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The Effect of Anesthetic Agents on the Human Immune Response

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CONTENTS

FOR MANY YEARS, researchers and clinicians have been concerned about the potential impact of anesthetic agents on human immune system function. This interest stems from a variety of theoretical and clinical observations centering around both the high rate of infections seen in postoperative patients[15] and the demonstrated bone marrow depression after prolonged anesthetic exposure.[5,48] Concern regarding the impact of anesthetic agents on immune system function has been heightened as a reflection of modern understanding of functional capabilities of the human immune system, including the cancer protective function of the immune system.[26,90] At the same time, the recent emergence of the acquired immune deficiency syndrome (AIDS) has stimulated researchers to determine the potential adverse effects of anesthetic agents on patients with pre-existing immunodeficiencies. The purpose of this review paper is to summarize previous clinical observations regarding the immunosuppressive effects of anesthetic agents, to correlate this information with the preclinical research data base that has accumulated, and to abstract the net impact of these understandings on clinical anesthetic administration in the future. This review will be specifically limited to human studies, using anesthetics at clinically relevant concentrations; it will not review allergic reactions to anesthetic agents (IgE-mediated and anaphylactoid responses). In order for the details of this review to be placed in their proper perspective, this article will begin with an overview of normal human immune system function, as currently understood.

Overview of Human Immune System Function

The primary purpose of the human immune system is to distinguish "self" from "nonself" and to clear "nonself" antigens from the body. "Nonself" antigens can range from bacteria, viruses, and fungi to cancer cells and transplanted organs. The precise mechanisms of immune recognition and elimination of antigens are still incompletely understood and are the subject of intense ongoing investigation. There are two known major components of immune system function: nonspecific and specific. Nonspecific immunity is a first line defense against "nonself" invaders. No prior exposure to the antigen target is required for the host to activate nonspecific immune system components; thus, a wide range of targets can be neutralized in a nonspecific fashion. Specific immunity, in contrast, refers to immune system components that seek out specific targets. The cells that confer specific immunity are only capable of interacting with a limited subset of closely related "nonself" invader molecules (antigens), and prior exposure is required for optimal function. Both specific and nonspecific immunity are composed of cellular and noncellular (humoral) components.

The specific and nonspecific components of the human immune system can be organized into five basic categories (fig. 1): 1) antigen processing (mediated by lymphoid tissue mononuclear phagocytes [cells that are referred to as monocytes when found circulating in the bloodstream]);

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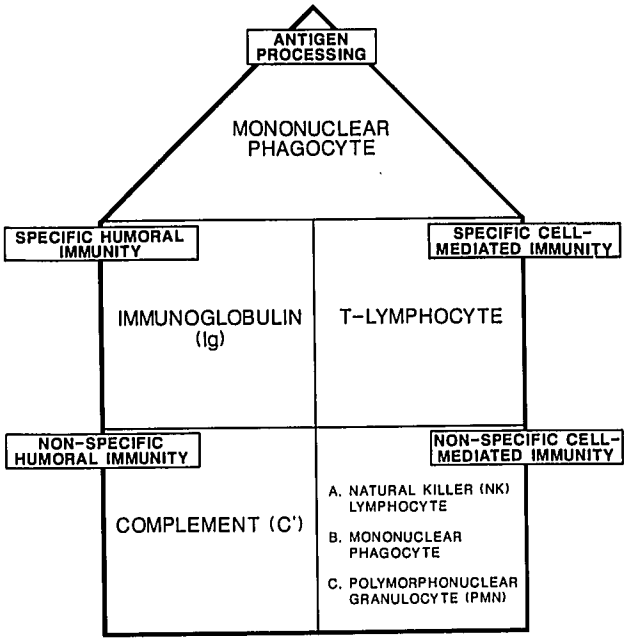

FIG. 1. Five functional components of the immune response: antigen processing, specific humoral immunity, specific cell-mediated immunity, nonspecific humoral immunity, and nonspecific cell-mediated immunity.

2) immunoglobulin (Ig), the specific component of humoral immunity (a product of B-lymphocytes); 3) complement (C'), the nonspecific component of humoral immunity (produced by mononuclear phagocytes); 4) T-lymphocytes, the specific component of cell-mediated immunity; and 5) the nonspecific components of cell-mediated immunity (natural killer [NK] lymphocytes, mononuclear phagocytes, and polymorphonuclear neutrophils [PMN]).

To understand the role and importance of the various subcomponents of the human immune system, it may be helpful to visualize these elements in a schematic representation. Figure 2 represents the specific and nonspecific elements of immunity that were displayed in figure 1, including a classification of the functions of the participating leukocyte subsets. Figure 3 lists some of the signals mediating interactions between immune system effector cells. These signals are termed biological response modifiers (BRM). BRM are polypeptides released by one leukocyte subset that can modulate the function of other subset cells in the local vicinity. The literature currently describes almost 100 BRM,[4] and the number continues to grow. Due to the rapid expansion of this research arena, the nomenclature used to describe BRM is confusing; colony stimulating factors (CSF), interferons (IFN) and interleukins (IL) are all distinct types of BRM. Only a few of the most important types will be described in this review.

Antigen Processing

Initiation of the immune response occurs at the level of the mononuclear phagocyte and is referred to as "antigen processing." The mononuclear phagocyte first ingests "nonself" antigen and chemically modifies it intracellularly. This modified antigen is then re-expressed on the plasma membrane of the mononuclear phagocyte. It is this membrane bound "nonself" antigen that becomes the primary stimulus for B-lymphocyte and T-lymphocyte activation.

Early in the immune system activation, the mononuclear phagocyte also releases a series of CSF. CSF are BRM that stimulate the bone marrow stem cells to produce additional leukocytes, amplifying the immune response. Mononuclear phagocytes secrete other BRM, including: interleukin 1 (IL-1) that activates the T-lymphocytes; interleukin 6 (IL-6) that enhances B-cell proliferation; α interferon, an antiviral protein that boosts NK lymphocyte killing; tumor necrosis factor (TNF), a protein directly capable of lysing tumors; and the C' components, which lyse cell membranes when activated.

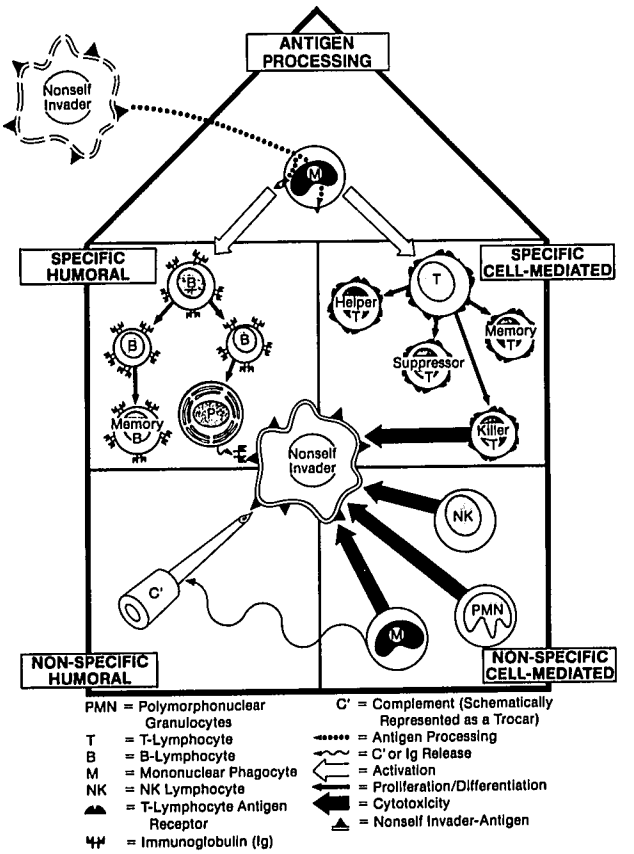

FIG. 2. Participating leukocyte subsets in the overall immune response: mononuclear phagocytes; B, T, NK phagocytes; and polymorphonuclear granulocytes (PMN).

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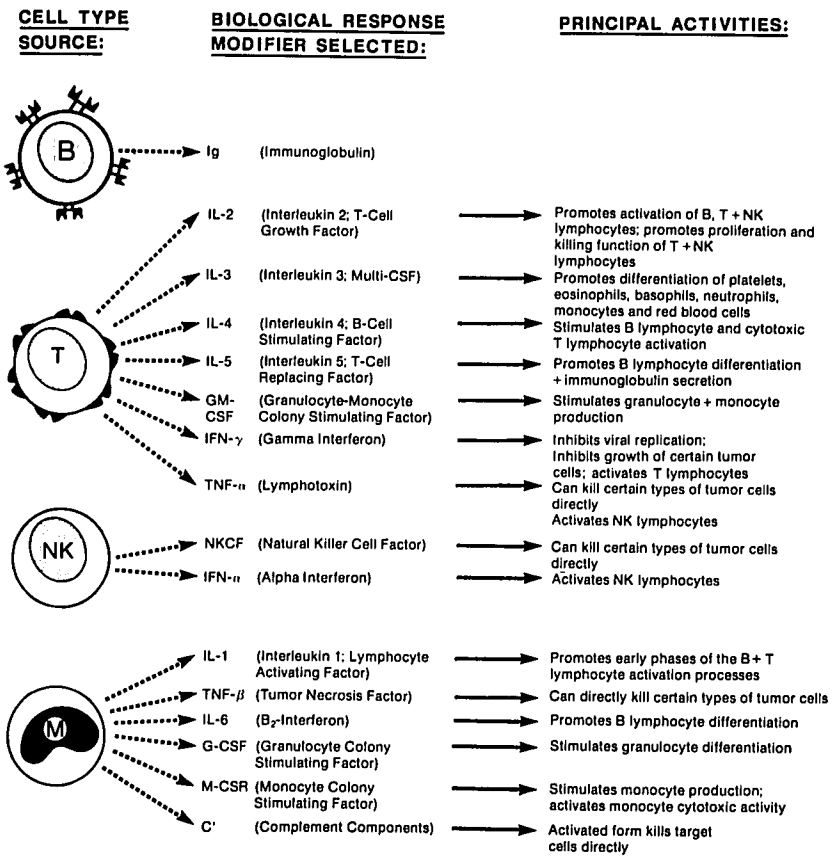

FIG. 3. Principle activities of biological response modifiers (BRM), including their leukocyte subset sources.

SPECIFIC CELL-MEDIATED IMMUNITY

T-lymphocytes function as clones (groups of identical and equally reactive cells) that have the ability to respond to a very limited number of closely related "nonself" antigens. This specificity is conferred to the T-lymphocyte clones by the antigen-specific receptors found on their cell surfaces. In response to mononuclear phagocyte signals, the appropriate T-lymphocyte clone becomes activated and releases a BRM, interleukin 2 (IL-2); this molecule is autostimulatory and amplifies the number of T-lymphocytes in the activated clone. Four major T-lymphocyte subsets are produced in response to activation: 1) helper T-lymphocytes; 2) suppressor T-lymphocytes; 3) antigen-specific killer T-lymphocytes; and 4) memory T-lymphocytes. The helper T-lymphocytes release a variety of BRM that are capable of increasing the activity of various immune system components. One of these is interleukin 4 (IL-4), one of the two signals required for B-lymphocyte proliferation. A second signal, interleukin 5 (IL-5), is required to promote the differentiation of expanded B-lymphocyte clones. A third helper T-lymphocyte BRM, γ interferon, is capable of enhancing the cytotoxic function of killer T-lymphocytes and mononuclear phagocytes. Suppressor T-lymphocytes assist in decreasing the activity of certain human immune responses. For example, secretion of soluble suppressors of Ig release (SF-Ig) causes plasma cells to decrease synthesis and release of immunoglobulins. The third T-lymphocyte subset, the antigen specific killer T-lymphocytes, bears receptors that allow the cells to identify and kill specific "nonself" invader tumor cells. One mechanism for tumor cell killing by killer T-lymphocytes is the release of a soluble factor known as lymphotoxin (LT), which is capable of lysing tumor cells directly. The final T-lymphocyte subset, the memory T-lymphocytes, are cells that do not directly participate in the primary immune response; these cells remain dormant but are easily activated for rapid initiation of secondary T-lymphocyte responses when required.

SPECIFIC HUMORAL IMMUNITY

B-lymphocytes are responsible for the specific component of humoral immunity. B-lymphocyte responses are initiated when the appropriate B-lymphocyte clone recognizes antigen on the membrane surface of a mononuclear phagocyte. The binding of B-lymphocyte surface immunoglobulin with this antigen, coupled with the receipt of the IL-4 signal from the helper T-lymphocyte, stimulates the proliferation of the B-lymphocyte clone. Following proliferation, B-lymphocytes require a second signal from the helper T-lymphocyte (IL-5), plus IL-6

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from mononuclear phagocytes, in order to differentiate into memory cells and plasma cells. Memory B-lymphocytes lie dormant in the immune system but promote rapid initiation of secondary humoral immune responses when needed. Plasma cells are immunoglobulin-secreting elements (the result of B-cell activation) and can be inhibited when SF-Ig is secreted by suppressor T-lymphocytes.

Nonspecific Humoral Immunity

Complement (C′) is the nonspecific component of humoral immunity; the complement (C′) cascade of proteins are secreted into the serum by mononuclear phagocytes. Immunoglobulin-coated invader targets are not capable of being destroyed simply by the binding of immunoglobulin to their surfaces. One mechanism of eliminating immunoglobulin-coated targets is by complement activation. Binding of immunoglobulin G or M (IgG or IgM) to a "nonself" invader cell activates complement components which then assemble into a "membrane attack complex." This activated complement can be thought of as a "trocar" that is capable of disrupting cell membranes. Activated complement is intended to lyse cell membranes of "nonself" invader cells, but it also may be harmful to normal cells in the area.

Nonspecific Cell-Mediated Immunity

There are three nonspecific components of cell-mediated immunity:[41] 1) NK lymphocytes; 2) mononuclear phagocytes; and 3) PMN. NK lymphocytes are of primary importance in the elimination of tumor cell targets, which may be mediated in part by release of a BRM known as natural killer cell factor (NKCF). The tumor-killing capabilities of NK lymphocytes appear to be augmented by their exposure to α interferon, a BRM released by mononuclear phagocytes.

A second component of nonspecific cell-mediated immunity is the mononuclear phagocyte. The mononuclear phagocyte has even broader killing capabilities than does the NK lymphocyte; its function can be dramatically increased following exposure to the BRM, γ interferon. Mononuclear phagocytes mediate part of their killing by the secretion of another BRM, tumor necrosis factor (TNF). The final component of nonspecific cell-mediated immunity is the PMN that is a short-lived granulocyte that has a killing capability similar to that of mononuclear phagocytes. PMN have a life span of approximately 6 h in the peripheral circulation and, compared with mononuclear phagocytes, release few BRM.

Review of Previous Data Regarding Effects of Anesthetic Agents on Immune System Function

Multiple *in vivo* and *in vitro* observations have been made regarding the effects of anesthetic agents on human immune system function. At first glance, the *in vivo* studies would appear to be more relevant, because they should represent events that actually occur in the human immune system. Unfortunately, clinical testing in this area has been confronted with serious methodological problems that have not been overcome to date; the primary difficulty involves separating the effects of the multiple intraoperative factors that impact on immune system function from the direct effects of anesthetic agents themselves.

Many normal functions of the immune system are depressed after exposure to the combination of anesthesia and surgery. The contributory role of anesthetic agents to the immune impairment is poorly understood, however, because there are few good studies of prolonged anesthetic exposure in the absence of surgery. It would appear that many of the immune changes seen in surgical patients are primarily the result of the surgical trauma (cautery, tissue, and organ manipulation) and endocrine responses (increased ACTH, catecholamines, and corticosteroids), as well as ancillary drug effects, rather than the result of anesthetic exposure itself.[18,57,61,105–107]

Most studies of immunocompetence *in vivo* have been done by laboratory testing of a sample of peripheral blood. These assays are a poor reflection of the ongoing immunologic activity at the tissue level because peripheral blood principally serves as a conduit allowing transfer and concentration of specific immune system cells at the sites of effector cell function.[93] Thus, all *in vivo* data based on peripheral blood sampling alone must be viewed with suspicion.

Because of uncontrollable variables influencing the data from most *in vivo* studies, many investigators have attempted to assay the potential immunomodulatory effects of anesthetic agents in the more controlled environment of *in vitro* research. A variety of methodologic and theoretical impediments also plague this area of inquiry.[88] Problems include: 1) the questionable relevance of *in vitro* testing results applied to *in vivo* clinical events; 2) the practice of studying leukocytes obtained from the peripheral blood of poorly screened donors (cells that may have limited correlation to actual immune system effector events); 3) the difficulty of purifying leukocyte subset cells without altering their native function;[92] and 4) the difficulty of preserving leukocyte subsets in culture for the prolonged periods necessary to perform many of the required laboratory assays. When comparing the most recent *in vitro* data on the immune effects of anesthetic agents with earlier studies, several areas of disagreement can be related to the dramatic advances in immunologic *in vitro* technology in the past decade. Until recently, procedures that purify subset cells other than PMN were not available. New laboratory techniques allow the isolation and purification of large numbers of the circulating and immune system reservoir human blood monocytes and

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lymphocytes of normal volunteers and patients. This "bulk collection" of immune system components from well-characterized normal volunteers and patients is felt to produce a leukocyte research substrate that is more reflective of overall human immune system reactivity.[95] In addition, separation techniques have been developed that allow the purification of monocytes, B-lymphocytes, T-lymphocytes, and NK lymphocytes with negligible impact on their baseline function.[92,93] Recently developed cell culture methods have also aided the *in vitro* assessment of immune system function.[96] Among these innovations is the development of a serum-free media that allows the cultured cells to be exposed to physiologic, tightly controlled, chemically defined media conditions that are reproducible from experiment to experiment. The cultured cells are not exposed to endotoxin or other potential contaminants usually found in standard media sources, including fetal calf serum.[96] In addition, the development of nonadherent labware provides for the suspension of cultured mononuclear leukocytes in a milieu very similar to that found in the body (in marked distinction to the standard polystyrene labware often used in earlier studies).[96]

A further exciting development in immunology has been the continuing elucidation of the role of BRM in immunoregulation (fig. 3). Sophisticated assays for measuring these BRM have allowed more accurate assessment of the microenvironment of immune system leukocyte subsets. Progress in this area is critical to the evaluation of the impact of anesthetic agents at the tissue level.

In the past, PMN were widely studied in both the clinical and *in vitro* setting. The extensive study of PMN was not due solely to the importance of the cell to immune system function, but rather to the relative ease of the study of this cell type. Even a superficial examination of the immunoregulatory process indicates that other cells, such as mononuclear phagocytes, are at least equally (and probably more) important to overall immune function.[91] Detailed research regarding these other leukocyte subsets in their purified form was not possible until recently when the above-cited cell separation and culture techniques were perfected.

Cultured human monocytes can now be exposed to inhalational agents under tightly controlled *in vitro* conditions analogous to those occurring clinically. Such a system was reported by Welch in 1981; granulocytes were exposed to halothane in a chamber for periods up to 60 min.[108] However, most important leukocyte subsets cannot be studied within such a short time frame. Monocytes, for example, must be maintained in culture for at least 48 h in order to adequately monitor many of their most significant immunologic functions.[1] When manipulating immune system cells, each step of their care (including isolation, purification, activation, exposure to anesthetic agents, and subsequent functional monitoring) must be performed under conditions that are as physiologic as possible. Only with the meticulous use of modern techniques will experimental results be reproducible and useful (after extrapolation) to the clinical setting. Our group has described one such *in vitro* system using highly purified leukocytes, calibrated Drager vaporizers, precision flowmeters, monitoring of anesthetic agent concentrations within the exposure chambers, constant temperature control, and serum-free media.[88]

In addition, there have been several prior reviews of the impact of anesthetic agents on immune system function.[18,57,61,105,106] These reviews often detail conflicting results from various research groups. As a result of such contradictory data, useful conclusions have been difficult to obtain. In addition to documenting the results of these prior studies, the authors of this review article evaluated the study designs employed by the prior investigators. As each study was reviewed, several study design elements were critiqued:

1) Were *in vitro* immune system components isolated from well-characterized normal volunteers? Were well-standardized patient groups selected for the *in vivo* studies?
2) Did leukocyte separation and manipulation techniques leave cells in their native state? Were purified leukocyte subsets used? Were negative selection techniques employed?
3) Were clinical-grade, serum-free suspension *in vitro* culture techniques used?
4) Were clinically relevant anesthetic delivery systems used during *in vitro* studies?
5) Did the *in vivo* study design allow for a distinction between effects of anesthetic agents alone *versus* effects of other intraoperative events (such as surgical trauma, blood transfusions, etc.)?
6) Did the *in vivo* study design allow for a distinction between alteration of leukocyte cellular function from effects of leukocyte immunoregulatory signals *versus* changes related to leukocyte trafficking (preferential compartmentalization in one or more immune system reservoirs)?

Many study designs were not optimal; often the primary impediment to reproducible results was the lack of sophisticated immune system research technology. An overall assessment of those *in vivo* and *in vitro* studies performed to date follows and is summarized (fig. 4).

Antigen Processing Studies

Study in this area of immune system function has been almost totally neglected, primarily because of the technical difficulties arising when separating and culturing mono-

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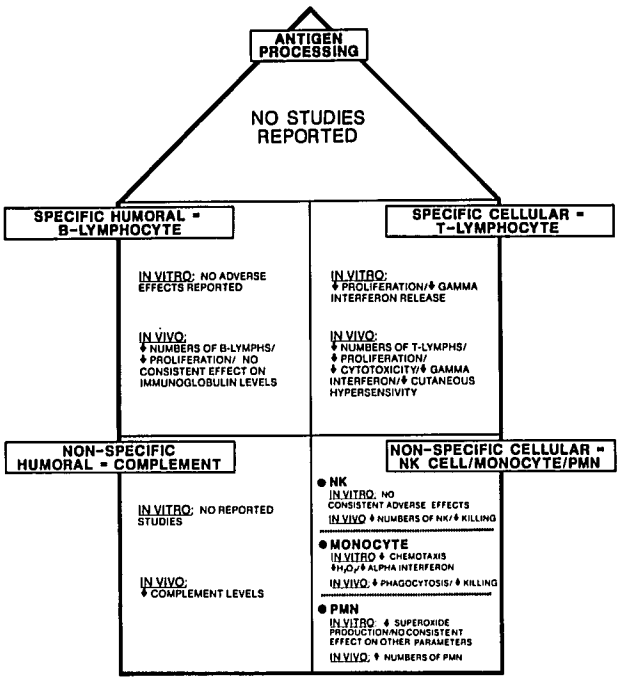

FIG. 4. Effects of anesthetic agents (primarily halothane) on *in vitro* function of immune components. The *in vivo* summary reflects the combined effects of both anesthetic agents and surgery on postoperative immune function.

cytes, but also because of the tedious nature of antigen-processing immunological research.

In Vitro. There have been no reported *in vitro* experiments testing the effect of anesthetic agents on the processing of "nonself" antigens by the monocyte.

In Vivo. There are no *in vivo* data that specifically test the effects of anesthetic agents on antigen processing. There has been evidence of impairment of the delayed cutaneous hypersensitivity response after major surgical procedures,[34,84] which could be the consequence of either a defect in antigen processing by the mononuclear phagocyte or an abnormality involving T-lymphocyte function itself.

Specific Cell-Mediated Studies: The T-Lymphocyte

In Vitro. There are comparatively few *in vitro* data focusing specifically on T-lymphocyte function. The effect of anesthetics on mitogen-stimulated cell proliferation is unclear. While several studies show a decrease in T-lymphocyte response to mitogens,[6,7,9,86] others show no change from control values.[8,35,89] The only reported study of BRM release by T-cells[88] showed a decrease in γ interferon following halothane exposure. Another study showed decreased migration of anesthetic agent-exposed lymphocytes toward chemical attractants.[58] To date, there have been no cytotoxicity studies performed using purified T-lymphocytes *in vitro.*

In Vivo. In contrast to the paucity of *in vitro* research, the *in vivo* T-lymphocyte arena has been extensively investigated. It has been repeatedly shown that the combination of anesthetics and surgical trauma decrease absolute numbers of circulating T-lymphocytes[30,37,42,47,53,54,71,74,76,84,97,101,110] and decrease T-lymphocyte proliferation in response to mitogens.[17,24,30,36,38,42,43,46,53,65,70,73,76,79,80,97,110] Cytotoxicity was measured in only one study[103] and found to be impaired. One study of BRM release reported that γ interferon production was significantly depressed postoperatively when general anesthetic agents were used. No effect was seen when epidural anesthesia was used.[38] One study[19] exposed volunteers to prolonged halothane or enflurane without a surgical procedure being performed. No significant effect was seen in the number of T-lymphocytes found or in their function. In chronically exposed operating room personnel[80,81] no measurable impairment of T-lymphocyte immune function could be detected. One study found no immune impairment resulted if only minor surgery was performed, but did occur in association with the trauma of major surgery.[46] It is unclear if a differential between patient groups in time exposure to anesthetic agents was a factor in the results of this study. Although not yet conclusively proven, postoperative T-lymphocyte immune impairment appears to be more correlated with the degree of surgical trauma than to the anesthetics used intraoperatively.

Several studies indicate that the postoperative T-lymphocyte impairment associated with major surgery is mediated by factors that are at least partially blocked by regional anesthesia.[36,38,71,101,110] One group[97] related the observed immunosuppressive effect to increased cortisol levels. One significant T-lymphocyte-mediated immune function that does not appear to be affected by regional blockade is delayed cutaneous hypersensitivity to antigens. Patients undergoing major surgical procedures show a postoperative impairment of delayed cutaneous hypersensitivity that is not blocked by the use of a regional anesthetic technique,[34] which may be the result of some specific T-lymphocyte function as yet not tested or may be due to an impairment of antigen processing.

Specific Humoral Studies: The B-Lymphocyte

In Vitro. In vitro data regarding B-lymphocyte activation are not evident in the research literature. Using a recently described *in vitro* exposure system,[88] our group assessed the proliferative capacity of human B-lymphocytes in response to mitogen stimulation after halothane exposure (4% halothane for 8 h). We found no significant differences from control cultures in proliferative ability.

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In Vivo. *In vivo* studies using a variety of anesthetic agents indicate that the combination of anesthesia and surgery decreases the number of B-lymphocytes and decreases their proliferative response to mitogens.[23,42,46,47,53,54,70,84,101,110] The effect on serum Ig levels is less certain; it is variously reported to be decreased,[14,23,51,67,72] increased,[47] or not affected.[24,80,84] Most of these studies made no attempt to distinguish between the effects of anesthetic agents themselves *versus* those of surgical trauma and endocrine responses. Similarly, no studies have been performed to determine whether changes (when noted) in Ig levels were due to alterations of protein synthesis or Ig trafficking events. One study[23] found that the observed Ig level depression was not present until surgical trauma had been initiated; similarly, another study[46] found no adverse effects after minor surgery, but did observe Ig level depression following major surgical cases. Other studies show a lack of demonstrable immune system impairment following chronic anesthetic agent exposure of operating room personnel.[80,81] These *in vivo* studies imply that specific humoral immunity impairment is more related to the degree of surgical trauma than to the specific anesthetic agent employed. It appears that the surgical process itself or associated perioperative conditions is the dominant factor responsible for most postoperative specific humoral immunity impairment.

The mechanism of this immune impairment following surgical trauma has not been defined. Two studies[101,110] found Ig level impairment when surgery was carried out with general anesthetic techniques, but not when regional techniques (spinal, epidural) were used. This immune system "sparing effect" of regional anesthetic techniques may be related to an inhibition of the neuro-endocrine axis, although there is some evidence that Ig levels are not related to patient blood glucose or cortisol levels.[72]

Nonspecific Humoral Studies: Complement

In Vitro. There are no available *in vitro* data on effects of anesthetics on complement component synthesis or on the activity of complement components following *in vitro* exposure to anesthetic agents.

In Vivo. There is evidence that there is a 10–20% decrease of acute-phase plasma proteins in the immediate postoperative period.[72] The combination of anesthesia and surgery is associated with a decrease in complement levels, which may represent complement pathway activation, since a rise in C_3 split products has been documented.[31]

Nonspecific Cell-Mediated Studies: NK Lymphocyte, Monocyte, and PMN

NK Lymphocyte—In Vitro. Little research has been performed regarding NK lymphocyte activity following *in vitro* anesthetic exposure; the data that do exist are conflicting. Two studies[29,89] showed no impairment of NK lymphocyte function after anesthetic exposure, but a third[112] observed a significant decrease in the ability of these cells to kill tumor targets.

NK Lymphocyte—In Vivo. The NK lymphocyte research data following intraoperative anesthetic exposure are consistent. There is a transient increase in NK activity intraoperatively,[28,100] followed by a decrease in activity for several days postoperatively.[52,77,78,97–102,104,113] This effect may be correlated with an increased number of circulating NK lymphocytes intraoperatively,[28] followed by a decrease postoperatively.[97,101] Although several hypotheses exist to explain this phenomenon, the most compelling is that it is endocrine-related, possibly a direct effect of cortisol release.[97] Whatever the precise mechanism, it is becoming clear that regional anesthesia may block, or at least blunt, postoperative NK immunodepression.[78,99,101]

Monocyte—In Vitro. Monocyte chemotaxis is impaired in response to a variety of anesthetic agents.[58,59] H_2O_2 production of purified monocytes (superoxide is necessary for many monocyte-related killing functions) was decreased after halothane exposure in one study.[89] Concomitant exposure of monocytes to γ interferon was protective against this halothane-mediated immunosuppression. Thiopental has been shown to decrease tumor cell cytolysis by mitogen-stimulated monocytes.[35] Another study examined the effect of anesthetic exposure on monocyte production of α interferon;[88] production of this BRM was decreased.

Monocyte—In Vivo. Monocytes respond to anesthesia and surgery by displaying decreased phagocytosis and decreased killing ability.[2,3,36,39] Some studies[21,36,39] indicate that this adverse effect can be negated by regional anesthesia. The mechanism of the sparing effect of regional anesthesia on this monocyte function may be due to blockade of the neuro-endocrine axis.[39]

PMN—In Vitro. PMN production of activated oxygen radicals (substances necessary for killing function) is impaired following *in vitro* halothane exposure.[62] Several investigators have found a decrease in killing ability of PMN exposed to anesthetic agents *in vitro;*[62,108,109] phagocytosis,[27,49,56,59,111] and chemotaxis are also decreased.[44,58,63] Other studies[16,20,32,44,64,109] have not confirmed changes in these PMN functional parameters. The lack of agreement among these studies may be related to the different specific anesthetic agents or laboratory techniques used.

PMN—In Vivo. Examination of *in vivo* data reveals that anesthesia and surgery consistently increase the number of circulating PMN[2,17,19,21,22,33,47,54,68,71,82,83,87] and even does so in normal volunteers who are anesthetized without subsequent surgical procedure.[19,33] Whether this increase is or is not related to the increased PMN release from the

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bone marrow or blood vessel demargination (catecholamine mediated release of PMN from blood vessel endothelium, to which they tend to adhere) has not been documented. Two studies[71,82] indicate that the granulocytosis seen postoperatively may be decreased by regional anesthetic techniques.

Phagocytosis has been reported by some researchers to be decreased after anesthesia and surgery;[2,3,11,49,51,66,85] other studies show no change in this PMN functional parameter.[2,22,32,54,68] This depression of phagocytosis was not seen when regional anesthetic techniques were used in one study,[2] but was found in another.[11] Chemotaxis studies following *in vivo* exposure are also inconclusive; several studies showed decreased motility postoperatively,[13,21,33,61,85,87] and others showed no change.[12,54] Thus, while anesthesia and surgery definitely increase circulating PMN cell numbers, it is unclear whether or not the function of these cells is modulated to any significant degree.

Conclusions and Future Perspectives

The postsurgical infection rate observed in immunologically normal individuals coupled with concern for the potential worsening of the pre-existing immunocompromised state of certain at-risk patient groups (such as patients suffering from AIDS) has promoted a sustained interest in defining the interface between immunology and anesthesia. Unfortunately, we still lack unified mechanistic insights into both medical disciplines. In the realm of anesthesia, work continues to delineate the intracellular events that occur in cells in response to anesthetic exposure. It is entirely possible that cell types from different tissues are impacted differently by these agents, further delaying the generation of a unified mechanistic theory of anesthetic action.[45] Similarly, in the realm of immunology, we are only beginning to understand how the human immune system identifies and eliminates an enormous range of potential "non-self" invaders. The identification of new mononuclear leukocyte subsets and the identification of the immunoregulatory BRM signals that control them have complicated this topic, as well as opened up new opportunities for further research.[40] This review article has summarized data from major studies performed to date that pertain to anesthetic agent effects on the human immune system. Inconsistencies in these data have been highlighted. Potential causes for incongruity have also been identified, including: 1) failure to segregate *in vivo* effects of anesthetic agents themselves from other intraoperative factors; 2) failure to ascribe observed *in vivo* abnormalities to altered protein or cell trafficking *versus* altered cell biology mechanisms; 3) failure to purify, maintain, and study immune system components in a clinically relevant fashion during the execution of *in vitro* studies; 4) failure to consider immune system components beyond the circulating peripheral blood compartment; and 5) failure to administer anesthetic agents during *in vitro* experimentation under conditions that correlate with clinical events. Several recent methodologic strategies in each research arena that may allow investigators to obtain more reproducible data in the future have been detailed.

In spite of the many inconsistencies found in the present data bank, one conclusion of this review and several previous reviews[18,57,61,105,106] is that the trauma of surgery is a significant factor in the observed postoperative immunodepression of immunologically normal individuals. Studies have shown that the greater the surgical trauma, the more profound the observed immune depression;[17,46] other studies have indicated that impairment of the studied immune component was not noted prior to the surgical incision, but occurred sometime after surgical trauma began.[3,23,66,79,87] The exact mechanism by which surgical stimulation impairs the immune response is not yet understood. The ability of regional anesthetic techniques to block (or partially block) some aspects of observed postoperative immune impairment may implicate the neuroendocrine axis. The contribution of anesthetic agents themselves to observed postoperative immune depression should not be underestimated. The multiple *in vitro* studies showing reproducible effects of clinically relevant concentrations of anesthetic agents on the function of some immune components cannot be ignored. Although these effects may be more subtle than the effects of surgical trauma, they may still prove to be of considerable clinical significance.

The effect of anesthetic agents on many important aspects of immune function has not been adequately studied due to technical difficulties in the laboratory and the rapid emergence of a better understanding of human immunology. BRM, for example, are critical elements of human immune function; with few exceptions, the effects of anesthetic agents on BRM have not yet been studied. Seemingly isolated alterations of immune function following anesthetic exposure (such as decreased γ interferon production of halothane-exposed lymphocytes[88]) may have far-reaching effects in specific clinical settings.[4] For example, as anesthesiologists treat ever-increasing numbers of patients with AIDS and other immunodeficiency syndromes, careful clinical research is warranted to monitor these patients for exaggerated postoperative immunosuppression, as well as to search for effective treatment interventions. Similarly, we are currently witnessing an increase in cancer-related operations in our progressively aging population. Recent evidence indicates that immunosurveillance mechanisms are not only important in the management of emerging malignancy *de novo*, but may also be critical to the successful elimination of microscopic residual tumor postoperatively.[90] Clearly, even transient impairment of tumor clearance mechanisms by anesthetic agents under such circumstances may be detrimental.

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Several studies cited in this review indicate that different anesthetic agents and techniques may be more sparing of postoperative immunocompetence; a change in clinical practice may be indicated if these effects are found to be convincingly reproducible. Alternatively, pretreatment of patients with immunocompetence enhancing BRM (such as γ interferon) may minimize postoperative morbidity. Future research investigations should identify those at-risk patient populations for anesthesia-related postoperative immunosuppression and offer clinical strategies for minimizing this risk. In addition, since many aspects of immune system function (such as cancer immunosurveillance) require longer time frames (years) for adequate scientific study, the anesthetic research community should develop strategies for monitoring potentially long-term dangers of anesthetic agent-mediated immunosuppression. The logical eventual direction for these research studies will be to examine the impact of anesthetic agents on immunoregulation, signal transduction mechanisms and the gene expression basis for immune system impairment. Research at the anesthesia-immunology interface can expect to continue to benefit from the molecular/technical research advances that are currently being observed in both disciplines.

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