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THE UNEXPECTED: ITS SIGNIFICANCE IN BIOLOGICAL RESEARCH*

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We have all read scientific papers which failed to reveal how a certain line of work started, or what actually led to the crucial observations. As published, all seemed tidy and well planned. The confusion and obvious lack of planning was passed over, but even more important, the considerable gains realized from the unexpected were clouded.

It is now opportune to describe such a personal experience, one which concerns my part in the development of micro filtration of blood. I am stimulated to do this by a frequently asked question: How did a neurologist become immersed in a study of the physical state of the circulating blood? Neurologists have been traditionally interested in blood vessels and their pathology, but until very recent years they have, as a group, avoided interest in the fluid flowing through these vessels.

My serious interest in blood began early in 1949, as the result of several observations about the disease multiple sclerosis. First, many of the attacks or relapses of the disease were sudden or apoplectic in onset. Second, the lesions often closely resembled those produced in experimental animals by micro-embolic occlusion of the cerebral microcirculation with rigid spheres 12 to 16 u in diameter or smaller (1). These observations suggested a vascular participation in this disease. Later, we observed blood cell aggregation (2), and slowing of the circulation after large butter fat meals (3), accompanied by a reduction in available cerebral oxygen (4), and abnormalities of the EKG (5). Other related observations confirmed the belief that exploration in this field could be profitable.

Capillary tube viscosity studies in the early 1950's showed no significant differences in blood viscosity between normal subjects and patients with multiple sclerosis, except possibly that the viscosity was slightly lower in the patients (6). This focused our energy to develop a means of detecting micro particles in the blood. It seemed likely that these particles, if numerous, could not be larger than the 12 to 16 u solid spheres previously studied.

Late in the 1950's, metal screens with multiple, precisely sized, small pores, became available. Different pore sizes were tested, and those 20 x 20 u square were adopted, (7), (8) and (9). Normal fresh blood forced through such a screen at a steady rate generated a pressure before the screen which could be measured continuously in mms. Hg.

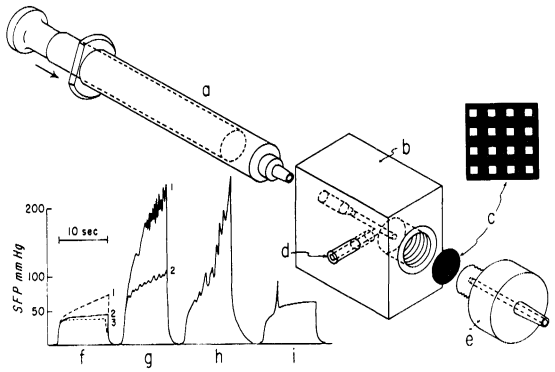

FIG. 1
Schematic of screen filtration pressure (SFP) apparatus. Diagram: (a) syringe with blood; (b) plastic block with 20 u pore screen; (c) pore screen held in place by (e); (f) shows normal SFP curves; (g) shows curve of hypotensive shock; (h) shows curve of

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stored blood; (i) shows effect of air bubble. Reproduced from "Series hemotologica," Vol. 1(2): 146-167. 1968.

There was a sharp rise in pressure related directly to hematocrit when the blood first contacted the screen, then a further slow increase during the ten second test, which slowly occluded the pores of the screen. The amount of occlusion varied, but even so the final screen filtration pressure (SFP) rarely exceeded 50 mm. Hg.

To test the reliability of our method, we needed a single large sample of blood appropriately anticoagulated. The obvious answer was the RED CROSS BLOOD BANK from where we obtained one unit of out-dated blood.

The first test resulted in a sudden and unexpected increase in SFP to 2000 mm. Hg. or more, and broke our strain gauge (7). We replaced the broken apparatus and tried one more sample. This time we were able to reverse the drive mechanism of the SFP machine early and prevent damage. It was apparent though that the second test confirmed the first, an increase in screen filtration pressure approximately 2000 mms. Hg. greater than we had observed in fresh blood samples.

Almost immediately, and for reasons not clearly thought out, I put a handful of pyrex glass wool in a funnel and poured about 100 cc. of the test blood through the wool. To our surprise, the filtered blood had a normal screen filtration pressure. It appeared that the aggregates had been removed from the blood, and upon examination they were clearly visible attached to the glass fibers. In the unfiltered blood, dark field illumination revealed clumps of platelets and polymorphonuclear leukocytes varying in size up to about 200 u in diameter. The great majority, however, were less than 25 u in diameter.

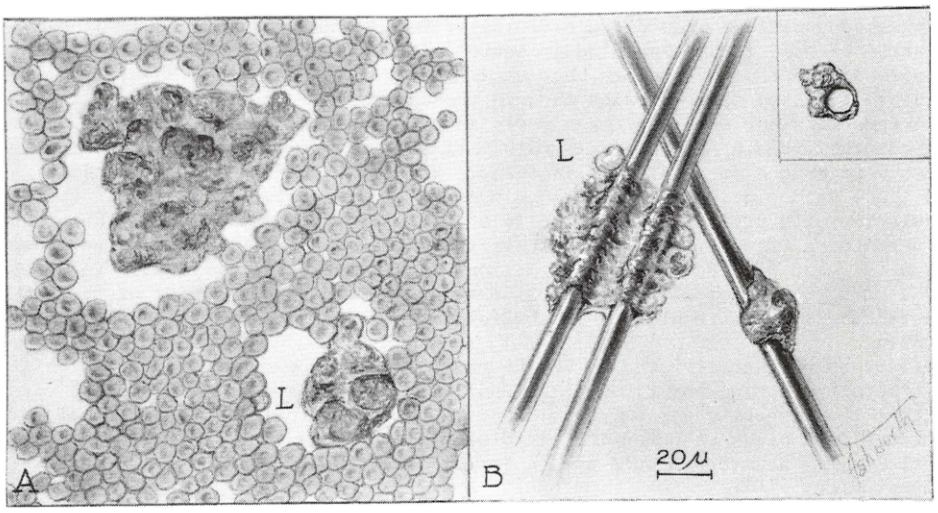

FIG. 2
"A" on left shows aggregates in wet blood smear. "B" on right shows glass fibers with aggregates attached. Reproduced from New England Journal of Medicine, Vol. 265: 728-733, 1961.

After examining about 50 samples of variously aged blood, anticoagulated by sodium citrate or heparin solution, I was convinced that something of practical importance had been observed, and work was begun which led to development of micro-emboli filters for transfusions.

Formation of Blood Element Aggregates During Blood Storage

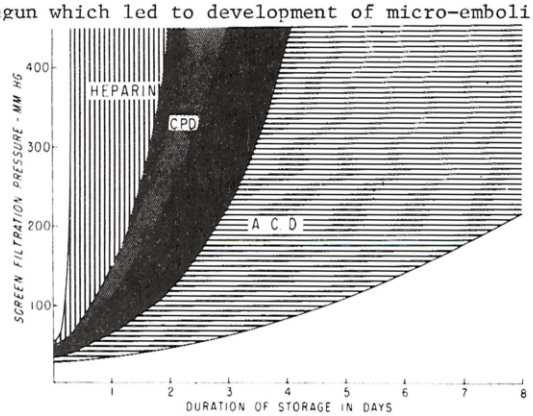

FIG. 3

Investigations soon were initiated to determine if aggregation of platelets and leukocytes might also occur in vivo as well as in vitro. In the next month, we did a series of bleeding shock, experiments in dogs (10) and (12). It was not totally surprising that as the blood pressure of the dogs fell the SFP increased from normal levels of 40-50 mm. Hg. to several hundred mm. Hg.

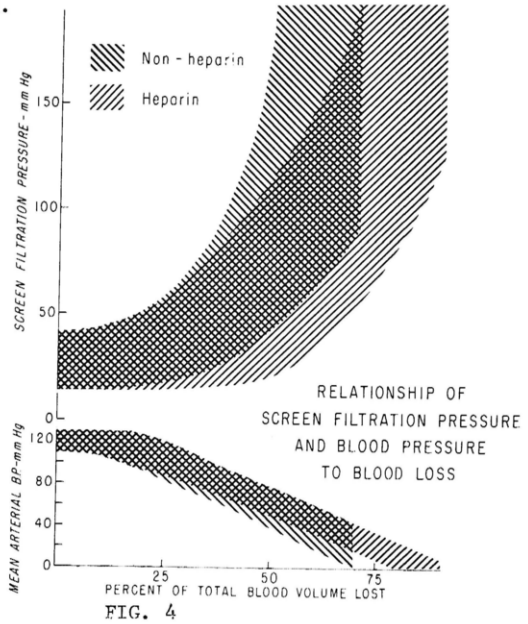

FIG. 4

Effect of falling blood pressure during exsanguination on the screen filtration pressure.
Reproduced from Circulation Research Vol. 14: 97-104, 1964

Small aggregates were observed in fresh blood smears with dark field illumination; filtration through glass wool returned the SFP to normal; and platelet leukocyte aggregates were revealed attached to the wool.

FIG. 5

Platelet-leukocyte aggregates attached to Dacron fibers 17 u in diameter.

This led to development of the cardio-vascular bypass filter for the suction line, and later for arterial line filtration.

On Sabbatical leave in Cologne, Germany, in 1961-1962, SFP examination, and filtration of blood circulating in an isolated cat head were studied at the laboratory-for normal and pathological physiology with Professor Hirsch (11), and Professor Isselhardt (12), with the support of the Director, Professor Schneider. These studies supported our growing belief that removal of these aggregates from blood would improve the micro circulation. On return to Portland, studies on surgical shock were continued with Professor Geoffrey Seaman (13) and (14), Doctor W. Hissen (13) and (14) and (17), Professor Sven Erik Bergentz (15), Professor Jack Fellman (16), Doctor Reid Connell (18) and (19) and (20) and Doctor Miles Edwards (21).

The original observations of aggregate formation in vitro and in vivo took about one to two months after the SFP machine became available. The demonstration of occlusion of pulmonary micro circulation and increased pulmonary artery pressure (17), and erosion of the vascular and perivascular tissues of lungs, kidneys and brains (18), (19) took longer.

By 1968, eight years after our first observations on aggregate formation, the testing of filters in patients was underway, and shortly thereafter filters for the suction line of an extra corporeal circulation for heart surgery were commercially available.

There remains one important aspect of this story yet to be told. It has no definite spot in the narrative, it hovered over us as a cloud through most of the developmental period.

Within a few months of our initial observations a patent was applied for. In 1963, when a preliminary design for a transfusion filter had been determined, I approached a major pharmaceutical house with the idea. License and option agreements were quickly reached. In the next two years experimental filters were built and tested, and finally clinical trails were started. The first tests of the transfusion filter were successful and created some enthusiasm. Because glass wool was difficult to handle, Dacron was substituted. This material had satisfied all requirements in the laboratory, but had to be thoroughly washed to rid it of a toxic surface active envelope. We had developed methods for this, but in the manufacture an important step was omitted. The next clinical tests were unsuccessful. A number of non-fatal toxic reactions developed. This experience frightened our big partner and all work was discontinued. In time we were able to free ourselves of the formal aggreements.

In the meantime, I realized that somehow we would have to prove our point without outside help. Cardiovascular surgery was fraught with serious brain, kidney and lung complications (22). I believed that this pathophysiologic damage was due to massive microembolism from the transfused blood and the surgical shock which patients suffered during the operation. We had shown that blood entering the body at the start of the bypass was "loaded" with aggregates, and upon leaving the body through the venous system, was virtually free of these micro emboli (23). I reasoned that the micro circulation of the body in the process of removing these particles from the blood, was becoming occluded. This caused ischemia and serious impairment of organ function.

A high volume, high capacity filter was needed, and one such filter was developed and tested in dogs in Doctor Albert Starr's experimental cardiovascular surgery laboratory. At about this time, Doctor John Osborn (24), who had been following our work, talked to me about such a filter for the suction line of the extra-corporeal system to be used at the Presbyterian Hospital in San Francisco by Doctor Donald Hill (25) on Doctor Gerbode's service. I supplied him with a pair of stainless steel cases which could be cleaned and repacked with Dacron for each operation. These worked well.

In the meantime, we fabricated a clean room using sheets of plastic, and air filters made of tightly packed Dacron. A wool washing technique for large volumes of wool was developed, and a distillation apparatus was purchased. All were installed in the basement of our home. Molds were purchased and plastic parts were extruded. When the original testing was completed, a disposable filter for the suction line of the extra-corporeal circuit was available.

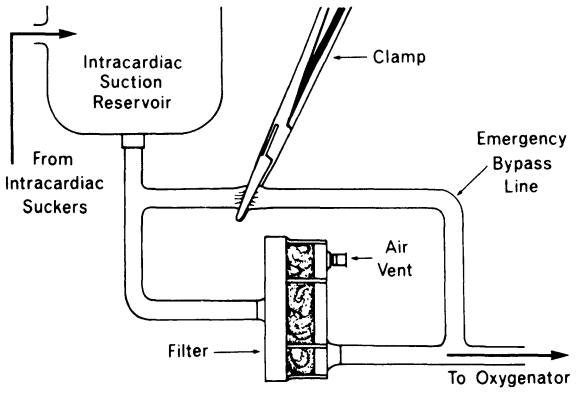

FIG. 6
Suction line filter in extra corporeal circuit d uring cardiovascular surgery. Reproduced from Journal of Thoracic and Cardiovascular Surgery. Vol. 60 (4): 575-581, 1970.

The success of this filter created an interest in the transfusion filter previously developed.

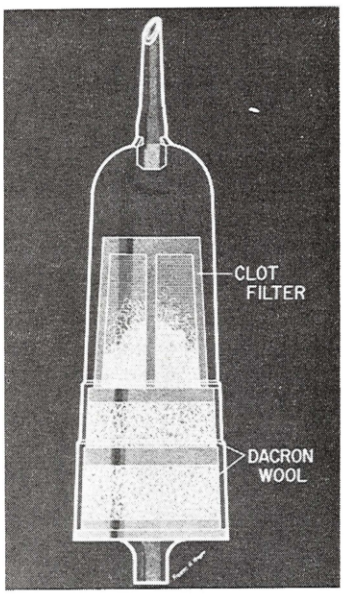

FIG. 7
Transfusion filter as originally introduced.

Later, a higher volume filter for the arterial line of the extra corporeal circuit was added.

Now, ten years later, there are a number of micro filters in clinical use. They vary somewhat in design. To some extent, they are surrounded by controversy primarily with regard to the desired convenience, capacity and efficiency. I believe, however, we can safely say that the improved understanding of micro emboli, and of methods for their removal are of substantial value in the prevention of tissue damage. As usual, the future is clouded, but it is reasonable to expect further developments and improvements. Possibly another unexpected observation will lead to development of other means for removing or neutralizing the damaging aggregates.

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