The Influence of Intracranial Aneurysm, Meningioma and Glial Tumor Surgery on Immunodepression

İntrakranial Anevrizma, Menenjiom ve Glial Tümör Cerrahisinin İmmündepresyona Etkisi

METİN TUNA, NUSA TUNA, CAN YILDIRIM, TAHSİN ERMAN, A. İSKENDER GÖÇER, SALİH ÇETİNER, FARUK İLDAN

Çukurova University School of Medicine, Departments of Neurosurgery, Anesthesiology and Reanimation(MT,NT) and Immunology(CY,TE,AİG,SÇ,Fİ) Adana, Turkey

Received: 25.12.1999 ⇔ Accepted: 13.4.2000

Abstract: The neurosurgical operations used to treat various intracranial pathologies may affect the immune system in different ways. The main goal of this study was to determine whether the surgeries for intracranial aneurysm, meningioma and glial tumor cause immunodepression. In each of these three surgical patient groups, we measured monocytic human leukocyte antigen-DR expression and the plasma levels of inflammatory cytokines (tumor necrosis factor-α, interleukin-1α, interleukin-6 and interleukin-8) in the preinflammatory response, and assessed whether these parameters could be used to predict postoperative infection. We also compared the different groups' length of stay in the intensive care unit, and the duration of surgery for each group, to determine whether these factors influence infectious outcome. Thirty adult patients were divided into three equal groups, according to whether they underwent craniotomy in the treatment of an aneurysm, meningioma or glial tumor. We measured human leukocyte antigen-DR expression and levels of tumor necrosis factor-α, interleukin-1α, interleukin-6 and interleukin-8 at four different time points, namely, the start of surgery (stage 1), 1 hour into the operation (stage II), 3 hours after surgery (stage III) and on postoperative day 3 (stage IV). There were no significant differences among the three groups, or between the infected and noninfected patients, with regard to age or the levels of human leukocyte antigen-DR expression, tumor necrosis factor-α, interleukin-1α, interleukin-6, or interleukin-8 at any of the four stages ($p > 0.05$ for all comparisons; Mann-Whitney U test). However, length of stay in intensive care and duration of surgery were both longer in the

Özet: Farklı intrakranial patolojiler için yapılan nöroşirürji operasyonları immün sistemi değişik olarak etkileyebilir. Bu nedenle, amacımız intrakranial anevrizma, menenjiom ve glial tümör cerrahisinin immündepresyona neden olup olmadığını; monositik human lökosit antijen-DR ekspresyonu ve plasma enflamatuar sitokin düzeylerinin (tümör nekroz faktör-α, interlökin-1α, interlökin-6, interlökin-8) postoperatif infeksiyonların prognostik göstergesi olup olamayacağını; yoğun bakımda uzun süre kalmanın ve uzun operasyon sürelerinin postop infeksiyonlardaki rolünü saptamaktır. Bu çalışma anevrizma, menenjiom ve glial tümör gruplarına ayrılan selektif kraniotomiye uğrayan 30 hastayı kapsamaktadır. Human lökosit antijen-DR, tümör nekroz faktör-α, interlökin-1-α, interlökin-6 ve interlökin-8 sonuçlarının değerlendirmesinde; her bir grubun dönemleri arasında {operasyonun başlangıcında (1. dönem), başlangıçdan 1 saat sonra (2. dönem), postop 3. saat (3. dönem) ve postop 3. gün (4. dönem)}, üç grubun aynı dönemleri arasında, ayrıca postop enfeksiyonlu ve enfeksiyonsuz iki grup arasında önemli bir fark bulunmadı ($P > 0.05$; Mann-Whitney U). Bununla beraber yoğun bakım ünitesinde kalış süresi ve ameliyat süresi infeksiyonlu hastalarda daha uzundu ($P < 0.05$). Sonuç olarak: intrakranial anevrizma, menenjiom ve glial tümör cerrahisinin immündepresif etkileri yoktur; monositik human lökosit antijen-DR ekspresyonu, plasma tümör nekroz faktör-α, interlökin-1-α, interlökin-6 ve interlökin-8 düzeyleri postoperatif infeksiyonların prognostik

individuals who developed infection ($p < 0.05$). The study results suggest that surgeries for intracranial aneurysm, meningioma and glial tumor do not cause immunodepression. Also, monocytic human leukocyte antigen-DR expression and plasma tumor necrosis factor-α, interleukin-1α, interleukin-6 and interleukin-8 levels representative of the preinflammatory response are not good predictors of postoperative infection. Prolonged stay in intensive care and longer duration of surgery are associated with the development of postoperative infection.

Key Words: Human leukocyte antigen-DR, immunodepression, interleukin-1α, interleukin-6, interleukin-8, tumor necrosis factor-α

göstergesi değildir; yoğun bakımda uzun süre kalmanın ve uzun süren intrakranial ameliyatların postoperatif enfeksiyonların gelişmesinde önemli rolü vardır.

Anahtar Sözcükler: Human lökosit antijen-DR, immündepresyon, interlökin-1-α, interlökin-6, interlökin-8, tümör nekroz faktör-α

INTRODUCTION

Postoperative infections continue to be a major problem in patients who undergo neurosurgery. Surgical trauma is generally considered to play an important role in altering the immune response. Changes in all parts of the immune response may depend heavily on the patient's specific intracranial pathology, and on other factors such as the amount of dissection required, the length of the operation, patient age, systemic illness, preoperative medication and blood transfusions received. The significant risk of infection after neurosurgery may be linked to disturbance of the immune response. Clearly, it would be very valuable to be able to identify patients who are immunodepressed after neurosurgery before any infection develops.

Patients who have suffered multiple trauma appear to go through a systemic hyperinflammatory phase, followed by monocyte deactivation. This deactivation is characterized by a decrease in monocytic human leukocyte antigen-DR (HLA-DR) expression and a shift toward secretion of antiinflammatory cytokines (12). These changes indicate severe immunodepression, and such patients are at high risk for developing infection (12,30).

Sterile neurosurgery is an interesting model for analyzing how particular types of sterile central nervous system (CNS) trauma affect immune competence (3). The specific immunologic changes that occur after neurosurgery may offer insight into how operating on the CNS affects a patient's immune system postoperatively. Further, it is possible that the surgical procedures used to treat intracranial pathologies impact the immune system in different ways. Our main aim in this study was to determine whether the different surgeries for intracranial aneurysm, meningioma and glial tumor cause immunodepression. We also sought to determine whether decreased monocytic HLA-DR expression and increased plasma levels of inflammatory cytokines (tumor necrosis factor-a [TNF-a], interleukin [IL]-1, IL-6, and IL-8 values), termed the preinflammatory response, predict postoperative infection. Finally, we examined whether a prolonged stay in the intensive care unit (ICU) and longer duration of surgery play roles in the development of infectious complications after these procedures.

MATERIALS AND METHODS

We studied 30 adult patients who underwent selective craniotomy, dividing them into three groups based on the type of CNS pathology that required surgery. Group I included 10 patients with intracranial aneurysms, Group II was made up of 10 patients with meningiomas, and Group III was comprised of 10 patients with glial tumors. We measured monocytic HLA-DR expression and plasma TNF-a, IL-1-a, IL-6 and IL-8 at designated time points, namely, the start of surgery (stage I), 1 hour into the operation (stage II), 3 hours postsurgery (stage III) and on postoperative day 3 (stage IV). None of the patients had any immunologic pathology or infection preoperatively.

We tried to avoid factors that might confound our immune response results. To this end, we limited the type of surgery studied to craniotomy, and only

included patients who had received the same numbers of blood transfusions and the same types and dosages of drugs. In the postoperative period, all patients received intravenous (i.v.) doses of cephtriaxone (1 g/day) and amikacin (500 mg/day) for the first 5 days, and i.v. dexamethasone (8 mg four times daily) for the first 3 days. For anesthesia, all patients were premedicated with midazolam (0.6 mg/kg i.v.). Anesthetic induction was achieved with an i.v. injection of fentanyl citrate (1.5 µg/kg) and 1% propofol (2.5-3 mg/kg). After intubation, anesthesia was maintained with total intravenous anesthesia using an infusion of 4-5 mg/kg/min propofol and 3 µg/kg/min fentanyl citrate. Each patient received a one-unit transfusion of whole blood.

Each individual was followed for 10 days postoperatively. Patients were considered to have an infectious complication if there was clinical evidence of a systemic response to infection. This was defined as the presence of two or more of the following signs in addition to clinical evidence of a site of infection: peripheral white blood cell count of $< 2 \times 10^9$ cells/L or $> 15 \times 10^9$ cells/L; temperature of > 38 °C; elevated and rising C-reactive protein concentration; and isolation of pathogenic microorganisms from blood, urine or cerebrospinal fluid.

We determined the percentage of monocytic HLA-DR expression in blood samples using a flow cytometry apparatus (Epics XL-MCL Coulter) and I2-FITC monoclonal antibodies (Coulter, lot # 707801). The method was as follows: One-milliliter samples of venous blood from each patient were added to tubes containing the anticoagulant EDTA. A 100 ml aliquot of each sample was then transferred to a 12C75 mm tube, and 10 ml of fluorescence-labeled monoclonal antibody (I2-FITC-lot # 707802 Coulter) was added. The mixture was incubated at room temperature for 10 minutes. Next, the tubes were placed in a Q-prep apparatus (Coulter-USA-6704203), and the following solutions were added, in order: 600 ml Immunoprep A (1.2 ml/L formate) to lyse the blood cells, 265 ml of Immunoprep B (6 g/L sodium carbonate, 14.5 g/L sodium chloride, 31.3 g/L sodium sulphate) to stabilize the leukocytes, and 100 ml of Immunoprep C (10 g/L formaldehyde, 14 ml/L buffer) to stabilize the membranes. Once all the solutions were added, the tubes were incubated in the dark for 20 minutes at room temperature. Then they were placed in the flow cytometry apparatus (XL-Coulter- USA) for determination of percentage HLA-DR present.

The level of plasma TNF-a was determined using a TNF-a kit (CytElisa TM), the IL-1-a level was determined with an IL-1-a kit (CytElisa TM), IL-6 with an IL-6 kit (CytElisa TM), and IL-8 with a Human IL-8 kit (ACCUCYTE TM). Each of these tests involved the microELISA method. All the kit test results were expressed in pg/ml, as determined using a Denley-We-Scan apparatus.

For statistical analysis, we used SPSS software to perform the Mann-Whitney U and Wilcoxon tests, with $p<0.05$ considered to indicate significance.

RESULTS

Of the 30 patients who underwent selective, sterile CNS surgery, 5 developed infectious complications in the first postoperative week. Two patients (one aneurysm patient and one with a glial tumor) developed wound infection, two others (one glial tumor patient and one with meningioma) developed urinary tract infection, and one of the meningioma patients developed pneumonia.

The patients who developed infectious complications had significantly longer ICU stays and surgery times ($p < 0.05$; Mann-Whitney U test) (Table 1) than the other 25 patients; however, infected and noninfected patients were similar regarding gender distribution, level of HLA-DR expression, and plasma levels of TNF-a, IL-1-a, IL-6 and IL-8 ($p > 0.05$) (Tables 1 and 2). There were no significant differences among the aneurysm, meningioma and glial tumor surgery groups in terms of age or duration of surgery ($p > 0.05$) (Table 3).

When the percentage HLA-DR antigen expression was compared within and among the

Table I: The clinical profiles of the 30 patients who underwent surgery.

	Patients with infectious complications	Patients with no infectious complications
No. of patients	5#	25
Age (years)*	46.4±16.5	42.4±12.3
Gender (M/F)	2 / 3	11 / 14
Duration of surgery (hours)*	6.3±2.4	3.5±1.2
Days in intensive care*	8±2.3	3±1.1

#Wound infection (n:2), urinary tract infection (n:2), pneumonia (n:1).

*Values are listed as mean ± standard deviation.

Table II: A comparison of cytokine levels and HLA-DR expression levels in infected versus noninfected patients. (Values are listed as mean ± standard deviation)

Parameter	Stage	Patients with infectious complications (%)	Patients with no infectious complications (%)
HLA-DR	I	40.3±16.2	43.4±18.7
HLA-DR	II	38.3±14.2	41.9±11.5
HLA-DR	III	41.7±30.3	44.3±17.9
HLA-DR	IV	49.6±15.8	58.4±13.4
TNF-α	I	60.2±15.8	56.2±14.4
TNF- α	II	58.3±15.3	52.0±14.7
TNF-a	III	63.5±16.8	57.3±19.4
TNF-a	IV	59.2±17.5	48.5±13.8
IL-1a	I	56.3±24.7	44.3±20.6
IL-1a	II	31.6±22.4	19.1±16.4
IL-1a	III	37.1±22.4	28.0±25.7
IL-1a	IV	44.5±24.2	33.4±25.3
IL-6	I	65.5±40.2	59.4±32.3
IL-6	II	59.0±43.2	40.5±31.6
IL-6	III	80.8±36.4	42.9±41.2
IL-6	IV	72.6±35.1	58.4±21.9
IL-8	I	8.4±1.3	8.1±2.2
IL-8	II	10.8±3.6	10±4.1
IL-8	III	8.9±1.2	8.5±1.8
IL-8	IV	10.1±3.2	9.4±2.8

Table III: Patient age and duration of surgery for the three different surgical groups.

	Group I	Group II	Group III
Age* (years)	40±19.5	43.7±11.2	50.3±15.6
Duration of surgery* (hours)	3.8±1.2	4.7±2.3	3.9±1.1

*Values are listed as mean ± standard deviation.

three surgical groups at the four different time points studied, each group showed a trend toward elevation at stage IV; however, these higher levels did not differ statistically from the levels at the other stages in each group ($p > 0.05$). In each group, we found no significant differences in HLA-DR expression among the four stages, nor did we find differences among the groups at any given stage ($p > 0.05$).

Regarding our assessment of the patients' preinflammatory responses, we noted trends toward elevation in TNF-a in the meningioma patients at stage III, in IL-1a in the aneurysm group at stage IV, in IL-6 in the meningioma group at stage IV, and in IL-8 in all groups at stage IV. However, none of these proved to be statistically significant increases above the levels of each parameter at any other stage, or in any other group ($p > 0.05$). Overall, there were no significant differences in the levels of TNF-a, IL-1a, IL-6, and IL-8 within and among the three surgical groups at the four different time points studied ($p > 0.05$) (Table 4).

Table IV: A comparison of cytokine levels and HLA-DR expression levels at the different stages in the three surgical groups. (Values are listed as mean ± standard deviation)

Parameter	Stage	Group I (%)	Group II (%)	Group III (%)
HLA-DR	I	43.2±16.3	41.3±17.2	39.3±18.9
HLA-DR	II	41.8±16.1	41±17.5	37.9±12.9
HLA-DR	III	43.±20.9	41.1±23.	43.3±17.9
HLA-DR	IV	58.5±11.4	48.7±11.5	45.2±16.2
TNF-α	I	59.6±17.7	58.3±12.2	55.8±17.9
TNF-α	II	54±14.5	65.6±18.7	55.6±17.9
TNF-α	III	54.7±15.2	56.9±19	64.7±24.3
TNF-α	IV	57.5±16.6	64.3±14.5	50.1±12.7
IL-1α	I	39.6±29.9	31.9±25.1	54.1±50.4
IL-1α	II	29±28.3	24±19.5	20.1±17.7
IL-1α	III	35.4±25.2	29.3±21.1	31.2±24.4
IL-1α	IV	43.9±37.6	26±20	35.1±29.7
IL-6	I	60.1±50.8	105.7±79.2	61.7±38.6
IL-6	II	58.4±51.6	68.7±53.1	41.8±37.8
IL-6	III	43.5±35.4	92.2±64.5	95.3±46.6
IL-6	IV	45.5±38.3	64.2±55.8	69.3±25.1
IL-8	I	8.2±3.7	8.3±2.5	8.0±2.3
IL-8	II	9.8±3.5	10.7±4.1	10.1±3
IL-8	III	8.7±1.5	8.8±2.5	6.6±1.7
IL-8	IV	10±3.6	9.5±3.4	9±2

DISCUSSION

The probability that a patient will develop infection after craniotomy is reportedly 9%, and studies have suggested that this significant risk is related to alterations in the immune response (8,26). Postoperative immunological changes are known to depend largely on the patient's primary pathology and on the surgical procedure involved (5,11,13,14,23,29). Many clinical and experimental studies have documented immunological shifts after trauma or hemorrhage. Anesthesia, the patient's

neuroendocrine response, blood or plasma transfusion, and the type of operation are all factors that have been proven to impair immunologic responsiveness (3,9,11,20,23,27,29).

Studies that have investigated immune response during surgery have demonstrated that minor surgery causes no detectable change in immunity, but that major surgical trauma alters the immune balance (22,23,27). HLA-DR expression is considered a meaningful parameter in the evaluation of immune response because it plays an important role in antigen presentation to T-lymphocytes, a key element of cellular immunity (29). It has been suggested that local intracranial inflammation affects the systemic inflammatory response by activating the hypothalamic-pituitary-adrenal axis and producing immunodepression, which is reflected by low HLA-DR levels (3,6,7,12,15,19).

Inflammation is the general human response to trauma. The clinical picture of this response is variable, and is influenced by several factors. In patients who are exposed to major trauma, the initial systemic inflammatory response appears to be followed by monocyte deactivation. As mentioned above, HLA-DR is important in the development of the antigen-specific T-cell response, and monocyte deactivation is characterized by decreased monocytic HLA-DR expression (measured as the percentage of positive cells or as the mean fluorescence intensity, an indicator of the average number of monocytic HLA-DR antigen complexes per cell). Another feature of monocyte deactivation is an observed shift toward the secretion of antiinflammatory cytokines, including IL-1 receptor antagonist and IL-10. The combination of decreased monocytic HLA-DR expression and cytokine secretion indicates that the patient is severely immunosuppressed, and is at high risk for developing infection (3,12,30).

Asadullah et al. (3) measured monocytic HLA-DR expression and the levels of cytokines TNF-a, IL-1b, IL-6 and IL-8 in the cerebrospinal fluid and plasma of patients who had undergone intracranial surgery. They observed reduced monocytic HLA-DR expression in some patients and also reported that all individuals with decreased HLA-DR expression developed infectious complications. However, they did not detect increased levels of cytokines in the patients' plasma at any time during the first few hours or the first 3 days postsurgery. Other authors have also reported that patients with very low levels of HLA-DR expression developed infection, and have suggested this is an indicator of immunodepression (7,12).

The cytokines secreted by monocytes are the types that are most important in the inflammatory response (27,29). One of these, TNF-a, is known to be particularly important in the pathogenesis of sepsis (21,28). IL-1 and IL-6 have been identified as important mediators of the hypothalamic-pituitary-adrenal axis response to immune system activation in vivo. It has been suggested that the systemic inflammatory response limits itself by activating the hypothalamic-pituitary-adrenal axis, resulting in downregulation of monocytic function (3,7,28). Research has shown that circulating concentrations of proinflammatory mediators, including IL-6, rise after trauma and blood loss (4). Hoch and colleagues (21) demonstrated marked increases in the plasma concentrations of IL-6 and IL-8 in the immediate postinjury period. As a group, inflammatory cytokines have been implicated as mediators of the immunologic changes that occur after hemorrhage, trauma, burn and septic shock (1,18,24).

Brain tissue is reported to be the source of many of the classic mediators of inflammation that are detected after various types of injury (16,17). Specifically, glial cells and some CNS tumors are known to produce significant quantities of cytokines (2,10,25). In our study, contrary to the above-mentioned results of Asadullah et al., we noted a trend toward increased HLA-DR expression in all three surgical groups on the third postoperative day compared to the previous stages; however, the observed increases were not statistically significant. Furthermore, there were no significant differences between infected and noninfected patients regarding HLA-DR expression. On the other hand, we did find that the patients who developed infection had had significantly longer stays in the ICU, and had undergone significantly longer surgeries than patients who did not develop this type of complication.

As noted previously, Hoch et al. (21) demonstrated marked increases in the plasma concentrations of IL-6 and IL-8 in patients who had suffered multiple trauma; however, our testing for TNF-a, IL-1-a, IL-6 and IL-8 revealed no significant differences among the levels at each stage within each surgical group, or among the levels at each stage when the three groups were compared. The same held true for our analysis of these factors in infected versus noninfected patients.

In conclusion, our results suggest that surgeries performed in the treatment of intracranial aneurysm, meningioma and glial tumor do not cause immunodepression. Our findings related to monocytic HLA-DR and the plasma TNF-a, IL-1-a, IL-6 and IL-8 preinflammatory response did not concur with other results that have been cited in the literature (3,7,12,21,30). Based on the changes we observed, these parameters do not appear to be good predictors of postoperative infection. However, our study does show that prolonged stay in the ICU and longer duration of surgery are associated with the development of infectious complications postsurgery.

Note: This study was presented, in part, as a poster at the May 19-23, 1999 Turkish Neurosurgical Society meeting - XIII Annual Scientific Congress.

Correspondence: Metin Tuna
Çukurova Üniversitesi Tıp Fakültesi
Nöroşirürji ABD
01330 Adana, Turkey
Phone: (90-322) 3386060 / 3212
E mail: metnus@superonline.com

REFERENCES

1. Abraham E: Host defense abnormalities after hemorrhage, trauma, and burns: Crit Care Med 17; 934-939, 1989
2. Aloisi F, Care A, Borsellino G, Gallo P, Rosa S, Bassani A, Cabibbo A, Testa U, Levi G, Peschle C: Production of hemolymphopoietic cytokines (IL-6, IL-8, colony-stimulating factors) by normal human astrocytes in response to IL-1-b and tumor necrosis factor-a. J Immunol 149; 2358-2366, 1992
3. Asadullah K, Woiciechowsky C, Döcke WD, Liebenthal C, Wauer H, Kox W, Volk HD, Vogel S, Baehr RV: Immunodepression following neurosurgical procedures. Crit Care Med 23; 1976-1982, 1995
4. Ayala A, Wang P, Ba ZF, Perrin MM, Ertel W, Chaudry IH: Differential alterations in plasma IL-6 and TNF levels after trauma and hemorrhage Am J Physiol 260; 167-171, 1991
5. Barth J, Petermann W, Entzian P, Wustrow C, Wustrow J, Ohnhaus EE: Modulation of oxygen-free radicals from human leukocytes during halothane- and enflurane-induced general anesthesia. Acta Anesthesiol Scand 31; 740-743, 1987
6. Benjamini E, Leshowitz S: Immunology, a short course. 2nd edition, Immunology 8; 175-182, 1991
7. Blalock JE: The syntax of immune-neuroendocrine communication. Immunol Today 15; 504-511, 1994
8. Blomstedt GC: Infections in neurosurgery: A retrospective study of 1143 patients and 1517 operations. Acta Neurochir (Wien) 78; 81-90, 1985
9. Brodsky JB: Toxicity of Nitrous Oxide in Nitrous Oxide/N2O, Eger EI II. New York, Elsevier Science Publishing Company, Inc., 1985; 259+62 p.
10. Chao CC, Hu S, Close K, Choi CS, Molitor TW, Novick WJ, Peterson PK: Cytokine release from microglia: Differential inhibition by pentoxifylline and dexamethasone. J Infect Dis 166; 847-853, 1992
11. Cullen BF, van Belle G: Lymphocyte transformation and changes in leukocyte count: Effects of anesthesia and operation. Anesthesiology 43; 563-569, 1975
12. Döcke WD, Syrbe U, Meinecke A: Improvement of monocyte function - A new therapeutic approach? In Reinhart K, Eyrich K, Sprung C (Eds), Sepsis - Current Perspectives in Pathophysiology and Therapy. Berlin: Springer-Verlag, 1994: 473-500.
13. Duncan PG, Cullen BF, Calverly R, Smith NT, Eger EI, Bone R: Failure of enflurane and halothane anesthesia to inhibit lymphocyte transformation in volunteers. Anesthesiology 45; 661-665; 1976
14. Eskola J, Salo M, Viljanen MK, Ruuskanen O: Impaired B lymphocyte function during open-heart surgery: Effects of anesthesia and surgery. Br J Anaesth 56; 333-337, 1984
15. Guillou PJ: Biological variation in the developement of sepsis after surgery or trauma. Lancet 342; 217-220. 1993
16. Hariri RJ, Ghajar JBG, Bahramian K, Sharif S, Barie PS: Alterations in intracranial pressure and cerebral blood volume in endotoxemia. Surg Gynecol Obstet 176;155-166, 1993
17. Hariri RJ, Ghajar JBG, Pomerantz KB, Hajjar DP, Giannuzzu RF, Tomich E, Andrews DW, Patterson RH Jr: Human glial cell production of lipoxygenase-generated eicosanoids: A potential role in the pathophysiology of vascular changes following traumatic brain injury. J Trauma 29; 1203-1210, 1989
18. Heinrich PC, Castell JV, Andus T: Interleukin-6 and the acute-phase response. Biochem J 265; 621-636, 1990
19. Hershman MJ, Cheadle WG, Wellhausen SR, Davidson PF, Polk HC Jr: Monocyte HLA-DR antigen expression characterizes clinical outcome in the trauma patient. Br J Surg 77: 204-207, 1990
20. Hisatomi K, Isomura T, Kawara T, Yamashita M, Hirano A, Yoshida H, Eriguchi N, Kosuga K, Ohishi K: Changes in lymphocyte subsets, mitogen responsiveness, and interleukin-2 production after cardiac operations. J Thorac Cardiovasc Surg 98; 580-591, 1989
21. Hoch RC, Rodriguez R, Manning T, Bishop M, Mead P, Shoemaker WC, Abraham E: Effects of accidental trauma on cytokine and endotoxin production. Crit Care Med 21; 839-845, 1993
22. Hole A, Unsgaard G: The effect of epidural and general anaesthesia on lymphocyte function during and after major orthopaedic surgery. Acta Anaesthesiol Scand 27; 135-141, 1983

23. Koenig A, Koenig UD, Heicappel R, Stoeckel H: Differences in lymphocyte mitogenic stimulation pattern depending on anesthesia and operative trauma: Halothane-nitrous oxide anesthesia. Eur J Anaesthesiol 4; 17-24, 1987
24. Michie HR, Manogue KR, Spriggs DR, Revhaug A, O'Dwyer S, Dinarello CA, Cerami A, Wolff SM, Wilmore DW: Detection of circulating tumor necrosis factor after endotoxin administration. N Engl J Med 318; 1481-1486, 1988
25. Peterson PK, Chao CC, Hu S, Thielen K, Shaskan EG: Glioblastoma, transforming growth factor-b, and *Candida* meningitis: A potential link. Am J Med 92; 262-264, 1992
26. Prittikangas CO, Salo M, Mansikka M, Gronroos J, Pulkki K, Peltola O: The influence of anaesthetic technique upon the immune response to hysterectomy. A comparison of propofol infusion and isoflurane. Anaesthesia 50(12); 1056-1061, 1995
27. Salo M: Effects of anaesthesia and surgery on the immune response. Acta Anaesthesiol Scand 36; 201-220, 1992
28. Shapiro L, Gelfand JA: Cytokines and sepsis: Pathophysiology and therapy. New Horizons 1; 13-22, 1993
29. Stevenson GW, Hall SC, Rudnick S, Seleny FL, Stevenson HC: The effect of anaesthetic agents on the human immune response. Anaesthesiology 72; 542-552, 1990
30. Wakefield CH, Carey PD, Foulds S, Monson JR, Guillou PJ: Changes in major histocompability complex class 2 expression in monocytes and T cells of patients developing infection after surgery. Br J Surg 80; 205-209, 1993