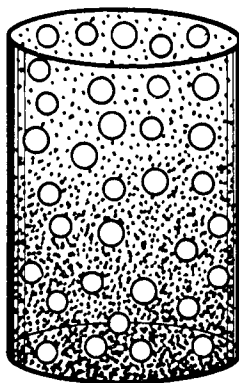


Platelet- Leukocyte Emboli

Origins, Effects & Treatment

R. L. Swank
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Microemboli composed of aggregates of platelets and leukocytes can become a serious threat to the microvasculature. These aggregates develop in blood stored for future transfusion, and during hemorrhagic and traumatic shock. During the use of the extracorporeal circulation, these causal factors combine together with the trauma of suction, pumping and oxygenation of the blood to produce wide-spread microembolism of the microvasculature resulting in pathophysiological alterations of the lungs, brain, kidneys, heart and liver, as well as other organs. This often leads to permanent damage and sometimes to death. It is important, therefore, that this phenomenon be examined, and that methods available to remove the microemboli or to prevent their access to the body be evaluated.

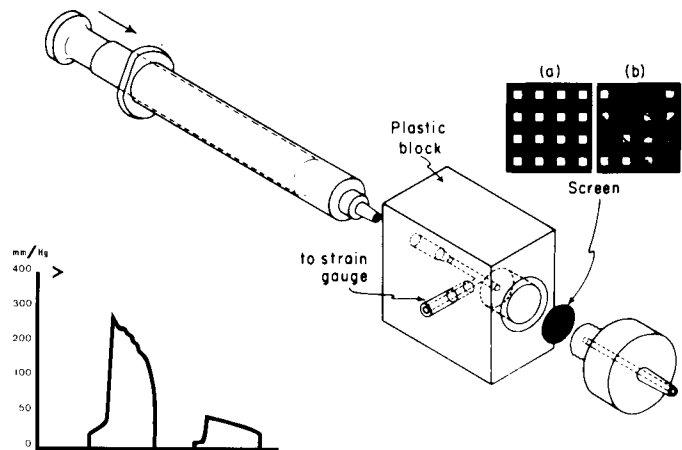


Figure 1 is a schematic illustration of the screen filtration pressure (SFP) apparatus. Blood is forced from a syringe at a constant rate through a screen with pores 20 x 20 x 20 μ for 10 seconds. Screen (a) is clean, screen (b) shows occluded pores after test. The pressure before the screen is monitored by a strain gauge and recorded on moving paper. Two curves are shown, the one to the right is normal, the left curve is for blood containing many aggregates. Read curves from right to left.

I. GENESIS OF PLATELET LEUKOCYTE AGGREGATION

Adhesiveness of platelets, and aggregation with leukocytes begin immediately after blood is withdrawn from the body^{1, 2}. Contact with foreign surfaces accelerates this process³. Within a few hours, heparin anticoagulated blood exhibits marked adhesiveness and/or aggregation of the blood elements as shown by the screen filtration pressure (SFP) method^{4, 5, 6, 7, 8, 9, 10, 11} (Figure 1), and in 24 hours this process is essentially complete (Figure 2). Acid citrate dextrose anticoagulated blood changes more slowly. In 3 days, all blood samples show marked adhesiveness and aggregation of the platelets and leukocytes, and within one week the process is nearly complete⁵. These observations have been confirmed^{6, 7, 8} using the SFP method, and the Coulter Counter⁹.

During exsanguination, the platelets become adhesive as the perfusion of tissues become inadequate. If the blood loss is rapid^{10, 11}, the SFP rises rapidly as the blood pressure falls (Figure 3), if the bleeding is slow the microemboli may form before the blood pressure falls, or even when the pressure is increased. In these two latter cases, it is likely that the blood pressure is maintained by early microembolism of the capillary beds of the body. This would limit the area of perfusion and lessen the volume of blood needed to prevent a fall in the arterial pressure.

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FORMATION OF BLOOD ELEMENT AGGREGATES DURING BLOOD STORAGE

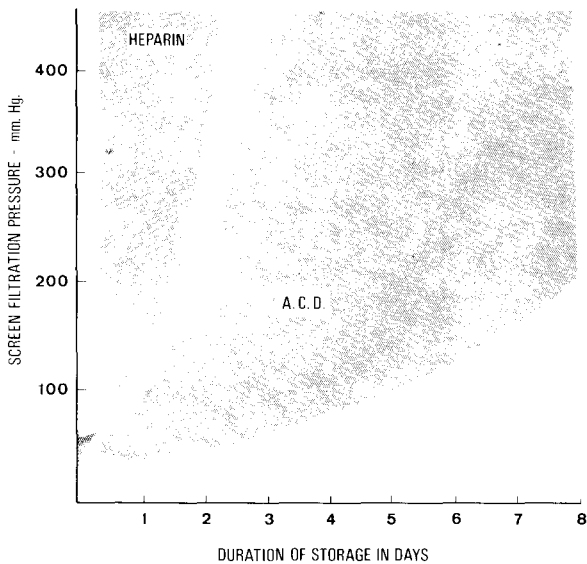


Figure 2 illustrates the rate of platelet-leukocyte aggregate formation in stored heparinized and acid-citrate-dextrose anti-coagulated blood as shown by the SFP apparatus (reproduced here with the permission of Biorheology).

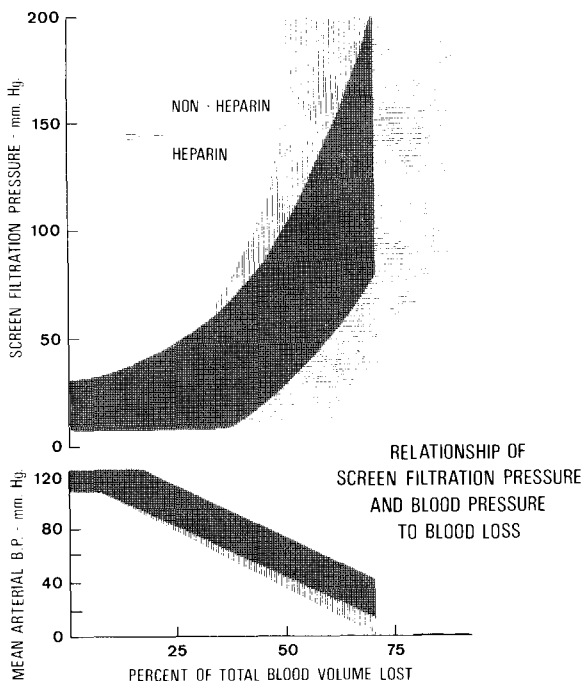


Figure 3 shows the relationship of SFP to mean blood pressure in dogs being exsanguinated. Total period of hemorrhage was 20 to 30 minutes (reproduced here with the permission of Biorheology).

To these two important factors are to be added trauma to the blood elements and activation of the platelets during use of the extracorporeal circulation, especially during open heart surgery. Coronary suction blood contains many microemboli of platelet-leukocyte and other origins¹², and also free hemoglobin from lysis of red cells. Unless removed, the emboli find their way into the oxygenated blood and re-enter the body of the patient. Another related, also ill-defined, cause of platelet leukocyte aggregation is the mixing within the oxygenator and also within the patient, of the donor and patient's blood traumatized by the extracorporeal circulation. These traumata activate the platelets and aggregation occurs when they come in contact with other platelets and leukocytes. Aggregates generated in this way can be numerous when no donor blood is included in the extracorporeal priming solution.

In the process of aggregate formation, the platelets lose about 30% of their negative electrical potential¹³ and become adhesive¹⁴. This loss of repulsion for one another and for other cells plus the adhesiveness are, no doubt, important physically in the genesis of the platelet-leukocyte aggregation. The chemical changes leading to these changes are unknown. It is known that in shock serotonin¹⁴, adrenalin, noradrenalin, and adenosine disphosphate are present in abnormally high concentrations. The fact that these same factors cause aggregation of platelets and leukocytes *in vitro* when added to blood in physiologic concentrations suggests the hypothesis that these biologic amines are important chemical factors in the phenomenon under consideration¹⁵.

II. SIZES AND NUMBER OF AGGREGATES AND THE EFFECTS OF FILTRATION

By light microscopy, most aggregates in human stored blood three weeks old are in the range of 10-40 μ in diameter. A few grow to be 100 μ and very few as large as 200 μ in diameter¹. When measured with the Coulter Counter, most emboli of this age are from 10 to 50 μ in diameter, a few as large as 164 μ in diameter⁹. Approximately 100 aggregates of all sizes are contained in 1 mm³ of blood, 90% of these less than 50 μ in size. This concentration of aggregates amounts to a total of 100,000,000 aggregates/liter of stored blood three weeks old. The numbers are not significantly less in two week old blood, but fewer have reached a size in excess of 50 μ in diameter.

Filtration of blood through a standard clot filter reduces slightly those emboli above 50 μ in diameter, but the total number remains essentially unchanged⁹. Filtration through the single layer 35 μ pore filter* eliminates the large emboli above 100 μ in diameter but increases slightly the number of emboli below 50 μ in diameter so that the total number of microemboli capable of occluding the microvasculature still remains unchanged (approximately 100,000,000/liter blood).

The Dacron wool filter** removes all the large aggregates and about 90% of all other aggregates including those 10 μ in diameter. This filter also removes microemboli smaller than 10 μ in diameter. This statement is based on the fact that smaller than 10 μ aggregates not detected by the Coulter Counter can be detected by the SFP technique. These are removed by the Dacron wool filters.

Two Dacron wool filters have been developed. One for the cardiotomy suction line in the extracorporeal circulation which is packed with Dacron wool 2 cm thick and

*Manufactured by Pall Corporation

**Manufactured by Pioneer Filters, Inc.

10 cm in diameter. This has a flow capacity of 5000 liters/min. The transfusion filter is smaller with a flow rate of from 80 to 300 ml/min depending upon the pressures applied to the bottle or bag of blood (Figure 4A & B).

Filtration of blood less than 24 hours old through Dacron wool reduces the platelet counts from 20 to about 40%. As the blood ages progressively more platelets are removed by simple filtration with Dacron wool¹⁶. The addition of 2 to 5 ug of adenosine diphosphate/ml to fresh blood activates (makes adhesive) the platelets for several minutes. If the blood is mixed and filtered through Dacron wool during this period, 90 to 95% of the platelets and up to 50% of the leukocytes can be removed¹⁵. Blood treated in this way has a very low resistance to flow in a capillary bed and the rate of perfusion in a partial veno-venous bypass can be significantly increased before swelling of the right heart and lungs occurs in the dog¹⁶. This method of preparing blood for priming the extracorporeal system has not been investigated in humans, although removal of platelets and leukocytes by centrifugation and washing the red cells in saline is employed by some cardiac surgeons.

The screen or pore-type filters are dependent on pore-size to remove aggregates and are otherwise non-selective. Examination of such filters with the scanning electron microscope¹⁹ revealed many pores occluded by aggregates and debris after filtration of a unit of blood (Figure 5). Because of the large size of the fiber strands woven together to form the screen, adsorption as a factor in removing aggregates would appear to be unimportant. As the pores become plugged and pressures up stream increase, the aggregated material, unless very tenacious, is extruded through the pores. Because of this "punch out" property (Figure 6), this type of filter leaks about 90% of the temporarily trapped aggregates which can then be caught in a Dacron wool filter (Figure 7). By this process of "leaking," the screen-type filter maintains low pressure and high flow rate.

Platelet-Leukocyte Emboli

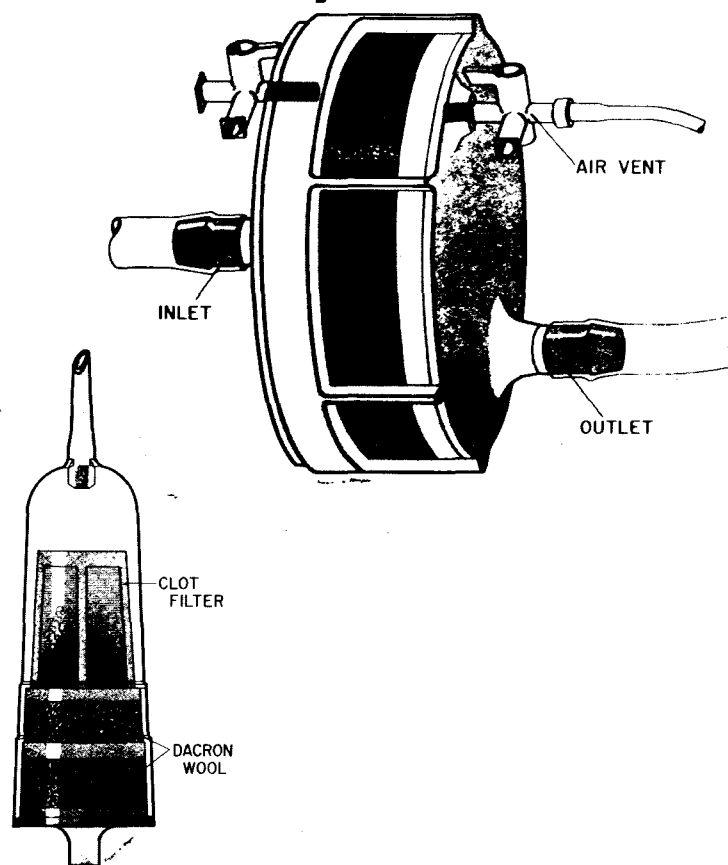


Figure 4 shows two Dacron wool filters. A is for continuous filtration in an extracorporeal system, and B is for transfusion.

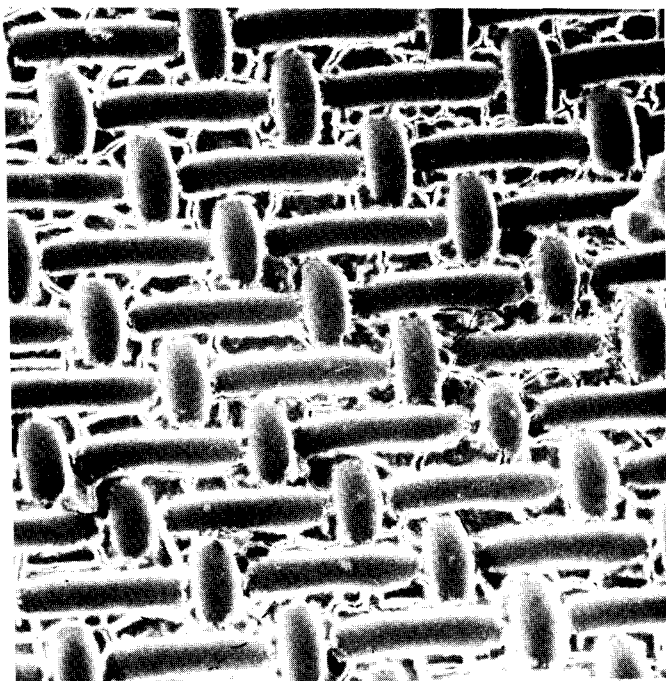


Figure 5 shows the 35 u pore filter (Pall filter*) with all pores occluded by platelet-leukocyte aggregates after passage of 250 ml of stored blood through the filter.

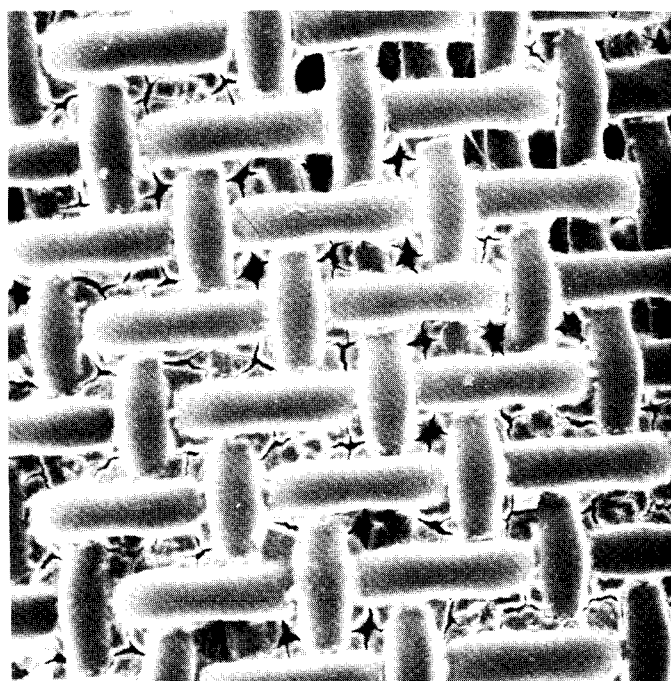


Figure 6 shows filter (same type as Figure 5) after passage of 500 ml blood. Many of the occlusive plugs of aggregate material have been extruded through the 35 u pores.

Platelet-Leukocyte Emboli

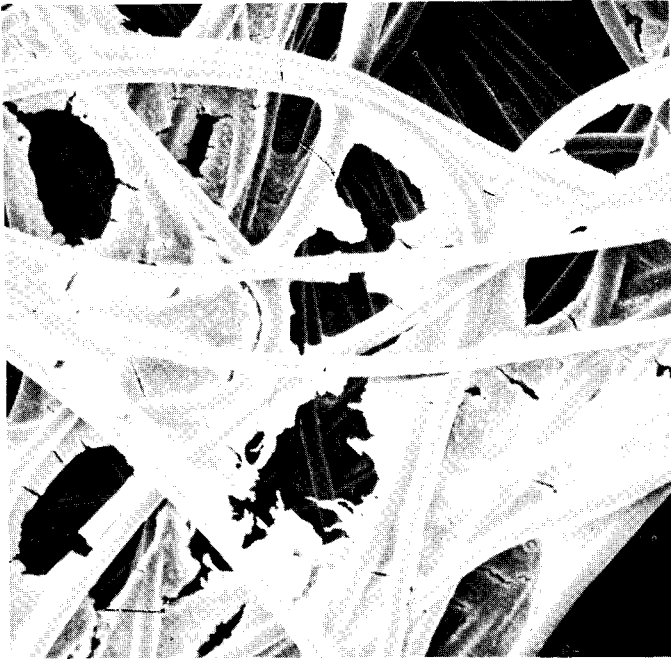


Figure 7 A Dacron wool filter (Figure 4A and B) was placed in line after the 35 μ filter shown in Figures 5 and 6. Note the collection of aggregates and debris in the Dacron wool which escaped from the 35 μ filter.

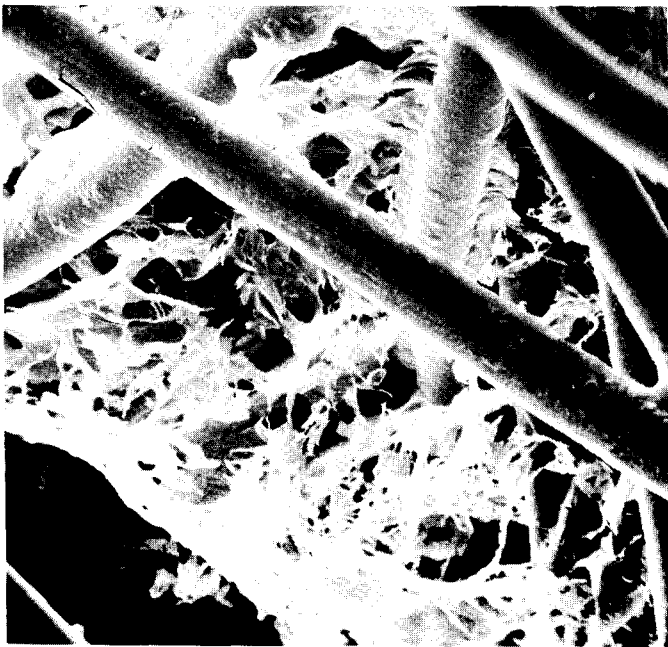


Figure 8 shows platelet-leukocyte aggregates and debris caught in the fibers of a Dacron wool filter (Figure 4A & B) after passage of 500 ml of stored blood. The filter was flushed with 500 ml of saline to wash out the red cells.

The Dacron wool filters consist of packed fine fibers to a depth of 2 cm in a plastic case. The pore size is variable but averages about 80 to 100 μ in diameter. The pores are irregular. Filtration is based **not** on pore size, but on adhesiveness of aggregates and debris for the small fibers. These materials adhere to the surface and/or encircle the fibers (Figure 8). They resist being washed away even when the filter is flushed with normal saline solution. Thus, aggregates much smaller than the pore size are removed if abnormally adhesive. Individual non-adhesive cells pass through the filter readily. Intact red cells are not retained in the filter.

III. PHYSIOLOGICAL EFFECTS OF MICROEMBOLISM IN PLATELET-LEUKOCYTE AGGREGATES

Many investigators have encountered a progressive increase in vascular resistance of isolated organs perfused artificially with donor blood²⁰. This has been attributed to vaso active substances as well as to particulate matter. Studies with the isolated cat head provided evidence that this increased resistance was due to aggregated blood cells, in particular platelets and leukocytes^{21 22}, and that filtration of the blood through Dacron wool prevented a rise in this pressure^{21 23 20}. In the latter studies, a normal E.E.G. could be recorded for several hours, whereas without filtration the electrical activity of the brain diminished and disappeared in a few minutes. More detailed studies²⁰ appear to have established the importance of filtration with glass or Dacron wool in perfusion studies. "Simplified blood" consisting of well-washed bovine red cells suspended in albumin-Ringer solution and defibrinated whole ox blood were used for perfusion. In addition to preventing an increase in vascular resistance, the filter also altered the metabolism of the brain. The average rate of CO₂ production by the brain during 1 hour from 4.4 to 6.3 ml/100 g brain per minute, the glucose content of the cortex at the end of the experiment rose from 10 \pm 1.5 mg/100 ml to 28 \pm 11.0 mg/ml and the lactate content of the cortex dropped from 135 \pm 7.9 mg/ml to 73 \pm 22 mg/100 ml when the filter was used.

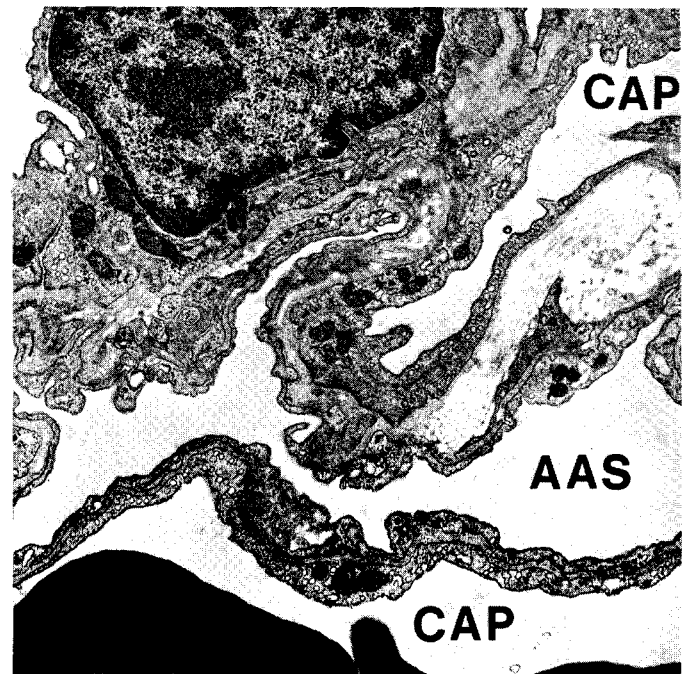


Figure 9 electronmicrograph of normal human lung showing intact capillary and alveolar lining cells. CAP, capillary, AAS, alveolar air space.

Additional studies in intact animals have shown that during hemorrhagic shock and as the result of transfusions of stored blood, pulmonary arterial pressure increased²⁴, and PCO₂ difference between alveolar air and arterial blood developed²⁵. Pulmonary vascular resistance as the result of transfusions has also been demonstrated to be increased²⁶. In humans in shock and after receiving multiple transfusions arterial PO₂ has been found markedly reduced²⁷. These evidences all point to pulmonary vascular occlusion, the cause of which appears, from light and electron microscopic studies described below, to be due to platelet-leukocyte aggregations. The increased vascular resistance during transfusion has been prevented by filtration of the blood through Dacron wool^{20 26}.

IV. PATHOLOGICAL EFFECTS OF PLATELET-LEUKOCYTE AGGREGATES

Platelet-leukocyte aggregates whether produced by blood storage, hemorrhagic or traumatic shock, or by ill-defined events in the extracorporeal circulation tend to produce identical pathological lesions^{28 29}. These consist first and principally of erosion of the endothelium of the microvasculature (Figure 9, 10, and 11). Next, the basement membrane and interstitial tissues feel the impact of the eroding effects. In the lungs, the alveolar epithelium is ruptured and red cells and plasma appear in the air sacs. The erosion of the endothelium occurs very quickly and varies in intensity with the number of aggregates. The erosion appears to be due to a combination of obstruction of the microvasculature by the aggregates which presumably is followed by a shift locally in the acid-base balance to the acid side. Disintegration of leukocytes takes place liberating lysosomes whose enzymes are probably principally responsible for the rapid erosion of the endothelium and surrounding tissues. Removal of these emboli from transfused blood by Dacron wool filtration (Figure 4B) prevents the pulmonary lesions in dogs.



Figure 10 human lung demonstrating a capillary obstructed by an aggregate of platelet-leukocyte material.

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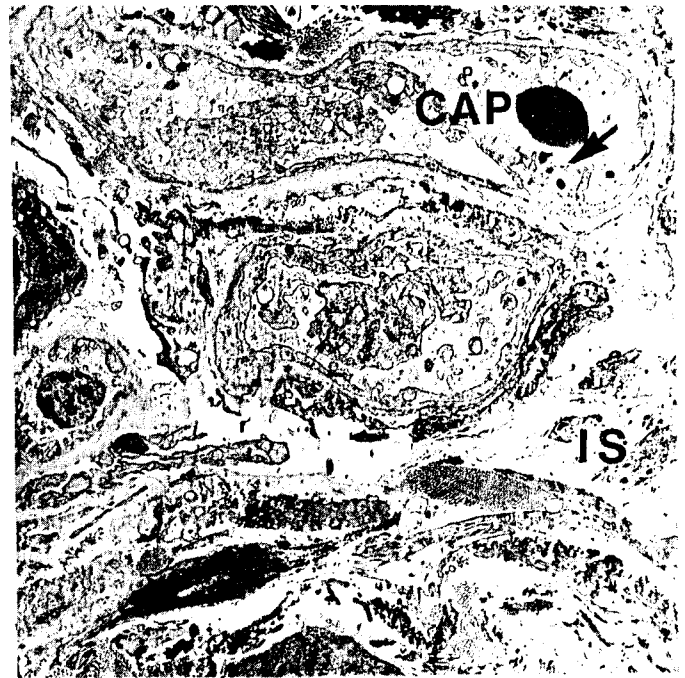


Figure 11 human lung one hour after cardio-pulmonary bypass. Note discontinuity of capillary endothelium at arrow and widespread perivascular edema. CAP, capillary, IS, interstitium.

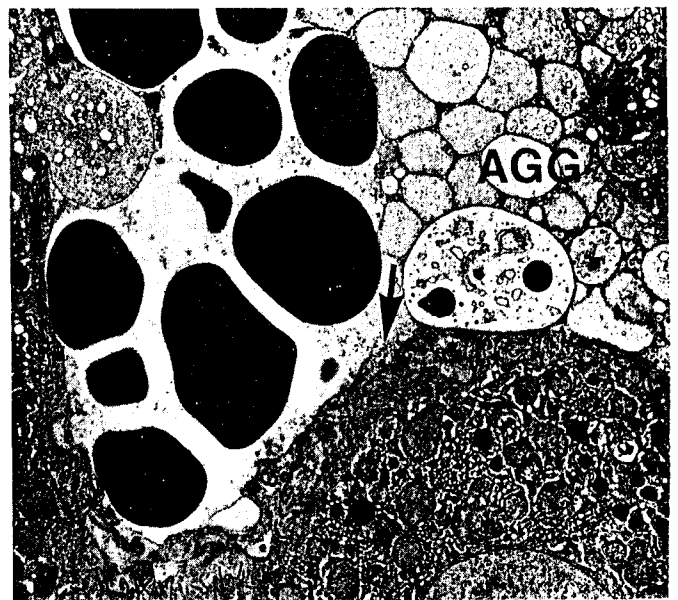


Figure 12 liver biopsy twenty minutes following transfusion of whole blood one week old through a standard clot filter. Note the aggregate (agg.) in the sinusoidal lumen and discontinuity in the endothelial lining at the arrow.

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“ . . . it seems not only reasonable but necessary that all adhesive emboli, regardless of size, be removed from the blood before perfusion into the body.

During shock, the first occlusive microemboli in the lung consist largely of platelets. In minutes, leukocytes are added making up the major bulk of the emboli. By the end of four hours, the platelets are diminished and soon almost absent, leaving leukocytes, many in the process of disintegration²⁸. If the platelets are first removed from the experimental dog by Dacron wool filtration in a partial veno-venous bypass, and then hypotensive shock is produced, these pulmonary lesions do not occur⁴.

It has been stated that the small emboli (those below 30 μ in diameter) are of no importance and do not cause pathophysiological lesions. Earlier studies have shown that severe lesions in the brain can be caused by paraffin spheres 4 to 12 μ in diameter¹⁸. It is also known that in stored blood from dogs, few aggregates become larger than 30 μ in diameter³⁰ yet major primary lesions in the lungs, and secondary ones in the brain, kidney and liver have been produced in the dog by transfusion of one week old blood¹⁷ (Figure 12). The emboli temporarily occlude blood vessels in the lungs, then clear the lungs to secondarily embolize other organs. It is clear that the small emboli can and do obstruct the microcirculation and produce well-defined pathological lesions. Because of the very large number, and the likelihood that they form nuclei to which other platelets and leukocytes adhere, it seems not only reasonable but necessary that all adhesive emboli, regardless of size, be removed from the blood before perfusion into the body. This is accomplished by filtration through a properly constructed Dacron wool filter (Figure 4B).

V. CLINICAL OBSERVATIONS RELATIVE TO MICROEMBOLIZATION

About 1960, many reports of neurologic and other complications following open heart surgery began to appear. In an attempt to evaluate the severity and frequency of neurologic complications, 10 patients who were to have double valve surgery were intensively studied clinically and by electroencephalography before and after surgery³¹. Each of these 10 patients developed focal neurological and psychiatric signs, and focal as well as generalized E.E.G. changes beginning 2 to 4 days after the operation. These abnormalities cleared in a few to 7 days (for a review of preceding literature, consult other papers^{31 32}). A similarly oriented study³² confirmed high frequency of neurological complications after open heart surgery.

Screen filtration pressure studies were performed in combat casualties in Vietnam²⁷. In minor injuries, the SFP values remained low in both venous and arterial blood. Seriously injured casualties exhibited a moderate but significant elevation of the arterial SFP. Patients in shock from this group exhibited even higher SFP values in the arterial blood. In venous blood, all SFP values are normal. In 10 seriously injured patients receiving high SFP bank blood, the SFP remained normal in the peripheral venous blood, and was double normal in central venous blood, and moderately elevated (less than in central venous blood) in the arterial blood. A reduction in PaO₂ was also observed in severely injured patients; a decrease from 80 in minor combat injuries in shocked cases after transfusion with more than 10 units of blood. Light microscopic studies revealed many pulmonary occlusions in patients who succumbed in a few days.

Because aggregates of platelets and leukocytes had previously been observed in the brains of patients who died after heart surgery³³, and similar emboli had been observed in the lungs and other organs postmortem^{35 35 27}, microembolization by platelet-leukocyte aggregates appeared to be a cause of the clinical symptoms mentioned above.



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The first clinical studies with Dacron wool filtration were reported from the Presbyterian Hospital of San Francisco using the continuous Dacron wool filter (Figure 4A) in the coronary suction line and for the donor blood during open heart surgery^{36, 37}. Several observations of importance were made. First post-operative confusion was markedly reduced, increases in hemolysis lessened, and the post-operative mortality reduced from about 20% to 6.5%. In the last study, there were 96 cases in which the filter was not used and 108 cases in which it was. Another comprehensive clinical study from Heidelberg¹² showed that the aggregate formation during surgery was very marked in suction blood and in unfiltered blood many of these aggregates reentered the body of the patient by the arterial line. When the suction blood was filtered, the aggregates were removed and the arterial blood remained free of aggregates. Post operatively, the patients whose blood was filtered suffered remarkably less prolonged unconsciousness and stupor than those in which the filter was not used (Table 1).

In another study of pulmonary changes in humans, the result of extracorporeal circulation^{38, 39}, pulmonary biopsies were studied before and 60 minutes after the end of bypass by electron microscopy. Severe and wide-spread pulmonary damage followed surgery in non-filtered cases. In these studies, the priming fluid contained two units of donor blood one day old. Platelet-leukocyte aggregates occluded the microcirculation and with the electron microscope, were easily identified post operatively. Perivascular edema and swollen and fragmented vascular endothelium and alveolar epithelium were widespread. Filtration through Dacron wool of both the coronary suction blood and of the donor blood added to the priming solution markedly improved the tissue fine structure. Very few aggregates were to be seen and the vascular endothelium and alveolar epithelium were intact. Perivascular edema was still evident but markedly reduced. When an additional Dacron filter was placed in the arterial line, the pulmonary fine structure appeared normal.

In this same group of patients, SGOT (serum glutamate oxalacetate transaminase) levels were determined daily in the patients post operatively³⁹. SGOT levels were very much higher in patients in which blood was not filtered than in those in which the suction and donor, or suction, donor and arterial blood were filtered through Dacron wool. These enzyme studies would appear to corroborate the pathology changes observed in these patients.

“When the suction blood was filtered, the aggregates were removed and the arterial blood remained free of aggregates.”

Table 1 shows post operative levels of consciousness in patients in which suction and donor blood was filtered or was not filtered¹².

TABLE I

| | Without Filter 59 cases | With Filter 97 cases |
|------------------|----------------------------|-------------------------|
| Mentally Clear | 20.2% | 72.2% |
| Light Somnolence | 10.5% | 12.4% |
| Deep Somnolence | 18.5% | 11.2% |
| Stupor | 20.3% | 2.1% |
| Comatose | 30.5% | 2.1% |

CONCLUSIONS

Storage of blood for future transfusion, hypotensive and traumatic shock, and use of an extracorporeal system are attended by increased adhesiveness and aggregation of platelets and leukocytes. The aggregates vary in size from less than 10 to about 160 u in diameter, the great majority being 32-50 u in diameter or less. These emboli, including the microemboli 32 u in diameter and smaller, occlude the microcirculation of various organs and cause physiologic and pathologic changes regardless of their origin. During transfusion, many microemboli traverse the lung microcirculation and secondarily embolize other organs of the body. Removal of the emboli by Dacron wool filtration alleviates the patho-physiologic damage which they cause, and markedly reduces the post operative confusion, stupor and unconsciousness following open heart surgery. Significant reductions in the mortality rate following open heart surgery have also resulted from use of Dacron wool filtration.

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