phistication of the clients and the value the seller or agent places on future business and reputation. The drawbacks of obtaining guidance and services from advisers whose interests diverge from those of the client are unfortunate but generally accepted, as long as there is full disclosure of the potential conflicts. Any such conflicts in GE's role should be known to the hospital, and GE surely recognizes that the success of its relationship with New York–Presbyterian and its ability to form other similar relationships depend on the hospital's continuing satisfaction with the arrangement.

If GE's quality- and process-improvement programs enable a hospital to make better use of its operating rooms, eliminate unnecessary duplication of tests, and shorten waiting times in clinics, the hospital and its patients benefit. But any consultant could also help a hospital's financial performance by pursuing strategies that do not benefit the public. Many academic hospitals could improve their bottom lines by cutting the amount of uncompensated care they provide and eliminating unprofitable services. They might also promote excessive use of high-margin services. For example, to the extent that physicians induce demand, any hospital that owns a scanner — and any physician who earns fees by interpreting scans — can raise revenues by performing scans for less critical or even dubious indications. Similarly, well-reported phenomena such as "DRG creep," "upcoding," and "unbundling" can increase health care expenditures without benefiting patients. Such practices may seem innocuous from the individual patient's point of view, if they merely raise health expenditures generally. But a physician or hospital that takes advantage of reimbursement anomalies can also jeopardize patients' health. Physicians and hospitals can be reimbursed more if a candidate for the placement of multiple coronary stents has the procedure divided among two or more hospital admissions than if they are placed as part of a single complex procedure. Is it plausible that clinical needs alone explain why so many patients have stents placed as part of multiple admissions?

No institution with a reputation to preserve — whether for-profit or nonprofit, medical center or consulting firm — can risk encouraging or engaging in any practice that might be construed as fraudulent or unethical. Nevertheless, one cannot presume that what is good for the hospital and the consultant is good for society. Does this imply that a successful partnership between GE Medical Systems and New York–Presbyterian Hospital will not serve the public interest and that such arrangements should be discouraged? I believe that would be the wrong conclusion. The problem is not that GE Medical and its competitors are seeking to make hospitals more efficient. The problem is that hospitals are not always rewarded for providing care that is both of the highest quality and appropriate. The task of GE Medical is to help the hospital respond to the incentives it faces. The responsibility of those of us who are concerned about the future of health care is to make sure that the incentives they face are the right ones. It is a responsibility that we cannot delegate.

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Cardiopulmonary Bypass after 50 Years

L. Henry Edmunds, M.D.

Related article, page 1635

A little more than 50 years ago, a hole inside a human heart was closed, with a machine maintaining life while the surgery was done. Within the next two years, four of eight children survived repair of complicated congenital heart defects in operations involving a similar machine. The heart–lung machine, as it was called, was invented and developed by John and Mary Gibbon (see Figure 1). Simultaneously, Forssmann, Cournand, and Richards developed cardiac catheterization that permitted anatomical and physiological diagnoses of heart disease during life. With the discovery and commercial production of the anticoagulant heparin, these two innovations spawned the modern surgical

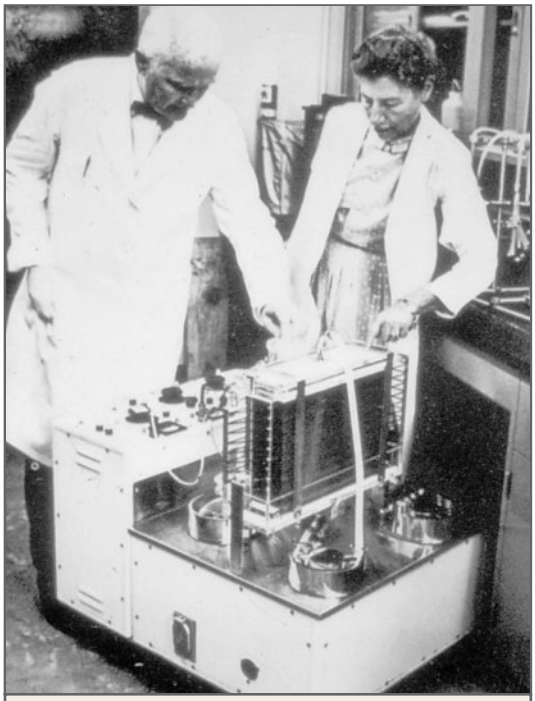

Figure 1. John and Mary Gibbon with the First Heart–Lung Machine.

Courtesy of TJU Archives at Scott Memorial Library, Philadelphia.

treatment of cardiovascular disease and launched a worldwide cardiovascular medical–industrial consortium. During the next 50 years, treatment of heart disease contributed to a 12.9 percent increase in life expectancy in the United States[1] and trillions of dollars of economic benefits. Still, cardiovascular disease is the primary or a contributing cause of 60 percent of all deaths in this country — albeit later in life than before.[2]

The early years were difficult; cardiac surgery was effective but not safe. Desperate patients clamored for help, but essential knowledge was vague or fragmentary or simply did not exist. Cardiovascular physiology, pathophysiology, biochemistry, pathology, pharmacology, and imaging were unborn or infant disciplines. Surgeons needed to learn pathological anatomy and physiology; how to expose, stop, start, incise, sew, and repair the heart; how to protect the heart during the process; and how to monitor and care for the patient afterward. The heart–lung machine was integral to this effort but, despite improvements, was among the major culprits causing suboptimal results. It was not until 1960 that doctors began to understand how the machine itself made patients sick.

Blood is the only tissue that comes into contact with both the patient and the machine, but normally blood does not exit the body and touches only endothelial cells. A monolayer of these special cells lines the entire cardiovascular system, which has an estimated surface area of more than 1000 m^2. Endothelial cells maintain both the fluidity of blood and the integrity of blood vessels by maintaining equilibrium between fluid and gel forms. When blood touches any other surface, such as the surgical wound or the heart–lung machine, both clotting and an inflammatory response are triggered. The thrombotic (clotting) response is attenuated by heparin, but heparin does not completely prevent clotting or the activation of complement, neutrophils, and monocytes, which are the principal mediators of the inflammatory response. This response produces a wide range of cytotoxins, cell-signaling proteins, and vasoactive substances that circulate and disrupt interstitial fluid balance and homeostasis. Both the thrombotic and inflammatory responses produce thousands of microembolic particles (measuring <500 μm) consisting of fibrin fragments, fat, platelet aggregates, and other particulate matter derived from or introduced into circulating blood. Microparticles obstruct arterioles that supply small nests of cells throughout the body and, together with cytotoxins, damage organs and tissues and temporarily disturb organ function.

Recovery is complete for most patients after use of the heart–lung machine, but subtle neurocognitive defects or worsened kidney function persist in a few. "Off-pump" myocardial revascularization is currently a popular method of avoiding the unwanted consequences of the heart–lung machine, but off-pump surgery is limited to operations on the surface of the heart.

Many factors affect the intensity of the thrombotic and inflammatory responses. The intensity varies depending on the biomaterials used (nontoxic plastics or metals), but even the most thromboresistant biomaterials initiate clotting (see Figure 2). The patient's age and coexisting diseases; the areal size of the synthetic surface; specific biomaterial; and the volume, rheology, and flow rate of the interfacing blood are major variables affecting the intensity of the response. For example, bioprosthetic

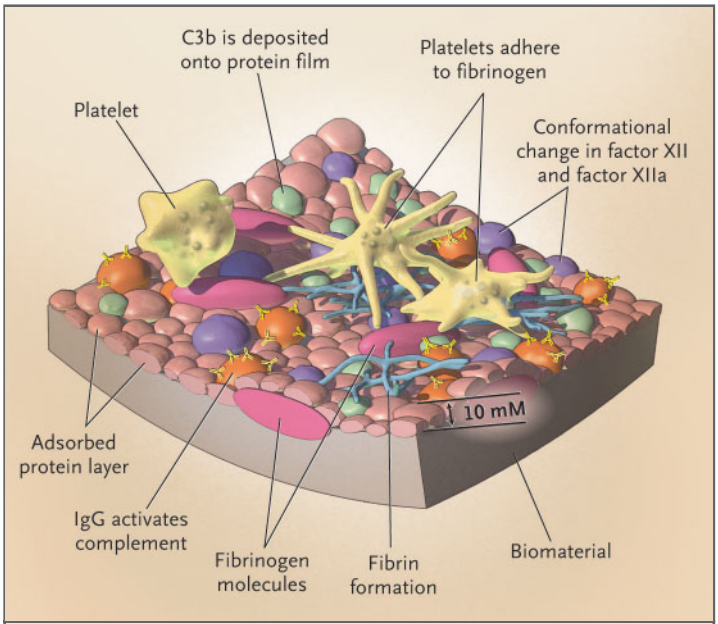

Figure 2. Initial Interactions between Plasma Proteins and Biomaterials.

When heparinized blood contacts a biomaterial surface, plasma proteins are instantly adsorbed onto the surface to form a dense, very thin, covering film that varies for different biomaterials and for differing mixtures of plasma proteins. Some adsorbed proteins, including coagulation factor XII, undergo conformational changes to expose reactive domains to circulating blood elements; thus, formation of thrombin and fibrin is initiated through the intrinsic coagulation pathway. Adsorbed IgG triggers complement activation, which is immediately amplified by the alternative pathway. Large amounts of C3b are generated and deposited on the adsorbed protein layer to catalyze activation of downstream complement proteins. During initial contact, fibrinogen is selectively adsorbed onto many biomaterials and expresses reactive sites on α and γ chains that bind platelet αIIbβ3. Thus, within one to two minutes, biomaterials initiate powerful thrombotic and inflammatory responses in blood.

heart valves present small, relatively thromboresistant surfaces and interface with large volumes of rapidly flowing blood. These valves trigger a weak clotting stimulus, but normal levels of anticoagulant proteins and enzymes are sufficient to prevent clots and circulating emboli. In contrast, the heart–lung machine, with a large biomaterial surface area (2 to 3 m^2), imperfect rheology, and exposure of blood to the surgical wound, produces a massive thrombotic and inflammatory stimulus, and perfusion is not possible without large doses of heparin or another anticoagulant.

The thrombotic and inflammatory responses can be suppressed for short periods through the manipulation of the biochemical and hematologic characteristics of blood. However, suppression confers risks of bleeding and infectious complications, and this strategy cannot be sustained indefinitely. Complete suppression of thrombin generation by new and better anticoagulants and the administration of specific inhibitors of complement, neutrophil, and monocyte activation, which are in the early or middle stages of development, will eventually prevent or reduce complications caused by contact between blood and the biomaterial surface during short-term applications of extracorporeal perfusion. Incremental improvements, such as those described by Mou and colleagues in this issue of the *Journal* (pages 1635–1644), and more compatible biomaterials or surface coatings will also contribute — a mite at a time.

Achieving control of the blood–surface interface without altering the composition of blood, however, is prerequisite for realizing the extraordinary and exciting possibilities introduced by the invention of the heart–lung machine. A surface that is truly nonthrombogenic, which consists of or is similar to a monolayer of endothelial cells, opens the door to the development of intracorporeal devices that can replace diseased parts of the cardiovascular system or that can process blood as done by the lung, liver, and kidney.

Two different approaches are currently being pursued toward this objective. One is to develop biomaterials and biomaterial surfaces that modify the adsorption of blood proteins so that clotting is not initiated, complement is not activated, and platelets, neutrophils, and monocytes do not adhere or express surface receptors. This approach also includes efforts to develop biomaterials that elude chemical anticoagulants, such as nitric oxide, that can be derived from blood precursors. The second approach, often termed "tissue engineering," envisions fabricating biomaterial or tissue scaffolds that can be seeded and covered with the patient's own endothelial cells outside the body. Once the monolayer envelops the scaffold, the new organ is surgically connected to the cardiovascular system.

Multidisciplinary teams scattered around the world are vigorously pursuing the dream of creating artificial internal organs. The obstacles are daunting but not insurmountable. Meanwhile, progress in controlling and treating cardiovascular disease continues at breakneck speed and involves legions of scientists, engineers, health care professionals, businesspeople, administrators, and count-

less others. The cardiovascular medical–industrial consortium remains healthy and is still growing rapidly. And it all began in February 1931, because a junior surgical fellow wondered how to save a young woman who was dying from a blood clot in her pulmonary artery.[3]

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