameter and were found in the portal, splenic and superior mesenteric vein. The clotting in the portal circulation is of the recurrent type and small in amount, and it appears to be the most important site of clotting. Of course, the occasional case of massive thrombosis of portal, splenic or mesenteric vein is well known.

The involvement of the pulmonary circulation by thrombi in cirrhosis is less frequent but is of great interest, since it is associated with pulmonary hypertension.

Many patients with cirrhosis of the liver and portal hypertension exhibit a profound cardiopulmonary circulatory disturbance. Murray et al,[44] studying a selected group of 24 patients with cirrhosis, found an increased cardiac output, an increased total blood volume, an increased peripheral blood flow, and an arterial oxygen unsaturation. They interpreted some of these changes as an evidence of shunting of systemic venous blood through pulmonary arteriovenous anastamoses.

Naeye[45] described five patients with portal hypertension due to cirrhosis and observed the anatomical changes characteristic of pulmonary hypertension. The hearts exhibited right ventricular hypertrophy and dilation. The pulmonary changes varied from moderate arterial intimal proliferation of endothelial cells and fibroblasts to advanced plexiform lesions that resembled recanalized thrombi. Recent emboli or thrombi in varying stages of organization were widespread throughout the small pulmonary vessels.

Portal venous thrombi were found in three of the patients, one of whom had organizing thrombi in collateral varicose esophageal and gastric veins. No other sites of origin for pulmonary emboli were found. The question of the nature of the fibrin deposits in the pulmonary circulation remains problematic. Two possibilities exist: They represent either (1) emboli from the primary thrombotic site in the portal veins, or (2) thrombi arising *de novo* in the lung. The enormously dilated collateral circulation would provide easy access of emboli to the lungs. On the other hand it is equally likely that they are thrombi formed because of the entry of procoagulant substances into the portal circulation from the gastrointestinal tract, substances which ordinarily are removed by the reticuloendothelial system, which is bypassed or "blockaded" in cirrhosis. The thrombi in the pulmonary circulation may be responsible in part for the pulmonary hypertension. A corollary to the concept is the idea that vasoactive amines (such as 5-hydroxytryptamine or tyramine) from the intestinal tract might also add to the pulmonary hypertension.

Whatever the mechanism, intravascular clotting may occur in patients with portal hypertension due to cirrhosis. The clotting is usually small in amount and chronic in duration, but enough to be detectable by studies of the hemostatic medium. In a few patients the pulmonary vascular bed is the site of considerable fibrin deposition.

At the San Francisco General Hospital we have found another cause of acute and massive disseminated intravascular coagulation in cirrhosis, namely Gram-negative bacteremia. A large number of patients with infection of this kind die of endotoxin shock. In these cases bacterial endotoxin is the trigger for the clotting episode. The source of the bacteremia is variable but often it is pneumonitis. The whole process is contributed to by the "blockaded" reticuloendothelial system

which in cirrhosis fails to remove quantities of bacteria that the normal liver could easily handle.

Another possible etiologic factor for intravascular clotting is the effect of the ingestion of alcohol. Lindenbaum and Hargrove[46] observed ten episodes of thrombocytopenia in five alcoholics with delirium tremens. Platelet counts rapidly returned to normal after ingestion of alcohol was discontinued, and thrombocytosis developed. Further studies are required to determine whether this is a direct or indirect effect of alcohol ingestion, and whether or not the platelet change is accompanied by changes in other clotting factors.

Plague

Plague has been known as a deadly and terrifying disease for at least 2,000 years. Although it is of little concern to a North American physician, it continues as a problem in parts of Asia. Its historical interest for the Western World prompts the inclusion of plague in this review.

In a sense the demonstration by Finegold et al[47] of disseminated intravascular coagulation in plague is a rediscovery. Glomerular capillary occlusion by fibrin thrombi was found in seven of twenty cases in a Philippine epidemic of plague in 1904 by Herzog.[48] They were also found in two of twenty-five cases of pneumonic plague from the Manchurian epidemic of 1910-1911,[49] and in approximately 40 percent of 75 cases of bubonic plague in Manila from 1912 to 1914.[50] For the past 30 years, the finding has been overlooked by students of plague.

Finegold's contribution was to demonstrate the generalized Shwartzman reaction in experimentally induced pneumonic plague in monkeys. He observed glomerular capillary thrombi in 80 percent of animals dying of the disease induced by pulmonary exposure to *Pasteurella pestis* and in six of seven injected subcutaneously. Glomerular capillary thrombi are the hallmark of disseminated intravascular clotting. The animals apparently died of endotoxin shock, before renal insufficiency became a factor. Studies of the hemostatic mechanism were confirmatory. Prolongation of the clotting time, prothrombin time, and partial thromboplastin time was associated with progressive thrombocytopenia. There was no evidence of a circulating anticoagulant, or of massive activation of the fibrinolytic enzyme.

With the advent of antibiotic therapy, infection with *Pasteurella pestis* has usually been successfully controlled wherever patients have had access to medical facilities. In occasional cases, however, people have died of plague despite successful antibiotic sterilization of their blood and tissues.[51] It is clear that these as well as many patients in antiquity died of endotoxemia with shock and disseminated intravascular coagulation.

(To be continued in October issue.)

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(References to be continued in October issue)

CONSERVATIVE THERAPY FOR HIATAL HERNIA

"I think . . . that hiatal hernia surgery is rarely needed if the patient is treated correctly. In my experience, the proportion of patients with hiatal hernia that have ultimately come to surgery is certainly much less than 5 percent. The indications for surgery . . . have been severe complications, such as stricture, that did not respond to medical therapy or ulceration of the esophagus that ultimately turned into stricture; but more than not I've . . . referred patients for surgery in whom medical therapy has failed. Years ago we talked about intractable ulcer disease and came to realize that this, in most cases, merely represented a posterior penetrating ulcer. In hiatal hernia disease, we do get intractable patients. Most of these I think I can categorize . . . into a psychological group of young women that have been unable to take their antacids and, for one reason or another, have absolutely not responded to medical therapy. In these cases, surgery has been recommended. But again I would state it is infrequently needed."

—LAWRENCE D. WRUBLE, M.D., Memphis

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