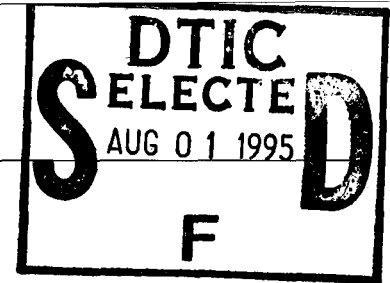


PRESIDENTIAL ADDRESS



# The Integration of Clinical Care and Laboratory Research

## A Model for Medical Progress

Basil A. Pruitt, Jr, MD  
Colonel, US Army Medical Corps

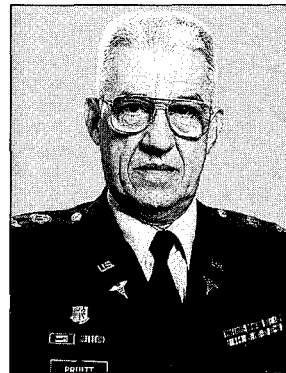
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**T**HE DUTIES of the President of the Western Surgical Association center on the delivery of this address, and as I was escorted to the podium 1 year ago, I began the mental search for a topic that would catch the interest of the membership. To help in that search, I have reviewed the Presidential Addresses delivered since 1947 and have classified those according to topic to avoid redundancy and to identify an ecologic niche (**Table 1**).

The box score of Presidential Address topics made it obvious that neither clinical activities nor research had been overworked. Accordingly, I have chosen to address both of those "orphan" topics and illustrate how the planned integration of clinical care and multidisciplinary laboratory research at the US Army Burn Center in San Antonio, Tex, has resulted in significant advances in burn patient care, all of which are applicable to other critically ill patients as well. I also propose to demonstrate that a center where such integration occurs can adapt to the exigencies of disaster care, conduct an effective teaching program at all levels of surgical education, and serve as a model that ensures continued medical progress in a milieu of managed care.

Medical research, as a planned and funded component of medical practice, is a relatively new development in the United States. In the late 18th and early 19th centuries, medical practice in the United States was focused on the obvious clinical problems of the day, with little, if any, consideration given to scientific research. Even if physicians had wished to conduct clinical studies, the requisite facilities and environment simply did not exist. The establishment of the conditions necessary for the development and maturation of an independent American medicine began in the 1700s with the immigration of European physicians to the United States and the reciprocal movement of US physicians to Europe for training. European centers enjoyed sequential temporal prominence as the preferred educational site for potential US physicians and surgeons. Britain and Scotland, particularly Edinburgh, were the favored venues in the 18th and the first fifth of the 19th centuries. From 1820 to 1860, France predominated, and Germany was favored throughout the remainder of the 19th century.<sup>1(pp4-18)</sup>

In the last half of the 19th century, the physicians who made the voyage to Europe learned about and at times



Basil A. Pruitt, Jr, MD

participated in the largely observational studies and experiments that described organ function, identified the causes of various diseases (infection and nutritional deficiencies are commonly cited examples), and confirmed the effectiveness of new therapeutic interventions. The development of basic science laboratories at the German medical schools facilitated the prompt applica-

tion of new findings to the care of patients. What was called "physiological medicine" emerged and was used to study clinical problems in the German hospitals.<sup>1(p19)</sup> That format of research had been used as early as 1842 by Richard Bright at Guy's Hospital in London, England, where he organized and conducted what is considered to be the first collaborative clinical and laboratory study as part of his work on kidney diseases.<sup>1(p19)</sup>

Even with the described transatlantic medical exchange, there was generally inadequate scientific preparation of physicians in the United States. In the 1860s, no basic science knowledge was required of entering medical students, there were no basic science laboratories for either undergraduates or medical students, and the medical school basic science teachers did no research and typically were part-time. In 1869, Yale University's Sheffield Scientific School, New Haven, Conn, offered a course of "Studies Preparatory to Medical Sciences," which appears to have been the first attempt in the United States to provide training in the scientific method for potential clinical investigators.<sup>1(p31)</sup> Two years later, in 1871, the first university laboratory for experimental physiology was established at Harvard Medical School, Boston, Mass, with Dr Henry P. Bowditch as director.<sup>1(p40)</sup> The second laboratory of physiology was established at The Johns Hopkins University School of Medicine, Baltimore, Md, in 1876, when Henry Newell Martin became professor of biology. Martin, who had a degree of doctor of science in physiology and who was also qualified in medicine, enthusiastically promoted research among his students, who included George Sternburg and Walter Reed,

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**Table 1. Western Surgical Association Presidential Address Topics, 1947-1993**

| Topic                                                                | No. |
|----------------------------------------------------------------------|-----|
| Psychosocial aspects, philosophy, organization, and delivery of care | 21  |
| History of surgery and history of the Western Surgical Association   | 13  |
| Surgical education                                                   | 10  |
| Clinical surgery                                                     | 1   |
| Medical research                                                     | 1   |

as well as seven of the original 24 members of the American Physiological Society.<sup>1(p44)</sup>

Even the productivity of these laboratories (Bowditch studied ciliary motion and nerve transmission and Martin devised a method of perfusing the isolated mammalian heart)<sup>1(p42),2</sup> and the proliferation of graduate schools, which were promoted by the Land Grant Act of 1862,<sup>1(pp58-59)</sup> failed to generate an appreciation of the importance of trained medical research personnel and specialized research facilities. Physicians, even in the latter half of the 19th century, were considered to be clinicians and not scientists.

The rapid development and maturation of clinical research in the United States in this century can be related to a number of factors, including new developments in the basic sciences that have been applied effectively to clinical problems, development of new scientific disciplines, the establishment of specialized scientific academic positions and facilities, and the development of defined, systematic educational programs for research. The aggregate effect of these factors has been to establish biomedical research as a regular scientific career.

The clinical surgical scientist template was formed only when full-time physicians began to populate university clinical departments. The establishment of full-time professorships met with vigorous vocal resistance and generated intense controversy that remains unresolved in some quarters even today. Institution of a full-time system was department specific, as exemplified by the clinical departments at The Johns Hopkins University School of Medicine. The Department of Pediatrics, directed by John F. Howland, readily adapted to a full-time format, whereas Lewellys F. Barker, who succeeded William Osler and had been a strong advocate of full-time clinical professorships, refused such an appointment in 1914.<sup>1(p58-59)</sup> In surgery, virtually no change was necessary to institute the full-time system since William Halsted's dedication to clinical research and small volume of private practice had made him a de facto full-time professor.<sup>1(p58-59)</sup>

Publication of the Flexner report<sup>3</sup> in 1910, in which severe criticism was leveled at the clinical departments of medical schools, stimulated measures to improve the quality of those departments by the establishment of more full-time professorships. In 1917, the Committee on Medical Research of the Association of American Medical Colleges published a report emphasizing that science should be brought to the bedside, with every faculty member having an obligation to conduct clinical investigations.<sup>4</sup> Over

the next three decades, clinical research laboratories and institutes were organized and established at numerous medical schools across the country. Financial support for full-time professorships, which were essential for the development of clinical research departments, was often provided in the form of grants from the General Education Board of the Rockefeller Foundation. Washington University in St Louis, Mo, received \$750 000 and Yale University, \$500 000 to establish full-time clinical teaching positions.<sup>1(p143)</sup> Departments of surgery frequently cited as placing emphasis on clinical research in the first half of this century included those of The Johns Hopkins University; Washington University; Vanderbilt University, Nashville, Tenn; the University of Rochester (NY); the University of Chicago (Ill); the University of Minnesota, Minneapolis; and the Mayo Clinic, Rochester, Minn. The latter institution recognized the importance of collaboration between the diagnostic services and the clinical sections. The enhanced productivity realized by the formation of research teams, including both clinicians and laboratory personnel, was exemplified in Dr Charles Mayo's studies and successful treatment of pheochromocytoma and Dr A. W. Adson's studies of the sympathetic nervous system and his subsequent clinical application of sympathectomy.<sup>1(pp374,377)</sup>

In 1930, the US Congress declared, "Scientific research is the most important function of the Federal Government as relates to public health" when they established the National Institutes of Health (NIH) (Bethesda, Md).<sup>5</sup> The budget of that organization has progressively increased, and it is now the principal federal agency supporting biomedical research. Until recently, clinical investigation had increased in proportion to funding, and the resulting productivity evident in the development of clinically beneficial pharmacologic and surgical interventions was met with increased popular support of such research. The success of government-directed research and development in World War II provided justification for the postwar expansion of NIH funding and proliferation of institutes. Continued NIH support for clinical research in the 1950s, 1960s, and 1970s was evident in the establishment of 74 general clinical research centers at medical schools and six program projects focused on trauma research.<sup>6</sup>

The US Army has had an even longer presence in clinical research than the NIH. Physiologically based clinical research began in the US Army on June 16, 1822, when William Beaumont was called to see the penetrating abdominal wound of Alexis St Martin,<sup>7</sup> and that tradition was carried forward in 1900, when Walter Reed identified the carrier of yellow fever.<sup>8</sup> The intensity of medical research in the military has always increased during times of war, as illustrated by the shock studies sponsored by the Medical Research Committee in World War I and the broad-based clinical studies of the Board for the Study of the Severely Wounded in World War II.<sup>9</sup> The increased funding and multiplication of NIH institutes after World War II were paralleled during and after World War II in the Army Medical Corps. A proliferation of categorical research units, the provision of secure funding, and ultimately, the formation of an independent medical research and development command have ensured

the continuity of focused clinical research activities within the Army Medical Department.

In 1947, the US Army Surgical Research Unit, originally established in 1943 (with Dr Edwin J. Pulaski as commander) to define the role of antibiotics in the treatment of war wounds, was moved to San Antonio, Tex, and assigned the new mission of caring for burn patients, teaching others about burn care, and conducting both clinical and laboratory studies of burn injury. That mission statement mandated the continuation by subsequent commanders (Dr Curtis E. Artz, Dr Edward H. Vogel, and Dr John A. Moncrief) of the multidisciplinary clinical and laboratory staffing of the unit and defined a primary patient care responsibility that to this day sets it apart from other military medical research units. Four integrated research programs serve as examples of the synergism that has been realized by the intimate collaboration of surgeons, other physicians, and allied scientists at what is now titled the US Army Institute of Surgical Research, San Antonio, Tex.

In the late 1950s, the use of the then-available antibiotics was associated with the frequent emergence of gram-negative bacteria in the wound flora of patients with burns. Conventional daily wound care effected débridement slowly; this resulted in a prolonged susceptibility of the wound to infection, which was most often caused by *Pseudomonas aeruginosa*, the predominant burn-wound pathogen of the time.<sup>10</sup> The emergence of *Pseudomonas* organisms in burn units preceded their emergence in other special care units by approximately a decade, and even today, tracking burn center infections allows one to anticipate epidemiologic changes in the flora of other critical care units.

The risk of invasive burn-wound sepsis was noted to be both age and burn-size related, as manifested by the high mortality rate in extensively burned patients, particularly those at either extreme of age.<sup>11</sup> The impression of our surgeons that the degeneration of the burn wound, which characteristically accompanied a fatal outcome, was a manifestation of infection was confirmed when pathologists were assigned to the burn center. The pathologists documented that uncontrolled proliferation of bacteria in the burn wound frequently led to the invasion of viable tissue and ultimately to hematogenous and lymphogenous spread of the invading organisms to remote tissues and organs in burn patients who died.<sup>12</sup>

An animal model of invasive burn-wound infection was then developed by Dr A. D. Mason, the surgical scientist who was and is the chief of the Laboratory Division of the Institute of Surgical Research.<sup>13</sup> That model reliably and reproducibly recapitulated the gross, microscopic, and clinical characteristics of invasive burn-wound sepsis and was used to confirm the prophylactic effectiveness of topical antimicrobial chemotherapy. The universal mortality of the model when bacterially seeded but untreated was converted to universal survival when seeded and treated by twice-daily topical application of a cream containing mafenide hydrochloride, which has since been changed to mafenide acetate.<sup>14</sup> Clinical application of that agent was attended by a striking decrease in *Pseudomonas* burn-wound sepsis and an asso-

ciated increase in the survival of burn patients<sup>15</sup> (Figure 1).

The elimination or control of one problem in critically ill patients often reveals and may accentuate, in a relative fashion, other clinical problems and causes of comorbidity. Even though the occurrence of invasive burn-wound infection has been reduced strikingly, infection in other organs remains the most frequent cause of death in burn patients, and the lungs are the most common site of infection.<sup>16</sup> The improvements in wound care have been associated with a marked change in the predominant form of pneumonia: the occurrence of airborne pneumonia now exceeds that of hematogenous pneumonia, and the formerly predominant causative organism *P aeruginosa* has been replaced by *Staphylococcus aureus*.<sup>16</sup> Moreover, the pneumonias that do occur are often associated with inhalation injury. In short, the control of infection in the burn wound has revealed the magnitude of the comorbid effects of inhalation injury and its bronchopneumonic sequelae.

In the mid 1980s, Shirani et al<sup>17</sup> reported that bronchopneumonia occurred in 38% of burn patients with inhalation injury, and they quantified the independent and additive age- and burn size-related mortality-enhancing effects of inhalation injury and pneumonia.

Identification of the clinical importance of inhalation injury promptly led to the development of a repro-



**Figure 1.** The use of effective topical chemotherapeutic agents, such as the mafenide acetate burn cream being applied to the wounds of this patient with extensive burns, and early excision essentially have eliminated invasive bacterial burn wound sepsis and have been associated with increased survival of burn patients.

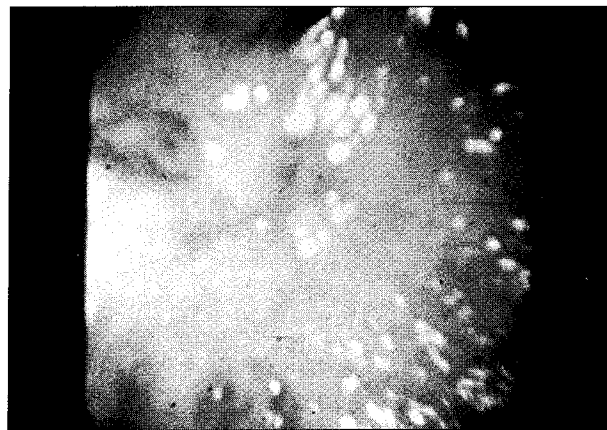


**Figure 2.** In the ovine model of inhalation injury, the morphologic changes mimic those in human patients. Note the finely particulate carbon particles evident on the mucosa of the right side of the trachea, edema of the airway mucosa indexed by foci of reflected light, and the mucoid membrane that has formed over the left side of the trachea and involves the bronchi.

ducible smoke-dose-responsive large animal model of inhalation injury in which the endobronchial changes mimicked those encountered in patients<sup>18</sup> (**Figure 2**). The use of that model enabled us to document the primary importance of small airway injury, demonstrate the disturbed matching of air flow and blood flow following inhalation injury, demonstrate the deleterious effect of ventilatory support using high concentrations of oxygen, and identify the beneficial effect of both pentoxifylline and an inhibitor of platelet activating factor.<sup>19-21</sup>

A primate model of inhalation injury has also been developed that was used to document the effectiveness of interrupted flow high-frequency positive pressure ventilation in maintaining lung volume and limiting the progressive atelectasis that occurs following inhalation injury.<sup>22</sup> That form of high-frequency ventilation has now been brought to the bedside of the burn patient. Prophylactic use of high-frequency positive pressure ventilation has been associated with a significant reduction in pneumonia in all patients with inhalation injury.<sup>23</sup> Moreover, the mortality in burn patients with clinically assessed mild inhalation injury is now no greater than that predicted on the basis of age and burn size, and the mortality in burn patients with clinically assessed severe inhalation injury has been significantly reduced compared with that in patients who received conventional ventilatory support.<sup>24</sup>

Stress ulceration of the upper gastrointestinal tract represents the third life-threatening complication that has been addressed effectively by an integrated program of clinical and laboratory investigation. In the 1970s, the technological developments that produced fiberoptic endoscopes permitted description of the natural history of stress ulceration in burn patients and documented that the incidence of gastritis and duodenitis was proportional to the extent of the cutaneous injury<sup>25</sup> (**Figure 3**). Additional clinical and laboratory studies evaluated the relationship of ulceration to changes in mucosal blood flow, mucous secretion, and gastric mucosal acid production.<sup>26</sup> The severity of mucosal disease was found to be related to acid production, and prophylactic antacid



**Figure 3.** Endoscopic examination reveals gastritic lesions as early as 5 hours after burn injury. Note the many focal dark gray areas of hemorrhagic change in the gastric mucosa and the characteristic bull's-eye lesion at the 10-o'clock position. The incidence of such changes is proportional to the extent of burn injury, and without antiulcer prophylaxis, the initially superficial erosions may progress to frank ulceration with surprising rapidity.

therapy was found to limit progression of the mucosal disease and significantly reduce the occurrence of hemorrhage and perforation.<sup>27</sup>

Subsequent studies confirmed that the histamine<sub>2</sub> receptor antagonist cimetidine exerted similar protective effects and was associated with more rapid repair of the mucosal injury.<sup>28</sup> In the 19 years since McAlhaney and Czaja demonstrated the protective effect of either neutralizing or reducing the production of gastric acid,<sup>27</sup> there have been only six burn patients treated at the US Army Institute of Surgical Research who have required surgical intervention for control of stress ulcer perforation or bleeding. In comparison with the 76 patients in whom such emergency surgery was required in the preceding 22 years, that represents a tenfold decrease. In each of the recent six patients who required surgical intervention, inadvertent cessation of prophylaxis had occurred prior to the bleeding episode.

The fourth program of integrated research was made possible by the installation of a dedicated study room in which the environmental conditions could be controlled. Using that room, we were able to define the neurohormonal changes that characterize postinjury hypermetabolism and orchestrate the distribution and utilization of nutrients.<sup>29,30</sup> Those studies have generated information defining the amount and type of nutrients necessary to maintain lean body mass in critically injured patients and have assessed the usefulness of pharmacologic intervention using human growth hormone, narcotics, inert gases, and most recently, insulin-like growth factor 1.<sup>31-33</sup> The animal component of those studies has documented that burn injury induces a resetting of thermoregulatory set points that control metabolic rate and that reduction of the bacterial content of the eschar is associated with a reduction in the magnitude of postburn hypermetabolism.<sup>34,35</sup> Those studies actually may have defined the specific energy cost of wound repair.

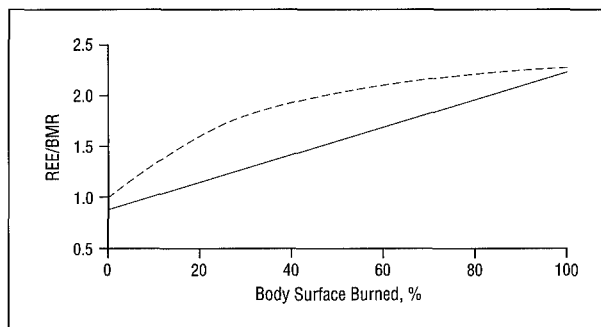
Recent clinical studies have confirmed that our current regimen of burn patient treatment is associated with a much reduced level of hypermetabolism compared with measurements made 20 years ago. In those recently stud-

ied patients, the metabolic rate is linearly, not curvilinearly, related to burn size and reaches levels of two to 2.5 times the predicted resting energy expenditure only when the burn involves 75% or more of the body surface<sup>36</sup> (**Figure 4**). These findings document a secondary benefit of improved wound care and emphasize the importance of bedside measurement of resting energy expenditure in order to match nutritional support to metabolic needs and avoid the complications of both underfeeding and overfeeding.

Consideration of the organization, environment, and personnel at the institution where this research occurred defines what I consider to be the essentials of the process by which effective integrated clinical and laboratory research can be carried out. A dependable and adequate number of patients is critical. Admission of 215 to 260 patients a year is ensured by use of the American Burn Association's major burn injury criteria for triage—and by the regulations of all three military services, which encourage transfer of patients with severe burns to the Institute of Surgical Research.<sup>37</sup> The medical and surgical specialists on the staff identify important clinical research questions in the course of providing care to those patients. Multidisciplinary staffing then facilitates the formation of research teams that consist of individuals whose discipline-specific expertises address the needs of individual research projects and programs. The active involvement of the laboratory staff, consisting of biochemists, physiologists, microbiologists, immunologists, and veterinarians, is essential for the conduct of correlative laboratory studies, the development of animal models, and the performance of specialized biomedical tests and assays.

Laboratory support capability must be state of the art, as illustrated by our use of the six-inert-gas technique to assess matching of air flow and blood flow in the lung in the inhalation injury studies, the use of stable isotopes and electron microscopy in the metabolic studies, and the microbiology culture techniques used in the wound infection studies. State-of-the-art technology is also required for physiologic monitoring in clinical studies. The importance of dedicated clinical study areas is illustrated by the essentiality of the environmentally controlled room in our studies of the metabolic response to injury.

When the disease process has been characterized in terms of pathogenesis and mechanisms of disease, the models or assays that have been developed can then be used to test therapeutic interventions. Following analysis of the data generated by such testing, promising interventions and therapeutic agents are taken back to the clinic for application to patients, initially to confirm safety and subsequently to generate statistical confirmation of clinical effectiveness and, in the best-case scenario, increased patient survival. Results of those studies must then be published to disseminate the findings to the medical community at large where, if additional studies and use confirm efficacy of the new treatment, it will be incorporated into patient care regimens. Clinical use of the new treatment typically begins the next iteration of the clinical and laboratory research cycle. Experience with new treatments quickly leads to the identification of treat-



**Figure 4.** Current techniques of burn patient care are associated with a linear and lesser increase in metabolic rate (expressed as REE/BMR) (solid line) as the extent of burn increases in contrast to the curvilinear increase (dashed line) reported in the mid 1970s (adapted from Carlson et al<sup>36</sup>). REE indicates resting energy expenditure; BMR, basal metabolic rate.

**Table 2. Benefits of Synergism of Integrated Clinical and Laboratory Research**

1. Importance of research topics ensured
2. Critical scientific mass maintained
3. Clinical relevance of animal models and model systems readily validated
4. State-of-the-art technology utilized
  - a. Clinical monitoring
  - b. Laboratory tests
5. Identification of new treatment limitations and side effects facilitated
6. Efficiency and economy of resource use optimized
7. Duplication of effort prevented

ment limitations and side effects and almost always to the emergence of other clinical problems and complications that previously were obscured by the problem for which the new treatment was developed. Those newly apparent problems then become topics of research projects. This reiterative process has been likened to the sequential opening of a linear array of doors.

The described integration of clinical and laboratory research results in a synergy that, among other benefits, ensures that the research process addresses clinically relevant problems in a fashion that will increase the understanding of disease and develop a solution to the research question or questions being asked<sup>38</sup> (**Table 2**). The clinical relevance of animal models and model systems is readily validated by the interaction between the clinical and laboratory personnel, and the clinical evaluation of laboratory findings is expedited by the ready access of the research team to patients with the disease of interest. Inclusion of allied scientists on the research team ensures the availability of state-of-the-art technology, and the inclusion of clinical personnel facilitates the identification of the limitations and side effects of promising new treatments developed in the laboratory as these treatments are evaluated in the clinic. Most importantly, the integration establishes the critical scientific mass that facilitates the free exchange of ideas and information among the members of the research team and the development of innovative approaches to research problems.<sup>39</sup> The close integration of clinical and laboratory personnel prevents duplication of effort within the institute and opti-

**Table 3. US Army Institute of Surgical Research (Houston, Tex) Teaching Activities, 1984-1993\***

| Educational Level | No. |
|-------------------|-----|
| Medical students  |     |
| Military          | 39  |
| Civilian          | 56  |
| Residents         |     |
| PGY 1             |     |
| Military          | 40  |
| PGY 2 and above   |     |
| Military          | 177 |
| Civilian          | 127 |
| Fellows           |     |
| US military       | 28  |
| US civilian       | 9   |
| Foreign           | 12  |

\*PGY indicates postgraduate year.

mizes the use of available resources to enhance research economy, efficiency, and productivity.

Secure funding is essential for research continuity, and it must be possible to employ the funds with flexibility. Reallocation of resources may be needed to exploit unexpected findings, rapidly expand promising studies, or in the case of burn and trauma centers, defray unanticipated patient care requirements generated by disasters and mass casualty situations. The stability of senior personnel ensures continuity of direction and effective mentoring activity and also makes available the institutional memory needed when unanticipated expansion of clinical activities is required.

The importance of experienced staff has been demonstrated repeatedly by the prompt responses of the Institute of Surgical Research to civilian disasters and military mass casualties. In 1989, within an 18-hour period, the staff organized and dispatched to Ufa, Russia, a 21-member team consisting of surgeons, nurses, registered practical nurses, respiratory therapists, a microbiologist, a microbiology technician, an anesthesiologist, a physical therapist, and an occupational therapy technician. The team members used the 7 tons of equipment and supplies that were sent with them to assist the Russian surgeons on-site in the care of more than 700 patients injured in a natural gas explosion. Similarly, in support of Operation Desert Storm in January 1991, the Institute dispatched three burn teams to Saudi Arabia to provide theater-wide burn care, dispatched a surgeon to establish a burn holding unit at a military hospital in Germany, and developed, in collaboration with the air force, a system for the transcontinental transfer of burn patients from that holding unit to the Institute of Surgical Research. Those actions ensured continuity and quality of care from point of injury until discharge from the tertiary treatment and study unit.

Both internal and external reviews must be carried out to document clinical relevance, scientific merit, and productivity of an integrated clinical research center. In the case of the Institute of Surgical Research, military relevance must also be ensured, and the frequency of burn injuries in combat makes clinical relevance synonymous with military relevance. The publication of re-

search findings in refereed medical journals is one accepted index of research productivity, and outcome analysis, in our case a probit or logit analysis of mortality, can be used to assess the quality of clinical care and document improvement in survival.

The academic achievement of staff members who have moved to other institutions may serve as another measure of the productivity of an integrated clinical research center and as an index of successful mentoring activity. Among the alumni of the Institute of Surgical Research, there are 86 who have attained the rank of professor in academic departments. Twenty-six of the alumni have become chairmen of medical school departments: 12 in surgery, four in plastic surgery, three in anesthesiology, three in medicine, two in urology, one in pediatric surgery, and one in physiology. Twenty alumni have become directors of other burn centers.

The clinical and laboratory integration described above establishes an environment of scientific curiosity and intellectual ferment that provides fertile soil for all levels of surgical education. The breadth and intensity of teaching at our institute is indicated by the medical students, interns, residents, and postdoctoral fellows who have spent time at our institute over the past 10 years (**Table 3**).

Just as integrated clinical and laboratory research at the US Army Institute of Surgical Research has led to improvement in the care of burn patients, similar research programs at civilian institutions have led to the development of effective nonsurgical treatment of peptic ulcer disease, pharmacologic treatment for cystic fibrosis and multiple sclerosis, the prevention of tooth decay, and a variety of vaccines.<sup>40,41</sup> Those developments, as well as improved nutrition, which has been heavily dependent on clinical research, have increased life expectancy in all industrialized countries during the past 100 years.<sup>42</sup> Advances in surgery, anesthesiology, and surgical critical care, largely resulting from clinical studies, have been credited with reducing the mortality rates of appendicitis, gallbladder disease, gastric and duodenal ulcer, hernia and intestinal obstruction, and benign prostatic hyperplasia. The mortality caused by those diseases decreased by as much as one 100-fold between 1968 and 1988.<sup>43</sup>

One would anticipate that the benefits that have accrued from integrated clinical and laboratory research would ensure continued support and perhaps even expanded funding, but such is not the case. In fact, a variety of budgetary, organizational, institutional, and personnel impediments are exerting progressively adverse effects on integrative clinical research. These negative factors range from the current reorientation of federal funding priorities to an apparent dearth of physicians adequately prepared or interested in clinical research.

In fiscal year 1993, the NIH provided \$174.1 million of extramural support to medical school departments of surgery compared with only \$84.9 million in 1984.<sup>44</sup> That apparently favorable trend is at risk as initiatives to decrease federal spending restrict expansion of medical research funding even though research receives only 3 cents of each dollar spent on health care.<sup>45,46</sup> The 1994 NIH budget of \$10 937 000 000 is being in-

creased by only 3.6% (just keeping abreast of inflation) to a 1995 level of \$11 334 000 000, or \$137 000 000 less than the President's budget request.<sup>47</sup> That trend is projected to continue since the Department of Health and Human Services has proposed a budget increase of only 4.2% to a level of \$11.8 billion for 1996.<sup>48</sup> In addition, proposals have been made in Congress to place a 50% cap on research grant indirect costs.<sup>49</sup> Fortunately, the Senate refused to approve the cap.

The Defense Department's budget for science has actually decreased in recent years. In fiscal year 1993, our institute's funding was decreased by 12%, and even though it increased in fiscal year 1994, that was only to cover the costs of caring for 43 patients burned when a plane crashed into a group of soldiers. In fiscal year 1994, only \$24.7 million was budgeted by the Army Medical Research and Development Command for all in-house and contract surgically oriented research. There is little prospect of even matching inflation in the current fiscal year, in which only a 0.9% increase will be realized in overall research and development funding by the Department of Defense.<sup>47</sup>

The current changes in research funding by the federal government have occurred despite a vigorous campaign mounted by the Federation of American Societies for Experimental Biology and other biomedical organizations, urging Congress to increase the 1995 NIH budget by 8.9% in order to support 25 000 new and continuing research project grants.<sup>50,51</sup> Those organizations have also asked the Department of Defense to maintain stable funding for the US Army Medical Research and Development Command, of which the Institute of Surgical Research is a component.

The tepid congressional support for biomedical research has been attributed to the systematic undervaluation of biomedical innovation.<sup>41</sup> The unfamiliarity of members of Congress and the public with the past accomplishments of NIH research and their lack of understanding that the NIH is the principal source of support for biomedical research performed at medical schools, nonprofit research institutes, and universities in the United States are also contributing factors.<sup>52</sup> The direct economic benefits of NIH research support to the general economy are also poorly understood. The competitive grants that were awarded by the NIH in 1990 provided full-time employment to more than 53 000 people.<sup>53</sup> Funds disbursed by the NIH have also been shown to provide needed support to the biotechnology industry and the Small Business Innovative Research Program.<sup>54</sup>

The support of clinical research by the pharmaceutical and biotechnology industries has also been constrained by concern over reduction of earnings caused by managed care and the threat of increasingly restrictive regulatory policies. Moreover, investigator reluctance to cede data management and analysis to commercial research sponsors has tempered acceptance of such support.

In recognition of the low rate of funding of NIH medical research proposals, several health system reform bills that included health research funds to augment NIH funding were introduced near the end of the 103rd Congress. When introducing his bill, Senator Hatfield noted

that medical research is "the cornerstone of cost containment" because it results in the curing of disease and improvements in the treatment of sick patients.<sup>55</sup> In light of that statement, it seems increasingly unsupportable that the insurance industry, which benefits from such cost containment, has essentially no research and development budget and provides so little support for integrated clinical research.

The increasing penetration of managed care plans into the health care system of the United States may also have a negative effect on clinical research. Such plans typically make no provision for teaching and research costs but, at present, usually provide for access to specialized treatment centers such as burn centers, trauma centers, and transplantation services.<sup>56</sup> It is my opinion that all such centers are fully compatible with managed care systems and function in many respects as self-contained mini-managed care programs. The clinical activities in such research centers typically revolve around a defined population in which the disease or condition of interest exists. In the case of a burn center, the use of nationally accepted criteria for admission eliminates the need for a gatekeeper's approval for admission. As in generic managed care systems, the specialized care is provided in a preselected treatment facility (the clinical research center) by a predetermined panel of physicians (the staff of the center). Care is typically rendered according to practice guidelines, which, for burn patients during the first 24 hours after injury, may consist of the recommendations contained in the *Advanced Burn Life Support Course: Instructor's Manual*<sup>57</sup> and the center's protocols and nursing service critical pathways thereafter. In the case of trauma centers, the *Advanced Trauma Life Support 1993 Instructor Manual*<sup>58</sup> provides early care practice guidelines, and in the case of transplantation services, treatment protocols commonly serve the same purpose. Finally, outcome analysis has been used to evaluate burn center performance for the past half century and is in no way a new or intimidating concept. In fact, logit or probit analysis of mortality data provides statistically rigorous documentation of the improvement in outcome that has occurred as a result of the integrated clinical research carried out at burn centers<sup>59</sup> (**Table 4**).

Managed care plans typically emphasize adherence to practice guidelines and thereby establish an austere cost-conscious environment that is hostile to innova-

**Table 4. Improved Survival of Burn Patients Admitted to the US Army Institute of Surgical Research (Houston, Tex), 1957-1991\***

| Starting Year† | Age, y |        |        |        |
|----------------|--------|--------|--------|--------|
|                | 5      | 21     | 40     | 60     |
| 1957           | 47.104 | 54.334 | 46.902 | 28.003 |
| 1967           | 45.599 | 53.553 | 45.376 | 24.584 |
| 1977           | 52.729 | 60.571 | 52.510 | 32.012 |
| 1987           | 72.154 | 81.905 | 71.881 | 46.391 |

\*Data for patients who were admitted within 48 hours of injury. Values are the percentage of body surface burned that is associated with a 50% chance of dying.

†Initial year of a 5-year window.

**Table 5. Administrative Impediments to Health Care and Research**

1. Accelerating proliferation of administrative positions
2. Increasing fraction of health care costs (US average, 24.8%)
3. Unjustified multiplication of forms to fill out, reports to prepare, and committees to meet
4. Inappropriate or inadequate qualifications of committees reviewing and evaluating integrated clinical research

tion and thereby likely to arrest medical progress in the name of cost savings. The association of an integrated clinical research center with a managed care system may exert an ameliorating effect on such treatment fixation. Recently proposed health care system reform measures that provide for ensured access to centers of excellence appear to recognize the value of such an association.<sup>60</sup> Interactions between the two organizations should permit the identification of further cost-saving treatments as a result of research activities that will, in turn, justify research support by the managed care plan and thereby benefit both organizations. Consequently, integrated clinical research centers are likely to survive health care system reforms and may well flourish.<sup>61</sup> Our institute has thrived within the army's managed care system, which is responsible for over 3 million (3 035 488) beneficiaries.

There are also institutional impediments to integrative clinical research at both the national and local levels. In recent years, reductionistic, commonly laboratory-based research has received an increasingly large proportion of NIH funding.<sup>62</sup> The overall success in obtaining NIH funding has decreased from a success rate of 45.3% in 1975 to 23% in 1990 and, at some institutes, to only 10% to 15% of grant proposals in recent years.<sup>63,64</sup> Two thirds or more of the NIH research grant portfolio is now held by persons with doctor of philosophy degrees, who engage largely in reductionistic research, and only about one fifth of the portfolio is held by doctors of medicine, who are more commonly involved in integrative clinical research.<sup>6</sup> The remainder of the portfolio is held by individuals with both degrees. The NIH study sections have apparently placed emphasis on the rapid exploitation of new technological developments and the precision of laboratory studies at the expense of less precise, more difficult to control integrative clinical research.<sup>62,65</sup>

There are a surprising number of administrative limitations to productivity and cost-effectiveness at all levels of health care and research (**Table 5**). One of the greatest of those impediments is the apparently limitless increase in administrators and administrative requirements. The excessive proliferation of those administrators, noted as early as 1984 by Wohl,<sup>66</sup> has continued to this day. Administrative costs in US hospitals overall averaged 24.8% of total spending in 1993 and, in individual states, ranged from 20.5% to 30.6%.<sup>67</sup> In a letter to the editor of the *New England Journal of Medicine*, Sweet<sup>68</sup> graphically displayed the extension of present trends in administrator multiplication and the reduction in hospital bed occupancy rate. She demonstrated that by the year 2026 there will be 2 508 600 adminis-

trators in US hospitals, which will, by that time, be devoid of patients.

It is my suspicion that administrators aggrandize their position by developing new forms and reports that require them to expand their staff simply to file the forms and, at times, even analyze the data. At the present time, our institute completes, on an annual basis, four overlapping progress reports for each research project. In addition to those, each directed inquiry results in a specific data call to supply information typically contained in those reports. These duplicative reports represent an inappropriate use of our investigators' time and, thus, an impediment to medical progress. Scientific research at universities is similarly burdened by federally mandated administrative impediments.<sup>69</sup> Inasmuch as physicians and investigators are required to justify their productivity and the quality of their outcomes, we must also insist that the reports, forms, and committee activities imposed on us by research and hospital administrators be justified on a cost-benefit basis to reverse the current multiplication of reporting requirements and the proliferation of bureaucrats.

Another administrative problem resides in the composition of committees that review clinical research reports and clinical research grant applications. The increasing number of reductionistic research grants has prompted some to call for a reorientation of the NIH institutional review groups and the Division of Research Grants. Suggestions have been made to increase the number of clinical investigators on the surgical study sections or, alternatively, to establish a patient-oriented research study section, to which each institute's overall pay line would be applied to approve patient-oriented research applications in the same proportion as other applications.<sup>62</sup> Others have arbitrarily proposed that 50% of available funds be targeted for investigator-initiated patient-based clinical research to redress the imbalance between laboratory and clinical research that has been created over the past two decades.<sup>70</sup> A subpanel of the National Cancer Advisory Board recently asked Congress to provide an extra \$60 million to be spent on research to expedite patient-care application of laboratory findings.<sup>71</sup>

Committees that are responsible for reviewing and assessing clinical research but have no members with the necessary experience or qualifications represent another problem. Six weeks ago, I received the review of our institute's 1993 independent research program, which indicated that the review panel had a basic appreciation of the importance of the clinical care and laboratory research integration that exists at our institute. However, the review went on to say that "the only problem is that it is not clear the world needs more burn research—or that animal models will remotely improve human medicine." That statement was so astonishing that I explored the composition of the review committee and found that there were no physician members, let alone surgeon members, who were knowledgeable about clinical research. The question about whether the world needs more burn research simply confirms the medical isolation of the panel members. That review panel may deem the world not to need more burn research, but the surgical and medical

research consultants on the NIH Trauma Research Task Force do not share that opinion. The recent report<sup>72</sup> by that task force lists 14 burn-specific and burn-related research priorities in support of reprogramming the NIH budget to provide more support for trauma and burn research (**Table 6**).

The statement in that panel's review about animal models, which is readily refuted by the examples of clinical progress that I have cited, is of particular concern because it indicates the extent to which the agenda of the antivivisectionists is being inappropriately advanced. The activities of the antivivisectionists, decried by Dr Charles W. Mayo in his Presidential Address in 1963,<sup>73</sup> have caused additional costs to be imposed on laboratory research, most often in the form of duplicative reporting requirements and, in recent years, terroristic vandalism that increases security costs.<sup>74</sup> The statements by this panel indicate a critical need for the review and, as necessary, revision of the composition of governmental and non-governmental committees charged with reviewing clinical research to provide the needed expertise and ensure a more equitable assessment of the accomplishments of integrative clinical and laboratory biomedical research.

Finally, the length of preparation for a research career, the relatively low level of remuneration, the increase in clinical practice obligations, and the difficulty encountered in obtaining research support as a principal investigator all act as disincentives to those surgeons considering a career in clinically oriented research. Preparation for a clinical research career is given little attention in medical school, where laboratory experience in modern medical science is commonly limited.<sup>6</sup> The lengthening of residency training programs and the 4-year clinical research training program or fellowship that appears necessary to enhance success in getting grants combine into a daunting duration of preparation for many potential investigators.<sup>75</sup> The indebtedness of many medical school graduates makes the income differential between private practice and a career in clinical research a disincentive for the latter.<sup>6,76</sup> Moreover, the increased competition-generated emphasis on practice income in the academic research center reduces the time available for research and blurs the distinction between private practice and a full-time faculty position.<sup>77,78</sup> In short, full-time faculty positions, which played such a central role in the development of clinical research, are being imperiled by the economic realities of the day. If present trends continue, such positions may only exist at integrated research institutes such as ours.

Economic realities are also evident in the chilling effect of the low rate of funding of grant applications submitted to the NIH. Recent success rates of NIH applications for new biomedical research grants have been less than 20% overall. In 1989, the success rate for RO1 grant renewal applications to the National Institute on Aging was 28.4% but was only 16.9% for new applications.<sup>79</sup> Such a funding rate for new proposals means that six applications must be submitted for each award received. This low rate of research grant approval appears to have caused a marked decrease in the number of NIH grant proposals submitted in 1993 by young investigators, which resulted in a 54% decrease in first NIH grant awards to in-

**Table 6. Burn and Wound Healing Research Priorities\***

1. Devise a population-based model using observational data to assess the effects of therapeutic interventions on burn patients
2. Develop accurate methods to assess burn size and burn depth
3. Develop a burn severity index
4. Establish a clinically relevant model of inhalation injury to assess treatment
5. Promote the study of receptor mediators of pain
6. Evaluate alternative analgesic delivery systems
7. Develop longitudinal studies of rehabilitation of burn patients
8. Assess the effects of pending litigation on disability resolution
9. Evaluate the effects of early intervention on psychological dysfunction
10. Develop programs to increase the use of smoke detectors and to prevent tap water scalds
11. Promote fire-safe construction
12. Increase emphasis on fire-safe cigarettes and cessation of smoking
13. Support basic studies of modulation of inflammatory response
14. Support basic studies of hormonal modulation of postburn hypermetabolism

\*Information taken from A Report of the Task Force on Trauma Research.<sup>72</sup>

vestigators under the age of 37 years.<sup>80</sup> Those factors and an alleged paucity of clinical research role models have been cited as the reasons for the declining interest of physicians and surgeons in clinical research careers.<sup>62,81</sup> The NIH has responded to those concerns by developing new programs to encourage research activity. Those programs begin at the medical student level with the medical scientist training program and include a series of career development awards, such as the clinical investigator award, the special emphasis research career award, and the career development award series, in which the physician-scientist award provides 5 years of phased supervised research training.<sup>6</sup>

In summary, the development of clinical research in the United States, which began in the 19th century, was dependent on the establishment of the required clinical facilities, the necessary laboratory capabilities, and a stimulating intellectual environment. Full-time faculty positions for appropriately trained clinical scientists ensured the successful integration of clinical care and laboratory research that accelerated patient-oriented research productivity in university medical centers and specialized treatment centers in the US Army Medical Corps and other organizations. The research conducted in such centers has improved the care and survival of surgical and other patients, increased overall longevity, and been of both direct and indirect economic benefit to our country. Those accomplishments must be made known to the members of Congress and government funding organizations, health care planners, our colleagues, and the public to ensure continued research funding and support as we work to overcome the financial, organizational, administrative, and educational problems that appear to be compromising integrative clinical and laboratory research.<sup>54</sup> We must also maintain the amalgamation of clinical excellence and laboratory research expertise in single organizational entities, which are able to achieve what neither of their component parts can accomplish alone. The integration of such organizations into

managed care systems must also be promoted to ensure continued improvement in the care of severely injured, critically ill patients and to realize the associated cost-savings. Last, it is essential that we increase the general understanding that new treatments and techniques are developed at high-technology research centers and medical schools, not at cost-competitive treatment facilities.<sup>82,83</sup>

As I noted above, each solution to a clinical problem typically reveals other previously inapparent problems, and such is the case with the four examples presented. Investigation of those newly obvious problems is already under way in current iterations of the integrated clinical care and laboratory research process. The ongoing studies will generate data from which solutions to continually evolving clinical problems can be developed. Those treatment advances will further improve the care and survival of burned and other surgical patients beyond that achieved to date and maintain the velocity of biomedical progress into the next century.

*The opinions and assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.*

*Presented at the 1994 Annual Scientific Session of the Western Surgical Association, Palm Desert, Calif, November 14, 1994.*

*Reprint requests to Library Branch, US Army Institute of Surgical Research, 2322 Harney Rd, Fort Sam Houston, TX 78234-6315 (Dr Pruitt).*

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