

## Review Article

# Anesthesia and Immunology

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THE INTERACTIONS of anesthesia and operation with components of the immune system may have considerable importance for both patients and anesthetists. Such interactions would have profound implications in drug reactions, transplantation surgery, and patient resistance to cancer and infection. Additionally, chronic exposure to trace amounts of anesthetics may alter immune defenses and possibly explain the reported increases in malignancies among operating room personnel.<sup>20</sup> While earlier reviews have suggested that anesthesia<sup>20</sup> and surgical trauma<sup>21-29</sup> may be associated with clinically important immunosuppression, recent observations have done much to quantify and characterize the nature of the immunologic lesion produced. It is the purpose of this review to update the previous surveys and attempt to correlate basic scientific observation with clinical practice. A brief overview of basic immunology is presented, followed by a more detailed account of the effects of anesthesia and surgery on immune competence.

### Basic Immunology

The immune system is a multifaceted mechanism by which the body resists the intrusion of substances and cells determined by the host to be foreign. Immune mechanisms are classically divided into two components,

"nonspecific" and "specific" immunity. While nonspecific immunity is genetically determined and does not require prior exposure to the antigens involved (as with the classic ABO blood groups), specific immunity is acquired and occurs only when there has been prior exposure to a particular foreign substance. These distinctions are somewhat arbitrary, for many acquired immune mechanisms, such as antibody production, are dependent upon intact nonspecific functions such as vascular inflammation and phagocytosis. Similarly, many nonspecific immune phenomena are facilitated by acquired responses.

### A. NONSPECIFIC IMMUNITY

#### *The Inflammatory Lesion (Figure 1)*

In response to localized foreign invasion there is an initial increase in regional blood flow, which serves to deliver plasma proteins and leukocytes to the areas of injury. Chemical mediators are released locally; in conjunction with circulating proteins, they act to increase endothelial permeability, increase venular sphincter tone, and redistribute arteriolar flow via regional shunts. As a consequence, stasis and hypoxia occur at the site of injury, with transudation of plasma proteins and fluid into the tissues. The net result is the reddened, swollen, hot, tender lesion of inflammation.

Usually the vascular response gives way to a cellular infiltrate. Circulating leukocytes accumulate in the region of injury, adhere to the vessel lining, and migrate into the surrounding connective tissue. The leukocytes must be metabolically active, and the direction of their migration is mediated via chemotaxis, substances released by damaged tissues and invading organisms that attract circulating leukocytes. The type of cell involved in the infiltrate varies with time and with the type of lesion produced. The neutrophil pre-

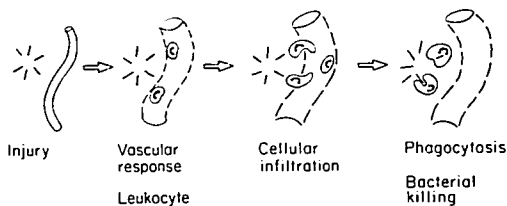
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FIG. 1. The steps in the inflammatory response. Tissue injury or bacterial invasion stimulates vascular dilatation and increased vessel permeability, aiding the delivery of plasma proteins, antibodies, and circulating leukocytes to the area. Leukocytes adhere to the vessel walls, migrate between the endothelial cells and enter the interstitial space. With the aid of opsonins from the plasma proteins, bacteria and cellular debris are phagocytosed and destroyed.



dominates in the early stages of most lesions and primarily protects against microbial organisms. Eosinophils tend to appear at sites of antigen-antibody reactions, while mast cells, and perhaps basophils, provide a source of mediators further to support the inflammatory response. Mononuclear phagocytes (macrophages) appear somewhat later to remove particulate matter and cellular debris. The lymphocyte, although lacking the ability to respond to chemotaxis or to phagocytose foreign particles, is central to the acquisition of acquired immunity and mediation of specific immunologic responses.

Many pharmacologic, pathologic, and genetic conditions may impair this "first line" of host defense.<sup>11,27,42,96</sup> The inflammatory response may be altered by drugs such as ethanol, salicylates, cortisone, colchicine or narcotics. Low-blood-flow states such as those associated with vasopressor therapy or shock will also reduce delivery of effector proteins and leukocytes to the area. Last, the inflammatory response will be limited in avascular tissue of devitalized areas or fatty planes.

#### Phagocytosis

Bacteria and cellular debris are primarily removed from the injury site by phagocytosis.<sup>140</sup> Leukocytes engulf particles and enclose them within a protective membrane, forming the encapsulated phagosome. Bacteria are then acted upon by hydrolyzing enzymes, derived from lysosomes, and killed. Although bacterial killing occurs within the cytoplasm of the phagocytosing leukocyte, the cell is protected from its own digestive enzymes by the phagosomal membrane.

Phagocytosis occurs by a process similar to normal muscle contraction, with actin and myosin proteins interacting with ATPase in the presence of calcium to effect movement of the cell wall as it surrounds the invader. Microtubules are necessary to provide structural support for the actin-myosin system, as well as being important for interaction of lysosomes with phagosomes. Energy for phagocytosis is obtained by glycolysis and glycogenolysis. The metabolic and phagocytic activity of the cell can be indirectly assessed by measuring the reduction of nitroblue tetrazolium (NBT) dye. NBT dye reduction is decreased in certain congenital and acquired disorders characterized by recurrent infection.<sup>106</sup>

How phagocytic cells discern what is to be removed from the site of injury is not known. Many microorganisms, particularly encapsulated ones, resist phagocytosis and hence have enhanced pathogenicity. Particles that have been coated with fresh serum or specific antibody are ingested avidly. This coating of particles, called "opsonification," can be accomplished by specific antibody, activated complement, and other unidentified thermolabile proteins of plasma.

Both congenital and acquired disorders of phagocytosis, usually manifesting as recurrent bacterial infections, have been described. Many drugs are also capable of inhibiting phagocytosis and bacterial killing, including agents affecting microtubular structure and function (cytochalasin B, colchicine, or elevators of intracellular cAMP), energy production and utilization (chelators of divalent ions), and lysosomal enzyme production (ethanol, hydrocortisone, antimalarials).<sup>140</sup>

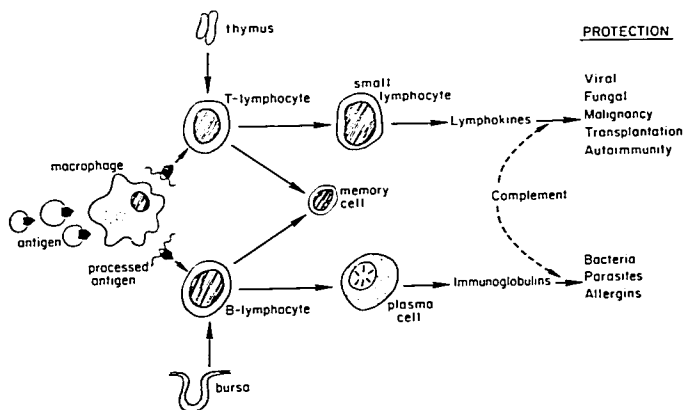


FIG. 2. Physiology of immunology. Structural determinants of a foreign particle or bacteria (antigens) are phagocytosed by macrophages, the information processed, then passed on to circulating lymphocytes in the form of RNA synthesized specifically for that antigenic structure. If it is received by B lymphocytes, there will be a morphologic alteration to form a plasma cell producing immunoglobulins (antibodies) to that antigen. Stimulation of T lymphocytes results in transformation to a small circulating lymphocyte producing chemical mediators (lymphokines) on direct cellular interaction with the antigen. Either type of lymphocyte can form a memory cell capable of an accelerated response to that antigen in the future. The protein cascade of the complement system can facilitate either humoral or cellular immune mechanisms. The usual protective roles of each type of immune cell are illustrated.

#### SPECIFIC IMMUNITY (FIGURE 2)

Acquired or specific immunity is an adaptive response to an antigenic stimulus that results in acquisition of immunologic memory and synthesis of a specifically reacting antibody. After phagocytosis of a particular antigen by the macrophage, part of the antigen (or RNA synthesized in the macrophage, according to the antigen's structure) is transferred to a small circulating lymphocyte. Upon receipt of this information the lymphocyte is stimulated and transforms into either a cell capable of a specific immune response against that antigen or a memory cell capable of more rapid response to the antigen in the future. Thus, as a result of prior experience with an antigen, the host becomes equipped with defense mechanisms specific to the antigen in question.

Immunocompetent effector lymphocytes are classified as either B lymphocytes (maturing under the influence of the human equivalent of the bursa of Fabricius of the

chicken) or T lymphocytes (maturing under the influence of the thymus). Although these cells are morphologically similar by light microscopy, they can be separated and characterized by their surface receptors as distinct in structure and function.<sup>123</sup> In response to antigenic stimulation the B cell is further transformed to a plasma cell capable of producing circulating antibodies against the antigen. Immunoglobulin production appears to reflect B cell function and hence the status of humoral immunity. These circulating antibodies confer humoral immunity that can be passively transferred from one individual to another with serum alone. The T cell, on the other hand, produces soluble mediators called "lymphokines," which may destroy the antigenic invader directly or "arm" other leukocytes against the antigen. This phenomenon, "cell-mediated immunity," requires direct contact of T cells with foreign cells, and may be passively transferred only by sensitized lymphocytes.

The transformation of the small, resting

lymphocyte to an immune effector cell may be mimicked *in vitro* by culture with non-specific mitogens such as phytohemagglutinin (PHA). This assay does not require prior exposure or sensitization of the cell. PHA stimulates the lymphocyte to enlarge and undergo mitosis, with associated increases in RNA, DNA and protein synthesis, which can be quantitated by radiolabelled precursor incorporation. Since PHA stimulates predominantly T cells, the amount of transformation *in vitro* is thought to reflect *in-vivo* T cell responsiveness.

In spite of the nonspecific stimulus supplied by PHA, it appears that lymphocyte transformation is a more sensitive technique to detect impaired cellular immunity than skin testing with common antigens. Lymphocytes from patients who have impaired cellular immune mechanisms do not transform well *in vitro*, and these patients appear to be at risk from neoplastic or bacterial challenge.<sup>108</sup> Steroids, radiation and antineoplastic drugs impair lymphocyte transformation as part of their clinically important immunosuppressive effects.<sup>125</sup>

#### Humoral Immunity

Plasma cells, the progeny of B lymphocytes, synthesize antibodies with structural specificity for the stimulating antigen. These circulating proteins are classified according to structure as IgA, IgD, IgE, IgG, or IgM antibodies, each of which subserves specific functions. IgG and IgM, together with complement,<sup>121</sup> play an important role in bacterial defense. IgE is important in sensitization reactions of the skin and respiratory tract, while IgA serves as topical defense at excretory sites such as the gut and upper respiratory tract. IgD has not yet been associated with any specific function in man.

Although rare, defects of humoral immunity do occur and are expressed clinically as increased susceptibility to bacterial pathogens. Indeed, bacterial surveillance appears to be the main function of the B-cell system. However, it has recently been shown that B cells are also important in certain cellular immune systems, such as tumor control, both as modifiers of T-cell function and possibly as effector K cells, described below.

#### Cellular Immunity

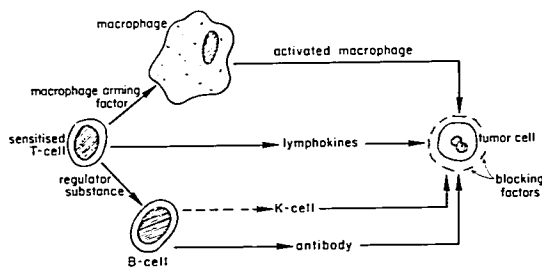
Cellular immunity is dependent upon competent T-lymphocyte function, and operates by direct cell-to-antigen interaction rather than by circulating immunoglobulins. Mediators that have effects on both the invading antigens and the other leukocytes mediating host defenses are released locally. Lymphokines such as chemotactic factor, migration-inhibition factor, macrophage-arming factor, and mitogenic factor direct and enhance the activity of macrophages and other phagocytosing leukocytes.<sup>45</sup> T cells also produce lymphotoxin, which is directly cytotoxic to foreign cells. Last, T cells appear to produce non-immunoglobulin factors capable of modulating B-cell function and hence humoral immunity.

T lymphocytes appear to play a dominant role in a variety of conditions, including viral, fungal and neoplastic diseases, rejection of transplanted organs, and delayed hypersensitivity reactions. In many of these situations, it would appear that T cells act as vectors to "arm" the macrophage, which then acts as the final effector of antigen control. Defects of T-cell function are associated with increased incidences of fungal, tuberculous and viral infections, as well as increased chance of neoplastic growth.

#### Tumor Immunity (Figure 3)

Tumor cells possess, in addition to regular membrane or transplantation antigens, further determinants called "tumor-specific" or "tumor-associated" antigens. It is postulated that host immunologic mechanisms act continuously to remove neoplastic cells from the body by acting on these foreign antigens. Clinical malignancy is thought to arise as a result of failure of this ongoing immunologic surveillance.<sup>64</sup> Support for this theory stems from the observation that impaired immune function, either congenital or acquired, results in a higher incidence of malignancy, particularly of lymphoid origin.<sup>151</sup> This concept has recently been re-examined, however, and it may be that the immune system serves only to protect the host from infection with oncotic viruses.<sup>150</sup>

Numerous cell types have been advanced as effectors of tumor immunity. T lymphocytes



tumor by B lymphocytes. K cells, the progeny of B lymphocytes, act with circulating antibodies to destroy the cell. "Blocking" factors can interfere with the tumor killing of any of the above mechanisms.

FIG. 3. Tumor immune mechanisms. Thymus-dependent lymphocytes (T cells) sensitized to antigenic determinants on the tumor cell lyse the tumor in several ways. Macrophages can be "armed" by T cells to an activated state capable of specific cytotoxic activity. Lymphokines produced by the T cell can lyse the tumor directly. T lymphocytes can regulate the production of antibody to the

appear to be critical in tumor defense, either acting autonomously or by "arming" macrophages with specific antitumor activity.<sup>45</sup> B cells may produce cytotoxic antibodies to the tumor,<sup>69</sup> while "killer" (K) cells, probably derivatives of B cells, are capable of tumor-cell lysis in the presence of specific antibody to the neoplasm.<sup>100</sup>

Serum factors that affect the capability of leukocytes to control tumor growth are also described. There are "blocking" antigen-antibody complexes that can mask antigenic determinants on the tumor cell from effector leukocytes. Circulating antigens, shed by tumor masses, may react with cytotoxic cells at a distance from the tumor, rendering the effector cells incapable of operating in the region of the tumor mass. "Unblocking" activity has been ascribed to free antitumor antibody capable of clearing these circulating inhibitors.

Much of the theory of tumor immunology has been developed from animal models using *in vitro* assays, leaving relevance to human malignancy open to question. Nevertheless, *in vitro* studies of patient responses to tumor-specific antigens, such as cytotoxicity assays, studies of lymphocyte transformation, assays of lymphokine production, and investigations of cutaneous hypersensitivity reactions, do seem to correlate with some aspects of the clinical course when serum and other factors are taken into account.<sup>119</sup> At present, however, there is no universally-accepted method of assessment of patient immune responses toward tumors. It is hoped that

future development of such an assay will permit better identification of patients at risk and allow more rational intervention of therapeutic measures.

## Influence of Anesthesia on Immunology

### ANESTHETIC EFFECTS ON LEUKOCYTES

The production, mobilization, and deposition of sufficient leukocytes at a site of infection or neoplastic growth is obviously crucial to proper immunologic function. There are data to suggest that all aspects of this response may be altered by anesthesia. Bone marrow depression and pancytopenia was first observed by Lassen<sup>91</sup> when patients were given 50 per cent N<sub>2</sub>O and *d*-tubocurarine for tetanus. A few of these patients died from overwhelming sepsis. Numerous subsequent reports have documented the toxic effects of anesthetics on dividing cells. Animals develop leukopenia following administration of N<sub>2</sub>O for two days;<sup>112</sup> ethylene, cyclopropane or acetylene for six days;<sup>2</sup> pentobarbital, thiopental, methohexital, thiamylal,<sup>61,115</sup> or halothane, 0.45 per cent, for 24–115 hours.<sup>18</sup> These effects are due to the inhibitory effects of anesthetics on mitosis<sup>63,111</sup> rather than delayed maturation or release from the marrow pool.<sup>18</sup> Despite the leukopenia a relative lymphocytosis is evident, possibly because of the lymphocyte's long life span and slow rate of division.

One must extrapolate these experimental data to clinical anesthesia in man with cau-

tion. These animals were exposed for prolonged periods (as long as six days) to concentrations of anesthetics below those required for surgical anesthesia yet far greater than those encountered in contaminated operating rooms. Anesthetic effects on leukocyte counts varied among animal strains and species.<sup>65</sup> Last, a change in resting leukocyte count may not necessarily reflect an impaired ability to generate an adequate response to infection.<sup>112</sup> Nevertheless, leukopenia can be produced by prolonged anesthesia in man, and this may be of clinical consequence, particularly in those patients with pre-existing bone-marrow suppression secondary to drugs or disease. Whether chronic exposure to anesthetics in low doses affects human leukocyte production is unknown.

In contrast to the reversible inhibition of granulocyte production seen with prolonged exposures, clinical anesthesia in healthy subjects does not appear to cause significant leukopenia. Indeed, volunteers undergoing morphine-N<sub>2</sub>O,  $\downarrow$  enflurane, or halothane- $\downarrow$  anesthesia without operation showed slight leukocytosis. Surgical procedures are capable of eliciting leukocytosis in proportion to the trauma involved but unaffected by the anesthetic technique employed.<sup>62</sup>

There have been several attempts to utilize the mitotic inhibiting property of anesthetics in the therapy of malignancy. Leukemic patients have been subjected to treatment with N<sub>2</sub>O with dramatic reductions in leukocytes.<sup>18,92</sup> However, remissions were short-lived and the leukocyte counts increased rapidly on withdrawal of the drug. Other investigators<sup>39</sup> have attempted to protect normal bone-marrow cells from cytotoxic drugs by inhibiting cell replication with anesthesia at the time of chemotherapy. Although the therapeutic index was improved by halothane in some cases, the results were variable and general conclusions could not be drawn.

In summary, it seems that reversible, dose-

dependent inhibition of cell replication is a function of all anesthetics in concentrations used in clinical practice. The effect on one rapidly multiplying pool of cells, the leukocytes, may be insignificant in healthy man during routine clinical anesthesia, but effects on other cell systems should not be excluded.

#### ANESTHETIC EFFECTS ON INFLAMMATION AND PHAGOCYTOSIS

Little is known concerning the effects of anesthetics on the initial vascular and early cellular response to infection or injury. Because anesthetic agents may induce profound alterations in regional distribution of blood flow and perfusion pressure, the establishment of an efficient vascular inflammatory response may be opposed. Leukocytic adherence to the vessel wall is inhibited by topically applied lidocaine in a dose-related manner,<sup>39</sup> but the effects of other anesthetics are unknown.

The migration of cells out of vessels into the interstitium is an active cellular process, which may also be inhibited by anesthetics. The spontaneous motilities of mouse leukocytes<sup>107,120</sup> and a variety of unicellular organisms<sup>15,133,151</sup> are decreased by halothane, methoxyflurane, cyclopropane, chloroform and ether. The effects are reversible, and may be secondary to anesthetic effects on microtubular systems necessary for modulation of the membrane structure.<sup>107</sup>

In contrast to random cell motility, the attraction of leukocytes to a nidus of infection is directional and under the influence of chemotactic factors. Although chemotaxis is impaired by ethanol and thermal injury,<sup>152</sup> the effects of anesthesia and operation have not been ascertained. Bruce<sup>33</sup> demonstrated reduced leukocyte mobilization to the mouse peritoneal cavity in response to *salmonella* or *Pseudomonas* lipopolysaccharide when mice were anesthetized with 1 per cent halothane, but the influence of altered splanchnic blood flow during anesthesia could not be excluded. In man, leukocyte mobilization, viewed through a skin window, is not inhibited by surgical procedures during cyclopropane, N<sub>2</sub>O and ether anesthesia.<sup>11</sup> However, ethanol, shock and diabetes are capable of inhibiting the response. The effects of anesthetics on

<sup>1</sup> Leck JH, Twomey PL, Hume B, et al. The Clinical Center and National Cancer Institute, National Institutes of Health, Bethesda, Maryland; personal communication.

<sup>§</sup> Dimean PG, Cullen BF, Calverly R, et al: Unpublished observations.

leukocyte mobilization and directional motility *in vitro* are unknown.

Phagocytosis in the presence of anesthesia and operation has been extensively studied both *in vitro* and *in vivo*. As early as 1911, *in-vitro* studies<sup>62,70</sup> showed reversible impairment of phagocytic activity of animal leukocytes when exposed to high concentrations of ether or chloroform in culture. More recent *in-vitro* studies using halothane and  $N_2O$ <sup>31,4</sup> demonstrated only minimal effects upon phagocytosis by human leukocytes. Local anesthetic inhibition of mouse macrophages<sup>120</sup> and human leukocytes<sup>25</sup> is demonstrable with concentrations of the drug probably achievable only at the site of local infiltration. Narcotics in clinical use have not been evaluated; however, levorphanol, the structural analog of morphine, can cause 80-90 per cent inhibition of phagocytosis and bacterial killing *in vitro*.<sup>158,160</sup>

The results of *in-vitro* studies of anesthesia and phagocytosis are difficult to evaluate because of species differences or because of concomitant surgical procedures. The administration of 1 per cent halothane impairs phagocytosis of peritoneal *salmonella* in mice,<sup>12</sup> but human studies after halothane- $N_2O$ , pentothal-Innovar- $N_2O$ , or morphine-*d*-tubocurarine- $N_2O$ <sup>29,4</sup> anesthesia, without operation, have shown only minimal impairment of latex particle phagocytosis by peripheral-blood leukocytes. NBT reduction is reduced after morphine- $N_2O$  anesthesia,<sup>1</sup> but this may represent a steroid effect rather than a direct effect of the anesthetic agents.<sup>26</sup> Reduced phagocytic activity by fixed macrophages of the reticuloendothelial system has been demonstrated during anesthesia in man<sup>91</sup> and in animals,<sup>90</sup> but in general, the effect of anesthesia on phagocytosis appears minimal.

In contrast, the effect of surgical trauma on circulating neutrophils and fixed macrophages of the reticuloendothelial system appears far more significant. In rats<sup>127</sup> anesthetized with ether and subjected to laparotomy, impaired colloidal clearance was felt to be due to impaired plasma opsonification activity.<sup>126</sup> Impaired clearance has also been demonstrated in dogs subjected to surgical stress.<sup>131</sup> or

ischemic-bowel-induced shock<sup>72</sup> under barbiturate anesthesia. In man, reticuloendothelial function is impaired by operation,<sup>66</sup> while peripheral leukocytes show exaggerated phagocytosis but reduced NBT reduction after thermal injury,<sup>41</sup> cardiac surgery,<sup>131</sup> and miscellaneous traumas.<sup>3</sup> This preservation of particle engulfment but inhibition of leukocyte metabolism is again suggestive of a steroid response to surgery, and indeed can be related to the extent of trauma.

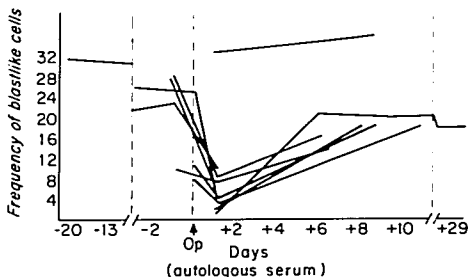
It would thus appear that the effect of anesthetics *per se* on phagocytosis is minimal, relative to the impairment associated with surgical trauma. Surgical trauma may stimulate release of cortisol or other circulating factors that may inhibit phagocytosis, cellular metabolic integrity, or plasma opsonification. Assuming that such inhibition may be secondary to nonspecific "stress" responses, unusually light anesthesia and excessive sympathetic stimulation would be more harmful than well-conducted, adequate anesthesia.

#### ANESTHETIC EFFECTS ON HUMORAL IMMUNITY

The influence of anesthesia on antibody production by sensitized B lymphocytes has been studied in both animals and man, but results are inconclusive. There is no firm evidence that anesthesia alters the level of circulating immunoglobulins. Since the half-life of  $\gamma$ -globulin in serum is approximately five days, any influence of operation or anesthesia should not be manifest until several days following the insult. Patients subjected to burns<sup>4</sup> or cardiopulmonary bypass<sup>67</sup> have reduced levels of immunoglobulins, probably due to general protein loss in the former case and denaturation of protein in the latter. Patients undergoing normal surgical procedures do not show significant alterations in either quantity or type of immunoglobulin present in the serum,<sup>25</sup> suggesting that the effects of anesthesia and operation are not significant. Ichihashi and Kondo<sup>90</sup> have suggested that antibody production in response to a specific antigen given at the time of operation is impaired; however, all patients in their study group had malignancies that might have altered basic immunologic responsiveness independent of operative influences.

<sup>4</sup> Rosenbamm KJ, Orkin F, Department of Anesthesiology, Hahnemann Medical College, Philadelphia, Pennsylvania: Personal communication.

FIG. 4. Lymphocyte transformation in response to PHA following cholecystectomy. Impaired transformation after operation is apparent immediately postoperatively and persists as long as two weeks. From Bergman,<sup>9</sup> reproduced with permission of the author and publisher.



Rats exposed to halothane show a dose-related reduction of antibody synthesis lasting two to six hours after anesthesia.<sup>78,156</sup> Prolonged exposure of rats to low concentrations of halothane, N<sub>2</sub>O and pentobarbital also results in impaired antibody synthesis as measured by the hemolytic plaque technique,<sup>157</sup> probably secondary to a reduction in the actual number of antibody-producing cells in the assay.<sup>78</sup> Prolonged exposure to lidocaine reduced antibody production in rabbits,<sup>90</sup> although the level of lidocaine obtained in the serum was not monitored. Other studies using different species<sup>79,86</sup> have failed to show any significant alteration in immunoglobulin production. In view of species variations, extrapolation of animal data to man is impossible, and hence definite effects of anesthesia on humoral responses in man remain to be demonstrated.

#### ANESTHETIC EFFECTS ON LYMPHOCYTE TRANSFORMATION

Lymphocyte transformation has been studied after exposure of the cells to various anesthetic agents *in vitro*. Halothane in concentrations greater than 0.5 per cent has been shown to inhibit lymphocyte transformation in a dose-related manner,<sup>11,10,17</sup> but the period of exposure must exceed 24 hours. This inhibition is not related to loss of cell viability or failure of labelled precursors to enter the lymphocytes, but is probably the result of inability of the resting cell to begin active mitosis.<sup>13,16</sup> Similar inhibition of lymphocyte transformation has been demonstrated with clinical concentrations of phenobarbital, but not thiopental or amobarbital.<sup>11</sup> No *in-vitro*

inhibition of lymphocyte transformation has been observed following exposure to clinically relevant concentrations of cyclopropane,<sup>95</sup> lidocaine,<sup>96</sup> and ketamine.<sup>95</sup>

In order to determine the effect *in vivo* of anesthesia alone, lymphocytes have been taken from human patients receiving various anesthetics without surgical procedures and put into culture with PHA. Serum factors from anesthetized patients may influence results under these circumstances, and it is important to determine whether altered responsiveness is due to serum or cellular influences. Although lymphocyte transformation is depressed following N<sub>2</sub>O/O<sub>2</sub>-halothane<sup>91</sup> and N<sub>2</sub>O/O<sub>2</sub>-morphine<sup>92</sup> anesthesia and following therapeutic anticonvulsant doses of phenobarbital,<sup>11</sup> no inhibition is observed following thiopental-N<sub>2</sub>O/O<sub>2</sub>-halothane,<sup>93</sup> enflurane, or halothane anesthesia in the absence of operation. § Furthermore, no alteration in lymphocyte transformation is detectable in operating room personnel exposed to trace concentrations of anesthetics for prolonged periods.<sup>88</sup>

In contrast to the variable results reported to occur with anesthetics alone in man, there appears to be a consistent inhibition of lymphocyte transformation associated with surgical procedures, demonstrable in the immediate postoperative period and persisting for as long as three weeks<sup>8,9,115,121,125</sup> (fig. 4). This appears to be a direct effect upon the cells, for it is not corrected by culture with

§ Mathien A, DiPadua D, Mills J, Anesthesia Laboratories, Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts: Personal communication.



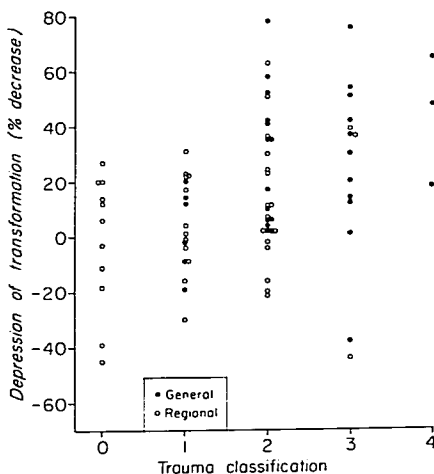


FIG. 5. Relationship of postoperative depression of lymphocyte transformation in response to PHA to an arbitrary scale of surgical trauma in 77 patients. Each point represents the response of one patient. There was no relationship to the type of anesthesia employed. From Cullen and van Belle,<sup>12</sup> reproduced with permission of the author and publisher.

normal serum,<sup>115,121</sup> nor can it be mimicked by cortisol added *in vitro* to the cultures.<sup>8</sup> The changes relate most closely to the extent of surgical trauma<sup>8,12</sup> (fig. 5), although duration of operation,<sup>111</sup> amount of blood transfusion,<sup>83,111</sup> presence of heart disease or cancer<sup>114</sup> may also be contributing factors. Attempts to relate postoperative depression of lymphocyte transformation to the type of anesthesia used have met with little success,<sup>12</sup> for general,<sup>83,111,125</sup> intravenous,<sup>125</sup> and conduction<sup>88</sup> anesthetics were all associated with the same magnitude of change in transformation.

#### ANESTHESIA AND THE STRESS RESPONSE

Reference has already been made to immunosuppression due to nonspecific "stress," particularly in those patients undergoing anesthesia for surgical procedures. Classically, stress is associated with elevated blood levels of adrenal corticoids and catecholamines, both potent immunosuppressives, but other endocrine changes are probably important as well.<sup>109,112</sup> Other factors such as cyclic nucleotides,<sup>129</sup> blocking factors resulting from tumor or tissue debris, and altered organ function secondary to trauma or manipulation, may

contribute to immunosuppression in response to surgical stress.

Direct effects of modern anesthetics on catecholamine levels during well-conducted anesthesia appear to be minimal. However, if anesthesia is light or if complications such as hypoxia, hypercarbia, or hypotension ensue, catecholamines may be released either directly or by central autonomic stimulation.<sup>10</sup> Additionally, the metabolism and distribution of normal concentrations of catecholamines may be altered by some anesthetic agents.<sup>68</sup> Hence, if catecholamines play a role in the immunodepression associated with surgical stress, well-conducted anesthesia should minimize the opportunity for their undesirable elevation.

The adrenal cortex is also stimulated by anesthesia and operation. Adrenal corticoid production is elevated to approximately three times normal at the termination of both halothane<sup>130</sup> and epidural<sup>32</sup> anesthesia for operation, although anesthesia without operation fails to elicit this effect.<sup>118</sup> While high doses of morphine (more than 1 mg/kg)<sup>37</sup> may obtund this response by inhibiting ACTH release, clinical doses of morphine are associated with some elevation of serum cortisol

even in the absence of operation.† Whether the elevations seen clinically are sufficient to block normal immune function remains to be shown, although *in-vitro* experiments using similar concentrations fail to show the amount of depression seen *in vivo*.<sup>8</sup> However, ACTH and cortisol may be acting not alone but with other hormones<sup>26</sup> to create a synergistic effect on immune reactivity.

### Clinical Implications

#### ANESTHESIA AND INFECTION

Any discussion of the influence of anesthetics on infection must consider the effects of the agent upon the microorganism involved, the concentration of the agent, and the milieu in which interaction occurs. Thus, while numerous volatile anesthetics, including ether, trichloroethylene, chloroform, halothane, and methoxyflurane,<sup>7,71,101,150</sup> have bacteriostatic effects on many organisms, they are demonstrable only at concentrations achievable in anesthetic apparatus. Concentrations achievable *in vivo* are generally associated with no bacteriostatic effect,<sup>7</sup> while conditions existing *in vivo* at the site of an inflammatory exudate would further minimize bacterial killing.<sup>71,101,102</sup> Clinical variations in oxygen concentrations have no effect on bacterial survival, while the elevated humidity in an anesthetic circuit lessens any bacteriostatic effects of the anesthetics.<sup>71</sup> In brief, while dry anesthetic gases may reduce bacterial contamination of anesthetic apparatus, there is no evidence of an effect on bacterial organisms *in vivo*.

No demonstrable bacteriostatic effect is achievable with usual stock concentrations of fixed agents such as thiopental (2.5 per cent), succinylcholine, or decamethonium<sup>7</sup>; however, very high barbiturate concentrations<sup>††</sup> will inhibit bacterial multiplication. Local anesthetics have bacteriostatic effects on a wide variety of organisms at concentrations achievable with topical application,<sup>129,153</sup> but a few common pathogens, such as *Staphylococcus aureus* and *Pseudomonas*, are relatively

resistant. Indeed, this has important clinical implications when obtaining bacteriologic information in ophthalmology or bronchoscopy, where use of a topical anesthetic greatly reduces the incidence of positive cultures.<sup>29</sup> Concentrations of lidocaine achieved systemically during regional anesthesia or after intravenous administration are insufficient to alter bacterial growth.

The overall effect of anesthetics on infectious disease is difficult to evaluate because of the many factors involved in the pathogenesis of disease. Hypoxia, uremia, metabolic and respiratory acidosis all increase the severity of infection in experimental animals.<sup>50</sup> Few studies, either in animals or in man, have addressed themselves to the modification of infection by anesthetics, and hence the applicability of the foregoing survey of suppressed immunity by anesthesia and operation remains to be adequately evaluated.

Ether anesthesia has been reported to facilitate experimental induction of influenza pneumonia in mice,<sup>154</sup> perhaps secondary to failure of the normal coughing reflex during anesthesia. Anesthesia has been reported to increase the death rate in mice injected with murine hepatitis virus,<sup>101</sup> an interesting observation that may help to explain the poor prognosis of patients anesthetized while clinically infected with hepatitis virus.<sup>71</sup> Halothane anesthesia was associated with an accelerated death rate in mice with salmonella peritonitis,<sup>12</sup> while the mortality from fecal peritonitis in mice was doubled by administration of halothane, 0.6–0.8 per cent.<sup>17</sup>

Studies of human postoperative infections shed little light on the role of anesthetic factors in development of these infections. The high incidences of chest infections after both local<sup>††</sup> and general<sup>†††</sup> anesthesia have been ascribed at least in part to impaired mucociliary function and bacterial clearance.<sup>††</sup> The incidence of wound infections is directly related to the duration of operation and anesthesia, but is further influenced by surgical technique and the presence of previous systemic disease.<sup>33,37,103,128,129</sup> Mac Lean *et al.*<sup>97</sup> suggest that the patient's immune status plays a highly

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significant role in postoperative infection, in relation to both incidence and severity. Unfortunately, little attention has been paid to the role of anesthesia in these studies, and few conclusions can be drawn about whether individual agents affect perioperative infection.

#### ANESTHESIA AND NEOPLASIA

As with infection, any study of the role of anesthesia in neoplastic disease must consider the effects of the agent on malignant cells as well as the effects on host resistance. There is an inherent danger in extrapolating *in-vitro* and animal data to the human situation, where ethical considerations prohibit adequately controlled studies. In addition, responses to operation and to stress have influences on resistance to malignancy that make the role of anesthesia even more difficult to delineate as an isolated factor. Nevertheless, there is evidence that anesthetics might influence the course of neoplastic disease.

Studies of cell cultures *in vitro* suggest that anesthetics have the same antimitotic effects on neoplastic cells that they have on normal cells.<sup>21-23</sup> In general, however, anesthetic inhibition of cell division requires prolonged exposure (more than 24 hours) and minimal effects would be expected during routine clinical use. Although this has not yet been studied, it is possible that host leukocytes, perhaps because of a more rapid mitotic rate, are more susceptible to antimitotic effects of anesthetics than are tumor cells, implying a condition suitable for enhanced tumor growth in spite of anesthetic-induced reduction in tumor mitotic rate.

Animal models have been used repeatedly to evaluate the effect of anesthesia on tumor growth. Several investigators have demonstrated enhanced numbers of "takes" of intravenously administered tumor cells during anesthesia.<sup>1,11,14,16</sup> However, this model may not be wholly analogous to the human situation, where the host has an opportunity to develop specific immunity prior to vascular dissemination of the disease. Experiments evaluating the growth and metastases of tumors arising in the host have shown enhanced,<sup>24</sup> unchanged,<sup>41,46</sup> or inhibited<sup>19,41</sup>

growth of tumor under anesthesia, probably reflecting differences in the tumor models used and the host animals under study. Inductions of spontaneous<sup>117</sup> and chemically-induced<sup>118</sup> tumors have been enhanced by barbiturate anesthesia in animals.

The effects of surgical procedures on experimental tumor growth and metastases have also been studied with animal models. Surgical removal of a primary tumor appears beneficial in protecting an animal from subsequent reinoculation with the same tumor, demonstrating the "unblocking" effect of removal of tumor mass on host defense mechanisms.<sup>24</sup> Minimal operation or stress may not be associated with any alteration in host resistance,<sup>22,125</sup> although coeliotomy,<sup>22,23</sup> manipulation of the liver,<sup>22</sup> and trauma<sup>22</sup> are associated with enhanced tumor growth, even when tumor cells had remained dormant for extended periods.<sup>22</sup> Some investigators have suggested that hormonal stress responses are unimportant for this enhancement because adrenalectomy or parenteral administration of steroids does not alter the effect,<sup>126,126</sup> although non-operative stress has, by itself, been associated with enhanced tumorigenesis.<sup>122</sup> The anesthesia used in these studies was often unspecified or not given to control animals; hence, the data cannot be meaningfully evaluated from an anesthetic viewpoint.

Although controlled studies in man are lacking, several observations appear pertinent. Patients who have previously had neoplasms with no evidence of metastasis occasionally experience reappearance of cancer after incidental anesthesia and operation.<sup>22</sup> In addition, tumor cells are often demonstrable in regional and central veins at the time of surgical resection of malignancy, in spite of acceptable operative technique.<sup>122</sup> Thus it may be that increased seeding of tumor at the time of resection, occurring at a time of lessened host resistance due to anesthesia and operation, sets the stage for post-operative exacerbation of the disease.

Recently it has been possible to monitor human host responses to cancer by the use of *in-vitro* assays such as those that measure the ability of leukocytes to recognize and react to antigens specific to the tumor. These

assays, by determining cellular immune responsiveness to the tumor in question, afford some idea of host resistance to the tumor and appear to correlate with clinical status and prognosis in most cases.<sup>25</sup>

Tumor-specific responses have been monitored in the perioperative period to determine the effects of operation and anesthesia on host resistance to cancer. A study of leukocyte migration inhibition in response to tumor antigens in 24 melanoma or mammary carcinoma patients showed impairment postoperatively for as long as 22 days.<sup>27</sup> Similarly, the inhibition of leukocyte adherence to test tubes was used to evaluate patients with mammary carcinoma, and again, inhibition was demonstrable postoperatively for 7-14 days.<sup>26</sup> The ability of host leukocytes to kill tumor cells has been assessed *in vitro* and is impaired for as long as seven days after operation in patients who have mammary carcinoma<sup>105,119</sup> and Wilms' tumor<sup>28</sup> (fig. 6). Tumor cell killing by sensitized leukocytes is also inhibited by local anesthetics,<sup>27</sup> barbitol,<sup>26</sup> and halothane<sup>27</sup> *in vitro*. To what extent anesthetics contribute to the inhibition seen postoperatively in man is not known.

Thus, surgical operations, by dissemination of tumor cells, in conjunction with altered host resistance due to anesthesia, stress, or other unknown mechanisms, may be harmful to cancer patients. Unquestionably, many patients have their neoplasms successfully removed surgically with little deleterious effect. However, the immunosuppressive effect of the procedure may be sufficient to decompensate the resistance of some patients where the tumor load is extensive. Under these circumstances efforts must be made to minimize the suppression caused by the procedure or to augment host resistance preoperatively, in order to obtain maximum benefit for the patient.

#### ANESTHESIA AND TRANSPLANT REJECTION

The optimum anesthetic technique for patients undergoing homograft transplantation is largely unknown. In many instances the success or failure of these procedures hinges upon the adequacy with which immune rejection of the transplanted organ can be de-

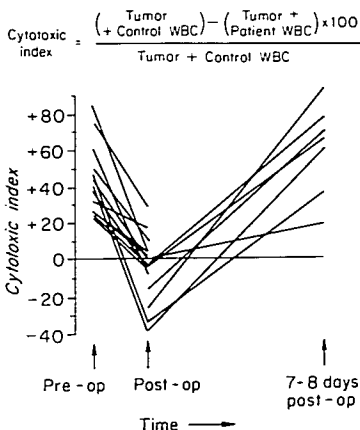


FIG. 6. Effect of simple mastectomy performed with N<sub>2</sub>O/O<sub>2</sub>-halothane anesthesia on the ability of peripheral leukocytes from 23 patients with mammary carcinoma to kill mammary tumor cells *in vitro*. Tumoricidal activity (expressed as a cytotoxic index) is reduced immediately postoperatively, and the reduction persists at least a week in 50 per cent of cases. From Vose and Moudgil,<sup>119</sup> reproduced with permission of the author and publisher.

pressed, and therefore any immunosuppression by anesthetics might be beneficial. Little work has been done to assess this possible effect in either animals or man, however. Graft rejection in mice and mongrel dogs is unaffected by prolonged halothane or N<sub>2</sub>O anesthesia,<sup>21</sup> although urethane is capable of prolonging graft survival in neonatal mice under experimental conditions.<sup>120</sup> Clearly, further animal and human studies, using other agents, techniques and dosage schedules, must be performed before any conclusion can be reached concerning the significance of anesthesia in modifying transplant acceptance.

#### ANESTHESIA AND ANAPHYLAXIS

The pathophysiology, clinical manifestations, and management of anaphylactoid and other drug reactions have been reviewed recently.<sup>5,26,116</sup> It is pertinent to consider

whether anesthesia, by suppression of immune responsiveness, affords protection against such catastrophic events. Here again, caution must be exercised in extrapolating animal data to the human situation, for considerable species variation exists for both mediators of anaphylaxis and end-organ responsiveness.

Anaphylaxis has been reported to occur with virtually all the fixed drugs used in clinical practice, including local anesthetics, induction agents, and muscle relaxants. Early work suggested that some anesthetic agents, particularly ether, may protect the experimental animal from otherwise fatal injections of antigens.<sup>24</sup> More recent evidence, however, fails to demonstrate any reduction in incidence or mortality from the syndrome by commonly used anesthetics.<sup>112</sup> The clinical manifestations of anaphylaxis may be modified by the pharmacologic actions of anesthetics on the cardiovascular and respiratory systems, but release of mediators by antigenic stimulation and the latter's interactions with target organs does not appear to be significantly affected.<sup>25</sup> Consequently, on the basis of present knowledge, the administration of known allergens during anesthesia cannot be justified, and great caution in drug selection should be exercised when patients have been known to manifest allergic phenomena in the past.

### Conclusions

If anesthetics are immunosuppressants, even if only during the time of operation with its associated neurohumoral reflex responses, there are many implications for the clinician who is caring for patients who have infections or neoplastic disease. Since neither the relative potencies nor the clinical significance of anesthetic effects on the immune system are known, no recommendation concerning anesthetic technique or choice of agent can presently be made. Elective procedures should be avoided if possible in the management of patients who have infections. If this is not feasible, effective antimicrobial and adjunctive therapy should be initiated preoperatively. The role of nonspecific immunostimulation with techniques such as BCG administration remains to be evaluated for patients known to be at

risk, such as those who have extensive malignancies.

Careful perioperative management by the anesthetist should help to minimize any immunosuppressive effect of the operative procedure. Theoretically, such factors as hypoxia, hypercarbia, hypotension, too light anesthesia, undue surgical trauma, and prolonged anesthesia and operation will enhance immunosuppression. Anesthetics, while perhaps directly contributing to the reduced immune responsiveness, are probably more important indirectly as modifiers of the total response to the procedure. At present, the relevance of such concerns to the anesthetic management of patients at risk remains speculative, to be elucidated by further clinical studies.

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