Host-Opportunist Interactions in Surgical Infection

Presidential Address

COL Basil A. Pruitt, Jr, MC, USA

The advances in general medical management and surgical care that have been made over the past half century have decreased morbidity in a broad range of surgical patients and have favorably influenced mortality, often in terms of length of survival rather than ultimate salvage. This specific, at times limited, medical progress may only be evident when at-risk groups are appropriately stratified, eg, the increased overall survival of patients with burns of 60% or less of the total body surface as contrasted with the prolongation of hospital stay but unchanged mortality of patients with larger burns (Table 1), and the increased immediate survival of patients with mechanical trauma overall as contrasted with the persistent late mortality of severely injured patients after resuscitation. The same partial success of initial surgical treatment coupled with intractable late mortality in critically injured and seriously ill patients is evident in transplant recipients and patients with cancer as well. In all high-risk patients, as exemplified by burn patients, the preponderance of residual morbidity and mortality is due to infection, and sepsis appears to be a common coexistent variable in the majority of critically ill patients who die (Table 2).

The persistent presence of infection as a complication in surgical patients and the pervasive effects of sepsis are well illustrated by the burn patient, who can be viewed as an infection model. Burn injury elicits the multisystem response characterized of all injury, with the magnitude of the response related to the readily quantifiable dose of injury, ie, extent of burn. The incidence of infection is similarly related to the severity of injury, and the occurrence of septic complications is influenced by the balance between host defenses and microbial invasiveness. Interactions between the host and opportunistic organisms not only affect that balance, usually by exaggerating pathophysiologic abnormalities, and adversely influence patient outcome, but also confound the diagnosis of sepsis. Those host-opportunistic interactions explain, at least in part, some of the limitations of current management of surgical infections, and a consideration of their effects indicates ways in which we can address both clinical and research problems related to surgical infection.

HOST FACTORS IN WOUND INFECTION

Host-opportunistic interactions may occur either locally to affect events at the site of injury or systemically to affect remote tissues and organs. In the burn wound, the absence of local blood supply, characteristic of a full-thickness burn, significantly influences the risk of infection by preventing delivery of the components of the host defense system and similarly the delivery of systemically administered antibiotics. The ischemia of the eschar also permits proliferation of the microorganisms that invariably colonize a burn wound (Fig 1). Other local host factors that influence the incidence of infection include tissue pH (acidosis predisposes to fungal infection) as well as wound temperature and moisture content. Moreover, the biochemical characteristics of the cells within a wound appear to influence the occurrence of certain burn wound infections, since herpes
Systemic changes induced by injury also exert burn size–related local effects that predispose the wound to infection, as reported at a previous meeting of this organization. Yurt et al demonstrated in an animal model that a partial-thickness burn resistant to bacterial inoculation became susceptible to invasive infection when an additional un inoculated burn injury was imposed. More recently, Yurt and Pruit have identified decreased wound neutrophil content eight hours after injury in animals with 60% burns as compared with those with 30% burns. Although the number of circulating neutrophils was similar in both groups, the increased sensitivity to chemotactic peptide and zymosan-activated serum implicate indiscrete neutrophil margination as a cause of the increased susceptibility to infection of the more extensive burns. This mechanism may also play a part in the early postinjury vascular changes in remote tissues and organs. Recent studies by Tvedten et al, showing a protective effect of catalase or superoxide dismutase treatment, implicate neutrophil-generated oxygen products in the acute lung injury produced by complement activation that commonly accompanies sepsis.

**MICROBIAL FACTORS IN WOUND INFECTION**

The type and density of microorganisms present on and in injured tissue change across time and influence not only the frequency of infection but the characteristics of those infections that do develop and the risk of systemic spread (Table 3). The initial flora of a burn wound is characteristically sparse and predominantly gram-positive. Consequently, wound infections occurring early after injury commonly elicit an erysipeloid response at the periphery of the wound or, in the case of staphylococcal infections, take the form of multiple well-demarcated microabscesses usually confined to the eschar with subcutaneous extension infrequent. By the end of the first week after injury, the more numerous wound bacteria are predominantly gram-negative. The virulence of such bacteria is influenced by toxin production (both endotoxin and exotoxins), production of enzymes such as collagenase, elastase, and a variety of other proteases, microbial motility, and both inherent and therapy-induced antimicrobial resistance.

In those patients in whom the density and invasive capacity of microorganisms at the nonviable/tissue interface exceed host defense capacity, invasion of viable tissue will occur. The importance of ensuing local host-opportunistic interactions in determining the course of the septic process is exemplified by the propensity of Pseudomonas organisms to proliferate around and invade the microvasculature and lymphatics (Fig 2). This pathogenetic characteristic explains the ischemic necrosis of tissue infected by such organisms and the frequent hematogenous dissemination from the primary focus of infection to remote tissues such as the lung. The propensity of the Phycycomycetes to invade and produce thrombosis of the local blood supply also explains the rapid centrifugal spread of ischemic necrosis characteristic of those infections.

**SYSTEMIC RESPONSES TO INJURY AND INFECTION**

**Metabolic Changes**

Other host-opportunistic interactions influence the systemic response to sepsis and the character of various organ and tissue changes brought about by infection. Sepsis-related alterations of metabolic processes illustrate the importance of these interactions in terms of the overall consequences of infection. Injury, including elective surgery, which is a controlled injury of variable magnitude, elicits a stereotypic biphasic metabolic response orchestrated in the early postinjury period by a configuration of neuroendocrine changes in which catabolic influences predominate. In the uncomplicated patient, the humoral factors affecting metabolism revert toward normal as healing proceeds and resume their normal relationships when the wounds are closed and convalescence begins. In the early stages of infection, a reversion of metabolic indexes to the early postinjury pattern or even an exaggeration thereof may be observed.

<table>
<thead>
<tr>
<th>Organism</th>
<th>% of Patients With Positive Surface Culture Results</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>0-2 Days After Burn</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>21.4</td>
</tr>
<tr>
<td><em>Staphylococcus epidermidis</em></td>
<td>70.0</td>
</tr>
<tr>
<td><em>Bacillus sp</em></td>
<td>32.1</td>
</tr>
<tr>
<td><em>Pseudomonas sp</em></td>
<td>7.0</td>
</tr>
<tr>
<td><em>Klebsiella sp</em></td>
<td>21.4</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>17.8</td>
</tr>
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</table>

*Table 1.—Burn Patient Mortality as Related to Extent of Burn*

<table>
<thead>
<tr>
<th>Mortality, %, by % of Body Surface Burned</th>
<th>0-30</th>
<th>31-40</th>
<th>41-50</th>
<th>51-60</th>
<th>61-100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before use of topical chemotherapy</td>
<td>4.3</td>
<td>44.4</td>
<td>61.1</td>
<td>78.3</td>
<td>89.1</td>
</tr>
<tr>
<td>With use of topical chemotherapy</td>
<td>3.8</td>
<td>18.1</td>
<td>32.2</td>
<td>47.3</td>
<td>83.8</td>
</tr>
</tbody>
</table>

*Table 2.—Causes of Death in Burn Patients: 1983 and 1984*

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>No. of Patients</th>
</tr>
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<tbody>
<tr>
<td>Sepsis</td>
<td>51</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>43</td>
</tr>
<tr>
<td>Burn wound infection</td>
<td>29</td>
</tr>
<tr>
<td>Bacterial endocarditis</td>
<td>9</td>
</tr>
<tr>
<td>Suppurative thrombophlebitis</td>
<td>6</td>
</tr>
<tr>
<td>Others</td>
<td>4</td>
</tr>
<tr>
<td>Acute inhalation injury</td>
<td>9</td>
</tr>
<tr>
<td>Myocardial infection</td>
<td>6</td>
</tr>
<tr>
<td>Associated injury</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>74</td>
</tr>
</tbody>
</table>

*Table 3.—Time-Related Changes in Burn Wound Bacterial Flora*
in clinical studies of infection and in laboratory studies of either infection or endotoxemia, alterations of carbohydrate metabolism at both the hepatic and peripheral tissue levels have been identified. The overall effect of severe sepsis on glucose metabolism in injured man, as described by Wilmore,26 is manifested by a decrease in glucose flow, an increase in glucose distribution space, and a decrease in the insulinogenic index. At the level of the peripheral tissues, a decrease in insulin sensitivity (perhaps even insulin resistance) has been attributed to sepsis.26 Specific changes in hepatic glucose metabolism associated with sepsis include decreased glucose-6-phosphatase activity, decreased glucose production, and decreased gluconeogenic responsiveness to alanine loading.26,27 The resulting energy failure occurs at a time when increased metabolic activity is needed. In bacteremic burn patients and a canine model of endotoxemia, McDougal et al28-32 found that altered glucose metabolism was accompanied by depression of indocyanine green clearance and that administration of insulin and hypertonic glucose significantly increased the glucose disappearance constant and hepatocyte clearance of the dye.

The effects of sepsis on postinjury protein metabolism are evidenced by an increase in albumin space (albumin synthesis rate is surprisingly well protected) and an increase in the peripheral release of amino acids associated with a reprioritization of protein synthesis.26 In instances of severe sepsis, visceral amino acid clearance is impaired and protein synthesis decreased.26

Studies recently completed indicate that a host-opportunist interaction also influences the early postinjury metabolic response to burn injury. In a murine model, burn injury produced an elevation of metabolic rate and both upper and lower critical temperatures. Bacterial inoculation of the surface of the burns of those animals markedly increased the metabolic response in untreated rats even in the absence of bacteremia. Postinoculation topical chemotherapy markedly limited the postinjury increase in metabolic rate to a level of 10% to 13% above that in unburned rats, and that modest increase appears to be the energy cost of the injury per se (L. H. Aulick, PhD, Albert J. McManus, PhD, Arthur D. Mason, MD, et al, unpublished data, 1985).
Fig 3.—Differences in free thyroxine index (open bar) and level of obtundation (hatched bar) distinguish between surviving (S) and nonsurviving (NS) extensively burned patients as early as third postburn day. Free thyroxine index is depressed and degree of obtundation is greater in nonsurviving patients as compared with those who survived. Single asterisk indicates free thyroxine index significantly (P<.05) lower than in survivors; double asterisks, level of obtundation significantly (P>.01) greater than in survivors.

Table 4.—Effect of Sepsis on Thyroid Function

<table>
<thead>
<tr>
<th></th>
<th>Triiodothyronine, ng/dL</th>
<th>Free Triiodothyronine, pg/dL</th>
<th>Thyroxine, µg/dL</th>
<th>Free Thyroxine, ng/dL</th>
<th>Thyreotropin, µU/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal range</td>
<td>100-200</td>
<td>230-669</td>
<td>5-11.4</td>
<td>1.3-3.8</td>
<td>&lt;3.5</td>
</tr>
<tr>
<td>Stable burn patients</td>
<td>94 ± 14</td>
<td>430 ± 59</td>
<td>5.5 ± 0.4</td>
<td>2.37 ± 0.5</td>
<td>6.5 ± 0.8</td>
</tr>
<tr>
<td>Burn patients with sepsis</td>
<td>51 ± 5</td>
<td>193 ± 14</td>
<td>5.0 ± 0.3</td>
<td>1.77 ± 0.13</td>
<td>7.3 ± 0.1</td>
</tr>
<tr>
<td>( p )</td>
<td>&lt;.01</td>
<td>&lt;.001</td>
<td>NS</td>
<td>&lt;.01</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 5.—Injury-Related Local Wound Changes Compromising Diagnosis of Wound Infection

<table>
<thead>
<tr>
<th>Impairment of local blood supply</th>
<th>Wound edema</th>
<th>Local neurological deficits</th>
<th>Presence of nonviable and injured tissue</th>
<th>Tinctorial changes</th>
<th>Textural changes</th>
<th>Posttraumatic fat liquefaction</th>
<th>Microbial proliferation in pooled secretions and exudates</th>
</tr>
</thead>
</table>

The sepsis-related alterations of nutrient distribution and utilization occur in a setting of increased catecholamine secretion, increased glucagon secretion, and a decrease in circulating levels of triiodothyronine and thyroxine (T₄). The global nature of the systemic effects of sepsis has been confirmed by the identification of patients in whom depressed circulating levels of triiodothyronine and T₄ failed to elicit an appropriate thyrotropin response (Table 4). In addition, a close correlation between depression of T₄ levels and obtundation as well as outcome has been observed in...
Table 6.—Physician Density in United States

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of Physicians per 100,000 Population</th>
</tr>
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<tbody>
<tr>
<td>1900</td>
<td>173</td>
</tr>
<tr>
<td>1910</td>
<td>146</td>
</tr>
<tr>
<td>1930</td>
<td>125</td>
</tr>
<tr>
<td>1970</td>
<td>148</td>
</tr>
<tr>
<td>1980</td>
<td>195</td>
</tr>
<tr>
<td>1983</td>
<td>212</td>
</tr>
</tbody>
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Table 7.—Quality Assurance of Clinical Trials

- Selection of a significant problem for study
- Direct Investigator participation in planning and design
- Appropriate study groups
- Comparable patients
- Comparable stage of disease
- Comparable treatment
- Defined exclusion criteria
- Preplanned statistical analysis
- Conclusions generated by Investigator
- Prepublication peer review of completed study

Fig 4.—Biopsy specimen shows dark-staining bacillary organisms in unburned tissue (from 12- to 4-o'clock position in central portion of field) confirming diagnosis of invasive burn wound infection. Presence of inflammatory cells in area of infection corroborates viability of that tissue as opposed to nonviability of burned tissue in upper right quadrant of this field (periodic acid–Schiff–Giemsa, original magnification × 400).

burn patients with fatal infections (Fig 3). More recently, Shirani et al have identified changes in the free concentration, dialyzable fraction, and resin uptake of the thyroid hormones that are consistent with the presence of a circulating inhibitor of thyroid hormone binding to transport proteins. Since the most profound depression of thyroid hormone levels occurs in patients with fatal complications, most commonly sepsis, it is tempting to speculate that infection plays a role in the generation of the thyroid hormone–binding inhibitor.

Immunologic Alterations

Injury also elicits a broad range of changes involving literally every component of the host defense system. Further perturbations of immunologic function are associated with infection. Life-threatening infections, particularly those caused by gram-negative organisms, are associated with reductions in opsonic activity, alterations in lymphocyte function and the distribution of lymphocytes within specific subpopulations, and alterations in neutrophil number and function. Studies in which chemiluminescence has been used to assay neutrophil function have shown that both the opsonic capacity of serum and the oxygenation index of polymorphonuclear leukocytes are depressed in burn patients with infection. In as yet unpublished studies conducted in 1981-1982, R. C. Allen, MD, in our laboratory has shown by means of enzyme-specific chemilumigenic probes that depression of neutrophil membrane–associated oxidase activity preceded depression of granule-associated peroxidase activity and that the change in oxidase activity was a reliable prognostic index of a fatal outcome.

INTERACTIONS COMPLICATING DIAGNOSIS OF INFECTION

These local and systemic effects of sepsis appear to increase in severity and velocity with time, and successful intervention to minimize or reverse the associated physiologic deterioration depends on early and accurate diagnosis of infection. At the level of the wound, the critical interactions that result in invasive infection occur at the junction of nonviable and viable tissue, a site usually inaccessible to surface cultures, which even in quantitative terms are unreliable in differentiating microbial colonization of nonviable tissue from microbial infection of viable tissue. Injury-related changes in the tinctorial and physical characteristics of the wound may also confound the clinical assessment of its microbial status (Table 5). Those limitations can be overcome and wound colonization can be most reliably differentiated from invasive infection by the microscopic examination of biopsy specimens obtained from a burn or other wound of a patient in whom clinical findings are equivocal (Fig 4). A newly developed frozen-section technique with a processing time of 30 minutes permits the identification of bacterial, fungal, and viral wound infections with a 96% accuracy.

The importance of early diagnosis of burn wound infection is well illustrated by the studies of McManus et al, previously reported to this Society, in which the five
survivors of 19 burn patients with documented burn wound invasion were patients in whom biopsy technique was used to make that diagnosis before septicemia was present. The applicability of biopsy diagnosis to other surgical infections is illustrated by the recent report of Stamenkovic and Lew, in which frozen-section soft-tissue biopsy specimens permitted earlier diagnosis and were credited with reducing the mortality associated with necrotizing fasciitis.

The problem of diagnosing and even defining systemic sepsis is even greater than that related to the diagnosis of wound infection. The systemic response to injury in the surgical patient characterized by hyperthermia, tachycardia, hyperventilation, altered mentation, and leukocytosis can lead to both underdiagnosis and overdiagnosis of sepsis. Although blood cultures have been relied on to confirm a diagnosis of systemic sepsis, their processing time, measured in days, and the effect of administered antibiotics mitigate their usefulness and reliability, respectively. Moreover, microbial products such as toxins can evoke changes in organ and cellular function. Staphylococcal α-toxin can induce pulmonary vascular hypertension, and pneumolysin has been found to inhibit the lymphocyte response to a variety of mitogens. Lymphocytes stimulated by bacteria may also liberate circulating factors such as monokines and prostaglandins that can alter carbohydrate metabolism. The fact that many of the systemic changes characteristic of sepsis can occur in the absence of an abnormal blood culture speak for the development of biochemical and/or physiologic criteria of systemic sepsis. Such criteria can be expected to reduce the uncertainty evident in studies in which the diagnosis of sepsis in the absence of positive cultures is based on the presence of a variable number of clinical signs, all of which are often present in uninfected injured patients. As a start in that direction, I am asking the Society's Scientific Studies Committee to address that problem during the forthcoming year.

INTERACTIONS COMPLICATING STUDIES OF INFECTION

The pathophysiologic interactions that influence the progression and spread of infection and complicate the diagnosis and management of clinical infections must also be kept in mind when designing and interpreting laboratory and clinical studies. Assessment of bacterial factors, such as microbial motility, that influence the development of wound infection is best carried out in a model employing surface inoculation that mimics the clinical situation. Models in which microorganisms are injected into subcutaneous tissue appear to be abscess models and evaluate systemic toxicity, but provide little information relevant to the pathogenesis of burn wound infection. The species specificity of bactericidal host defense mechanisms must also be kept in mind when designing laboratory studies, as emphasized by the recent study of Simmonds et al., in which an absence of xanthine and uric acid in human peritoneal macrophages confirmed the insignificance of xanthine oxidase generation of superoxide anion in man in contrast to its importance in the mouse.

Caution is also warranted in clinical studies in which the difficulty in diagnosing infection and the effects of variable therapeutic interventions may complicate interpretation of results. The effects of injury severity and time after injury on the metabolic and immunologic changes in uninfected surgical patients, and the secondary changes in those systems that result from infection, speak for careful attention to patient homogeneity and stratification. Appropriate classification of patients with intra-abdominal infections is facilitated by the stratification scheme developed by Meakins et al., which includes both an anatomic definition and a physiologic assessment. Since the effects of sepsis change across time, serial reclassification and patient "tracking," as advocated by Siegel, may be needed to increase the usefulness of that classification scheme. At any rate, temporal relationships must be considered with particular care before assigning infection causality to an observed metabolic or immunologic change.

MEDICINE-GOVERNMENT INTERACTIONS

Relationships similar to those that determine the occurrence, course, and consequences of infection in surgical patients influence the medical profession in general and surgery in particular. The most pervasive influences have been governmental, involving both personnel and funding, generating problems analogous to those of organism density and nutrient supply in a surgical infection. In the 1960s, changes in medical school funding were made to increase the supply of physicians. That program has continued during a period of ongoing high influx of graduates of foreign medical schools (4,730 received initial medical licenses in 1983) and has resulted in an oversupply of physicians, whose numbers (5.02 × 10⁶) now approach those of the critical bacterial density in surgical wounds.

In the three-year period, 1980 to 1983, the number of physicians in the United States increased by 11.1%. In 1983, there were 501,958 physicians in the United States, of whom 111,161 were graduates of foreign medical schools. That physician population now provides 215 physicians per 100,000 population, as compared with 125 per 100,000 in 1930, 145 per 100,000 in 1970, and 185 per 100,000 in 1980 (American Medical News, Oct 19, 1984, p 17) (Table 6). This increase in physician density, which is global in nature (Wall Street Journal, Oct 4, 1984, p 36), appears to have been arrested in the United States, since the number of graduating medical students has remained essentially static since 1982. Even so, the projected number of first-year students for 1988 is 16,457, only a 0.2% decrease from the 16,518 in 1984, and the 16,759 medical graduates projected for 1989 is virtually identical to the 16,730 projected for 1985. Reduction of the physician-population ratio will come about only as the general population increases. This increase in the proportion of physicians in the population is in certain respects a mixed blessing. The proliferation of physicians has been paralleled by the emergence and rapid proliferation of corporations that provide health care. An increasing number of physicians employed by health care corporations are at risk of having their practice of medicine and conduct of clinical research influ-
enced by considerations of profit by a third nonphysician party, the corporation. Although it has been claimed that the corporate practice of medicine decreases the cost of health care, at least one published study indicates that a common strategy has been to maximize profit by both patient selection and use of ancillary services. Conversely, potential benefits of a physician excess include an increased applicant pool for available residency (there are only 1.2 postgraduate year 1 positions for each US medical graduate) (minutes of the Joint Council of Academic Societies/Organization of Student Representatives meeting, Washington, DC, Nov 7, 1982), fellowship, and faculty positions and less pressure to increase the salaries paid such personnel.

**FRAGMENTATION AND PROLIFERATION OF MEDICAL SPECIALTIES**

One result of the interaction between government and medicine that has produced the increase in physicians is the fragmentation of surgery and the proliferation of medical specialties. The development of new technology, increased understanding of the physiology and biochemistry of organ systems, and an increase in the requisite technical sophistication have in the past and can in the future justify subdivision of a traditional specialty. However, at least some of the current requests to create new specialties are not based on a physiologic or anatomic system and appear to be guided by a territorial imperative to fence progressively smaller slices of a finite pie. In the field of surgery, there are currently two formal requests pending for the establishment of new certificates of special competence, and other special interest groups are considering such requests. The American Board of Medical Specialties already certifies in 74 specialties, while the Royal College of Physicians and Surgeons of Canada certifies in only 41 specialties. One cannot help but wonder how the traditional specialties in Canada have been able to resist capitulating to the demands for exclusiveness by special interest groups.

Applications on the part of the American Boards of Internal Medicine, Anaesthesiology, Neurologic Surgery, Pediatrics, and Surgery to issue certificates of special qualifications in critical care were approved at the recent annual meeting of the American Board of Medical Specialties. In the field of surgery, in which proper residency training includes the provision of care for critically ill and injured patients, the need for that field of special competence, based primarily on the physical location of the patient within the hospital, is unclear. As Maloney has pointed out, the establishment of such a field of special qualifications increases the possibility that by administrative fiat we will become itinerant surgeons within our own treatment facilities. The American Board of Medical Specialties recognized this hazard and approved the referenced certificates with the following qualification: “The possession of a certificate of special qualifications in critical care should not be used to interfere with the relationship between the patient and his primary physician and/or other specialists involved in the care of that patient” (memorandum of the American Board of Surgery, April 2, 1986). We must, as individuals and as a Society, insist upon such noninterference. The knowledge and skills of the physician with a special interest in critical care can be utilized in consultative format when appropriate, but we should simultaneously maintain the integrity of the traditional surgeon-patient relationship and avoid what could be interpreted as abandonment if we relinquish responsibility at the door of the intensive care unit.

The broad scope of the surgical infection problem that affects patients treated by virtually all surgical specialists speaks against the development of surgical infection as an exclusive specialty. Nevertheless, the velocity of surgical fragmentation shows no signs of decreasing. To avoid phagocytosis by one or more special interest group, we should define what constitutes the field of interest that we call surgical infection and maintain that field as an integral part of general surgery.

**ALTERATIONS IN FUNDING OF MEDICAL CARE AND RESEARCH**

Coincident with the increase in physicians, there have been changes in government funding of both medical care and medical research. The program of prospective payment for the care of patients with specific diagnoses may have little influence on health care costs overall by virtue of what has been termed “diagnosis creep.” “Cost shifting,” another host response to funding changes, appears likely to impose a greater financial strain on tertiary referral centers, but will ensure matching of patient care needs with the clinical resources available at academic medical centers. That mechanism will also facilitate clinical research by concentrating at such centers those patients appropriate for clinical investigation.

Governmental funding for medical research has also been constrained. The budget of the National Institutes of Health (NIH), which is the main source of biomedical research money in the United States, has not kept pace with inflation. In fiscal year 1984, the total NIH budget was $4.476 billion. This level of funding represented only slight growth in terms of constant dollars and permitted the funding of approximately 5,400 grants, generally those with a priority score of 150 or less. The chilling effect of such highly competitive funding (only about a third of approved grants are funded) prompted a Congress concerned about federal deficits and budgetary constraints to approve a total NIH budget for fiscal year 1985 of $5,149,700,000 to support 1,500 additional grants. The fiscal year 1985 budgets of the National Institute of Allergy and Infectious Disease and the National Institute of General Medical Sciences (those institutes from which our members are most likely to draw research support) increased from $305.7 million to $359.6 million and from $366.8 million to $424.5 million, respectively. Despite this favorable Congressional appropriations action, the fundable priority score may not rise and the number of funded grants may not increase. The Office of Management and Budget has instructed NIH to “forward fund” approximately 675 of the 5,000 grants it will make in 1985 to expend, during the current fiscal year, those funds exceeding the budgetary limit requested by the Presi-
In this way, NIH research support would remain essentially constant, and the elevation of the funding base for future years that would result from funding the additional 1,500 grants will be prevented.

The diagnosis-related group payment scheme may also have a restrictive effect on clinical investigation; in the field of surgical infection, it may specifically increase reliance on other sources of support for clinical trials. The risks of dependency on industry-sponsored trials, as enumerated by Kunin, include limited investigator design input, design bias, inappropriate patient exclusion, proprietary data analysis, prolongation of hospital stay to collect data, sponsor-biased conclusions, and selection of a nonproblem for study. In spite of all these risks, valid industry-sponsored clinical trials have been and can be carried out. The design, conduct, and interpretation of any clinical trial will be optimized and the potential hazards minimized by direct investigator involvement in the design, data analysis, and interpretation of the study (Table 7). The ultimate assurance of quality and validity in such studies is the editorial review process of refereed journals, and all of us who serve on editorial boards must apply the same scientific standards to those clinical trials that we do to other studies.

**SURGEON-NONSURGEON INTERACTIONS**

Other interactions impinging on the field of surgical infection include those between surgeons and basic scientists and between surgeons and infectious disease specialists. In both of these areas, misunderstandings may hinge on self-definition. It has been pointed out that assumption of the title "basic scientist" may be a snobbery similar to the arrogation of the title "intellectual" by the literary community. Perhaps the same mechanism accounts for the recent differentiation of cognitive medicine from those forms of medical care that involve procedures. What appears to be an oversupply of basic scientists has ameliorated this terminology barrier, as the number of basic scientists occupying positions in clinical departments has increased. The increasing number of grant applications emanating from clinical departments for which a basic scientist is listed as the principal investigator gives evidence of the increasing involvement of those scientists in surgical research. Optimum application of the expertise of the basic scientist to clinically relevant problems depends on effective two-way interdisciplinary communication and maintenance of an environment that fosters the professional development of all of the investigators.

The expertise of infectious disease specialists can, in many instances, be applied to the benefit of patients with surgical infections. It is important, however, that the surgeon maintain effective communication with those specialists and participate in infection control committee activities to develop useful definitions of specific surgical infections, such as those of the burn wound, and prevent unwarranted closure of special care units by inappropriate application of epidemiologic data. The report presented by Mason et al at this meeting, which verifies the mortality-enhancing effect of gram-negative bacteremia in burn patients, also shows that gram-positive bacteremia exerts no such effect and, in fact, may even enhance survival. Those findings would certainly question closure of a burn unit merely because of recovery of staphylococci from the burn wounds of a patient.

**ANIMAL RESEARCH-ANTIVIVISECTION INTERACTIONS**

A last opportunist that is adversely affecting medicine as a whole and surgical research in particular is the revivified antivivisectionist movement. This movement, which had its beginnings in the 17th century as a response to Cartesian rationalizations that animals were machines without feelings, received public and even medical support that led to the passage of the British Cruelty to Animals Act in 1876. Subsequent recognition of the importance of animal research and acceptance of such studies by the medical profession were paralleled by a decline in public support of antivivisection in both the United Kingdom and the United States.

A resurgence of the animal welfare groups in the United States paralleled the increase in biomedical research after World War II and led in 1966 to passage of what is now called the Animal Welfare Act. That act, which deals principally with facility improvement, is now regarded as ineffective by the animal welfare groups since it does not touch on research-related pain or the development of alternative models. The resurgence of the antivivisection groups and the increased criticism of animal research have been related to a variety of factors, including public perception of the fallibility of science, an increased level of social criticism during the past 20 years, increased moral concern about nonhuman species, and societal sensitivity to exploitation.

The new-found vigor of this movement has been directed into legislative efforts to restrict animal procurement from pounds, develop research alternatives, regulate painful research, accredit animal laboratories, and establish animal studies committees. Several bills in both the Senate and the House were not brought to a vote in the last Congress, but there are already similar bills before the present Congress (S 657, sponsored by Senator Robert Dole, and HR 5725, sponsored by Congressman George Brown). Nonlegislative initiatives have taken the form of a temporary ban on both in-house and extramural research use of cats and dogs in projects funded by the Department of Defense, for a several-month period that began in October 1984 and ended in early 1985, and militant actions ranging from picketing to theft of research animals, destruction of data, and bomb threats (San Antonio Sunday Express News, April 21, 1985, p 9A, and the President's Weekly Activities Report, Association of American Medical Colleges [AAMC], Jan 8, 1985). Animal theft has been justified on the basis of "rescuing animal slaves," and antivivisectionist propaganda includes the use of data and illustrative material three or more decades out of context (San Antonio News, July 28, 1985, p 1A). Of more than passing interest are the proposals by some members of the movement for the use, in lieu of animals, of prisoners, various groups of disadvantaged people, and even those holding unpopular political beliefs (San Antonio Light, July 29, 1983, p 1C). In the March 28, 1985,
1985, issue of Nature, the newest initiatives to protect the
rights of nonhuman life were detailed.4 In that report of an
alleged meeting at Oxford University, the formation of the
Vegetable Liberation Front was announced, and transfec-
tion of bacteria was classified as a subtle form of oppression.
One speaker was quoted as saying that "even bacteria have
rights."

INFLUENCE OF PROFESSIONAL SOCIETIES ON
INTERACTIONS

There are two broadly based organizations that address
the problems impinging on medical care, education, and
research. The Council of Academic Societies provides
groups such as ours with a means to participate in the
formulation of the host response to the opportunists gener-
ating those problems. The AAMC, of which the Council of
Academic Societies is a constituent group, has made impor-
tant representations on the part of medicine in the fields of
health care economics, specialty fragmentation and all
levels of physician education. In the latter area, the AAMC
Panel on the General Professional Education of the Physi-
cian and College Preparation for Medicine has recently
published their report, entitled Physicians for the 21st
Century, in which emphasis is placed on breadth of educa-
tion and individualized programs of study.6 The association
has also played a key role in combating the activities of the
anti-vivisectionists, as exemplified by its mobilization of
Congressional support, which in 1983 prevented the total
prohibition of animal research within the military medical
services. The second organization, now called the National
Association for Biomedical Research, has a national mem-
bership and represents both industry and academia in the
areas of legislation and regulation, and public education
related to the use of laboratory animals in research.

To address the threat posed by the antivivisectionists, I
propose that this Society become an institutional member of
the National Association for Biomedical Research and
support the activities of that organization to combat unwar-
ranted limitations on medical research that would imperil
medical progress. I also propose that the Society make
application for membership in the Council of Academic
Societies of the AAMC to support that organization's efforts
as they are exerted on our behalf in the areas of medical
care, health care, and biomedical research.

The expanding membership and the scientific vigor of our
Society serve as indexes of its rapid maturation. Our
Scientific Studies Committee has already developed a sys-
tem to classify intra-abdominal infections that makes possi-
ble the assessment of treatment effectiveness and outcome
in patients stratified on the basis of anatomic site and
physiologic response to infection. That committee intends
to develop guidelines for the design and conduct of clinical
studies of infection and, as noted above, has been charged
with developing a clinically useful definition of sepsis. The
work presented at this fifth annual meeting provides fur-
ther insight into the host-opportunistic interactions that
determine the course of surgical infections, and such stud-
ies will lead to further improvement in the care of the
surgical patient. As a mature academic society, we must
also meet our broader responsibilities by working with
others having similar interests in developing the responses
that must be made to those forces that, if untempered, have
the potential of compromising medical care and thwarting
medical research.

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