

# Endothelium as an organ system

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The endothelium is a highly dynamic cell layer that is involved in a multitude of physiologic functions, including the control of vasomotor tone, the trafficking of cells and nutrients, the maintenance of blood fluidity, and the growth of new blood vessels. Over the past several decades, advances in basic research of the endothelium have far outstripped those in the clinic. One explanation for this growing bench-to-bedside chasm relates to the inflexible and largely outdated nature of the present-day medical infrastructure. The constraints of medical subspecialization have

created a conceptual blind spot, namely, the inability to appreciate the endothelium for what it is: a cell layer that is teeming with life, every bit as active as any other organ in the body. The overall goal of this review is to bring the endothelium “to life” and to argue that future breakthroughs in biomedicine are contingent on acceptance of the endothelium as a *bona fide* organ system. (Crit Care Med 2004; 32[Suppl.]:S271–S279)

KEY WORDS: endothelial cells; endothelium; organ

## Acknowledging the Bench-to-Bedside Gap

The endothelium, which lines the blood vessels of the vascular tree, is a truly pervasive cell layer, weighing 1 kg and covering a total surface area of 4000–7000 m<sup>2</sup> (1). Endothelial cells from a single human, when lined end-to-end, would wrap more than four times around the circumference of the earth. The endothelium is not inert; it is highly active, participating in several physiologic processes, including the control of vasomotor tone, the trafficking of cells and nutrients, the maintenance of blood fluidity, and the growth of new blood vessels (2).

According to the *American Heritage Dictionary*, an organ is defined as “a differentiated part of an organism, such as an eye, wing, or leaf, that performs a specific function.” The *Webster’s Revised Unabridged Dictionary* defines an organ as a “natural part or structure in an animal or a plant, capable of performing some special action (termed its function),

which is essential to the life or well-being of the whole.” Based on these definitions, the endothelium surely qualifies as an organ. However, that is not to say that the endothelium is widely accepted or recognized as an organ system. Indeed, the terms “endothelial cells” and “endothelium” are conspicuously absent from the 64-page July 2003 index of *Scientific American Medicine*. In the 15th edition of *Harrison’s Principles of Internal Medicine*, the index refers only to “endothelial injury, in sclerosis” and “endothelial cell(s), interactions with lymphocytes; vascular proliferation” (3)—phrases that capture an infinitesimal cross-section of the field.

There are no national or international societies for the study of the endothelium. As physicians, few of us are attuned to the health of this cell layer as we interview and examine our patients. Diarrhea, syncope, or jaundice equivalents do not presently exist for the organ. There is no “endothelial box” to circle or check off as we move through the review of systems. Moreover, the endothelium is not amenable to the traditional maneuvers of inspection, palpation, percussion, and auscultation—nor, for that matter, to standard diagnostic interrogation.

Despite this, there has been an explosion of interest in the field of endothelial cell biology. A recent PubMed search using the keywords “endothelium” and “endothelial cells” netted a total of approximately 70,000–80,000 articles. These numbers reflect the enormous expenditure of resources, in the way of research

dollars and investigator time and effort. Moreover, the data have unquestionably advanced our understanding of the basic properties of the endothelium. Why, then, is there such a disconnect between bench and bedside? Why does the endothelium continue to fly well under the clinical radar screen? How can a better understanding of the role that the endothelium plays in pathophysiology improve evidence-based medicine? These questions will be addressed in the sections that follow.

## Explaining the Bench-to-Bedside Gap

The tendency to overlook the endothelium in clinical practice is explained in part by the hidden and enigmatic nature of this cell layer. The endothelium rarely shows its hand, at least in the classic ways that we, as physicians, are trained to detect. Like the hematologic system, the endothelium is highly diffuse, extending to all reaches of the human body. Yet, unlike blood cells, the endothelial lining is tethered to the blood vessel wall and therefore inaccessible and poorly amenable to study. Although assays do exist for circulating markers of “activated” endothelium, these are indirect measures of endothelial function and provide little in the way of useful information. Pathologic specimens of the endothelium are not routinely available, and even if they were, the findings would not necessarily correlate with function.

A second reason for the under-appreciation of the endothelium relates to his-

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torical legacies and infrastructural barriers. Traditionally, vascular biology (and by extension, endothelial cell biology) has been linked to the field of cardiology. The connection is steeped in history, its roots dating back to William Harvey's elucidation of the circulatory system in the early 1600s. After Harvey's seminal work, the prevailing view of the cardiovascular system was that of a closed circulatory loop consisting of a pump and series of conduit vessels, with the singular role of delivering oxygen and nutrients to the various tissues of the body. During the next 400 yrs, clinical and basic research focused largely on the pump: namely, the coronary arteries, the contractile appara-

tus, the conduction system, and the conduit vessels in so far as they affected the heart itself (e.g., in hypertension). These developments contributed to and were reinforced by the founding of a large clinical discipline (cardiology), a powerful societal infrastructure (the American Heart Association), successful public awareness campaigns, generous private and public funding, and enormous progress in research and development. The importance of these milestones cannot be overestimated. They have provided an invaluable platform for advances in endothelial cell biology and have led to improved detection, prevention, and treatment of vascular diseases.

During the past 40 yrs, however, two seminal observations have dramatically altered the way we think about the endothelium, and, when taken together, these make the case for a more complete synthesis of the field. First was the recognition that the endothelium is not an inert barrier but rather a highly active cell layer that is involved in a wide variety of homeostatic processes. The second important observation was that the endothelium, in traversing each and every organ, establishes a dialogue that is unique to the underlying tissue—in effect, marching to the tune of the local micro-environment. The endothelial-tissue interface plays an important role not only in maintaining the health of an organism, but also in dictating the focal nature of vascular disease states. Viewed from this perspective, the endothelium transcends all clinical disciplines. Although one would have been hard pressed 20 yrs ago to identify more than a handful of diseases in which the endothelium played a prominent role, today it may be argued that virtually every disease involves the endothelium, either as a primary determinant of disease or as a victim of collateral damage (Table 1).

These developments have created a quandary of sorts. On one hand, we are standing at the cusp of a golden age in vascular biology that should see a synthesis of the field of endothelial biomedicine and the recognition of the endothelium as a clinically relevant organ system. On the other hand, the existing infrastructure in medicine is poorly qualified to usher the field into the 21st century. In the sections that follow, I will briefly summarize the important themes in endothelial cell biology and underscore the importance of bridging the bench-to-bedside gap in this field.

### Primer on Endothelial Cell Biology

Although there are no fewer than 80,000 published articles on endothelial cells, certain important themes emerge (Table 2). First, the endothelium is not inert but rather is metabolically active. Second, the endothelium is analogous to an input–output device, sensing changes in the extracellular compartment and responding in ways that are beneficial or, at times, harmful to the host. Third, endothelial cell phenotypes vary in space and time, giving rise to a phenomenon termed endothelial cell heterogeneity or

Table 1. List of diseases involving the endothelium

Disease	Selected References	No. of Cross-References of the Disease Term with the Terms Endothelium/Endothelial Cells <sup>a</sup>
Hematology–oncology		
Cancer	(34, 35)	6133/9487
Hemoglobinopathies		
Sickle cell disease	(36–39)	237/157
Thalassemia	(40, 41)	29/35
Hemachromatosis	(42)	
Myeloproliferative diseases	(43, 44)	68/73
Bone marrow transplantation	(45, 46)	169/189
Transfusion medicine	(47–50)	282/297
TTP/HUS	(51, 52)	125/100
Coagulation	(7, 53)	2622/2016
Infectious disease		
Infection	(54–56)	2820/3141
Sepsis	(33, 57)	891/741
Cardiology		
Atherosclerosis	(58–63)	7318/3727
Congestive heart failure	(64–67)	570/228
Valvular heart disease	(68, 69)	158/82
Pulmonary		
Asthma	(70, 71)	251/285
COPD	(72, 73)	55/39
Pulmonary hypertension	(74–76)	771/397
ARDS	(4, 77)	182/159
Nephrology		
Acute renal failure	(78–80)	139/125
Chronic renal failure	(81–83)	269/152
Gastroenterology		
Peptic ulcer disease	(84, 85)	64/74
Inflammatory bowel disease	(86, 87)	147/162
Hepatitis	(88, 89)	197/315
Cirrhosis	(90, 91)	389/461
Pancreatitis	(92, 93)	85/92
Rheumatology		
Rheumatoid arthritis	(94–96)	436/600
Scleroderma	(97–99)	250/204
Endocrinology		
Diabetes	(100, 101)	2900/1693
Neurology		
Stroke	(102–104)	824/469
Multiple sclerosis	(105, 106)	186/207
Other		
Preeclampsia	(107, 108)	437/327

TTP, thrombotic thrombocytopenic purpura; HUS, hemolytic-uremic syndrome; COPD, chronic obstructive pulmonary disease; ARDS, adult respiratory distress syndrome.

<sup>a</sup>Based on a PubMed search done on August 30, 2003.

Table 2. Important themes in endothelial cell biology

1	The endothelium is metabolically active
2	The endothelium is an input–output device
3	Endothelial phenotypes vary in space and time
4	The endothelium displays emergent properties

vascular diversity. Fourth, the endothelium displays nonlinear dynamics and emergent properties and therefore can be fully understood only in the context of the whole organism. Each of these themes is briefly discussed below.

**Endothelium Is Not Inert.** Until the first half of the last century, the endothelium, when viewed through the lens of low-resolution microscopy, was considered to be little more than an inert layer of nucleated cellophane. However, the notion that the endothelium is an inert barrier has long since given way to more realistic views of the cell layer as a highly metabolically active organ.

**Endothelium Is an Input–Output Device.** Each endothelial cell may be viewed as an input–output device (Fig. 1). This model surely is not unique to the endothelium. Nevertheless, it helps to explain virtually every aspect of endothelial cell function in health and disease. Input arises from the extracellular environment and may include soluble mediators, cell–cell interactions, oxygenation, hemodynamic forces, temperature, or pH. The output is manifested as the cellular phenotype and may include any number of responses, including alterations in vasomotor tone, permeability, hemostatic balance, cell survival, cell proliferation, and inflammation. The intrinsic properties of the endothelial cell—the so-called set point—whether genetically predetermined or environmentally programmed, serve to channel and filter the information flow, linking input with output in ways that differ from one endothelial cell to another. All three elements (input, output, and set point) depend on time and location within the vascular tree (see next theme).

**Endothelial Cell Phenotypes Vary in Space and Time.** Perhaps more so than other tissues (the brain being an exception), endothelial cell phenotypes vary in both space and time. Endothelial cells display marked heterogeneity in structure and function. For further details, the

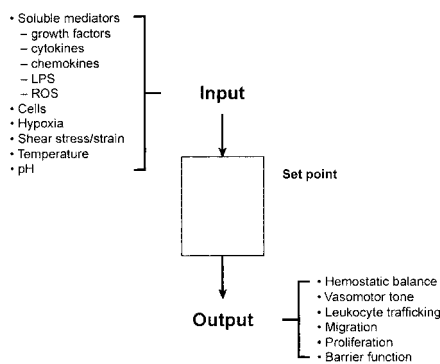


Figure 1. Endothelium as an input–output device. *Input* arises from the extracellular environment; *output* is manifested as the cellular phenotype; the *set point* represents the intrinsic properties of the endothelial cell. *LPS*, lipopolysaccharide; *ROS*, reactive oxygen species.

reader is referred to a number of recent reviews (2, 4–6). In taking creative license, I have previously drawn an analogy between the endothelium and a complex circuit board that is hardwired (to a point) to meet the demands of the underlying tissue and that is highly vulnerable to short-circuiting as a result of focal vasculopathic disease states (7). To carry the computer analogy one step further, one might envision the blood vessels as the hardware of the system and the endothelium as the software.

**Emergent Properties.** Although some properties of the endothelium are evident at the level of the individual cell, others are only expressed at higher orders of organization (6). Indeed, the more one moves through the hierarchy of organization, from single cell to blood vessel to organ to organism, the more one appreciates the emergence of new properties—the *sine qua non* of nonlinear systems. As endothelial cell biologists, our comfort zone (if not intellectually, then at least from a publication and funding standpoint) lies at the reductionist end of the spectrum. An important challenge for vascular biologists is to learn how to leverage the strengths that are inherent in each level of study for diagnostic and therapeutic gain.

### Endothelial Cells in Disease

Many terms have been used to describe the endothelium in disease, including activation, dysfunction, damage, injury, necrosis, derangement, and denudation (Table 3). Of these descriptors, endothelial cell activation and endothelial cell dysfunction are perhaps the most

commonly used and misused. Both terms are clarified below.

**Endothelial Cell Activation.** The term “activation” all too often implies a binary state: either off or on. According to this toggle hypothesis, quiescent endothelial cells express an anticoagulant, anti-adhesive, and vasodilatory phenotype, whereas activated endothelial cells express procoagulant, pro-adhesive, and vasoconstricting properties. However, the notion that endothelial cell activation is an all-or-nothing phenomenon is a gross oversimplification. Several important qualifications are in order.

For one, endothelial cells follow a spectrum of response and are thus more analog than they are digital in their behavior. This point is readily demonstrated in any number of published dose–response studies, in which the addition of a soluble mediator to endothelial cells results in concentration-dependent changes in cellular phenotype, whether at the level of protein or messenger RNA expression or of cell function.

Second, what constitutes activation for one cell type at a particular point in time may not meet the definition of activation at another site or moment in time. Consider, for example, the natural anticoagulant thrombomodulin (TM). Cell culture studies would have us believe that TM is down-regulated in activated endothelial cells, leading to reduced activation of protein C and hence increased thrombin generation (8–10). Faust et al. (11) demonstrated that in skin biopsies from patients with meningococemia, TM expression was reduced in the endothelial lining of dermal blood microvessels, providing convincing support for this phenomenon *in vivo*. However, if we step back and survey the distribution of TM under normal conditions, we learn that, to begin with, TM is not even expressed in the human brain (12). According to the toggle hypothesis, these findings would suggest that the blood–brain barrier is in a perpetual state of activation. This, of course, is not the case. Rather, the findings indicate that local hemostasis in the brain is balanced by natural anticoagulant mechanisms other than TM. More importantly, the observations emphasize the importance of interpreting endothelial cell activation in an appropriate context.

Third, not all inflammatory mediators are created equal. For example, in DNA microarray experiments, treatment of human umbilical vein endothelial cells with tumor necrosis factor- $\alpha$  and inter-

Table 3. Endothelium descriptors in disease

Descriptor	Synonyms	Definition	Phenotypes	Caveats
Endothelial cell activation		Time- and site-averaged phenotype of endothelial cells exposed to an inflammatory stimulus (some investigators might include other stimuli, e.g., angiogenic).	Typically consists of some combination of procoagulant, proadhesive, proliferative, vasoconstricting, vasodilating, or increased cell permeability properties	<ol style="list-style-type: none"> <li>1. What constitutes activation in one site or moment in time may not meet definition for activation at another site or point in time—hence the term time- and site-averaged</li> <li>2. Activation may occur locally or systemically</li> <li>3. Activation may be adaptive (functional) or nonadaptive (dysfunctional)</li> <li>4. Normal, healthy endothelium is highly active</li> </ol>
Structural loss of integrity	Endothelial cell damage, injury, or derangement	A breach in structure, which may be associated with dysfunction or activation	Cellular contraction, increased length of cellular projections, cellular swelling; bleb formation; vacuolation, perinuclear lucency, loss of pinocytotic vesicles, nuclear chromatin clumping, apoptosis, desquamation (sloughing, detachment, denudation); cytolysis, necrosis	Definition of structural integrity is site- and time-dependent
Functional loss of integrity—endothelial cell dysfunction	Endothelial cell damage, injury, or derangement	A breach in behavior that represents a net liability to the organism		Dysfunction is in the eye of the beholder

leukin-1 $\beta$  results in overlapping but non-identical patterns of gene expression (13). We have shown that thrombin, but not tumor necrosis factor- $\alpha$  or lipopolysaccharide, induces platelet-derived growth factor-A expression in several different types of primary human endothelial cells (S. Wu, W. C. Aird, unpublished observations). Inhibitors of mitogen-activated protein kinase p38 completely abrogate thrombin-induced, but not tumor necrosis factor- $\alpha$ -induced, leukocyte recruitment in human umbilical vein endothelial cells (14). As a final example, treatment of human umbilical vein endothelial cells with tumor necrosis factor- $\alpha$ , but not lipopolysaccharide, results in a biphasic change in protease-activated receptor-1 messenger RNA levels, with an initial decrease and a subsequent rebound above baseline (15). Taken together, these observations suggest that although inflammatory mediators induce overlapping changes in endothelial phenotypes, each mediator engages the endothelium in its own unique way.

Fourth, the very term activation implies that normal endothelium is by de-

fault inactive. Nothing could be further from the truth. The intact endothelium constantly senses and responds to changes in the local extracellular environment, such as might occur in the setting of transient bacteremia, minor trauma, and other common daily stresses, most of which we are not even consciously aware of. In other words, endothelial cell activation is not an all-or-none response nor is it necessarily linked to disease. Instead, endothelial cell activation represents a spectrum of response and occurs under both physiologic and pathophysiologic conditions.

Finally, in approaching endothelial cell activation, the notion of a “master switch” may be elusive. For example, the *Egr-1* gene has been shown to play a critical role in the control of such diverse processes as coagulation, inflammation, and vascular repair (16–19). However, mice that are null for *Egr-1* are viable, and although homozygous females are infertile, these animals must be significantly manipulated to otherwise elicit a phenotype. Thus, *Egr-1* is, by and large, dispensable for survival—at least in se-

lected inbred strains of mice raised in a stress-free environment. Moreover, we have previously demonstrated that the *Egr-1* gene is regulated in ways that differ from one endothelial cell to the next (20). In other words, the *Egr-1* transcription factor may be a switch of sorts for some, but probably not all, types of endothelial cells in the intact vasculature. Finally, we have recently shown that the addition of inflammatory mediators to microvascular endothelial cells harvested from the heart of *Egr-1*<sup>-/-</sup> animals results in the up-regulation of many of the putative *Egr-1* target genes (S. Wu, W. C. Aird, unpublished observations). Taken together, these observations raise the possibility that the *Egr-1* gene is a redundant signal transducer in certain subsets of endothelial cells.

In the case of certain nonendothelial lineages, cell type-specific transcription factors have been implicated as master switches in lineage determination, cellular differentiation, or phenotype. Examples include MyoD and GATA-1 in skeletal muscle cells and erythroid cells, respectively (21, 22). However, using a series of

co-culture, transplantation, transgenic, and Hprt targeting assays, we and others have proposed a model of endothelial cell-specific gene regulation that emphasizes the critical role of the extracellular environment (23–25). According to this model, the expression of a single gene within the endothelial lining is governed not by a common transcriptional control mechanism or master switch—in other words, there may be no MyoD equivalent in the endothelium—but rather by a constellation of vascular bed-specific signaling pathways, each beginning in the extracellular environment and ending at distinct regions of the promoter. This model is fitting for an input device, pointing to an elegant, if not predictable, mechanism for integrating and fine-tuning signal input at the level of the gene promoter (Fig. 2).

**Endothelial Cell Dysfunction.** Whereas endothelial cell activation refers to a change in phenotype, the term “dysfunction” describes the cost of that behavior to the organism. The functional state of the endothelium is ultimately in the eye of the beholder. Consider, as an example, endothelial cells that die during the process of wound healing. When viewed from the perspective of the individual cell, such behavior may be deemed dysfunctional. However, from the standpoint of the whole organism, the local kill of endothelial cells in the “line of duty” is anything but dysfunctional. Strictly speaking, the term endothelial cell dysfunction should be reserved for cases in which the endothelial cell response, whether local or systemic, represents a net liability to the host.

Assigning liability scores is, of course, a subjective exercise. An evolutionary biologist might argue that endothelial cell dysfunction is most relevant in its effect on an individual’s reproductive ability. A physician would surely expand the meaning of dysfunction to embody the myriad maladies whose origins are linked in one way or another to endothelial cell misbehavior. However, this is easier said than done. First, most endothelial response patterns likely evolved as adaptive mechanisms to serve and protect the host. Although it is certainly true that these responses may cross the line to maladaptation (or dysfunction), it is not always clear when that threshold is reached. Second, little is known about the cause-effect relationship between endothelial cell phenotypes and pathophysiology.

Practically speaking, most of us would agree that endothelial cell dysfunction underlies such disease states as atherosclerosis and severe sepsis. It seems likely, however, that the endothelium contributes to morbidity or mortality in many ways of which we are not yet aware of. As we continue to hone our diagnostic tools, we will undoubtedly uncover many previously unappreciated levels of endothelial cell dysfunction. Until then, the term dysfunction should be employed judiciously and with the appropriate caveats.

Finally, because endothelial cells display site-specific properties, the extent and nature of endothelial cell dysfunction is critically dependent on the location within the vascular tree. For example, in the blood–brain barrier, endothelial cell dysfunction occurs when there is loss of tight junctions and secondary leakiness

of resident microvessels. In contrast, endothelial cells in liver sinusoids are normally fenestrated and become dysfunctional when they acquire an abnormally tight barrier, a process that has been termed capillarization (26).

## Therapeutic Implications

When applying the concepts of endothelial cell activation and endothelial cell dysfunction to a consideration of therapeutics, it is important to recognize that endothelial cells may be activated—for example, they may express a phenotype that is characteristic of an inflammatory response—without being dysfunctional. Indeed, there are many instances in which endothelial cell activation is a welcome response, including wound healing, physiologic angiogenesis, and local defense against pathogens and foreign bodies. Following on from the themes developed earlier in this review, therapy should be reserved for cases in which the phenotype of the endothelium (regardless of whether it meets our definition of activated) represents a net liability to the host (Table 3).

The notion that endothelial cells resemble input–output devices and that their behavior is not binary but continuous has important therapeutic implications. The goal in treating the endothelium is not to reset the switch but rather to fine-tune and recalibrate the cell, nudging it back to its ideal state.

An important challenge is to learn how to determine the nature of that ideal state. Indeed, endothelial cell dysfunction often arises from otherwise adaptive responses (or at least ones that were adaptive in the ancestral environment) that are overzealous, sustained, or spatially or temporally misplaced. As more effective treatments become available for attenuating dysfunctional endothelium, it will be important to avoid overshooting the desired effect or “lobotomizing” the cells (Fig. 3). In this respect, it will serve us well to remember that a healthy endothelium is an active endothelium. Finally, given that endothelial cell phenotypes vary according to time and location in the vascular tree—in both health and disease—it will be essential to target therapy to specific vascular beds.

## Activated Protein C: A Case Study

A consideration of severe sepsis and activated protein C therapy helps to illu-

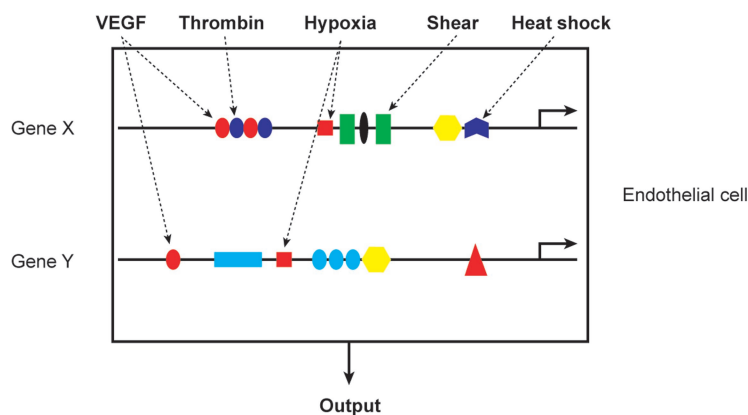


Figure 2. Modular mechanism of endothelial cell-specific gene expression. The expression of genes (designated *gene X* and *gene Y*) in a given endothelial cell (shown as an input–output device) is mediated by a constellation of site-specific signaling pathways beginning in the extracellular environment and ending at the level of the gene promoter. Input signals shown include vascular endothelial growth factor (*VEGF*), thrombin, hypoxia, shear stress (shear), and hyperthermia (heat shock).

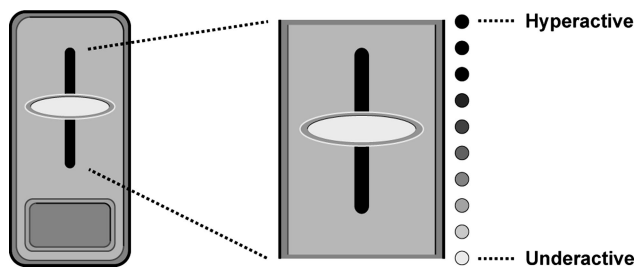


Figure 3. Endothelium as an analogue switch. The behavior of the endothelial cell as distinct from its genetic code is more analogue than it is digital. An important goal in therapy is to recalibrate the switch, nudging the cell back to its ideal state—without overshooting the desired end point (e.g., rendering the cell underactive or “lobotomized”).

**T**he goal in treating the endothelium is not to reset the switch but rather to fine-tune and recalibrate the cell, nudging it back to its ideal state.

minate the bench-to-bedside chasm. The pathophysiology of sepsis involves a complex nonlinear interplay between multiple cell types, including monocytes and endothelial cells, and myriad soluble mediators derived from activation of the inflammatory and coagulation pathways (27). Over the past decade, >10,000 patients have been enrolled in >20 placebo-controlled, randomized, phase III clinical trials. The vast majority of these therapies have failed to improve survival in patients with severe sepsis. A notable exception is activated protein C. In the PROWESS study, recombinant human activated protein C was shown to reduce 28-day all-cause mortality in patients with severe sepsis (28).

The results of the PROWESS trial have created an identity crisis for intensivists and hematologists alike, not to mention investigators from many other disciplines. The critical care field has finally come across an agent that saves lives in severe sepsis. However, the biological plausibility for this agent’s mode of action is mired in a maze of inflammation and coagulation pathways. Although recombinant human activated protein C is thought to inhibit both inflammation and coagulation, recent studies argue against a significant anti-inflammatory role for this agent (29) and suggest (albeit indirectly) that its anticoagulant effect may in fact be undesirable (30). It is conceivable, if not likely, that recombinant human activated protein C exerts its action, at least in part, through the attenuation of endothelial cell activation or apoptosis (31–33). The extent to which this is true will remain unknown as long as the intact endothelium continues to defy ready diagnostic interrogation.

At a clinical level, an under-appreciation both for the nonlinear nature of the host response to infection and the importance of the endothelium as an organ

system may have an impact on patient care. In some cases, physicians who lack a full understanding of sepsis pathophysiology and the potential mechanisms of action and risk-benefit profile of recombinant human activated protein C may avoid prescribing the agent for fear of the unknown. In other cases, poorly informed clinicians may administer the agent, unprepared for its potential complications. Finally, there exist a growing number of physicians genuinely interested in broadening their understanding of the complexities of the host response and in learning more about the endothelium as a component of this response. Owing to the bench-to-bedside gap in the endothelial field, these individuals currently have limited resources. As long as an understanding of the role of the endothelium eludes the clinical mainstream, the potential for developing a new class of sepsis drugs, capable of attenuating endothelial cell dysfunction, will remain unrealized. A better understanding of the endothelium in health and disease and the development of new tools to assay the endothelium *in vivo* should help to redirect research and development along more productive lines.

### Bridging the Bench-to-Bedside Gap

Clinical progress in endothelial cell biology will depend on several factors. First, clinicians should begin to view the endothelium as a discrete organ system—one that has pathophysiologic determinants and diagnostic and therapeutic potential. Second, there must be coordinated efforts to teach and educate physicians about the endothelium, not simply to “bring them up to snuff” but to train the next generation to develop and implement new diagnostic and therapeutic tools. Finally, there is an urgent need

for improved technology for observing and tracking the endothelium in real time.

I have made the argument that the current infrastructure of medicine is incapable of moving the field of endothelial cell biology into the clinic at a pace that is commensurate with advances at the bench. There are at least two solutions to this problem. One is to design a new clinical discipline in endothelial biomedicine. Training might constitute an added qualification to such specialties as cardiology, pulmonology, or hematology, to name just a few. It may be argued that a new discipline in endothelial biomedicine would only add to the fragmented state of medicine, that it would deny the complexity of the cardiovascular system and organism as a whole, or that it is too early—that there are insufficient diagnostic and therapeutic tools to justify a separate field. The counter-argument is, of course, that a new discipline would in fact represent a synthesis of an otherwise highly scattered field and would provide a necessary framework for bridging the bench-to-bedside gap.

An alternative approach is to improve the communication between and within existing clinical and basic disciplines. Endothelial cell investigators from different disciplines tend to represent a minority in their respective fields and have little opportunity to interact with one another. For example, a researcher studying the blood–brain barrier may spend a great deal of time interacting with neurologists and neuroscientists but remarkably little time with endothelial cell biologists whose work focuses on other vascular beds. As another example, a clinician–scientist in pulmonary medicine interested in understanding the molecular basis of pulmonary hypertension and improving treatment for this condition is

unlikely to cross paths with a hematologist who studies the role of the endothelium in thrombotic thrombocytopenic purpura. Both investigators are studying a common cell type and stand to gain from one another's knowledge. An important goal is to transcend the arbitrary barriers to interdisciplinary communication to foster intellectual cross-fertilization and progress. Transcending these barriers will require concerted effort on the part of many—in the way of collaborative basic research, inter-institutional and industry consortiums for developing novel diagnostic and therapeutic tools, and multidisciplinary team approaches to patient care. These and other efforts to synthesize the field are important first steps toward tapping the full potential of the endothelium.

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