Review Article

Anesthesia and the Immune Response

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THE COMPLEXITY of modern surgery frequently necessitates prolonged general anesthesia, which interferes with the immune response, suggesting that general anesthesia may affect postoperative infections, tumor growth, anaphylaxis and response to organ transplantation. This review summarizes evidence that anesthesia interferes with the immune response, particularly in these areas. The components of the immune response are described briefly, in simple terms, avoiding controversial areas. A recent monograph[51] summarizing current concepts of immunology is available for greater detail.

The Immune Response

Originally, immunology comprised the study of resistance to infection. Bacteriologists were the first to investigate the manner in which the host develops specific resistance to microorganisms by the production of antibodies. Later, it became apparent that acquired hypersensitivity to specific foreign proteins developed in the same way. Thus, the immune response can protect the individual (resistance to infection) or harm him (anaphylaxis). There are two basic types of immune response. One is manifested principally by circulating humoral antibodies and the other, frequently referred to as delayed hypersensitivity, is mediated by antibody-containing cells.

Cells present in, or derived from, lymphoid tissue mediate immune responses[74] and are involved in two distinct components of these responses: an afferent mechanism, concerned with recognition of antigen, and an efferent mechanism which determines the reaction of the host. The primary event of the afferent response is phagocytosis of the antigen by either fixed cells (reticuloendothelial) or circulating phagocytes (macrophages, neutrophils). This phagocytic function is enhanced by serum factors called "opsonins," which include serum complement and antibody. Once within the phagocyte, the antigen is prepared for the lymphocyte, which determines the efferent response.

That lymphocytes are involved in immunologic activity was established by the demonstration by Ehrich and Harris[29] that antibody production in lymph nodes is associated with lymphocytic hyperplasia. In the lymph from a node draining a site of antigenic injection, they found that increases in antibody titer and in cell content went hand in hand. Fagraeus[31] noted that among the cells that constitute lymphoid tissue, plasma cells seemed best suited to rapid immunoglobulin production. The most direct evidence of antibody synthesis in plasma cells was offered by Coons,[24] who demonstrated the presence of antibodies in the cells of lymphoid tissue by fluorescent antibody staining techniques.

The characteristic response to antigenic stimulation of lymphoid tissue is cell division. The proliferative changes that follow secondary antigenic stmiulation are usually much more pronounced than those which follow the first injection of antigen. The rate of increase in production of antibodies following a second injection of antigen (the "secondary" response) is more rapid than that following the first injection (the "primary" response).[38] Coons[24] found antibodies in cells scattered throughout

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lymphoid tissue four days after a primary stimulus, but only after six to eight days could these cells be clearly identified as plasma cells. In a secondary response, the antibody appeared within two days, and plasma cells were more numerous at that time.

The origin of plasma cells is controversial. Their precursors appear to be large lymphocytes in both blood and lymph. Gowans[42] showed that small lymphocytes constitute a recirculating pool of cells which pass freely from blood to lymph, whereas large lymphocytes are located chiefly in the gut, where they apparently develop into plasma cells. He further demonstrated that small lymphocytes of rats were divided into a short-lived (less than two weeks) population and a long-lived (several months) variety. A possible role of the small lymphocyte in the immune response has been suggested only recently. Gowans[43] irradiated animals to the point where they lost immunologic competence, then transfused them with small lymphocytes obtained from nonimmune donors. He found that the irradiated recipients were once again able to respond to antigen with production of the appropriate antibody. These findings indicate that small lymphocytes are involved in the primary immune response. When, on the other hand, the animals were transfused with small lymphocytes obtained from immunized donors, they responded to the first injection of antigen in a typical secondary manner, showing that the small lymphocyte is also involved in the secondary immune response. Thus, in the case of the formation of circulating humoral antibody, there is indirect evidence that through a series of rapid cell divisions, lymphocytes give rise to antibody-producing cells which themselves are either large lymphocytes or, more probably, plasma cells.

In cell-mediated immunity antigen also stimulates the rapid proliferation of cells which are endowed with the ability to synthesize antibodies against the stimulating antigen and are more likely to be lymphocytes of medium size than plasma cells. Brent and Medawar[10, 11] have suggested that this form of immunization consists simply of the generation of more cells with the same specificity. Thus, the nonimmune animal is assumed to possess lymphocytes capable of reacting with antigen but too few in number to inactivate it. Immunization would involve division of these lymphocytes in rapid succession to form large numbers containing the appropriate antibody. In the case of a homograft, for example, the antigenic stimulus would cause lymphocytes to divide until sufficient numbers were available to destroy the graft. This would require a selective shift to rapid cell division by the lymphocytes which possessed appropriate receptors for the antigen peculiar to that homograft.

The clinical manifestations of the immune response will depend upon the antigen and the particular cellular reaction elicited. Antibodies may be immunoglobulins, which circulate or are fixed to specifically sensitized cells. These, in turn, will promote a variety of reactions, such as enhancement of phagocytosis of antigen, hemolysis, activation of serum complement causing inflammation, and cellular release of substances such as histamine, serotonin and lysozyme. The clinical consequences of these events run the gamut from resistance to infection, anaphylaxis, and natural resistance to development of cancer to tissue transplant rejection.

Effects of Anesthesia on the Immune Response

Present evidence indicates that anesthesia interferes with both the afferent and efferent components of the immune response, but mostly the afferent system. Mobilization of phagocytes is inhibited during anesthesia. The formation of a peritoneal neutrophilic exudate in response to appropriate injection is inhibited by halothane (Fluothane) in the mouse[13] and rabbit.[62] The focal accumulation of neutrophils from abraded skin of the rabbit ear is markedly obtunded by diethyl ether or halothane.[14] These observations may be explained by an effect of the anesthetic either on capillary integrity or on the neutrophil itself. The former appears unlikely because the rate of extravasation into the peritoneal cavity of Evans blue dye injected intravenously into mice given intraperitoneal bacterial endotoxin is unaffected by halothane.[14] On the other hand, ether and halothane cause in neutrophils morphologic changes[13] which resemble the "stiffening" found in amebae[15] exposed to these anesthetics. This might be expected to

interfere with transvascular diapedesis of cells toward the site of antigen deposition, since this process requires alteration of the leukocytic form during passage through the capillary wall. Cellular locomotion is known to be inhibited by anesthetics [12, 66, 75] *in vitro*.

Once the leukocyte has reached the antigen, it must phagocytize the substance as the next step in the immune response. Sixty years ago, Graham [45] showed that ether inhibits phagocytosis by human and rabbit leukocytes. In 1916, Hamburger [48] reported that very low concentrations of chloroform *in vitro* stimulated phagocytosis by equine leukocytes, but as the concentration increased there was a reversal of the effect with complete cessation of phagocytosis. Recently, the same type of inhibition was shown during halothane anesthesia in mouse, rabbit and man.[13, 63] Since phagocytosis can be limited by anesthetics *in vitro*, it appears that the explanation lies in a direct depressant effect of the agent upon these cells. There may also be a diminution of activity of opsonins which promote phagocytosis, since normal leukocytes from unanesthetized patients and animals became inhibited in their capacity for phagocytosis when added to sera from individuals anesthetized with ether [45] or halothane.[63] These sera were almost certainly free of residual anesthetic. Batrak and Chaplinskii [7] anesthetized rabbits with ether and two to four days later found that sera from these animals were less effective in protecting mice against paratyphus infection than normal serum. This delay in recovery of serum antibacterial activity has been noted by others [54, 62] but has not been investigated thoroughly for its significance. Similarly, the hypothesis [61] that ether and chloroform reduce complement fixation by dissolving serum lipoids remains to be substantiated.

The apparent decrease in concentration of opsonins probably results from an effect of anesthesia on the lymphocyte. Prolonged exposure to any of the commonly used anesthetic agents causes a circulating leukopenia.[2-4, 17, 47, 64, 78] The lymphopenia seen soon after exposure probably has immunologic significance. *In vitro* studies by Nunn *et al.* with halothane [75] and Trowell with barbiturates [94] have demonstrated direct, toxic effects of these agents on lymphocytes. Findings included decreased motility, morphologic changes and death of some cells.

In vivo studies in rodents have revealed a time-dependent significant reduction in splenic antibody-producing cells after two hours of 1 per cent and four hours of 0.5 per cent halothane.[102] The numbers of cells remained depressed for various periods of time, directly dependent upon the duration of exposure to the anesthetic. Similar studies in rats and mice treated for 24 hours with halothane, nitrous oxide or pentobarbital demonstrated even greater depression of these cells.[54, 55, 103] In rats, recovery of normal antibody-forming capacity did not occur until 72 hours after the end of anesthesia, and the reduction in antibody production appeared prior to death of any cells. These changes in lymphocytic function are reflected in a decrease in antibody titer and complement fixation, which does not occur until 24 to 48 hours after anesthesia.[7, 54, 62] Anesthetics do not alter the activity of preformed antibody [34, 45] and this, coupled with the finding that serum antibody titer changes lag 24 hours behind antibody production by lymphocytes,[56] makes a strong argument for a direct anesthetic inhibition of antibody production. Since the immune response involves rapid proliferation of appropriate lymphocytes, and virtually all anesthetics inhibit cell division, the reaction wherein lymphocytes divide and initiate the efferent arm of the response may be blocked.

It is possible that the effect of anesthesia on the immune process is nonspecific, since anesthesia affects the sympathoadrenal system. Most of the studies cited were done in rats and mice, whose small lymphocytes are particularly sensitive to corticosteroids.[85] Both the number of lymphocytes and the phagocytic capacity of macrophages are depressed by steroids. Anesthetic agents *per se*, as well as "stress" of surgical trauma and blood loss, exert a variety of effects on the sympathoadrenal complex.[96, 97, 99] The reaction to noxious stimuli which we call "stress" can be divided into several phases. The first is a period of catecholamine release, characterized by a leukocytosis during which both neutrophil and lymphocyte counts are elevated, a change consisting predominantly in alterations of distribution and mobilization of cells.[27] A similar pic-

ture is caused by ether.[9, 21, 68, 86] The second phase results from ACTH liberation and is characterized by persistent neutrophilia but with concomitant lymphopenia. The latter probably represents cell destruction caused by corticosteroids.[27, 69] With prolonged exposure to halothane [19, 103] and nitrous oxide,[47] the first change is lymphopenia and neutrophilia. Humphrey *et al.*[53] have reported wide variation in peripheral leukocyte counts in man after an hour of halothane anesthesia. The only anesthetic agent administered to their patients was halothane, which has been shown to increase adrenocortical activity.[77] In addition, the patients were operated upon, a stimulus also known to increase adrenocortical activity.[72, 77] The variations in peripheral leukocyte counts reported by Humphrey, therefore, may reflect the degrees of adrenocortical activity at the moments the samples were obtained. In contrast, barbiturates do not stimulate catecholamine release, but inhibit ACTH secretion,[96, 97, 99] and the early leukocytosis caused by ether does not occur. In animals given barbiturate anesthesia there is an immediate decrease in peripheral leukocytes, predominantly the neutrophils, which reverses upon awakening.[44, 86, 95] The lymphocytes are either unaffected or elevated slightly.

Green has reported differences in sensitivity to the leukopenic effects of nitrous oxide among various strains of rats.[46] Cell destruction by nitrous oxide was greatest in aggressive, active wild rats and least in docile, domesticated rats. Perhaps wild rats have a high degree of sympathoadrenal activity which is partially responsible for the greater sensitivity of their leukocytes. Parbrook found that anesthesia produced more leukopenia and greater mortality in wounded rats than in normal rats.[78] The Jerne plaque technique was used to study antibody production by splenic lymphocytes of adrenalectomized rats, but the experiments were unsuccessful because these animals do not tolerate anesthesia well.[102] In the same study, the administration of morphine for five days in an attempt to reduce ACTH production produced only equivocal results. There is, then, a suggestion that the hypophyseal–adrenal axis may play a significant role in anesthetic immunosuppression. Further studies would help to define the relative effects of anesthesia, operative stress, and sympathoadrenal systems on the immune response.

Infections

Around the turn of the century, there were a number of reports claiming increased susceptibility of animals to a variety of bacterial infections following administration of central nervous system depressants. Many of these studies suffered from inadequate descriptions of technique, and often they contained few animals. In 1903, Snel[88] reported that ether, chloroform and chloral hydrate increased the mortality from anthrax in guinea pigs. This effect was noted to be in proportion to the duration of anesthesia. Rubin[82] made similar observations in studies of rabbits infected with streptococci or pneumococci and anesthetized with ether or chloroform. He concluded that both the depth and the duration of anesthesia were important in potentiating these infections. More recently, Bruce[13] studied the effect of six hours of 1 per cent halothane anesthesia on the mortality of mice given serial dilutions of *Salmonella typhimurium* intraperitoneally. The eventual mortality rate was not changed by anesthesia, but deaths which were to occur in the anesthetized group did so rapidly, usually during or immediately after the administration of anesthesia, compared with the slower progressive rates of death in the control groups. Olsen and co-workers[76] found that four hours of 1 per cent halothane not only accelerated the deaths of mice but also reduced the LD_{50} of *Pseudomonas acruginosa.*

It appears that anesthetics enhance infection by depression of phagocytosis and inhibition of mobilization of phagocytes into the area of infection. Long ago, Graham[45] observed reductions in phagocytosis by human and animal leukocytes when exposed *in vitro* and *in vivo* to five different species of bacteria during ether anesthesia. Goldstein *et al.*[40] have found that cyclopropane and methoxyflurane reduce murine pulmonary bactericidal activity. In the study cited above,[13] Bruce observed tenfold reductions in the numbers of phagocytized salmonellae and consequent increases in the numbers of free bacteria in the peritoneal cavities of the mice given halothane anesthesia. In addition, there were reductions in the numbers of neutrophils present in the peri-

toneal cavities which paralleled earlier findings [12] of decreased extravasation of neutrophils into the peritoneal cavities of mice anesthetized with halothane and given intraperitoneal injections of *Pseudomonas* lipopolysaccharide. Kosciolek [63] reported *in vitro* studies of phagocytosis by neutrophils in blood removed from men and rabbits anesthetized with ether or halothane. Both agents depressed the uptake of staphylococci by these cells. In this study, the patients were being operated upon when the blood samples were withdrawn, so that surgical stress might have accounted for the results. However, the rabbits had no surgery, and the results for rabbits were similar to those for patients. This suggests that anesthesia was the predominant cause of the depressed phagocytosis. Reductions of neutrophils in the peritoneal cavities of the rabbits were also noted, as was a circulating lymphopenia, most pronounced six hours after anesthesia, which gradually returned to normal 60 hours later.

There is no specific evidence that anesthesia predisposes man to bacterial infections.[58] In the cooperative ultraviolet light study conducted in five institutions by the National Research Council [80] the incidences of wound infections in surgical patients were found to be related directly to duration of the procedures; infections occurred in both clean and contaminated cases. Unfortunately, the anesthesia techniques were not reported, but an inquiry revealed that the patients were categorized as having received either regional or general anesthesia, the agents unspecified.[13] The only operation for which large groups of patients were given either regional or general anesthesia was elective herniorrhaphy. The incidences of wound infections in the two groups were the same, but the majority of patients had received prophylactic antibiotics, which precludes a meaningful interpretation of the data. The demonstration that the degree of leukocytic depression is related to duration of exposure to anesthetics [82, 88, 102] suggests there might be a causal relationship of prolonged anesthesia to postoperative infection. A definitive, prospective study of this problem would be worthwhile.

In animal studies referred to above [7, 54, 62] antibody and complement titers decreased progressively from normal on the day of anesthesia to low points about three days later, and did not return to control levels until the fifth day after the end of anesthesia. Wounds likely to become infected usually are not closed primarily until five to six days after the initial operations. While this practice is founded upon the empirical observation that wounds closed earlier tend to become infected and heal poorly, it may be more than coincidence that the optimal time for closure coincides with return of the immune response to normal.

A discussion of infections should include those due to viruses, but for acute viral infections at least, the problem appears to be significantly different from that of bacterial infection. Viruses are classified according to their sensitivity to liquid ether *in vitro*, some viruses being inactivated by it and others not.[6] The effect is due to direct toxicity to the virus. Studies suggest that a variety of anesthetics,[26, 89, 91] particularly ether, protect animals from some viral infections. This is especially true for those conditions caused by viruses classified as ether-sensitive. Since the *in vivo* concentration of ether necessary for this protection is much less than the virucidal concentration *in vitro* [90] the mechanism probably is not the result of an effect on the virus but is due to an effect on the animal itself which somehow prevents replication of the virus. The influence of anesthesia on the specific mechanisms of immunity evoked by viral infections has not been studied. This is a fertile field for future investigation.

Anaphylaxis

Quill [81] and Carron [22] have reviewed the older literature concerning anaphylaxis. Animal studies of the influence of anesthesia on this manifestation of the immune response have been inconsistent and contradictory. One reason for this is the differences in the anaphylactic responses among species.[101] Ether will protect guinea pigs from anaphylaxis but affords little protection to mice.[22] The route of administration of the antigen is also important, with intravenous injection producing the most consistent results,[101] although Parish *et al.*[79] found that ether did not protect guinea pigs when the antigen was given intravenously but did when the antigen was applied topically. This protection was related inversely to anti-

body titer, being most pronounced when the titer was low. Ether appears to be the anesthetic agent which most consistently protects against anaphylaxis in animals.[22, 79] In the guinea pig, halothane, nitrous oxide, cyclopropane, and pentobarbital provide little protection.[22, 79] Carbon dioxide narcosis prevents anaphylaxis in the guinea pig,[79] suggesting that respiratory acidosis if inadvertently produced during ether anesthesia might account for part of its protective action. Anesthetics appear not to interfere with the reaction of preformed antigen and antibody,[34, 102] so if protection is provided it must be by interference with the mediators of the response to anaphylaxis (*e.g.*, histamine, 5-hydroxytryptamine) and their actions on the end organs involved in the response.

Anaphylactic reactions in patients during deep general anesthesia appear to be rare. Reactions during induction of anesthesia [5, 25, 39, 57, 60, 84, 87] and on emergence from anthesia [67, 81] have been reported. Wheezing followed injection of succinylcholine in one asthmatic patient during both deep cyclopropane and deep ether anesthesia.[32] This low incidence of reactions may indicate that anesthesia interferes with anaphylaxis in man. Katz *et al.*[59] recorded the reaction of an anesthetized patient to penicillin and suggested that anesthesia modified the classical signs of anaphylaxis. They speculated that some inexplicable reactions of patients during anesthesia might fall into this category. The clinical signs of a reaction to a transfusion of incompatible blood, such as hypotension and bronchospasm, may be masked by anesthesia, even though the antigen–antibody reaction takes place and hemolysis and coagulation defects develop.[100] Frolov [34] has reported that ether anesthesia does not interfere with antigen–antibody reactions in rabbits, but that the manifestations of the reactions are modified, decreasing mortality. In the past it was common practice to administer antitoxins during anesthesia rather than before or after, in order to prevent allergic reactions to horse serum.[22, 81] Usual doses of tetanus and gas bacillus antitoxin did not produce anaphylaxis when given intravenously during ether anesthesia to patients shown preoperatively to be sensitive to the serum.[22] Quill reported the death of a surgical patient following the injection of tetanus antitoxin, but this apparently occurred postoperatively and, presumably, during or after emergence from anesthesia.[61]

Thus, the clinical literature concerning the effect of anesthesia on anaphylaxis is also confusing and contradictory. The agents appear to offer some protection, but the circumstances favoring this are obscure. Information to date is insufficient to warrant the intentional administration of a known allergen to an anesthetized patient.

Tumor Immunity

The tendency toward the development of malignancy in the host may be balanced by immunologic tumor suppression. In 1955, Mitchison [71] established that immunity to transplantable tumors in the mouse could be conferred by transfer of cells from lymph nodes draining a tumor homograft. Subsequent animal work has been reviewed by the Hellstroms,[50] who also reported their studies of a variety of human tumors. In almost every patient tested they found a strong cellular immunity to antigens present only in the patient's neoplastic cells. It appears that the cancer cell is antigenic and that a cell-mediated immune response of the host inhibits tumor growth. Good and Finstad [41] have described the relationship between lymphoid tissue, immunity and malignancy as a phylogenetic phenomenon. Among animal species, the more highly developed the immune response, the more the animal is given to the development of malignancy. It seems that evolution carries the penalty of susceptibility to cancer, but this trend is balanced by the concomitant development of protective mechanisms of immunity. Interference with this balance would favor malignancy. Good and Finstad note that patients receiving effective immunosuppressive therapy develop cancer far too frequently for this to be due to chance, that immunosuppression in animals aids the experimental induction of malignancy by carcinogens, and that carcinogenic chemicals are also immunosuppressive if given in appropriate dosages. With this degree of interaction, interference with immune mechanisms by anesthetics would be expected to influence the course of tumor development.

In 1916, Gaylord and Simpson studied the effects of chloroform and ether anesthesia on transplanted mammary carcinoma in mice.[36] Animals which were anesthetized with chloroform briefly to the point of unconsciousness each day for ten consecutive days following implantation of tumors had an accelerated rate of "takes." They concluded that, "loss of blood and the use of anesthetics appear to injure the natural resistance of a certain number of mice." More recently, two studies [1, 93] have demonstrated that 30 to 60 minutes of anesthesia with pentobarbital, ether or chloroform caused a significant increase in the number of rats developing tumors following inoculation of Walker 256 carcinosarcoma. Similar findings in rats anesthesized with hexobarbital or ether and injected with sarcoma 45 were reported by Timoshechkina.[92] On the other hand, a report [83] of the growth of tumors following intravenous injection of S-91 melanoma cells into mice concluded that, "there is no significant effect of anesthesia, operation or cortisone administration on the number of artificial pulmonary metastases of S-91 melanoma." The results of this paper are suspect because 100 per cent of control animals developed metastases and the authors did not specify the details of the anesthetic, saying only that they gave "anesthesia, intraperitoneally." For such an important area, the studies are too few in number and poor in quality.

Although little work has been done on the short-term effects of anesthesia on tumor growth and the immune response has not been directly implicated by any of the studies, there have been attempts to assess the effects on lymphoid tissues of long-term exposure to anesthetics. It is well known that the analog of the excitement phase of clinical anesthesia exists in many cellular processes.[49] For example, very low doses of chloroform stimulate phagocytosis by leukocytes [48] before this function is depressed by increasing concentrations of the anesthetic. If cell division is hindered by clinical concentrations of anesthetics, might it be accelerated by subanesthetic amounts? There is some evidence [33] that low concentrations of ether and halothane exert mild stimulation of cell division in mouse heteroploid cell cultures, but this area is largely unexplored. Its importance is underscored by the finding of an increased incidence of death from neoplasms of the lymphoid tissues among anesthesiologists.[16] This finding prompted a study in which rats were exposed to 0.01 per cent halothane in air daily for eight hours, five days per week for six months.[65] Neither changes in peripheral blood counts nor pathologic changes were found in rats receiving this treatment. The spleens of the rats exposed to halothane were double the sizes of the spleens of their litter-mate, paired controls, although the histologic patterns of the spleens were normal. In another study,[18] mice were exposed to 0.1 per cent halothane in air, seven hours daily for 15 weeks. This treatment produced a significant increase in mortality, but the cause of death of the animals could not be determined. The occasional finding of patches of lymphoid hyperplasia in the spleens of the surviving mice which received halothane was of questionable significance.

Transplants

Several investigators have described the effects of central nervous system-active drugs on tissue immunity. Reserpine prolongs the time of rejection of skin grafts in rats.[28] Phenothiazine derivatives will protect skin homografts in rabbits [30] and rats,[37] and rabbit corneal transplants as well.[8] The immunosuppression produced by chlorpromazine or reserpine is reversed by hypophysectomy and adrenalectomy.[37] Eyal *et al.* found that large doses of promethazine, perphenazine and chlorpromazine (in order of decreasing activity) increased skin graft survival in rats.[30] These authors consider the initial event following injection of the drugs to be a preservation of cell, lysosomal and mitochondrial membrane, which results in less intracellular antigen's becoming liberated in the host for the production of antibodies. The above observations are largely empirical, with little data concerning mechanisms of action. However, they do suggest some hormonal control of immunosuppression, since it can be reversed by hypophysectomy and adrenalectomy.

In contrast to the considerable number of reports concerning these drugs, the information regarding inhalation anesthetics is meager. Bruce and Wingard [19] found that prolonged halothane administration did not prolong the

viability of skin grafts in rats, and although 70 per cent nitrous oxide inhaled for long periods caused significant reductions in leukocytes in dogs, it did not increase the survival times of transplanted kidneys in these animals. No other data concerning the effects of general anesthetics on transplants are available at the present time.

Discussion

The area which has received the most attention is that of acute bacterial infection. The animal experiments cited above support the contention that anesthesia *per se* increases the morbidity from bacterial infections. Cellular processes such as peritoneal extravasation of neutrophils and phagocytosis by these cells are depressed by volatile anesthetics. This is an important component of natural host resistance to infection. In a study whose results were published in 1936, guinea pigs were given intracutaneous injections of nine different bacteria.[70] With all nine pathogens, the diameters of skin lesions were enhanced when the animals were given epinephrine or put into dehydration shock by hypertonic solutions administered intraperitoneally. The degrees of enhancement by these treatments varied among the bacteria, but *E. coli*, Pseudomonas, Proteus, and *Cl. welchii* had the most prominent effects. The increased diameters of the lesions were interpreted as representing interference with natural body responses to the pathogens, in the form of either inhibition of access to the lesions or attenuation of action of bactericidal elements of the blood in the lesions. The most interesting finding, however, was that infections several hours old were not influenced by these maneuvers. Similarly, infections more than three to five hours old were insusceptible to the actions of intravenous antibiotics given in doses that were effective when given earlier in the course of the infection. In a more recent review,[20] this and other studies are cited as demonstrating that the effectiveness of natural host resistance is contingent upon the ability to act on the invading bacteria as soon as they arrive in the tissue. An inhibitory action of anesthetics on human cellular defense mechanisms would clearly interfere with reactions to bacterial invasion occurring at the time of anesthesia and operation.

In terms of temporal relation to the surgical procedure, anesthetic effects probably play a role in morbidity in the early postoperative period. As outlined previously, these first few days are when antibody production and complement fixation are at their nadir following anesthetic-induced immunosuppression. If bacterial contaminants have gotten a head start at the time of operation, due to interference with cellular defense mechanisms, and then are not combatted by appropriate antibodies in the next few days, it seems likely that postoperative morbidity from infection will be enhanced, even though there is no direct experimental proof of this in patients.

In the quoted study of peritoneal neutrophil mobilization,[12] halothane completely blocked the extravasation of neutrophils into the peritoneal cavities of mice following intraperitoneal injection of bacterial endotoxin. If this degree of inhibition were produced by cortisone, it would not be reversible for several days,[35, 72] but it was reversible immediately upon cessation of halothane inhalation. This offers some support to the idea that the effect of the anesthetic is more specific than some sort of "stress" reaction. It would naturally follow that if an anesthetic has a specific inhibitory effect on normal defenses during the time it is being given, and if these defenses are critical in the early stages of bacterial invasion, then the duration of anesthesia should be as brief as possible. The tendency in the medical community to regard anesthesia as innocuous, with dangerous periods existing only during induction and emergence, does not seem justified. We suggest that morbidity may be influenced in a subtle fashion by the duration of anesthesia. We have been discussing infections in which humoral antibody is a predominant mediator of immunity, which would include not only acute bacterial infections but also viral hepatitis.[98] It is logical to speculate that there is a possible relationship of anesthetic-induced immunosuppression to the development of postoperative hepatitis. Perhaps, in some of these cases, latent viral hepatitis which had been kept under control by natural defense mechanisms becomes active as the scale is tipped in favor of the virus.

Most viral, fungal, and protozoal, and many bacterial diseases, as well as natural resistance

to cancer, are thought to involve a different form of immune response. The term, "cell-mediated immunity"[23, 52] is used to describe this form of immunity, previously called "delayed hypersensitivity." In this situation, the antibody appears to be produced by and to remain fixed to a cell, the sensitized lymphocyte. Little work on the effect of anesthesia on the system has been done, although numerous model experiments are available into which anesthesia might be incorporated to study its effects.

Numerous studies could be done, and some are fairly obvious. The degrees of infectivity of a variety of bacteria and viruses could be investigated in animals anesthetized at different times in relation to deliberate infection with the pathogens. The well-known model of bacterial peritonitis in the dog, wherein an appendectomy is performed and the appendiceal stump is left open, could be used with general anesthesia lasting minutes to many hours. The mortality rates associated with these differences in anesthesia times could be evaluated as a function of anesthesia time, of peritoneal cell counts, of quantitative peritoneal and blood cultures, and of development of antibody titers. A further study of the efficacy of antibiotics in these animals, with and without anesthesia, would shed light on the question of whether prophylactic antibiotic therapy is an adequate substitute for a swift surgical procedure in the subject known to be infected preoperatively. Although our studies of skin and kidney grafts in rats and dogs, respectively, indicated that halothane and nitrous oxide did not prevent or modify the course of rejection, more work along this line is indicated. The effects of anesthesia on tumor "takes" should be pursued further.

These are areas which offer abundant opportunities for clinical research. It would be important if one were to demonstrate that the response of man to the presence of bacteria in his peritoneal cavity was altered by anesthesia. This would require a cooperative venture between surgeons and anesthesiologists, with a standardized method of sampling the contents of the peritoneal cavity and quantitating both the cell content therein and the numbers and types of bacteria present. Controls would be necessary, for which regional anesthesia could be used. Along the same line, a series of patients known to have bacterial peritonitis preoperatively could be operated upon using either regional or local anesthesia and their morbidity and mortality rates compared with those of similar patients having general anesthesia. Again, this would require careful design and strict attention to an experimental protocol in order to achieve meaningful results.

If animal studies were to indicate that allergic responses, mediated by a delayed hypersensitivity mechanism, were obtunded by anesthesia, the possibility of modification of acute allergic reactions by long-term exposure to anesthetics might be investigated in man. Poison ivy is an example of this sort of reaction, in which the delayed hypersensitivity reaction is concurrent with the presence of antigen, and once the eliciting allergen is destroyed, the disease process ceases.[98] Could an allergy-provoked drug reaction or an attack of bronchial asthma be aborted by long-term administration of anesthetics? There have been so few animal studies of the effects of anesthesia on the immune defenses against cancer and homografts that to suggest clinical studies along these lines would be premature. However, should meaningful data accrue in basic studies, clinical research along these lines could easily be envisioned.

If we look critically at the subtle effects of the process called general anesthesia, we learn that this is not a physiologic state at all. Through some of the studies outlined, we may develop a rational, scientific basis for our long-held intuitive feeling that general anesthesia must be conducted by the most direct route in the shortest time consistent with good practice.

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Surgery

PERIPHERAL PALSIES Sudden development of palsy or paresis in the distribution of the femoral or sciatic nerves in patients who are anticoagulated suggests that a spontaneous hematoma within the psoas muscle or its sheath has occurred. Groin tenderness and some ecchymoses are frequent findings. The occurrence of these hematomas does not correlate with prothrombin times longer than the therapeutic range. Normal CSF and spinal roentgenograms exclude the diagnosis of a herniated disc or a peripheral hematoma. The prognosis is poor, even when surgical evacuation of these hematomas is attempted. (*Parkes, J. D., and Kidner, P. H.: Peripheral Nerve and Root Lesions Developing as a Result of Hematoma Formation during Anticoagulant Treatment, Postgrad. Med. J. 46: 146 (March) 1970.*)