

# Surgeons, Surgery, and Immunomodulation

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• With the definition over the past 15 years of the altered immune state of surgical patients as a result of disease itself and surgical therapy, there have been multiple approaches to the modulation of immune status in experimental or clinical situations, but with conflicting or unhelpful results. The variable that has never been assessed is the significance of the surgeon as an immunomodulator. The expediency and the quality of the surgical act in a variety of surgical diseases have a positive effect on the immune system. Indeed, the data indicate that correction of shock, drainage of infection, excision or drainage of necrotic material, restoration of body composition, and solid basic care all have a positive influence on patients' immune responses. An immunomodulator might get credit if the role of surgical care is not properly assessed. A framework for the study of immunomodulators with the integration of clinical behavior is outlined.

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The infectious complications of surgical illness and trauma continue to have a major impact on morbidity and mortality. Advances in trauma care and a clearer understanding of the physiologic characteristics of surgery, shock, and surgical illness have led to increased salvage of early mortal illness and injury, but at a cost in late complications, such as multiple-system organ failure and the septic syndrome. Control of infection and infectious complications remains, therefore, an important objective.

Most surgical patients are widely acknowledged to have some reduction of host resistance because of underlying or primary significant diseases, operation(s), trauma, and/or complications; therefore, they should be considered immunocompromised. This state has led to a search by many groups for an immunomodulator, a "Holy Grail,"<sup>1</sup> to correct this state, a quest that to present has not been successful. Surgeons and surgery will be shown to have an important influence on host factors that can contribute to the reduction of infection and its impact on morbidity and mortality, indicating that the immunomodulator is quality and details of care. Until these clinical aspects of modification of host responses are clearly understood and standardized, pharmacologic modulation must be viewed with some skepticism.

## THE SURGICAL PATIENT: AN ALTERED HOST

Acquired immunodeficiency is a common, almost normal state for surgical patients.<sup>2</sup> Descriptive immunological studies of a wide variety of surgical diseases,<sup>2</sup> trauma of all types,<sup>3,5</sup> and operations<sup>6-9</sup> and their complications<sup>10-13</sup> have demonstrated a broad-based set of abnormalities that touch all aspects of the immune response. Who has these abnormalities? Do they really matter? The answer to the first question is that patients likely to have significant changes in immune response can be identified either by classification in a population known to be abnormal—burns, major trauma, malnutrition, or septic complications—or by the presence of abnormal skin test results, which, while they do not identify defects, indicate which patients are likely to have defects in host defenses.<sup>2,12,14</sup> Patients known to be abnormal already do benefit from clinical immunomodulation; clinical practice has adapted to many aspects of these patients and not only restores immune responses but also restores the patients to health. Patients with abnormal skin test results are likely to be an appropriate population for the study of immunomodulation. However, before this is possible, better criteria are needed for the patient truly at risk for septic morbidity and mortality.

Does it matter that surgical patients have major immune defects? The clinical evidence seems overwhelming but does suffer from "being associated" with complications.<sup>2,5,10,12,13</sup> Direct cause and effect have been hard to prove but have been seen most convincingly when surgery and its adjuvant therapy have restored immune responses along with health.<sup>10,12</sup> The concordance of acquired defects and septic deaths has been recently shown by Moss et al.<sup>15</sup> The determinants of infection provide a useful framework to integrate clinical approaches to show that surgeons and surgery can be immunomodulatory.

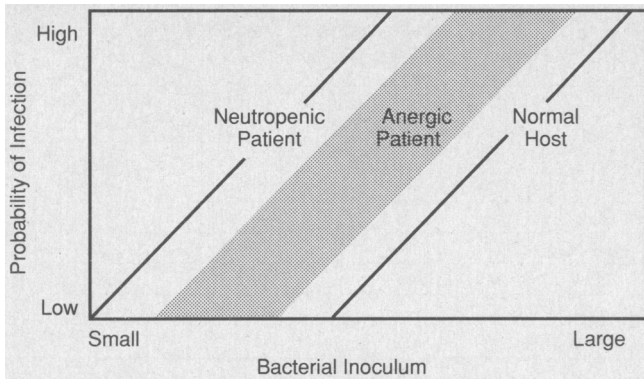
## THE DETERMINANTS OF INFECTION

The development of an infection is a dynamic process involving many factors that can be classified into three determinants: (1) the *microorganism(s)* producing the infection, (2) the *environment* in which infection takes place—the local defenses, and (3) the *host defense mechanisms*, the systemic responses to bacteria established in tissue—the immune system.<sup>2</sup> There is normally a continuing interaction among these factors; there are frequent breaks in mucosal and cutaneous barriers that, although organisms are present, do not become infected. In addition, the commensal flora prevent pathogenic organisms from invading, and those that do invade are dis-

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The anergic patient represents the surgical patient at increased risk of infection. As host defenses approach normal, resistance to infection increases, and a larger inoculation can be tolerated with a low incidence of infection.

persed by local (environmental) and systemic responses. There is a dynamic balance between the determinants.

If all the interwoven factors could be identified and weighted, an equation would result.

$$P(\text{infection}) = K + A(\text{bacteria}) + B(\text{environment [local factors]}) + C(\text{host defense mechanisms [systemic factors]})$$

The schematic approach is presented to introduce the concept of sepsis as a process in which the surgeon can and indeed does influence each determinant.<sup>2</sup> All surgeons have been faced with the patient who appeared to have a negligible injury or a good operation but who rapidly dissolved in pus. Any one of the three determinants might be responsible: an extraordinarily virulent organism, a technical error, or abnormal resistance to infection, with an inability to contain even the slightest microbiologic contamination. More likely, a combination of small abnormalities in two or even three determinants is responsible.

### CLINICAL MODULATION OF THE IMMUNE RESPONSE

The surgeon wears two hats: one as the physician required to manage all the needs of his or her patient, and the other as the physician who can perform an operation and fix the problem. Both roles can have profound implications for the immune system. Before immunomodulation can be considered as a pharmacologic issue, it must be examined from a clinical point of view. Clinically, it seems obvious that correction of the etiologic or underlying factors that led to the anergic immunocompromised state might improve the situation. Therein lies one of the great values of descriptive biology. The benefits are seen by changes in clinical behavior.

#### The Surgeon as Immunomodulator

If the term *anergic patient* is used to represent the compromised surgical patient, the Figure represents the clinical challenge. The challenge is to take a patient with a high probability of infection and care effectively for this problem without causing infection. Years of discussion have changed behavior, and it is useful to show that clinical approaches change to meet a better understanding of a problem. The clinical goal is to move the region indicating increased susceptibility to infection ("Anergic Patient" in the Figure) to the right (toward "Normal Host"), allowing the patient to cope with a larger inoculum of bacteria while having the same or a lower risk of infection. The first step is a nonoperative approach to modulating the host.

There have been significant changes in the approach to preoperative assessment in recent years. The approach to the

cardiovascular system has changed radically since Goldman et al<sup>16</sup> clearly defined risk factors and has changed further since the studies of Del Guercio.<sup>17</sup> The maintenance or restoration of normal physiologic characteristics—here, blood volume, oxygenation, and perfusion—becomes the key to preventing complications. Hunt's work<sup>18</sup> demonstrating the importance of Pao<sub>2</sub> and tissue oxygen levels in wound healing and resistance to infection extends the importance of maintaining and supporting normal physiologic characteristics.

In the traumatized or bleeding patient, rapid resuscitation, control of blood loss, and restoration of blood volume are the key elements to avoid late ischemic effects, such as acute tubular necrosis, peripheral ischemia, stroke, myocardial infarction, intestinal ischemia with ulcers, adult respiratory distress syndrome, and multiple organ failure.<sup>19</sup> There is clear evidence that resistance to infection is altered at the time of shock and for up to 5 days after shock.<sup>20,21</sup> In both time frames there is an inoculum effect; that is, infection rates are markedly altered by numbers of bacteria. Shocked animals require many fewer organisms to generate infection compared with normal animals.<sup>20</sup> These results would be expected in the short term, because altered perfusion decreases the inflammatory response and resistance to infection at the time of contamination.<sup>20,22</sup> However, the resistance to infection is reduced for up to 5 days. This effect can only be mediated through a significantly altered systemic immune response, as all local perfusion defects will have long been corrected. These observations are further supported by Rush et al,<sup>23,24</sup> who have shown the role of shock in the development of systemic infection in humans and animals. Hemorrhage has also been shown, as a function of volume of blood loss and transfusion requirements, to be associated with anergy.<sup>25</sup>

The implications for care are clear. Bleeding and trauma, the basic causes of shock, usually require a surgical solution. Resuscitation and management of the bleeding source with speed and efficacy are critical to reducing the late systemic effects of shock. Prevention and control of hemorrhage in the operating room is crucial both for early and late effects. Once shock has occurred, the surgeon must behave as if the patient were immunocompromised, with alterations of both local and systemic host resistance.

The incidence of postoperative infections—wound, urinary, and pulmonary—have been substantially reduced over the last 15 years.<sup>26,28</sup> Antibiotics are a part of the improvement, but the totality of preoperative and postoperative care has improved significantly. The literature abounds with reports of major operations that in the past were associated with major infectious morbidity and mortality now being done with vastly improved results and much reduced rates of infection.<sup>28,29</sup> The aspects of care responsible for the improvement include the following: better fluid management, maintenance of tissue perfusion and oxygenation, early mobilization, a better understanding of metabolism, and preoperative preparation.

A fine example of the efficacy of total care is seen in the management of Crohn's disease by Hill et al.<sup>30</sup> They integrate preoperative preparation, drainage, details of care, control of inflammation, and nutritional support with eventual surgical repair, and their results are excellent. Patients with Crohn's disease, when ill, are known to have major abnormalities in their immune systems that correct themselves following control of the disease by either medical or surgical therapy (Table 1). The appropriate treatment modulates the immune response and should be thought of as a biologic response modifier. Controlling the disease controls its expression, one aspect of which is immunosuppression.

Control of the stress response—the inevitable reaction to trauma, surgery, and infection—has been shown recently to

	Before Treatment	After Treatment
Severity of disease by Crohn's disease activity index*	341.2 ± 33.0	63.7 ± 23.1
Skin test results, No. of patients		
Reactive	0	10
Relative anergy	7	0
Anergy	3	0
Neutrophil chemotaxis, $\mu\text{m}^*$	103.7 ± 3.2	126.6 ± 2.3
Neutrophil delivery to skin windows, $\times 10^{*6}$		
6 h	0.5 ± 0.2	11.4 ± 2.0
12 h	25.2 ± 12.5	144.4 ± 23.1

\*Values are mean  $\pm$  SD.

be feasible.<sup>31-33</sup> While this may be a two-edged sword, as manipulating biology always is, the benefits may be significant for patients with respect to improved control of infection, decreased catabolism, and earlier return to function. Nutrition,<sup>33-36</sup> prostaglandin inhibitors,<sup>37</sup> and regional anesthesia<sup>32</sup> can all influence the stress response, as, indeed, can control of infection.

The failure of immune responses can perhaps be best seen in a patient with persistent tertiary peritonitis,<sup>38</sup> in which the peritoneum is unable to localize infection or produce pus, leading to a thin, watery peritoneal fluid and no localization or fibrin formation. Wound granulation tissue appears unhealthy, with a pallid, ragged look and no evidence of healing. During the period required to control the infection and remove necrotic material, supportive care, particularly nutrition, is mandatory to maintain the patient's hypermetabolism. With control of infection, ie, supportive care, dressings and drainage (open or closed), nutrition, and antibiotics, there is a sudden, dramatic change in the appearance of the wound's granulation tissue, and fibrous adhesions develop in the peritoneum. The frequency of dressing changes can be seen to influence the response. When the frequency of dressing changes is inadequate, hypermetabolism and organ failure occur, clearing with better wound management and control of the local infection.

Nutrition is believed in but not completely proved as an immunomodulator.<sup>34,36</sup> There can be no doubt of its importance in supportive care of the critically ill and in the maintenance or restoration of body composition. Nutrition has great importance in underdeveloped countries. Refeeding can exacerbate the signs and symptoms of infection by restoring the host's response to infection. The use of specific amino acids is showing promise, specifically glutamine<sup>39</sup> and arginine.<sup>40</sup> The data are promising and the maintenance of fuel and energy requirements<sup>34</sup> is essential, but the exact role of nutrition per se and of specific nutrients as immunomodulators is uncertain and requires further exploration.<sup>36</sup>

### Surgery as Immunomodulation

The surgical act modifies the immune response. There is a wealth of data showing that surgery, as a function of its duration, complexity, and magnitude, directly influences the immune reactions.<sup>6-9</sup> Surgery is immunosuppressive. In this context, the quality of surgery can significantly influence the development of infections and other complications.

The importance of the surgeon and technique can best be seen in the interplay between the determinants of infection and the surgeon's role in prevention of wound infection.<sup>41</sup> With

Operation	Improvement in Skin Test Results	
	No. of Patients	Mean No. of Days
Biliary tract surgery	11	5.7
Resection of colon cancer	8	6.6
Relief of bowel obstruction	5	8.2
Control of hemorrhage	5	5.8
Miscellaneous	3	5

preoperative care, the surgeon can give his or her patient the best chance to resist infection by improving host variables and diminishing potential bacterial contamination. In the operating room, bacteria can be controlled; an operation done perfectly leaves a wound that is best able to resist infection. For example, in a patient with 12 hours of fecal peritonitis, the wound should not be closed primarily. Infection rates are 50% to 70%, and infection has important sequelae. Cruse<sup>26</sup> and Olsen et al<sup>27</sup> have shown that keeping individual surgeons informed of their wound infection rates keeps infection rates low. Hemostasis has been shown by Polk and Lopes-Mayor<sup>42</sup> to be critical to the number of bacteria required to infect a wound. Without antibiotics, poor hemostasis reduces by 2 to 3 logarithms (from 10 000 organisms to 10 to 100 organisms) the number of bacteria required for a 20% wound infection rate in a contaminated wound.

Many variables under the surgeon's control have an impact on the determinants of infections,<sup>41</sup> and those factors that influence wound infection also influence the development of deep infections at the operative site and, therefore, the results of major surgery.<sup>42</sup> However, rather than a simple wound infection, the resulting infection or complications will be more serious, and the mortality rate may increase. The principles of gentle tissue handling, atraumatic anatomic dissection, careful hemostasis, preservation of the blood supply, and anastomoses without tension will improve results. In addition, modern anesthesia and monitoring techniques have eliminated the demand for speed, which was once a measure of skill. The surgeon's persona should no longer be linked to the duration of the procedure; results count.

In published series, there is considerable variation in infectious morbidity after hepatic resection.<sup>29,43,44</sup> Subphrenic abscesses remain common in published reports and therefore in unpublished series, yet it is possible to do resectional surgery of the liver with very low (1%) mortality and infection rates.<sup>29</sup> Crist et al<sup>29</sup> recently compared results over time and showed that pancreatoduodenectomy can be performed with very low morbidity and mortality rates. Thus, excellence of surgical technique and the preservation of local and systemic host responses by gentle, nontraumatic surgery has a major role as a potential immunomodulator.

Can the operation itself restore immune responses? Unequivocally, yes; resection of pathology or inflammatory foci and drainage of abscesses can return altered host defenses to normal.<sup>2</sup> Specifically, complement components,<sup>45</sup> fibronectin,<sup>11</sup> neutrophil chemotaxis,<sup>10</sup> and skin test results,<sup>13</sup> among other factors, show clear improvement. There is no immunomodulator as effective as the drainage of infection. Resection therapy can similarly have a profound effect on the immune system. Table 2 shows a variety of surgical conditions, all of which had improvement in skin test results following surgery, showing the connection between the operation and improvement in immune function.<sup>13</sup>

The presence of ascites uncontrolled by salt restriction, bed rest, and diuretics is invariably associated with a serious state of malnutrition and altered immune competence.<sup>46</sup> If ascites cannot be controlled, the prognosis is dismal. Peritoneovenous shunting, when performed in a meticulous manner,<sup>47,48</sup> permits cirrhotic patients to recover body composition<sup>49</sup> and immunocompetence via a number of mechanisms.<sup>46</sup> Shunts must be placed with zero mortality and low morbidity to be effective. Placing shunts, however, allows immunomodulation, as control of ascites is associated with recovery of appetite, sense of health, and other imponderables, leading to some recovery of liver function.

### Unintended Effects of Therapy

Pharmacologic regimens have many effects, some of them unintended. These unintended effects can, in precarious situations, create complications. The use of cimetidine or antacids for the prevention of stress ulcer and hemorrhagic gastritis is very common in surgical intensive care units. The unintended effect is overgrowth of bacteria and a gastric reservoir of organisms, with a loss of acidity; it is now clear that this is responsible for many if not most nosocomial bacterial pneumonias in the intensive care unit.<sup>50-52</sup> In addition, there is now evidence that bacteria in the proximal gut may be associated with multiple organ failure and its associated infectious complications.<sup>53</sup> Incidental data from Driks et al<sup>50</sup> indicate that, in patients with a normal gastric acid barrier, ie, those treated with a cytoprotective agent, there is improvement not only in infection rates but also in noninfectious respiratory morbidity and death, suggesting that the stimulus to multiple organ failure is controlled.

The question of steroids and septic shock is now resolved.<sup>53,54</sup> Steroid therapy does not improve outcome in septic shock or the septic syndrome, despite positive results in animal models, and steroid therapy appears to substantially increase mortality rates from secondary infection, although it does not increase the incidence of secondary infection.<sup>55</sup> This can only be the result of an altered systemic host response. The infection rates are the same, but the immunocompromised patient is less able to resist the same number of bacteria, showing the significance of the interplay between determinants.

It has been suggested recently that transfusions have immunosuppressive effects. The effect seems most clear in transplantation. Studies in colorectal<sup>56</sup> and other cancers suggest that the onset of recurrences and long-term survival may be influenced by transfusions. The improved immune response following resection of Crohn's disease<sup>56</sup> is impaired if transfusion is required, although transfusion may be associated with decreased recurrence rates. The increased susceptibility to infection in many animal studies is almost impossible to confirm clinically, but these results are very suggestive.<sup>57,58</sup> Many potential confounding variables may contribute to the increased immunosuppression, and these must be explained before firm conclusions can be reached. Transfusion requirements in major surgery are being reduced by a variety of modern clinical techniques.<sup>59</sup> However, in a trial of immunomodulation, transfusions themselves would become a confounding variable.

### Summary: Clinical Behavior and Immunomodulation

Despite the sense that little has happened in the field of immunomodulation, this clinical review shows that there has been progress. Biologic insights have been translated into changed clinical practice, and traditional clinical activities have been shown to positively influence biology. However, the results are diffuse and gradual and therefore hard to recognize. Biologic immunomodulation must be approached

Table 3.—Steps to Clinical Trials of Immunomodulation of Infection

Definition of specific defects in vitro and their correction by an agent Animal models of defects with infection and improvement of abnormalities and outcome The in vivo correction of defects in the patient population to be studied A clinical trial in specifically defined and stratified surgical patients with acquired immunodeficiency
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on the groundwork of clinical progress and must incorporate all the modulatory factors mentioned above to ensure that study results are accurate.

### AN APPROACH TO TOMORROW

In the future, whichever of the many immunomodulatory regimes becomes clinically feasible, a specific framework for evaluating its therapeutic importance must be developed. In addition to the usual criteria of study design, two specific issues must be integrated into studies assessing biologic response modifiers and surgical sepsis. The first set of criteria are outlined in Table 3. The request that the agent correct immune defects in vitro, then in vivo in animals with outcome efficacy, and that the same steps should be followed in clinical application seems to be a minimum requirement to determine which drugs might be suitable clinically. There must be an orderly and sequential approach to efficacy to avoid the many stuttering steps taken in the many disappointing attempts to bring biologic response modifiers into the clinical setting. Levamisole provides an excellent example of enthusiasm and hope interfering with judgment. Sketchy studies suggested efficacy in many areas, and suddenly there was a tidal wave of applications and articles. Levamisole is making something of a comeback in the adjuvant care of colon cancer and is again caught up in controversy between enthusiasts and those concerned with rigorous evaluation. It appeared to be successful in preventing infection following surgery,<sup>13</sup> yet, after a careful assessment, a second set of criteria became apparent.

In this study, the control group showed that surgery itself could correct all of the immune variables assessed. Testing an immunomodulator under the circumstances described by Fielding et al<sup>60</sup>—in a multicenter trial, differences in anastomotic leak rates and mortality rates in patients who had undergone colorectal surgery were demonstrated to be surgeon-related—would not lead to comprehensible results. Maintenance of local and systemic host defenses and control of bacteria—functions of surgical technique—should make results from all centers equivalent. It would then be possible to study a biological response. Therefore, the clinical aspects of care and their evident significant immunomodulatory influence need to be carefully integrated into the study design and standardized to ensure that confounding variables based on the quality of care do not influence conclusions. The early sections of this article showed that surgery and surgical practice have measurable effects on the immune responses.

### CONCLUSION

To bring biologic modulation of the immune response to clinical application, two significant additions must be made to the usual design of a clinical trial. First, the agent must be demonstrated to fulfill the steps outlined in Table 3 to have a minimum chance of success. Second, clinical behavior clearly alters the immune response, either its upregulation or downregulation, and clinical behavior must be totally integrated into study design and standardized to ensure that studies will give an answer supported by the data and devoid of enthusiasts' hyperbole.

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