SURGERY AND THE IMMUNE RESPONSE

M. Salo
Departments of Anaesthesiology and Medical Microbiology
University of Turku, SF-20520 Turku, Finland

In the last few decades the treatment of surgical patients has continuously advanced. Anaesthetic and surgical techniques have greatly improved. The treatment of hypovolemia is nowadays better mastered. Great progress has been made in the maintenance of renal and pulmonary function. The advances have reduced the numbers of immediate and early deaths after surgery. At present, many of the patients with a fatal outcome die later from infectious complications which are still the major hazard during convalescence. Increasing attention and research is therefore directed to changes during and after operation in the immune response. As a result, our understanding of immunological events is constantly improving and we are better equipped to control immune responses in patients at risk and thus reduce morbidity and mortality from infections.

IMMUNE RESPONSE TO SURGERY

During surgery a local inflammatory reaction arises at the site of tissue injury, possibly with systemic effects and the specific immune response is affected. The distinction of changes in the inflammatory reaction and the immune response is rather an academic than a practical question in surgical patients since both mechanisms interact to ensure survival of the body.

The immune response to surgery is characterized by temporary decreases in neutrophil functions and in the phagocytic capacity of the mononuclear phagocyte system (MPS,RES), activation of the complement and overall decreases in cell-mediated immunity and lesser decreases in humoral immunity. These changes are progressive, depending on the extent of the operation.

Neutrophil Functions

Neutrophils are the first cells to appear at the site of bacterial invasion and tissue injury, but their mobilization to skin abrasions is depressed after surgery[1,2]. This has also been shown *in vitro*[3] tests. Neutrophil adherence is decreased for a day after nephrectomy[3] and open-heart surgery[4], but increased thereafter[2,4]. Neutrophil motility towards chemotactic attractants (chemotaxis) and spontaneous migration are depressed *in vitro* for some hours to some days after operation[1-3,5]. The extent of the depression is related to the extent of surgery and it may be due to an

M. Paubert-Braquet et al. (eds.), *Lipid Mediators in the Immunology of Shock*
© Plenum Press, New York 1987

intrinsic defect in neutrophil chemotaxis, serum inhibitors or abnormalities in chemotactic factor generation.

Serum opsonic capacity for facilitation of ingestion of particles to be phagocytosed is slightly depressed after surgery. A decrease in serum opsonic capacity can be observed *in vitro* after cholecystectomy[6] and major abdominal surgery[7] but only at high serum dilutions, which makes the significance of the decrease clinically less important. By contrast, an opsonization defect may be of practical importance in inflamed and poorly perfused tissues and in serum in patients with major postoperative complications, burns or severe infections.

No changes in neutrophil ingestive capacity have been observed after major abdominal surgery[7], nephrectomy[3] or abdominal hysterectomy[8]. The bactericidal capacity of neutrophils is unaltered for *Staph. aureus* after nephrectomy[3] and increased after open-heart surgery[9] but decreased for candida after abdominal hysterectomy[8]. Several studies have measured various microbicidal-related neutrophil variables such as oxygen consumption, nitroblue tetrazolium (NBT) reduction, iodination, chemiluminescence and different enzyme activities. The chemiluminescence responses of granulocytes in phagocytosis of zymosan are depressed for less than one day after nephrectomy and abdominal hysterectomy[5] and are on preoperative levels on the first postoperative day in phagocytosis of zymosan, *Staph. aureus* and *E. coli* after major abdominal surgery[7,10] but depressed for 3-4 days after open-heart surgery[11]. A postoperative decrease has also been observed in NBT reduction[1], neutrophil myeloperoxidase activity[8] and in the activities of the intraneutrophilic granule proteins β-glucuronidase, lysozyme and B_{12}-binding protein[12], but no changes were observed in myeloperoxidase-mediated iodination or hexose monophosphate shunt activity after elective general surgery[13].

Anaesthesia in itself produces changes in neutrophil functions. Halothane anaesthesia produces in man a reversible concentration-dependent depression in neutrophil random migration and chemotaxis[14], which is also observed in patients under enflurane and morphine anaesthesia before the start of surgery[15], but inhalation of 60 % v/v nitrous oxide increased neutrophil chemotaxis[16]. Halothane + N_2O + O_2 and thiopentone + N_2O + O_2 anaesthesia decrease ingestion of latex particles and NBT reduction by neutrophils[17]. When separated neutrophils are exposed in tissue culture to increasing concentrations of inhalational, intravenous or local anaesthetics, a dose-dependent inhibition of random and directed motility, ingestion and microbicidal functions of neutrophils is observed[18-21].

Mononuclear Phagocyte System Functions

Both parts of the mononuclear phagocyte system (MPS,RES), monocytes and tissue macrophages, are affected by surgery. The numbers of monocytes in blood circulation increase postoperatively. Their chemotactic motility, ingestive capacity, chemiluminescence responses and lysozyme production have been observed to be increased *in vitro* for about a day after abdominal surgery and decreased thereafter for a week[22,23]. By contrast, the spreading of monocytes on plastic surfaces, which is thought to reflect their phagocytic capacity, is decreased after hip replacement under general anaesthesia and increased under epidural analgesia[24]. Monocyte-mediated cytolysis is decreased after hip replacement under general[24] and combined epidural and general anaesthesia[25], but not after operation under epidural analgesia[24]. This decrease is mediated by serum factors. By contrast, monocyte-mediated haemolytic activity was increased after open-heart surgery in the immediate postoperative period[9].

The number of monocytes which phagocytose latex particles or reduce NBT is decreased after halothane + N_2O + O_2 and thiopentone + N_2O + O_2 anaesthesia[17]. In *in vitro* exposure to 1.7 % v/v enflurane, 0.8 % v/v halothane, 0.2 % v/v methoxyflurane and 70 % v/v nitrous oxide decreases monocyte chemotactic responses[18]. *In vitro* exposure to thiopentone of monocytes

depresses their cytolytic capacity in a dose-dependent way but no such depression occurs when monocytes are exposed to a wide range of concentrations of fentanyl, morphine, diazepam, pancuronium or bupivacaine[26].

The total MPS phagocytic capacity, for which the fixed macrophages in the liver (Kupffer cells) and spleen are largely responsible, is depressed after traumas of various origins. This can also be seen after surgery[27]. The depression is only slight even after uncomplicated major surgery[6], it is seen in the immediate postoperative period and it is followed by a period of hyperfunction. Anaesthesia in itself with cyclopropane, diethyl ether, halothane, neurolepts and epidural analgesia may also cause an impairment in MPS phagocytic functions[28]. The impairment may be greater when surgery is performed under halothane instead of combined anaesthesia with the use of neurolepts[29].

The decrease in MPS phagocytic functions is thought to be associated with decreased concentrations of plasma fibronectin which acts as a MPS opsonin. Fibronectin concentrations are decreased for some hours after cholecystectomy[30] and for 1-2 days after major surgery[31]. Other suggested mechanisms for postoperatively decreased MPS functions are decreased blood flow of MPS organs and various inhibitory effects.

Complement

The complement, which is necessary for the inflammatory reaction, neutrophil functions, lysis of cells, bacteria and viruses and participation in many effector systems, is activated in a controlled way in connection with various operations[32] including abdominal[33] and cardiovascular surgery[34]. This activation has been shown in decreased haemolytic complement (CH_{50}) values, decreased concentrations of complement components and as the appearance of complement split products into the blood circulation. Many complement components are acute phase reactive and increase unspecifically during the inflammatory reaction. The profiles of complement activation are slightly different in different studies, but the activation of alternate and also of the classic pathways has been suggested to occur during surgery.

A high degree of complement activation can be observed during extracorporeal circulation in open-heart surgery patients[35,36]. The conversion rate of C_3 which in normal health is less than 5 % of total plasma C_3 protein increases during extracorporeal circulation to more than 30 %[37,38] and plasma C_{3a} concentrations may be increased severalfold[35]. C_{5a} is also thought to be released in parallel with C_{3a}, but C_{5a} is readily attached to neutrophil receptors and therefore cannot be in equal concentrations measured in plasma samples. Complement activation during extracorporeal circulation may be somewhat slighter when membrane oxygenators are used instead of bubble ones[36]. Besides extracorporeal circulation, protamine administration during cardiovascular and open-heart surgery may also result in high C_{3a} concentrations[39]. The high levels of activated complement components during open-heart surgery are, however, usually without harmful clinical sequelae.

No differences in complement activation were seen when the patients were anaesthetized with neurolept, halothane or epidural anaesthesia for aortofemoreal surgery[34]. Studies in trauma patients show that the extent of trauma and the presence of nonvital tissue or abscesses affects complement activation. In minor trauma, complement concentrations increase above reference values over a week, but in major trauma they may remain at low levels for a longer time[40].

Cell-mediated Immunity

The effects of an operation on cell-mediated immunity have been well-documented, since cell-mediated immunity responses have a central role in host defences and modern immunological methods were first available for the study of these variables of the immune response. These studies include

quantification of effector cell numbers and measurement of their functional variables.

Quantification of Lymphocytes and Their Subsets. Leucocytosis in peripheral blood, an increase in the proportions of neutrophils and monocytes and a decrease in the proportions of eosinophils and lymphocytes occur during and after operation. The numbers of lymphocytes in peripheral blood remain however unaltered during surgery of mild to moderate trauma and decrease after major surgery. The values return to preoperative levels within one or two weeks[41,42].

In minor surgery no changes are observed in the proportions or numbers of T and B lymphocytes, effector cells of cell-mediated and humoral immunity, respectively. As the extent of surgery increases, the numbers of T and B lymphocytes in peripheral blood tend to decrease and their proportions simultaneously change in favour of B cells[42-46]. The numbers of T lymphocyte subpopulations T helper/inducer and T suppressor/cytotoxic cells also decrease, but their proportions either remain unchanged or change in favour of T suppressor cells after operations with increasing trauma severity[42-48].

Changes in Functional *in vitro* Test Values. Most studies of the immune response in surgery deal with *in vitro* measurement of lymphocyte proliferative responses to mitogens, antigens and allogenic cells in peripheral blood samples from patients undergoing an operation. An impairment of T lymphocyte proliferative responses has been observed after operations from minor to major surgery[43,49-53]. Responses to phytohaemagglutinin (PHA) and concanavalin A (Con A), the widely used T lymphocyte mitogens, already start to decrease during operation. They are lowest at the end of surgery and usually return to preoperative values after uncomplicated surgery over a period of 1 to 10-14 days. Similar decreases in lymphocytic responses have been observed to antigens such as purified protein derivative of tuberculin (PPD), streptokinase-streptodornase, mumps and candida and to allogenic cells in a mixed lymphocyte culture. The decreases may be greater in neonates and young children than in older children and adults[54,55]. A decrease in lymphocytic responses can be observed after operations done under general or regional anaesthesia. Some studies show smaller changes in lymphocyte proliferative responses after operations done under regional analgesia than after those done under general anaesthesia[52,53], but this depends on how well afferent neurogenic impulses from the area of surgery can be blocked and perhaps also on how general anaesthesia is performed. However, what is considered more important than anaesthesia in determining the postoperative lymphocyte proliferative responses is the extent of surgical trauma[41,56].

Other functional cell-mediated immunity test values are also depressed postoperatively. Such changes have been found when the effects of lymphokines, effects of lymphocytes on target cells and antibody-dependent cellular cytotoxicity were measured[43]. The sensitivity of lymphocytes to prostaglandin E_2 is increased postoperatively[50] and the amount of serum needed to halve PPD-induced lymphocytic responses is smaller after operation than before it[48]. Natural killer (NK) cell activity is increased during operation but decreased after operation up to a week. This has been observed after hip replacement[57], major abdominal surgery[58] and open-heart surgery[59]. NK cell activity may fall even to undetectable values in patients with postoperative complications[60].

Delayed Hypersensitivity Skin Test. In studies of the effects of an operation on delayed hypersensitivity skin test results, two basically different ways to express the results are used: measurement of reaction diameters/areas induced by recall antigens or grading of patients into reactive, relatively anergic and anergic ones on the basis of to how many antigens they react with an induration of at least 5 mm in diameter. The two types of studies give slightly different results.

Those studies measuring the diameters or areas of the indurations show decreased delayed hypersensitivity skin test reactions after nephrectomy[61] and major abdominal surgery[62,63]. By contrast, those studies grading patients into reactive, relatively anergic or anergic ones show no effects of minor or uncomplicated major abdominal surgery on delayed hypersensitivity skin test results[64,65]. Even after major cardiovascular surgery less than half of patients became anergic[65].

Humoral Immunity

A general consensus is that humoral immunity is less affected by surgery than cell-mediated immunity, but, on the other hand, humoral immunity variables have been studied much less. As shown above, the numbers of B lymphocytes decrease in peripheral blood postoperatively as the extent of surgical trauma increases, although less than the numbers of T lymphocytes. Lymphocyte proliferative responses to *Staph. aureus* strain *Cowan I* (StaCw I), which mainly stimulates B lymphocytes to transform, are decreased on the first day after minor orthopaedic surgery and hip replacement and recover by the 3-4th postoperative day (Salo, unpublished). Several studies also show a postoperative decrease in lymphocytic responses to pokeweed mitogen (PWM), which stimulates both T and B lymphocytes[43].

Serum immunoglobulin concentrations decrease postoperatively, especially after major surgery. However, such changes are more likely to be due to haemodilution and loss of protein into extravascular tissues than to disturbances in immunoglobulin production. *In vitro* studies show that the numbers of immunoglobulin synthetizing and secreting cells in peripheral blood decrease after open-heart surgery[66] and there is a simultaneous decrease in the synthesis and secretion of IgG, IgM and IgA into the culture supernatants after PWM stimulation. However, such decreases in immunoglobulin production cannot be observed after hip replacement or minor orthopaedic surgery (Salo, unpublished).

The opinion that humoral immunity is less affected by anaesthesia and surgery is partly based on animal studies measuring specific antibody responses. These studies show that IgG and IgM antibody production is well maintained in response against different types of antigens during anaesthesia and that antibody responses may even be enhanced during surgery[43]. However, recent studies show that the level of IgG anti-tetanus toxoid antibody production is lower in surgical patients than in controls. The impairment is greater in anergic than reactive patients[67]. Depressed antibody production has also been observed in burned patients[68] but no general agreement exists on postoperative antibody responses.

CHANGES IN PATIENTS WITH MALIGNANT DISEASE

Basically similar changes in the immune response are found in patients with malignant and benign disease. Some differences have been found in changes reported below but there is no evidence that the general patterns of postoperative immune response changes differ in these patients. During major abdominal surgery, the patients' nutritional state unlike the malignancy of the disease had an effect on postoperative lymphocytic responses[69]. However, when a tumour has been an immunologic burden to the patient, its removal may improve immune responses[70].

The postoperative increase in monocyte numbers and in their phagocytic capacity in patients with benign disease was not observed in patients with malignant disease[23,71]. Lymphocytic proliferative responses to mitogens and bacterial antigens decrease postoperatively but in patients with malignant disease lymphocyte responses to tumour antigens may also be depressed. Depressed lymphocyte cytotoxicity to tumour cells has been measured postoperatively in patients with mammary carcinoma[72], Wilms' tumour[73] and malignant melanoma[74] and depressed leucocyte migration inhibition in

patients with malignant melanoma and breast cancer[75]. These responses usually return to preoperative values within a week.

Generation of cytotoxic cells is depressed after major abdominal surgery in patients both with malignant and benign disease[76]. No such increases in NK cell activity was found during surgery in patients with disseminated malignancy as was observed in patients with benign disease or localized primary tumours[77] and the postoperative decrease in NK cell activity was of longer duration in patients with malignant disease[74,78]. However, NK cells were equally unaffected by 2 % v/v halothane and 66 % v/v nitrous oxide in patients with benign and malignant disease[79].

Another difference between patients with malignant and benign disease is found in postoperative antibody-dependent cellular cytotoxicity (ADCC, killer (K) cell function) reactions. ADCC responses decrease postoperatively in patients with advanced malignancy and in septic and cachetic patients but not in patients with benign disease or early cancer[80]. This difference like that found in NK cell activity may, however, be due to other reasons, e.g. the nutritional state, than malignancy. Accordingly, in another study K cell activity was equally depressed after surgery in patients with benign and malignant disease[81].

Halothane anaesthesia depresses mitogen-induced lymphocytic responses more in tumour-bearing mice than in controls[82]. However, halothane anaesthesia in patients decreased cytotoxicity as much as balanced anaesthesia without the use of halogenated anaesthetics[74].

ETIOLOGY OF THE CHANGES

Anaesthesia

In general, anaesthesia is considered to have a smaller role than surgery in decreasing immune responses during operation. The effects of anaesthesia on the immune response are twofold. Self-evident is the protective role of anaesthesia as it makes the operation painless and reduces responses to surgery. The immune depressing effects of anaesthesia may manifest through its direct effects on host defences but also through its indirect effects on the endocrine and metabolic balance, oxygenation, ventilation and tissue perfusion, i.e. through its effects on the internal milieu of the cells.

Most intravenous, inhalational and local anaesthetics depress mitogen-induced lymphocytic responses, when separated lymphocytes are exposed *in vitro* to increasing concentrations of the anaesthetic[43]. Similar observations have been made on cytotoxicity, NK cell activity and immunoglobulin production by lymphocytes and on granulocyte functions.

Animal studies show decreasing effects of anaesthesia on several variables of the immune response. Most studies deal with the effects of halothane but effects of other anaesthetics have also been studied[43,83]. Although most studies are carefully conducted the risk always remains, especially in handling small animals, that disturbances in homeostasis may contribute to the extent of changes.

Few studies have been made of the effects of clinical anaesthesia on man. During balanced anaesthesia with thiopentone + N_2O + analgesics + muscle relaxants before the start of surgery no changes were observed over 1-2 hrs in the PHA- or Con A-induced lymphocyte proliferative responses[43]. 5-7 hrs' anaesthesia with halothane or enflurane did not affect PHA-induced lymphocyte responses in volunteers[84] but another study found a decrease in PHA-induced lymphocytic responses after 3 hrs' halothane anaesthesia[85]. More changes in the immune response due to anaesthesia may arise in patients with disturbed homeostasis and in those with marginal immunocompetence. Anaesthesia may also have other effects on host defences, such as those on cilial function[86] and on thoracic duct lymph flow and bacterial clearance when high positive end-expiratory airway pressures (PEEP) are used during controlled ventilation[87].

The immune response during surgery may be modified to some extent by blocking afferent impulses from the operation area with regional analgesia, which is possible at lower abdominal and lower extremity surgery, where granulocyte and lymphocyte numbers, mitogen- and antigen-induced lymphocyte proliferative responses, monocyte functions and serum suppressive activity change less by high epidural analgesia than general anaesthesia[24,52,53,88,89]. By contrast, no differences in the immune response were observed when minor surgery was performed under halothane anaesthesia with spontaneous ventilation, balanced anaesthesia with mechanical ventilation or regional analgesia[90].

Operative Trauma

The degree and extent of operative trauma are considered to be crucial in the postoperative changes of the immune response but not exclusively. Surgical trauma is basically different from accidental trauma in producing changes in the immune response since during surgery the anaesthetist and surgeon are able to minimize by prophylactic and therapeutic measures homeostatic disturbances. Therefore, the changes in the immune response produced by a surgical trauma can be expected to be slighter than those after an equal accidental trauma.

Correlations have been observed between the extent of surgical trauma and the changes in leucocyte and differential counts, numbers of lymphocytes in peripheral blood and mitogen- and antigen-induced lymphocyte proliferative responses[41,56]. A similar correlation has been found between the extent of surgery and T lymphocyte, their subtype and NK cell numbers and the plasma volume needed to halve PPD-induced lymphocytic responses[48].

Other Factors

The effects of blood transfusion depend on the situation in which blood is needed and on the blood preparation used. Blood transfusion may sometimes further deteriorate trauma-decreased immune responses but in some cases it may improve immune responses, since the maintenance of sufficient oxygenation and tissue perfusion is of primary importance for the patient and the adequacy of his immune response. The clinically significant deleterious effects of blood transfusion are suggested by reports on a worse prognosis in patients with colorectal or some other cancer who received blood transfusion compared to those who did not[91].

Several drugs including many antibiotics, cytostatics and corticosteroids are known to disturb immune responses. Severe malnutrition with its immunosuppressive effects is deleterious to the patient undergoing surgery. Psychological factors may be important in postoperative immunosuppression, but immobilization, disturbed diurnal rhythm and preoperative fasting are less important.

MECHANISMS OF THE CHANGES

The main mechanisms of the postoperative decrease of cell-mediated and humoral immunity consist of the neuroendocrine response induced by surgery and anaesthesia, immunosuppressive factors liberated from the surgical area[65] and pharmacologic effects of drugs given during and after the operation. Among the mediator mechanisms can be distinguished the effects of corticosteroids, catecholamines, prostaglandins and the imbalance between proteases and protease inhibitors[92].

These mechanisms lead to postoperative redistribution of neutrophils and lymphocytes and to functional changes in effector cells. Intravascular leucocyte populations are not equal during and after the operation to what they were before it. Moreover, these cells represent only a small fraction

of cells which participate in the immune response. The effector cells in the tissues might therefore react in other ways than the cells found free in the blood circulation[1].

Activation of suppressor cells is currently under active investigation. Increased suppressor T lymphocyte function has been observed in man after burns[93] and, after surgery, monocytes have been observed to be suppressive in the cytotoxicity reaction[76]. By contrast, decreased Con A-induced suppressor cell function has been found after open-heart surgery[94] and after hysterectomy[95]. The suppressor system thus seems to be very complex and maximum suppression may be observed with a combination of different suppressors[96]. The lymphocytes may moreover be postoperatively increasingly sensitive to endogenous suppressors, such as prostaglandin E, as shown in connection with coronary bypass surgery[50].

The leucocyte transmitters, interleukins 1 and 2, may also have a role in the changes. The ability of leucocyte suspensions *in vitro* to produce interleukin 1 which is an initiator of the immune response, an inducer of the acute phase response and a factor in protein catabolism is at preoperative levels on the fifth day after operation[97]. However, the kinetics of its production during surgery is not known in more detail. By contrast, the capacity of T helper cells to produce interleukin 2, which causes rapid proliferation of effector cells to adequate numbers, is depressed after major surgery for a week but not after minor surgery[98]. Removal of adherent cells abolished the decrease in interleukin 2 production which suggests a monocyte-mediated mechanism in the decrease.

CLINICAL SIGNIFICANCE OF THE ALTERATIONS

The inflammatory reaction and immune response are part of the general physiological response to surgery and occur in interaction with other homeostatic mechanisms. The inflammatory reaction is not only important in defence against microbes but also in wound healing and repair of damaged tissue. The postoperatively depressed immune response is considered to be beneficial to the patient in preventing the body from reacting against its own antigenic structures exposed and released during operation. However, autoantibodies appear in spite of postoperatively depressed immune responses after noncardiac and open-heart surgery[99]. During open-heart surgery, lymphocytes may become sensitized to cardiac mitochondrial antigens[100]. The levels of various anti-heart antibodies and the degree of migration inhibition correlate with the frequency of the postpericardiotomy syndrome suggesting the clinical importance of these autoimmune phenomena.

The changes in the immune balance during surgery may also impair resistance to infections. To what extent the changes in the immune response contribute to the rise of postoperative infections depends on the situation as a whole, since changes also occur in outer host defences and the degree of bacterial contamination varies. Unfavourable location of the surgical trauma, presence of traumatized tissue with haematoma and poor oxygenation and tissue perfusion of the local area may also favour the rise of infection. Surgically broken epithelial barriers and the presence of the intubation tube, intravenous and other canules and catheters all give access to the microbes into the interior. Moreover, changes occur in the mucociliary clearance, secretions and in the natural microbial flora. The functions of complement, granulocytes and MPS, which react first in the blood and tissues against invading organisms, are only slightly affected by uncomplicated surgery causing minor or medium trauma. The complement is capable of mounting an inflammatory reaction and generating chemotactic and opsonic substances, and immunoglobulins are available.

Thus, changes in the immune response are not exclusively responsible for postoperative infections but may contribute to their rise. This is especially true if the disturbances in the immune response are severe and prolonged or the patient is preoperatively immunocompromised. Decreases in

the postoperative immune response may thus manifest as increased sensitivity to postoperative infections[101], recrudescence of latent infections[102], reactivation of a virus without causing infection[103] or as a rise of an opportunist infection. The correlation between postoperatively decreased immune responses and frequency of postoperative septic complications and mortality has been best documented by the delayed hypersensitivity skin test. Those patients who are anergic or become anergic postoperatively are at most risk to develop sepsis and die[104].

Another suggested deleterious consequence of postoperatively decreased immune responses is the spread of malignant disease. Although surgery is certainly the most effective method of treating cancer, there are reports of rapid dissemination of cancer shortly after radical surgery and exacerbation of cancer after surgery for an independent or related condition[105]. Although these observations cannot be generalized and the proof of a possible connection is not conclusive, this may point to decreased host defences of clinical importance when large amounts of malignant cells may be free in the blood circulation during surgery. Significantly, there is an abundance of animal studies showing connections between anaesthesia, surgery, immune response and spread of malignancy[106].

Massive complement activation in itself may be harmful to the patient. Massive activation in bacteremia may result in shock during surgery[107], and in endotoxemia it is with other activated mediator systems a major mechanism in the induction of septic shock. C_{5a} in excessive amounts may lead to leucostasis and endothelial damage, and contributes to the rise of adult respiratory distress syndrome (ARDS). Massive stimulation of neutrophils by complement and other chemotactic factors may result in their inability to respond to chemotactic stimuli and to move to the site of microbial invasion.

RECOMMENDATIONS FOR PATIENT CARE

The maintenance of homeostasis is of primary importance for the immune response. The body is able to correct even severe alterations in the immune response if failures in the vital functions can be corrected and the underlying disease can be treated.

High age, malnutrition, certain drugs and diseases are known to affect immune responses preoperatively. These factors should always be taken into account. The best results in the correction of malnutrition have been obtained in severely malnourished patients with preoperative nutrition of at least a week's duration. The use of drugs known to be immunosuppressive must be considered on an individual basis.

In anaesthesia its general performance is more important than the selection of some special anaesthetic agent or method. This means good anaesthetic management and careful maintenance of homeostasis. Halothane with its well-documented immunosuppressive effects cannot be recommended in patients with severe infections. The need to modify operation-induced responses by high analgesic doses or epidural analgesia must primarily be considered from other viewpoints than that of the immune response.

Since the extent of operative trauma is crucial for the postoperative immune response, an atraumatic approach to operation with minimal blood loss is also recommendable from the immunological viewpoint. An open question is what the most suitable time is to make the final reconstructions in the multiple trauma patient. This also concerns patients with postoperatively decreased immune responses before further elective operations. In view of endocrine and metabolic alterations, a stabilization period has been recommended after the primary operations. It might also be beneficial for the immune response. By contrast, in patients with nonvital tissue, abscesses or other toxic processes, immediate operation is a prerequisite for restoration of the immune response although the immune response may transiently be further compromised by the operation.

In experimental work several possibilities already exist in the modification of the immune response by specific and unspecific means[47,108,109,110]. Ibuprofen, cimetidine, levamisole and interleukin 2 can prevent changes in postoperative immune responses. In the future, these and other immunomodulators may be given prophylactically or per- and postoperatively to high-risk surgical patients to improve their immune responses. This, however, requires a good understanding of the basic immune mechanisms by the operative team and laboratory services available for measurement.

REFERENCES

1. J.H. Wandall, Leucocyte mobilization and function *in vitro* of blood and exudative leucocytes after inguinal herniotomy, Br.J.Surg. 69:669 (1982).
2. J.S. Morris, J.L. Meakins, and N.V. Christou, In vivo neutrophil delivery inflammatory sites in surgical patients, Arch.Surg. 120:205 (1985).
3. T.K. Bowers, J.S. O'Flaherty, R.L. Simmons, and H.S. Jacob, Postsurgical granulocyte dysfunction: studies in healthy kidney donors, J.Lab.Clin. Med. 90:720 (1977).
4. J. Palmblad, Activation of the bactericidal capacity of polymorphonuclear granulocytes after surgery, measured with a new in vitro assay, Scand. J.Haematol. 23:10 (1979).
5. J.S. Solomkin, M.P. Bauman, R.D. Nelson, and R.L. Simmons, Neutrophils dysfunction during the course of intra-abdominal infection, Ann. Surg. 194:9 (1981).
6. J. Perttilä, E.-M. Lilius, and M. Salo, Effects of anaesthesia and surgery on serum opsonic capacity, Acta Anaesthesiol.Scand. 30:173 (1986).
7. W.C. van Dijk, H.A. Verbrugh, R.E.N. van Rijswijk, A. Vos, and J. Verhoef, Neutrophil function, serum opsonic activity, and delayed hypersensitivity in surgical patient, Surgery 92:21 (1982).
8. H. El-Maallem, and J. Fletcher, Effects of surgery on neutrophil granulocyte function, Infect.Immun. 32:38 (1981).
9. B. Schildt, L. Berghem, G. Holm, C. Jarstrand, G. Lahnborg, J. Palblad, and K. Rådegran, Influence of cardiopulmonary bypass on some host defence functions in man, Scand.J.Thorac.Cardiovasc.Surg. 14:207 (1980).
10. J. Perttilä, M. Salo, and A. Rajamäki, Granocyte microbicidal function in patients undergoing major abdominal surgery under balanced anaesthesia, Acta Anaesthesiol.Scand., submitted (1986).
11. J. Perttilä, O.-P. Lehtonen, M. Salo, and R. Tertti, Effects of coronary bypass surgery under high-dose fentanyl anaesthesia on granulocyte chemiluminescence, Br.J.Anaesth. , in press (1986).
12. J.M. Davies, K. Sheppard, and J. Fletcher, The effects of surgery on the activity of neutrophil granule proteins, Br.J.Haematol. 53:5 (1983).
13. L. Bröte, and O. Stendahl, The function of polymorphonuclear leukocytes after surgical trauma, Acta Chir.Scand. 141:565 (1975).
14. G.E. Hill, T.H. Stanley, J.K. Lunn, W.-S. Liu, J.B. English, E.A. Loeser, R. Kawamura, C.R. Sentker, and H.R. Hill, Neutrophil chemotaxis during halothane and halothane-N_2O anesthesia in man, Anesth.Analg. 56:696 (1977).
15. T.H. Stanley, G.E. Hill, M.R. Portas, N.A. Hogan, and H.R. Hill, Neutrophil chemotaxis during and after general anesthesia and operation, Anesth.Analg 55:668 (1976).
16. G.E. Hill, J.B. English, T.H. Stanley, R. Kawamura, E.A. Loeser, and H.R. Hill, Nitrous oxide and neutrophil chemotaxis in man, Br.J.Anaesth. 50:555 (1978).
17. B.F. Cullen, R.B. Hume, and P.B. Chretien, Phagocytosis during general anesthesia in man, Anesth Analg 54: 501 (1975).
18. G.C. Moudgil, J. Gordon, and J.B. Forrest, Comparative effects of volatile anaesthetic agents and nitrous oxide on human leucocyte chemotaxis *in vitro*, Can.Anaesth.Soc.J. 31:631 (1984).

19. W.D. Welch, Effect of enflurane, isoflurane, and nitrous oxide on the microbicidal activity of human polymorphonuclear leukocytes, Anesthesiology 61:188 (1984).
20. R. Hammer, C. Dahlgren, and O. Stendahl, Inhibition of human leukocyte metabolism and random mobility by local anaesthetics, Acta Anaesthesiol.Scand. 29:520 (1985).
21. M. Nakagawara, K. Takeshige, J. Takamatsu, S. Takahashi, J. Yoshitake, and S. Minakami, Inhibition of superoxide production and Ca^{2+} mobilization in human neutrophils by halothane, enflurane, and isoflurane, Anesthesiology 64:4 (1986).
22. J.P. Neoptolemos, P. Wood, N.W. Everson, and P.R.F. Bell, Monocyte function following surgery in man, Eur.Surg.Res. 17:215 (1985).
23. N.W. Everson, J.P. Neoptolemos, D.J.A. Scott, R.F.M. Wood, and P.R.F. Bell, The effect of surgical operation upon monocytes, Br.J.Surg. 68:257 (1981).
24. A. Hole, G. Unsgaard, and H. Breivik, Monocyte functions are depressed during and after surgery under general anaesthesia but not under epidural anaesthesia, Acta Anaesthesiol.Scand. 26:301 (1982).
25. A. Hole, Per- and postoperative monocyte and lymphocyte functions: Effects of combined epidural and general anaesthesia, Acta Anaesthesiol.Scand. 28:367 (1984).
26. A. Hole, Depression of monocytes and lymphocytes by stress-related humoral factors and anaesthetic-related drugs, Acta Anaesthesiol. Scand. 28:280 (1984).
27. A. Donovan, The effect of surgery on reticuloendothelial function, Arch.Surg. 94:247 (1967).
28. B. Löfström, and B. Schildt, Reticuloendothelial function under general anaesthesia, Acta Anaesthesiol.Scand. 18:34 (1974).
29. A. Doenicke, and W. Kropp, Anaesthesia and the reticulo-endothelial system: comparison of halothane-nitrous oxide and neuroleptanalgesia, Br.J.Anaesth. 48:1191 (1976).
30. A.B. Robbins, J.E. Doran, A.C. Reese, and A.R. Mansberger Jr, Effect of cholecystectomy on cold insoluble globulin, Arch.Surg. 115,1207 (1980).
31. W.O. Richards, W.A. Scovill, and B. Shin, Opsonic fibronectin deficiency in patients with intra-abdominal infection, Surgery 94:210 (1983).
32. R.E. Lewis Jr, J.M. Cruse, and J.V. Richey, Effects of anesthesia and operation on the classical pathway of complement activation, Clin.Immunol.Immunopathol. 23:666 (1982).
33. J. Hahn-Pedersen, H. Sørensen, and H. Kehlet, Complement activation during surgical procedures, Surg.Gynecol.Obstet. 146:66 (1978).
34. H.J. Wüst, H.-W. Fiedler, H. Trobisch, and O. Richter, Fibrinolyse- und Komplementsystem-Profile während aortofemoraler Bypassimplantation, Anaesthesist 31:564 (1982).
35. D.E. Chenoweth, S.W. Cooper, T.E. Hugli, R.W. Stewart, E.H. Blackstone, and J.W. Kirklin, Complement activation during cardiopulmonary bypass, N.Engl.J.Med. 304:497 (1981).
36. N.C. Cavarocchi, J.R. Pluth, H.V. Schaff, T.A. Orszulak, H.A. Homburger, E. Solis, M.P. Kaye, M.S. Clancy, J. Kolff, and G.M. Deeb, Complement activation during cardiopulmonary bypass, J.Thorac.Cardiovasc.Surg. 91:252 (1986).
37. B.J. Collett, N.B. Abdullah, D. Vergani, and R.J. Ware, Complement activation during cardiopulmonary bypass (abstract), Br.J.Anaesth. 55:914P (1983).
38. J. Watkins, and G. Wild, The early diagnosis of impeding coagulopathies following surgery and multiple trauma, Klin.Wochenschr. 63:1019 (1985).
39. P.G. Loubser, Complement activation during surgery with and without cardiopulmonary bypass (abstract), Anesth.Analg. 65:S90 (1986).
40. M. Heideman, C. Saravis, and G.H.A. Clowes, Effect of nonviable tissue and abscesses on complement depletion and the development of bacteremia. J.Trauma 22:527 (1982).

41. M. Salo, Effect of anaesthesia and surgery on the number of and mitogen-induced transformation of T- and B-lymphocytes, Ann.Clin.Res. 10:1 (1978).
42. E. Fosse, H. Opdahl, A. Aakvaag, J.-L. Svennevig, and S. Sunde, White blood cell populations in patients undergoing major vascular surgery, Scand.J.Thorac.Cardiovasc.Surg. 19:247 (1985).
43. M. Salo, Effects of anaesthesia and surgery on the immune response, in: "Trauma, stress and immunity in anaesthesia and surgery", J. Watkins, and M. Salo, ed., Butterworth, London (1982).
44. A. Hole, and O. Bakke, T-lymphocytes and the subpopulations of T-helper and T-suppressor cells measured by monoclonal antibodies (T11, T4, and T8) in relation to surgery under epidural and general anaesthesia, Acta Anaesthesiol.Scand. 28:296 (1984).
45. J.F. Hansbrough, E.M. Bender, R. Zapata-Sirvent, and J. Anderson, Altered helper and suppressor lymphocyte populations in surgical patients, Am.J.Surg. 148:303 (1984).
46. S. Madsbad, K. Buschard, O. Siemssen, and C. Røpke, Changes in T-lymphocyte subsets after elective surgery, Acta Chir.Scand. 152:81 (1986).
47. J.F. Hansbrough, R.L. Zapata-Sirvent, and E.M. Bender, Prevention of alterations in postoperative lymphocyte subpopulations by cimetidine and ibuprofen, Am.J.Surg. 151:249 (1986).
48. T.W.J. Lennard, B.K. Shenton, A. Borzotta, P.K. Donnelly, M. White, L.M. Gerrie, G. Proud, and R.M.R. Taylor, The influence of surgical operations on components of the human immune system, Br.J.Surg. 72:771 (1985).
49. H. Kehlet, M. Thomsen,M. Kjaer, and P. Platz, Postoperative depression of lymphocyte transformation response to microbial antigens, Br.J.Surg. 64:890 (1977).
50. J.S. Goodwin, S. Bromberg, C. Staszak, P.A. Kaszubowski, R.P. Messner, and J.F. Neal, Effect of physical stress on sensitivity of lymphocytes to inhibition by prostaglandin E_2, J.Immunol. 127:518 (1981).
51. R.M. Keane, A.M. Munster, W. Birmingham, R.A. Winchurch, T.R. Gadacz, and C.B. Ernst, Suppression of lymphocyte function after aortic reconstruction, Arch.Surg. 117:1133 (1982).
52. P. Whelan, and P.J. Morris, Immunological responsiveness after trans-urethral resection of the prostate: general versus spinal anaesthetic, Clin.Exp.Immunol. 48:611 (1982).
53. A. Hole, and G. Unsgaard, The effect of epidural and general anaesthesia on lymphocyte functions during and after major orthopaedic surgery, Acta Anaesthesiol.Scand. 27:135 (1983).
54. P. Ryhänen, Effects of anesthesia and operative surgery on the immune response of patients of different ages, Ann.Clin.Res. 9:suppl 19 (1977).
55. P. Puri, J. Brazil, and D.J. Reen, Immunosuppressive effects of anesthesia and surgery in the newborn: I Short-term effects, J.Pediatr.Surg. 19:823 (1984).
56. B.F. Cullen, and G. van Belle, Lymphocyte transformation and changes in leukocyte count: effects of anesthesia and operation, Anesthesiology 43:563 (1975).
57. E. Tønnesen, H. Mickley, and N. Grunnet, Natural killer cell activity during premedication, anaesthesia and surgery. Acta Anaesthesiol. Scand. 27:238 (1983).
58. E. Tønnesen, M.S. Hüttel, N.J. Christensen, and O. Schmitz, Natural killer cell activity in patients undergoing upper abdominal surgery: relationship to the endocrine stress response, Acta Anaesthesiol. Scand. 28:654 (1984).
59. P. Ryhänen, K. Huttunen, and J. Ilonen, Natural killer cell activity after open-heart surgery, Acta Anaesthesiol.Scand. 28:490 (1984).

60. E. Tønnesen, M.M. Brinkløv, A.S. Olesen, and N.J. Christensen, Natural killer cell activity in a patient undergoing open-heart surgery complicated by an acute myocardial infarction, Acta Pathol.Microbiol. Immunol.Scand.(C) 93:229 (1985).
61. M.S. Slade, R.L. Simmons, E. Yunis, and L.J. Greenberg, Immunodepression after major surgery in normal patients, Surgery 78:363 (1975).
62. W.C. van Dijk, H.A. Verbrugh, R.E.N. van Rijswijk, A. Vos, and J. Verhoef, Neutrophil function, serum opsonic activity, and delayed hypersensitivity in surgical patients, Surgery 92:21 (1982).
63. N.-C. Hjortsø, and H. Kehlet, Influence of surgery, age and serum albumin on delayed hypersensitivity, Acta Chir.Scand. 152:175 (1986).
64. J.B. Pietsch, J.L. Meakins, and L.D. MacLean, The delayed hypersensitivity response: application in clinical surgery, Surgery 82:349 (1977).
65. G.A. McLoughlin, A.V. Wu, I. Saporoschetz, R. Nimberg, and J.A. Mannick, Correlation between anergy and a circulating immunosuppressive factor following major surgical trauma, Ann.Surg.190:297 (1979).
66. J. Eskola, M. Salo, M.K. Viljanen, and O. Ruuskanen, Impaired B lymphocyte function during open-heart surgery, Br.J.Anaesth. 56:333 (1984).
67. C.W. Nohr, N.V. Christou, H. Rode, J. Gordon, and J.L. Meakins, *In vivo* and *in vitro* humoral immunity in surgical patients, Ann.Surg. 200:373 (1984).
68. J.J. Wood, J.B. O'Mahony, M.L. Rodrick, R. Eaton, R.H. Demling, and J.A. Mannick, Abnormalities of antibody production after thermal injury, Arch.Surg. 121:108 (1986).
69. P. Neuvonen, J. Takala, M. Salo, T. Havia, and R. Heinonen, Prolonged impairment of cell-mediated immunity after major abdominal surgery in malnourished patients, Clin.Nutr. 1:283 (1983).
70. J.A. Roth, S.H. Golub, E.A. Grimm, F.R. Eilber, and D.L. Morton, Effects of operation on immune response in cancer patients: sequential evaluation of in vitro lymphocyte function, Surgery 79:46 (1976).
71. I Crzelak, W.L. Olszewski, and E. Engeset, Influence of operative trauma on circulating blood mononuclear cells: analysis using monoclonal antibodies, Eur.Surg.Res. 16:105 (1984).
72. B.M. Vose, and G.C. Moudgil, Effect of surgery on tumour-directed leucocyte responses, Br.Med.J. 1:56 (1975)
73. S. Kumar, and G. Taylor, Effect of surgery on lymphocytotoxicity against tumour cells, Lancet 2:1564 (1974).
74. F. Møller-Larsen, A. Møller-Larsen, and S. Haahr, The influence of general anesthesia and surgery on cell-mediated cytotoxicity and interferon production, J.Clin.Lab.Immunol. 12:69 (1983).
75. A.J. Cochran, W.G.S. Spilg, R.M. Mackie, C.E. Thomas, Postoperative depression of tumour-directed cell-mediated immunity in patients with malignant disease, Br.Med.J. 4:67 (1972).
76. S. Miyazaki, T. Akiyoshi, S. Arigana, F. Koba, T. Wada, and H. Tsuji, Depression of the generation of cell-mediated cytotoxicity by suppressor cells after surgery, Clin.Exp.Immunol. 54:573 (1983).
77. C.D. Griffith, R.C. Rees, A. Platts, A. Jermy, J. Peel, and K. Rogers, The nature of enhanced natural killer lymphocyte cytotoxicity during anesthesia and surgery in patients with benign disease and cancer, Ann.Surg. 200:753 (1984).
78. A. Utchida, R. Kolb, and M. Micksche, Generation of suppressor cells for natural killer activity in cancer patients after surgery, JNCI 68:735 (1982).
79. C.D.M. Griffith, and M.B. Kamath, Effects of halothane and nitrous oxide anaesthesia on natural killer lymphocytes from patients with benign and malignant breast disease. Br.J.Anaesth. 58:540 (1986).
80. J.A. McCredie, H.R. MacDonald, and S.B. Wood, Effect of operation and radiotherapy on antibody-dependent cellular cytotoxicity, Cancer 44:99 (1979).
81. J. Micheels, G. Degiovanni, and A.M. Cayet, Effect of surgery and anaesthesia on cell mediated immunity, Acta Anaesthesiol.Belg.30:Suppl:33 (1979).

82. R.E. Lewis Jr, J.M. Cruse, and J. Hazelwood, Halothane-induced suppression of cell-mediated immunity in normal and tumour-bearing $C3H_f/He$ mice, Anesth.Analg. 59:666 (1980).
83. J. Thomas, M. Carver, C. Haisch, F. Thomas, J. Welch, and R. Carchman, Differential effects of intravenous anaesthetic agents on cell-mediated immunity in the Rhesus monkey, Clin.Exp.Immunol. 47:457 (1982).
84. P.G. Duncan, B.F. Cullen, R. Calverly, N.T. Smith, E.I. Eger II, and R. Bone, Failure of enflurane and halothane anesthesia to inhibit lymphocyte transformation in volunteers, Anesthesiology 45:661 (1976).
85. A. Doenicke, B. Grote, H. Suttmann, K.-J. Graf, U.V. Sprecht, H. Ott, B. Sarafoff, and C. Bretz, Effects of halothane on the immunological system in healthy volunteers, Clin.Res.Rev. 1:23 (1981).
86. K.S. Lee, and S.S. Park, Effect of halothane, enflurane, and nitrous oxide on tracheal ciliary activity in vitro, Anesth.Analg. 59:426 (1980).
87. M. Last, L. Kurtz, T.A. Stein, L. Wise, Effect of PEEP on the rate of thoracic duct lymph flow and clearance of bacteria from the peritoneal cavity, Am.J.Surg. 145:126 (1983).
88. J. Rem, M.R. Brandt, and H. Kehlet, Prevention of postoperative lymphopenia and granulocytosis by epidural analgesia. Lancet i:283 (1980).
89. A. Hole, Per- and postoperative monocyte and lymphocyte functions: effects of sera from patients operated under general or epidural anaesthesia, Acta Anaesthesiol.Scand. 28:287 (1984).
90. A.E. Edwards, L.W. Gemmell, P.P. Mankin, C.J. Smith, J.C. Allen, and A. Hunter, The effects of three differing anaesthetics on the immune response, Anaesthesia 39:1071 (1984).
91. R.S. Foster Jr, M.C. Costanza, J.C. Foster, M.C. Wanner, and C.B. Foster, Adverse relationship between blood transfusions and survival after colectomy for colon cancer, Cancer 55:1195 (1985).
92. P.K. Donnelly, B.K. Shenton, A.M. Alomran, D.M.A. Francis, G. Proud, and R.M.R. Taylor, The role of protease in immunoregulation, Br.J.Surg. 70:614 (1983).
93. J.L. Ninnemann, Immunosuppression following thermal injury through B cell activation of suppressor T cells, J. Trauma 20:206 (1980).
94. M. Salo, E. Soppi, O. Lassila, and O. Ruuskanen, Suppressor lymphocytes during open heart surgery, J.Clin.Lab.Immunol. 5:159 (1981).
95. I. Crzelak, W.L. Olszewski, and A. Engeset, Decreased suppressor cell activity after surgery, J.Clin.Lab.Immunol. 16:201 (1985).
96. J. Lundy, and C.M. Ford, Surgery, trauma and imme response. Evolving the mechanism, Ann Surg 197: 434 (1983).
97. J.J. Duncan, L.L. Moldawer, B.R. Bistrian, and G.L. Blackburn, *In vitro* leukocyte endogenous mediator production is not impaired following surgical stress in moderately malnourished patients, JPEN 8:174 (1984).
98. T. Akiyoshi, F. Koba, S. Arinaga, S. Miyazaki, T. Wada, and H. Tsui, Impaired production of interleukin-2 after surgery. Clin.Exp.Immunol. 59:45 (1985).
99. B. Maisch, P.A. Berg, and K. Kochsiek, Clinical significance of immunopathological findings in patients with post-pericardiotomy syndrome I. Relevance of antibody pattern, Clin.Exp.Immunol. 38:189 (1979).
100. S. Specter, A. Cerdan, C. Cerdan, K. Chang, and H. Friedman, Cell-mediated immune responsiveness to cardiac extracts by peripheral blood leukocytes from patients after myocardial infarction or open-heart surgery, Clin.Immunol.Immunopathol. 30:19 (1984).
101. J.W. Alexander, and R.A. Good, "Immunobiology for surgeons" p. 125, W.B. Saunders Co, Philadelphia (1970).
102. S.J. Eykyn, M.V. Braimbridge, Open heart surgery complicated by post-operative malaria (letter), Lancet ii:411 (1977).
103. C. Porteous, J.A. Bradley, D.N.H. Hamilton, I McA. Ledingham, G.B. Clements, and C.G. Robinson, Herpes simplex virus reactivation in surgical patients, Crit.Care Med. 12:626 (1984).

104. L.D. MacLean, Host resistance in surgical patients, J.Trauma 19:297 (1979).
105. P.H. Lange, K. Hekmat, G. Bosl, B.J. Kennedy, and E.E. Fraley, Accelerated growth of testicular cancer after cytoreductive surgery, Cancer 45:1498 (1980).
106. J. Lundy, E.J. Lovett III, S. Hamilton, and P. Conran, Halothane, surgery, immunosuppression and artificial pulmonary metastases, Cancer 41:827 (1978).
107. I. Brandslund, B. Teisner, P. Hole, J.G. Grudzinskas, and S.-E.Svehag, Complement activation in shock associated with a surgically provoked bacteriaemia, Acta Pathol.Microbiol.Immunol.Scand. (C) 91:51 (1983).
108. M. Salo, Immune response to shock, in: "Treatment of shock. Principles and practice", J. Barrett, and L.M. Nyhus, ed., Lea & Febiger, Philadelphia (1986).
109. H. Miwa, T. Kawai, H. Nakahara, and K. Orita, Decrease in cell-mediated immunity by surgical intervention and its prevention by levamisole, Int.J.Immunopharmacol. 2:31 (1980).
110. T. Akiyoshi, F. Koba, S. Arinaga, T. Wada, and H. Tsuji, In vitro effect of interleukin 2 on depression of cell-mediated immune response after surgery, Jpn.J.Surg. 15:375 (1985).