# History Repeats Itself

## *Connections and Causality in the Study of Surgical Infections*

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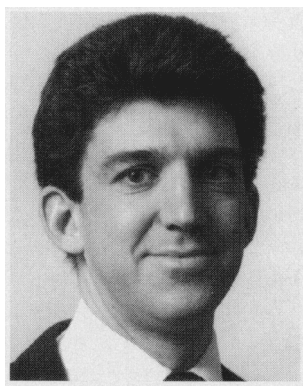
*Those who cannot remember the past are condemned to repeat it.*—George Santayana, 1922[1]

TODAY, I have chosen to discuss several disparate areas of social and biological evolution that led to surgery, and more particularly the study of surgical infection becoming a discipline within the field of medicine. I am sure that all of you are quite familiar with George Santayana's quotation that I have used for the epigram of my address.[1] Herein I will pursue several areas of the study of physiological evolution that have led to a number of important theories of causes and causality, as well as societal evolution, and examine some seemingly disparate connections with the past. I strongly believe that these connections have led to much of our current progress in the study of surgical infectious disease but also serve to put our current research in perspective.

Interest in historical cycles pervades literature and science. For example, even Salvador Dali took an interest in this topic when he entitled perhaps his most famous painting *Persistence of Memory*.[2] As surgeons, we are particularly interested in connections. The verb "to connect" is derived from the Latin *conectere,* which is in turn derived from the verb *nectere,* meaning "to bind."[3] We are quite used to thinking of surgical connections in terms of joining, fastening, or linking objects, but, of course, other definitions include placing or establishing things within various intangible relationships and forming associations in thought or logic. Paralleling these definitions are a number of obvious "surgical connections." We make tangible connections when we examine patients and perform surgery. The current catchword for these processes is "procedural." However, we perform many intangible or cognitive processes as well in both the experimental and clinical arenas. We test hypotheses, evaluate research data that leads to testing additional hypotheses within experimental and clinical settings, and establish intangible connections on a daily basis in the clinical setting with diagnoses and clinical trials. It is of interest that this points out an important connection with regard to the current health care cost crisis, to which I will return later. As we will see, many tangible and intangible connections have been used repeatedly in formulating theories of causality in the study of surgical infectious diseases.

Before proceeding, let me digress by briefly mentioning some of the types of reasoning that we use to establish connections. We pride ourselves as surgical scientists on our use of rational thought based on experience, reason, eclectic approaches, and deductive and inferential thinking. We typically try to avoid irrational thought in our clinical and experimental venues. I believe, however, that one of the most powerful types of rational reasoning is that of analogy, which often entails establishing connections. In both art and science, we are reminded that things are not necessarily as they seem, whether by looking closely into a mirror, as is demonstrated by René Magritte's painting, *Not to Be Reproduced,*[4] or into a microscope, through which we may be able to establish connections by close observation and clear thinking.

For example, on the surface, one finds it hard to believe that sex, evolution, and microbes created many of our current problems with health care costs. I find these seemingly disparate connections, however, rather intriguing and would like to pursue several lines of reasoning with you in which we will examine how sex and evolution led to the development of modern society, how a variety of potent forces within modern society led to the rise of the field of surgery, how surgery promoted the development of systemic sepsis, and how this highly morbid disease process may contribute substantially to health care costs. The logic of this syllogism, obviously, is that sex caused our current health care costs. First, let us examine how sex, evolution, and microbes have conspired against us.



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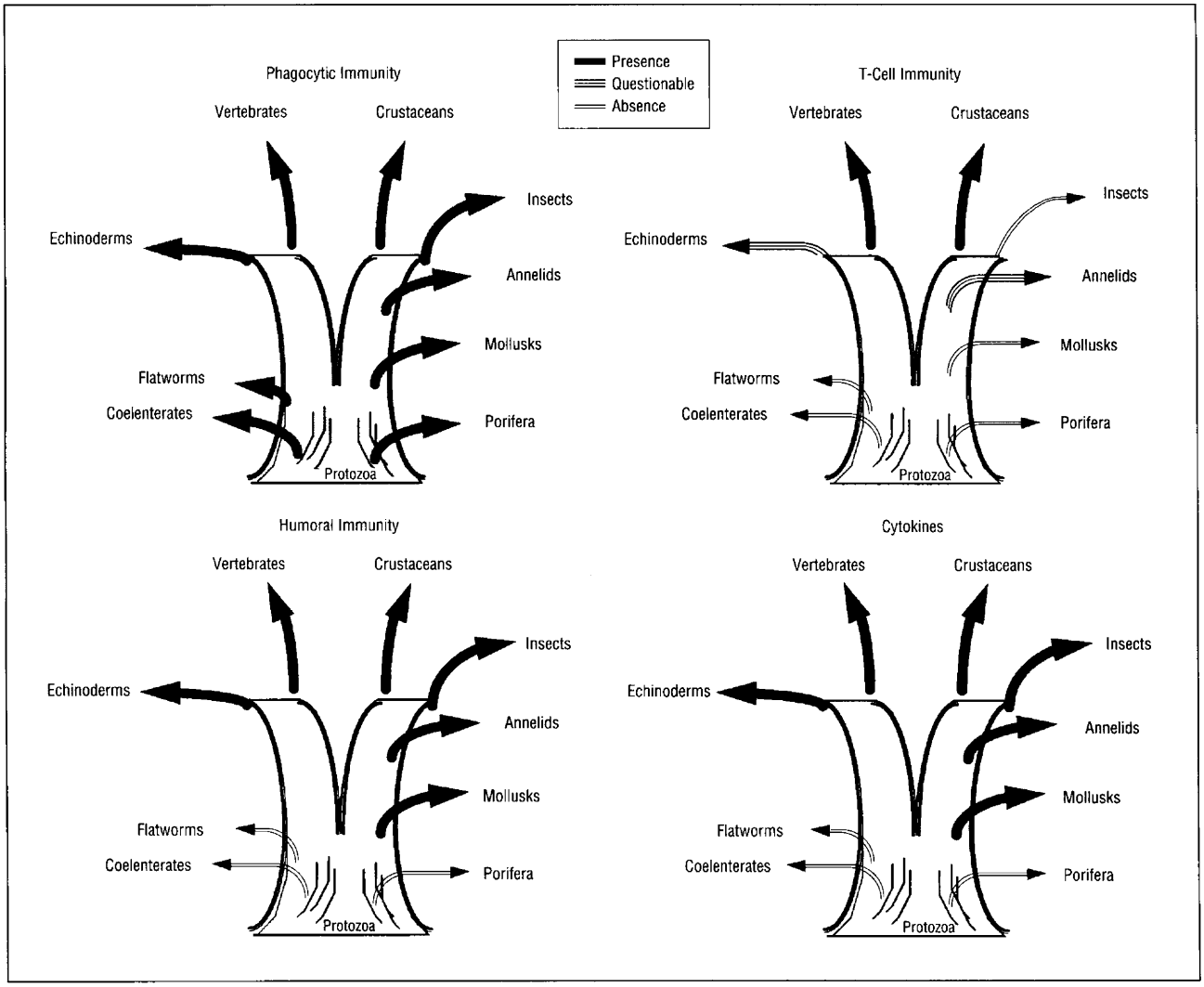
## SEX, EVOLUTION, AND MICROBES

Evolution has acted to propagate a variety of species, the vast majority of which are extinct. A number of theories have been invoked to explain the process of evolution, Darwin's theories of evolution having assumed precedence over Lamarck's concept of acquired characteristics. More recently, however, the "selfish gene" theory has been promulgated, the concept being that the smallest genetic unit on which evolution acts is not the species itself but the gene.[5] Effects of evolution are related to gene transmission, dimorphism, mating of young healthy individuals, and thus sex. Evolution probably does not act on sterile or nonbreeding individuals, which obviously would include patients in intensive care units. Sexual dimorphism is perhaps one of the most critical factors that influences evolution. Charles Darwin recognized this when he devoted the entire second portion of the *Descent of Man* to an examination of sexual selection.[6] This factor played an important role in early vertebrate evolution. Early on in the process of evolution toward primates, however, two events occurred that were probably closely intertwined. These are the loss of organ regeneration and the concurrent appearance of an advanced immune system and host defenses. If current phylogenetic studies indeed represent the manner in which evolution occurred, these events appear to have taken place as reptiles evolved from amphibians. In fact, there are several hundred million years of evolutionary "pressure" that have produced some of our current health care problems.

The two factors that served in large part to dictate the impact of evolution on the interaction of man and the environment are injury and trauma and infectious and noninfectious disease processes, as either common occurrences or cataclysmic events. These factors have shaped our physiological and societal evolution, and the development of modern surgery has been greatly influenced by injury in the form of wounds and infectious diseases in the form of intermittent plagues. Wounding most certainly is due to the aggressive nature of *Homo sapiens*, particularly with regard to the territorial behavior of the individual and groups. Early in the history of man, there was recognition of the interplay between wounds, infection, and surgical manipulation. In fact, virtually all wounds became infected and infection was associated with high mortality. Wounds were treated by early physicians who were also surgeons. Treatment was based on trial and error and individual physician experience, yet many forms of effective therapy that varied for different cultures were discovered. In virtually every ancient society, the wound was viewed as a window into the body and an experimental laboratory for early physicians. Thus, the treatment of wounds led to formulation of medical dogma in each and every ancient culture.

For example, the early Egyptians recognized some form of circulation of the blood based on the doctoring of wounds. In addition, some primitive remedies such as the use of pulverized malachite or honey in wounds may have been extremely effective, as noted by the modern-day experiments of Majno.[7] The Greeks and Romans employed a variety of remedies that included the use of red wine, poultices of herbs, and other compounds that may have had antibacterial properties. They also were proponents of "laudable pus," since infection was so common that it was considered the norm after wounding. These experiments were based on trial and error. Medical dogma arose solely from inferential data; for example, most disease processes were deemed to be an imbalance of various humors that consisted of either fire, water, air, or earth. It is of interest that the Chinese developed an explanatory system of medical dogma extremely similar to the Greco-Roman one, the latter of which pervaded medicine for hundreds of years and was used as the basis of medical beliefs throughout Europe until the Renaissance.

MEDIEVAL MEDICAL dogma probably would not have changed without the occurrence of an unusual chain of events in the 13th and 14th centuries detailed by historian James Burke.[8] First, an increase in travel and commerce occurred between 1200 and 1300 AD. As the population concurrently increased, climatic factors led to a number of years in which heavy rainfall occurred and a series of crop failures took place. On this weakened society, the scourge of bubonic plague or "Black Death" was visited. One third to one half of the entire population of Europe and Asia died. The plague swept out from western Asia across Europe beginning in 1347 and reached across nearly all of the continent and even to the islands of England and Iceland by the end of the 14th and beginning of the 15th centuries. The bubonic plague had an enormous impact on mankind during that period of time. Dereliction of land occurred based on decimation of the population. Without people to farm the land, inflation rose nearly 400%. However, because there were fewer people, real wages per capita rose and living conditions actually improved. Probably in reaction to the wholesale slaughter of society, huge demands for luxury and extravagance occurred, particularly with regard to dress. The aristocracy bought silk, and peasants bought linen as well as other accoutrements and garb. Even medieval physicians of the time adopted unusual garb in an attempt to demonstrate their position in society and to ward off the plague.[9] This demand for woven goods created a by-product market of linen rags that supported the paper industry in its infancy. Simultaneously, there was increasing demand for written transmission of knowledge. However, the death during the plague of the cognoscenti who could copy manuscripts and the scarcity




*Evolution of host defense as depicted by a phylogenic tree. Top left, Phagocytic immunity arose in primitive life forms, while humoral (bottom left) and T-cell (top right) immunity arose later, the latter being confined to vertebrates. Bottom right, Cytokines, however, appear to have evolved concurrently with phagocytic immunity (compare top left and bottom right).*

of manuscripts themselves provided the momentum that eventuated in Johannes Gutenberg's invention of moveable type in the creation of the first practical printing press. This series of events facilitated a dissemination of knowledge in art, science, and medicine that set the foundations for the formation of modern society.

## THE RISE OF THE FIELD OF SURGERY

Let me now examine how a variety of forces in modern society led to the rise of the field of surgery. This is a series of events with which I am sure you all are quite familiar, but some of the connections that can be made with prior events are rather intriguing. To summarize briefly, the studies of van Leeuwenhoek in microscopy and of Pasteur in microbiology set the stage for acceptance of the concept of fomitic disease transmission, ie, the transmission of microbial disease by infected material. This acceptance provided the conceptual groundwork for the control of infection. In fact, these events were really repercussions of the effects of the bubonic plague carried into the 19th and 20th centuries, in that some of those forces that shaped modern society also fostered additional, ongoing medical problems. Specifically, linen rags were shipped in abundant supply to large paper mills, and a lucrative industry arose in which this material was scavenged from various parts of the world. Unfortunately, numerous epidemics related to the importation of infected rags occurred, and there were outbreaks in the United States of a variety of diseases.[10(p405)] These occurrences fostered the demand for explanations, and thus the fomitic theory encountered modern bacteriology in its infancy. When 10 million people died in India and China during 1890 through 1902, identification of the causative gram-negative plague bacillus occurred owing to the work of Kitasato and Yersin.[11]

Thus, wounds and plagues represent those factors in the environment that have shaped many if not most

**Mortality Reported in Clinical Trials With Patients Given Antiendotoxin Monoclonal Antibodies E5 and HA-1A or Placebo***

| Patient Subgroup | Mortality, % | | | | | |
|---|---|---|---|---|---|---|
| | E5 Antibody | Placebo | P | HA-1A Antibody | Placebo | P |
| All patients with sepsis | 40 | 41 | NS | 39 | 43 | NS |
| Patients with gram-negative bacteremia | | | | 30 | 49 | 0.014 |
| Shock, present | ... | ... | ... | 33 | 57 | 0.017 |
| Shock, absent | ... | ... | ... | 27 | 40 | NR |
| Patients with gram-negative bacterial sepsis | 38 | 41 | NS | ... | ... | ... |
| Shock, present | 45 | 40 | NS | ... | ... | ... |
| Shock, absent | 30 | 43 | .01 | ... | ... | ... |
| Bacteremia, present | 27 | 37 | NR | ... | ... | ... |
| Bacteremia, absent | 33 | 46 | NR | ... | ... | ... |

*Adapted from Burd et al.[16] NS indicates not significant; NR, not reported.*

theories of causality in medicine and surgery. Initially, these events were attributed to divine acts, miasmas in the environment, and subsequently microbial toxins alone; more recently it has become clear how important host-microbe interactions are in these processes. These events have had a great deal of influence on surgical thinking. It was thought initially that infection was beyond control in both medicine and surgery. Even during the first portion of this century, many surgeons believed that infections were common and need not be controlled. Another thread, however, that pervades this field is that it was hazardous for medical practitioners to treat such infections in many cases. For example, surgeons treating patients with plague by lancing buboes frequently died.

More important for the development of modern surgery and the study of surgical infection was the occurrence of postmortem dissection wounds and deaths. Perhaps the most famous of these deaths is that of Dr Jakob Kolletschka, whose finger was pricked by an assistant during an autopsy. He died several days later, and his friend, Dr Ignaz Semmelweis, noted that this event was similar to the puerperal fever that he was studying in obstetrical wards. Determined to find the cause of his friend's death, Semmelweis ascertained that medical students often transmitted what we now know to have been streptococcal infection to postpartum patients as they left the autopsy suite to perform deliveries. He thereby established the principles of antisepsis.[10(p414)] An interesting modern-day parallel that concerns surgeons and infectious pathogens is the transmission of bloodborne hepatitis B and C and human immunodeficiency virus to surgeons and other health care workers in the course of treatment of infected patients. The current acquired immunodeficiency syndrome epidemic certainly has some parallels with that of bubonic plague, although the geographic distribution is somewhat different. Some intriguing parallels can be drawn between our current dilemma of identifying the causative pathogen of the acquired immunodeficiency syndrome and of having few treatment options and little control over the disease and that of the medieval physician dealing with bubonic plague to which I previously alluded.

Those events led to the hope that control of infection was possible and indeed set the stage for the performance of elective surgery. The two factors that made such surgery possible were antisepsis as promulgated by Lister and the development of anesthesia.[10(p426)] However, this expansion of criteria for surgery coupled with our inability to regenerate after wounding and an extremely effective local host defense response to infection has led to the recognition and characterization of the host systemic inflammatory response over the last several decades. A number of intriguing connections can be drawn between plagues and systemic sepsis, and it is fascinating how markedly both processes have influenced medical thinking. I would contend that these processes are both examples of evolution gone awry. Plague is caused by excessive bacterial virulence, while systemic sepsis is caused by excessive host virulence. In numbers, bubonic plague probably is the most frequent cause of systemic sepsis in history. Thus, as we look over those connections that led to the rise of surgery, I think it is apparent that control of infection led to our ability to perform elective surgery, and this has coincided with the increasing occurrence and our recognition of the host systemic inflammatory response. As we shall see, we are literally victims of our own evolutionary success.

## THE EVOLUTION OF THE HOST SEPTIC RESPONSE

Let us then look in somewhat more detail at how this evolution has occurred. Vertebrates, which include ourselves, occupy a rather insignificant portion of the phylogenic tree, and this holds true from the standpoint of various types of host defenses. Perhaps it is not surprising that phagocytic host defenses appeared to have evolved very early on, even in primitive multicellular animals such

as sponges and mollusks. Humoral immunity, however, occurred somewhat later in evolution, and the complexity of primitive mollusk host defense proteins pales in comparison with the surfeit of immunoglobulins due to immunoglobulin gene rearrangement found in vertebrates. T-cell immunity occurs even later in evolution. The most complex life forms with T-cell subsets once again occur in vertebrates, although some echinoderms and annelids appear to possess some type of progenitor system. It would appear, however, that cytokines occur in a phylogenic distribution very similar to that of phagocytic host defenses (**Figure**).[12-14]

THE CONNECTION that we can draw here is that it is indeed fortuitous that even relatively primitive invertebrates possess what was then termed "cellular," ie, phagocytic, immunity. Thus, in 1883, Eli Metchnikoff was able to observe the accumulation of phagocytes around a rose thorn that was inserted into a starfish larva. He subsequently postulated that phagocytosis was a general defense mechanism of all animals. Recent experiments that recapitulated these studies indicate that internal release of the cytokine interleukin (IL) 1 probably was responsible.[13,15]

Invertebrates constitute 95% of all animal species. The primitive phagocyte, the coelomocyte, also termed *hemocyte, amebocyte,* or *plasmatocyte,* is derived from mesodermal stem cells and is similar to monocytes and macrophages in vertebrates. This cell exhibits phagocytic activity in that it is attracted to sites of injury and/or the presence of foreign bodies, undergoes aggregation, and is capable of ingesting or killing microbes. It is surprising that invertebrates are capable of secreting a number of cytokines into the internal milieu.

One of the most common primitive cytokines is tumor necrosis factor (TNF) $\alpha/\beta$, which appears to be a progenitor of vertebrate TNF-$\alpha$ and TNF-$\beta$. It is of interest that there are separate invertebrate IL-1 cytokines. A number of other cytokines have been described in insects as well as echinoderms. Invertebrate TNF-$\alpha/\beta$ demonstrates activity in the L929 cytotoxicity assay similar to that of vertebrate TNF-$\alpha$. Interferon (IFN) $\gamma$ enhances stimulation of cytotoxicity similar to that of TNF-$\beta$. Invertebrate IL-1$\alpha$ and IL-1$\beta$ are both active in invertebrate and vertebrate systems, stimulating coelomocyte phagocytosis and proliferation, thymocyte activation, fibroblast proliferation, and cytotoxicity. Both are cross-reactive with vertebrate forms of IL-1. Also, vertebrate IL-1 stimulates coelomocyte phagocytosis and proliferation. There appears to be an inducible cytokine cascade present in invertebrates as well, in that mollusk immunocyte stimulation by IL-1 is due to initial secretion of TNF-$\alpha/\beta$.[12-14]

It would appear that these primitive cytokines evolved concurrent with humoral immunity. Most probably, they served as regulatory signals for the inflammatory response, as these cytokines are highly conserved through evolution. Invertebrates lack those cytokines such as IL-4, IL-5, IL-7, IFN-$\alpha$, and IFN-$\beta$ that act primarily as regulators of B-cell and T-cell immunity. It has been postulated that some cytokines were initially pheromones, perhaps important in the evolution of multicellular animals, and their activity may have been subverted as the internal milieu evolved. For example, IL-2 is capable of acting as a chemotactic agent in some unicellular species.[13]

## CLINICAL TRIALS OF THE TREATMENT OF SEPSIS IN RELATION TO CURRENT HEALTH CARE COSTS

Let me conclude by commenting on how seemingly disparate problems relate to some of our current dilemmas regarding health care costs. We are certainly all familiar with the concept that macrophage activation due to microbial cell wall compounds as well as other agents leads to a host of mediators being released, many of which are cytokines. Some of these cytokines, predominantly TNF-$\alpha$ and IL-1$\beta$, as well as other mediators perhaps yet to be described contribute to provoking the host septic response. This response is certainly beneficial in moderation, particularly when it occurs at the local site of infection. From an evolutionary standpoint, it assuredly evolved for selfish reasons, being extremely active in young individuals acting to promote health for mating, so that in a nutshell it would appear that the septic response evolved from sex. Unfortunately, it did not evolve to promote survival after mating and gene propagation occurred.

Some of the problems in dealing with this disease process are illustrated by two of the larger clinical trials that have been performed with agents that are purported to bind well to endotoxin (**Table**).[16,17] Even if these were extremely effective anti–endotoxin-binding agents, such therapy would be fraught with hazard due to the lack of rapid diagnostic tests for endotoxin and cytokines. Thus, it is not surprising that in the overall group of treated patients in each study, no salutary effect was observed because nearly two thirds of the patients had gram-positive bacterial or fungal infection as the cause of their septic event. These studies do serve to point out, however, that in the 1990s, the mortality rate of this disease process remains at 40%. Use of these agents without an appropriate diagnostic test for either endotoxin or gram-negative bacteremia would lead to significant numbers of patients receiving unnecessary therapy. In addition, if these agents had reached the market, they would have been extremely expensive: somewhere between $8000 and $10 000 per treatment course. Some authors, including myself, have estimated as much as a $1.6 billion potential market for this form of therapy.[18] Already there has been a proliferation of these agents directed against specific organisms such as antiendotoxin antibodies or those that I term here "organism-independent," which block later

steps in the host septic response such as anti–TNF-α monoclonal antibodies or IL-1 receptor antagonist. Unfortunately, the efficacy of these agents remains in question, most probably due in large part to our lack of understanding of the complexity of the host defense response. This lack of understanding comes at an unfortunate time and does not bode well for this type of clinical research. Health care costs in the United States have been increasing steadily as a percentage of the gross national product. Intensive care unit treatment costs for patients with sepsis are extremely high, and the addition of new reagents would only compound this already significant problem. Unfortunately, it seems likely that these types of studies will be curtailed as the potential costs of these agents pales even in comparison to that of antibiotics.

## CONCLUSIONS

Thus, let us return to this syllogism examining a number of disparate connections in which I hope that I have shown you how many of our current societal problems are related to such basic physiological forces as sex and evolution. If we are to make further progress in this field, we need to carefully examine our theories of causality of infection and sepsis. Fortunately, we have gone beyond believing these events are due solely to divine intervention, imbalance of body humors, direct effects of microbial toxins, and the endocrine stress response. We should recognize, however, that our current theories regarding microbial toxins that provoke the cytokine response may be nothing more than dogma and may eventually be viewed in a fashion similar to these previous theories. It is already becoming clear that complex interactions exist between various components of host defenses that we do not yet understand. Thus, it seems clear that we must put current theories continually in historical perspective and not become enamored with a single dogmatic point of view. Current theories of causality certainly are based on scientific observation, however, in contradistinction to the medieval view that the imbalance of humors caused various types of disease.

As we learn more about cytokine regulation, the complexity of the system appears enormous. It is clear that cytokines exert pleiotropic effects that can be both beneficial and deleterious. For many cytokines, it is unclear whether stimulation is provoked by serial or parallel, or both, types of pathways. Cytokines appear to be subverted extracellular signaling devices, yet we often do not recognize how these signals act to regulate the "set point" of host defenses that promotes health. This set point can be conceived as acting to prevent infection through the induction of local host defenses. Obviously, global immunosuppression and the systemic host septic response are examples of alterations in this homeostatic mechanism. We need to continue to ask how we can measure this set point and thereby learn how we can best regulate it. With regard to cytokine abrogation, we need to determine whether or not we can actually separate local from systemic effects and determine the effects of other systems such as the hormonal milieu and age on cytokine homeostasis. In conducting our research, perhaps we will find doorways where we least expect them that will lead us to these answers.

In conclusion, I would urge you to look for connections, perhaps disparate connections, in your clinical practice and research problems. Although rational observation is to be applauded, I think that it behooves us to recognize that a certain amount of skepticism is healthy, particularly whenever we confront what appears to be dogma. Finally, I think that it is often wise to consider past theories of causality in our field in relation to existing convictions in an attempt to both challenge our current theories and place them in clear perspective. I would like to thank the membership for the honor of serving as your president over the next year.

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