British Journal of Surgery 1994, **81**, 1747–1751

Effect of ranitidine on soluble interleukin 2 receptors and CD8 molecules in surgical patients

H. J. NIELSEN*†, T. MYNSTER*, S. JENSEN‡, J. HAMMER† and H. NIELSEN§

*Department of Surgical Gastroenterology 235 and †Surgical Immunology Laboratory, Hvidovre University Hospital, Hvidovre, and ‡Department of Surgery F, Bispebjerg University Hospital, and §Department of Clinical Microbiology, State University Hospital, Copenhagen, Denmark
Correspondence to: Dr H. J. Nielsen, Department of Surgical Gastroenterology 235, Hvidovre University Hospital, DK-2650 Hvidovre, Denmark

The effect of perioperative immunomodulation with the H_2-receptor antagonist ranitidine on postoperative changes in soluble interleukin (IL) 2 receptor and soluble CD8 levels was assessed in 24 patients undergoing major elective abdominal surgery. Eleven patients were randomized to receive intravenous ranitidine 100 mg twice daily for 4 days from skin incision, followed by oral ranitidine 150 mg twice daily for a further 5 days; 13 control patients received no ranitidine. Routine blood analysis, clinical data, duration of surgery, anaesthesia, antibiotic prophylaxis and perioperative blood transfusion were similar in the two groups. Serum concentrations of soluble IL-2 receptor and CD8 were measured before operation (day 0) and in the morning of postoperative days 1, 3 and 9 using commercial enzyme-linked immunosorbent assay kits. In patients treated with ranitidine, the serum level of soluble IL-2 receptor increased from day 0 to day 9 ($P < 0.01$); in control patients it decreased from day 0 to day 1, did not change significantly by day 3 and increased by day 9. The change from day 0 to day 1 was significantly different between the two groups ($P < 0.01$). Five of the 13 control patients developed postoperative infectious complications. No significant differences were shown in soluble CD8 concentration during the postoperative period. The postoperative change in soluble IL-2 receptor level may reflect lymphocyte activation status; ranitidine appears to promote activation of mainly CD4-positive lymphocytes since serum levels of CD8 were unchanged. Ranitidine may, therefore, improve immune function during major surgery.

Despite therapeutic advances, infectious complications remain a major cause of postoperative morbidity and mortality. Transient impairment in immunocompetence is induced by major surgery, trauma and burns[1–5], and immunosuppression before and after surgery increases the risk of developing postoperative infectious complications[6–8]. The mechanism underlying trauma-induced immunosuppression has not been fully elucidated, but several peptides and suppressor molecules[9–11] are believed to participate in a process in which downregulation of interleukin (IL) 2 production and release plays an important role[12,13]. IL-2 transduces its signal by binding primarily to high-affinity IL-2 receptors expressed by lymphocytes and natural killer cells[14]. When activated, an IL-2 receptor subunit with low affinity is released from lymphocytes[15,16] and, since this soluble receptor may retain its ability to bind IL-2[17], increased concentrations of soluble IL-2 receptor measured after traumatic events or infection have been suggested to participate in immunosuppression[15,18,19].

The CD8 molecule is expressed on the surface of T lymphocytes with suppressor and cytotoxic activity, and CD8-positive cells are classified as belonging to these subsets[20]. Following immune stimulation the CD8 molecule appears to be shed in a soluble form[21], and this may reflect specific activation of suppressor and cytotoxic subsets[22].

It has been shown previously that the H_2-receptor antagonist ranitidine can improve immunosuppression induced by trauma, blood transfusion and sepsis[23–28], presumably by reducing the production of suppressor-active peptides by CD8-positive suppressor lymphocytes. The purpose of the present study was to evaluate the effect of ranitidine on postoperative changes in serum levels of IL-2 receptor and CD8 to establish whether IL-2 receptors are shed particularly from activated CD8 positive cells after trauma and whether these receptors can participate in immunosuppression.

Paper accepted 19 April 1994

Patients and methods

Twenty-four consecutive patients, men and women aged 46–79 years, scheduled for major elective abdominal surgery entered the study. None had clinical signs of infectious disease and none had received systemic steroids, non-steroidal anti-inflammatory drugs, theophylline, insulin, cytotoxic agents, antiviral drugs, H_2 blockers or other known immunomodulatory agents within 4 weeks before entry to the study. Hepatic and renal function were normal on routine laboratory analysis, and no patient underwent blood transfusion before operation. Patients with known endocrine disease, and alcohol and/or drug abusers, were not asked to participate. In addition, patients aged more than 80 years, and those with a serum albumin level below 480 μmol/l, or body-weight less than 90 per cent of normal, were excluded.

Patients were randomized to receive perioperative adjuvant treatment with ranitidine 100 mg intravenously twice daily for 4 days starting at the time of skin incision, followed by oral ranitidine 150 mg twice a day for a further 5 days, or no adjuvant treatment. The laboratory staff were unaware of the randomization. Routine blood analysis was performed before operation (day 0) and on postoperative days 1, 3 and 9. Serum for analysis of IL-2 receptor and CD8 was drawn in the morning immediately before skin incision and in the morning of days 1, 3 and 9 after surgery. Serum was frozen at −80°C until all samples had been collected. To avoid day-to-day variation all samples were thawed simultaneously and analysis was performed using reagents with the same batch number.

Analysis of IL-2 receptor and CD8 in serum was performed using commercially available solid-phase sandwich enzyme-linked immunosorbent assay test kits (T Cell Science, Cambridge, Massachusetts, USA). Thus, the soluble IL-2 receptor analysis is based on the binding of receptor to a solid phase-bound antibody recognizing the Tac epitope on the human IL-2 receptor[29], and detection of the bound antigen by a horseradish peroxidase-conjugated antibody recognizing a different epitope on the human IL-2 receptor[30]. Soluble CD8 analysis depends on the availability of anti-CD8 monoclonal antibody (Mab) C9, and a second horseradish

peroxidase-conjugated anti-CD8 Mab B12 recognizes a different epitope on the human soluble CD8 molecule[21]. Serum levels of both IL-2 receptor and CD8 are expressed in units per millilitre.

The duration of surgery, blood loss during the operation and amount of blood transfused in the perioperative period were recorded. To avoid an amplifying influence of whole blood on trauma-induced immunosuppression only SAG-M blood transfusion was used, and only when needed[31,32]. The operations performed are shown in *Table 1*. All patients received general anaesthesia with or without combined epidural analgesia with bupivacaine, mepivacaine and/or morphine; there was similar use of anaesthesia between the two groups. Standard antibiotic prophylaxis was given as a preoperative single intravenous dose of cefuroxime 3·0 g and metronidazole 1·5 g. Postoperative infectious complications were treated with cefuroxime 1·5 g and metronidazole 1·0 g twice daily for 3–5 days.

Data were recorded on a standard form and were entered for computer analysis using the BMDP program (BDMP, Los Angeles, California, USA) for SPSS (SPSS, Chicago, Illinois, USA). Differences between groups were assessed statistically with the χ^2 test and the Mann–Whitney U test when appropriate. Differences within groups were analysed with the Wilcoxon rank sum test. $P < 0{\cdot}05$ was considered significant. All values are given as median (range).

The Helsinki II declaration of written informed consent was obtained and the study protocol was approved by the ethical committee of Copenhagen Hospitals.

Results

Eleven patients received adjuvant ranitidine treatment and 13 were operated on without adjuvant therapy. There were no side-effects of ranitidine treatment. Clinical data are shown in *Table 2*. There was a longer duration of surgery in the patients treated with ranitidine and postoperative wound infection occurred in five control patients; all other parameters were similar in the two groups. Routine blood analysis and differential leucocyte counts were similar in the two groups (data not shown). Postoperative infections detected clinically on days 5–7 were wound infection in three patients and perineal infection in two; pus was drained spontaneously or with surgical intervention.

Table 1 Operations performed

	Ranitidine ($n = 11$)	No ranitidine ($n = 13$)
Gastric resection	2	1
Low anterior resection	2	1
Abdominoperineal resection	1	3
Sigmoid resection	3	4
Right hemicolectomy	1	1
Closure of sigmoid colostomy	1	2
Exploratory laparotomy	1	1

Table 2 Clinical data

	Ranitidine ($n = 11$)	No ranitidine ($n = 13$)
Age (years)*	58 (46–78)	63 (50–79)
Height (cm)*	172 (161–182)	167 (159–181)
Weight (kg)*	70 (58–95)	73 (59–100)
Sex ratio (M:F)	3:8	8:5
Cancer	7 of 11	9 of 13
Duration of operation (min)*	180 (60–265)	145 (50–215)†
Blood loss (ml)*	750 (300–1500)	1050 (200–2100)
Blood transfusion	5 of 11	5 of 13
Wound infection	0 of 11	5 of 13†

*Values are median (range). †$P < 0{\cdot}05$ *versus* patients treated with ranitidine

The serum level of IL-2 receptor in normal age-matched subjects ($n = 8$) in this laboratory ranged from 155 to 480 (median 340) units/ml. Median preoperative levels of IL-2 receptor in serum were significantly increased in patients compared with those in healthy controls ($P < 0{\cdot}05$) (*Fig. 1*); in particular, high preoperative levels were detected in the 16 patients operated on for malignant disease compared with normal concentrations in the eight patients with no malignancy ($P < 0{\cdot}05$) (*Fig. 1*). There was no significant difference between preoperative levels of soluble IL-2 receptor in ranitidine-treated and control patients, although the pattern of changes in the two groups was different (*Fig. 2*). In ranitidine-treated patients the serum IL-2 receptor level increased significantly from day 0 to day 9 ($P < 0{\cdot}01$). The difference in the change from day 0 to day 1 was significant in the two groups ($P < 0{\cdot}01$, *Fig. 2*).

Soluble IL-2 receptor levels in the five control patients with postoperative infectious complications and in the eight

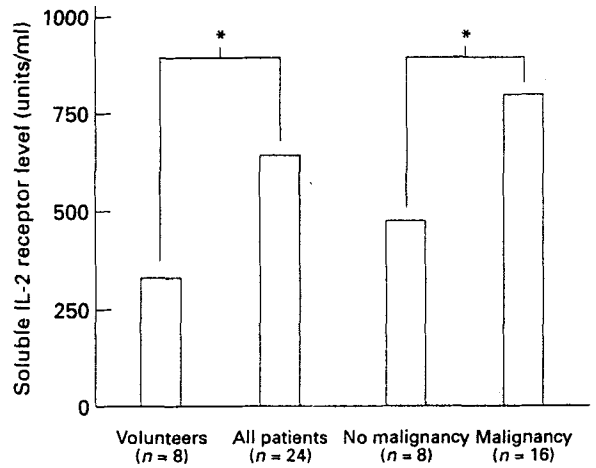

Fig. 1 Median soluble interleukin (IL) 2 receptor levels in eight healthy volunteers compared with preoperative levels in 24 patients. Of the 24 patients, 16 had malignant disease. *$P < 0{\cdot}05$

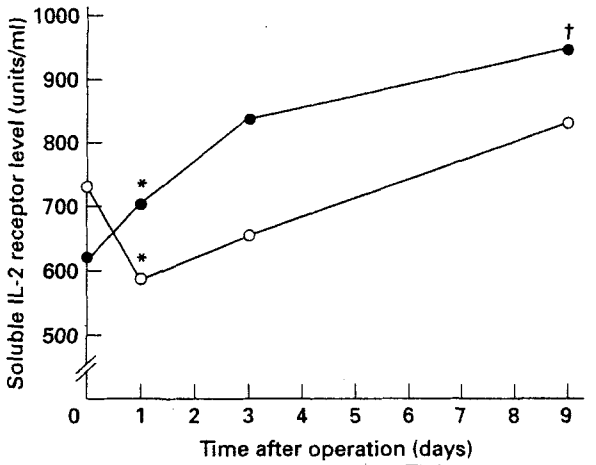

Fig. 2 Median soluble interleukin (IL) 2 receptor levels in 11 ranitidine-treated patients (●) and in 13 control patients (○) undergoing major elective abdominal surgery. *$P < 0{\cdot}01$ (change from day 0 to day 1 in controls *versus* change from day 0 to day 1 in ranitidine-treated patients); †$P < 0{\cdot}01$ (day 9 *versus* day 0). There was no significant difference between observed values in the two groups on any day

without infection are shown in *Fig. 3*. From day 0 to day 1 the concentration of IL-2 receptor in serum decreased significantly in the patients with infection ($P < 0{\cdot}05$) (*Fig. 3*), followed by a significant increase from day 1 to day 9 ($P < 0{\cdot}05$). In patients with no infection only small and insignificant changes were measured from day 0 to day 9.

The soluble CD8 concentration in normal age-matched subjects ($n = 8$) in this laboratory ranged from 138 to 687 (median 365) units per ml. There was no significant difference between healthy controls and patients, and the preoperative CD8 level was similar in the serum of ranitidine-treated and control patients (*Fig. 4*). Soluble CD8 levels were unchanged and within the normal range in the postoperative period and were similar in the two groups on all days, except for a significant increase from day 1 to day 3 in patients receiving ranitidine ($P < 0{\cdot}05$) (*Fig. 4*). There was no difference in soluble CD8 concentration between the five control patients with infection and the eight without.

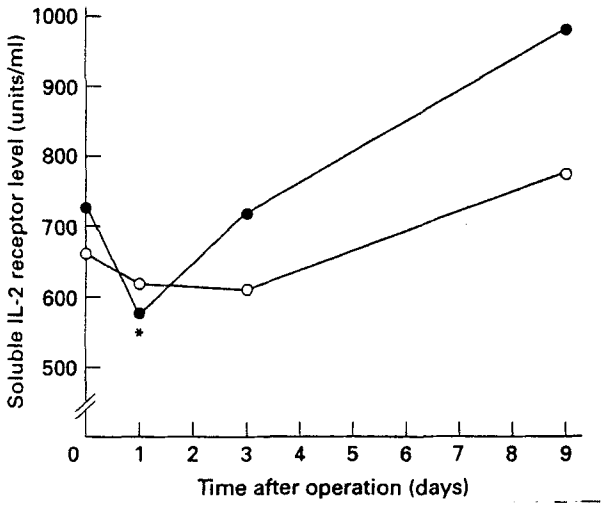

Fig. 3 Median soluble interleukin (IL) 2 receptor levels in five control patients with postoperative infectious complications (●) and in eight control patients without (○). *$P < 0{\cdot}05$ (day 1 *versus* days 0, 3 and 9). The values in non-infected patients did not change significantly. The difference between groups on day 9 was not significant

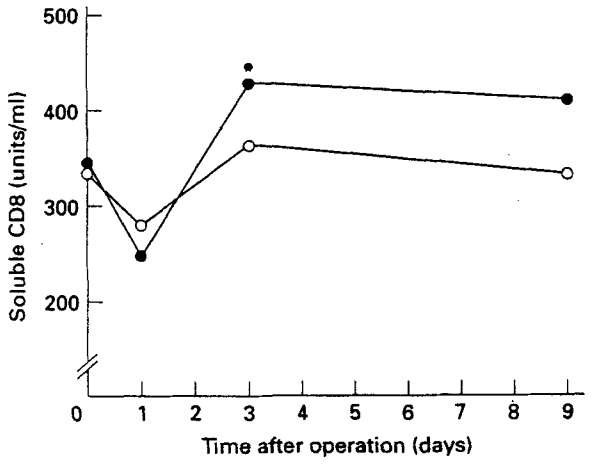

Fig. 4 Median soluble CD8 levels in 11 ranitidine-treated patients (●) and in 13 control patients (○) undergoing major elective abdominal surgery. *$P < 0{\cdot}05$ (day 3 *versus* day 1). There was no difference in CD8 concentration between the two groups

Discussion

Major surgery has repeatedly been shown to suppress immunocompetence[5,7,8]. This is considered to be important for impaired host defence against micro-organisms and probably against dissemination of malignant cells during cancer surgery[7,8,33]. The precise mechanism underlying post-traumatic immunosuppression has not yet been established, but circulating immunosuppressive substances, as well as complex lymphocyte–macrophage interactions and hyper-activation of granulocytes, have been described[2,7–11,28]. Downregulation of IL-2 production and/or release seems, however, to play a major role in a process leading to decreased immune reaction to foreign antigens[12–14,34,35]. Binding of IL-2 to its receptor is an important initial step in the regulation of T lymphocyte activation[14–16]. There are three known forms of cell-surface IL-2 receptor: the 55-kDa α-chain, the 75-kDa β-chain and the 64-kDa γ-chain, which have different affinities for IL-2 binding[36]. The highest binding affinity demands close approximation and expression of all three receptor chains. In the absence of stimulation by antigen, the density of cell-surface IL-2 receptors on the majority of T cells present in peripheral blood is not sufficiently high to induce proliferation. In the presence of antigen, however, T cells are induced to synthesize and secrete IL-2 as well as to synthesize cell-surface IL-2 receptors[16]. On activation, T cells release a soluble form of the low-affinity 55-kDa receptor[29,30], which has a molecular mass of approximately 45 kDa. The major difference between the soluble and cell-surface forms of the low-affinity IL-2 receptor is that the 45-kDa receptor comprises only the ligand-binding domain and lacks both transmembrane and cytoplasmic domains[37]. Increased concentrations of soluble IL-2 receptor have been found in patients with leukaemia[38], autoimmune disease[39] and human immunodeficiency virus infection[40], and in traumatized patients[18]. The increased preoperative levels of soluble IL-2 receptor in patients with malignancy shown in the present study (*Fig. 1*) supports previous findings in those with solid tumour[16]. The soluble IL-2 receptor may retain its ability to bind IL-2[17,41] and may therefore contribute to immuno-regulation, both in activated systems and in immunosuppression[16,36]. IL-2 has been shown[42] to regulate expression of its own receptor *in vitro*, and high-affinity IL-2 receptor production and expression has been shown[42] to decrease and the low-affinity expression to increase 8–10-fold on activation with recombinant IL-2 and antigen; however, the magnitude of the lymphocyte proliferative response correlates with the density of high-affinity binding sites[36,42]. Therefore, the increased expression of the low-affinity receptor may not participate in T cell proliferation[36]. This hypothesis may be supported by the finding that lymphocytes stimulated with antigen without exogeneous IL-2 proliferate to a much lower extent, and that low-affinity binding sites are metabolized with a half-life of 6·4 h compared with 2·6 h for high-affinity receptors[42].

Trauma-induced suppression of IL-2 production[12] may therefore lead to decreased production and degradation of IL-2 receptors, resulting in low levels of soluble receptor as seen in control patients on days 1 and 3 after operation (*Fig. 2*). The increased levels observed on day 9 may correlate with normalized IL-2 production after major surgery[12]. The significant increase in soluble IL-2 receptor levels in the five control patients with postoperative infection may be partly explained by secondary increased low-affinity expression on CD4-positive helper T cells, B cells and natural killer cells following prolonged antigen challenge and suppressed IL-2

production with increased release of the soluble subunit. A tumour-induced decrease in IL-2 production[35] may also partly explain the increased preoperative serum levels of IL-2 receptor found in patients with malignancy (*Fig. 1*).

The soluble CD8 molecule is released from activated peripheral blood mononuclear cells *in vitro*[21]; it is a 52-kDa homodimer that is 5 kDa smaller than its membrane-bound counterpart[43]. Release of CD8 does not apparently result from cell destruction but rather from immune stimulation[21,44]. Increased concentrations of CD8 are found in the serum of patients with disease of the immune system[21,22,45,46]. Furthermore, changes in soluble CD8 level are found to parallel changes in the number of cells expressing CD8-HLA-DR[21]. It has therefore been suggested that analysis of soluble CD8 may reflect the activity of CD8-positive cells[47]. The finding that CD8-positive cell counts are unchanged during major surgery[48] and the fact that levels of soluble CD8 remained the same in the present study (*Fig. 4*) suggest that soluble IL-2 receptors released by CD8-positive cells may play only a minor role in immunoregulation.

The increase in soluble IL-2 receptor levels in patients treated with ranitidine (*Fig. 2*) may indirectly reflect an improvement in IL-2 production, with increased expression and release of the 55-kDa subunit. Although ranitidine may block H_2 receptors on different cells, cells expressing CD8 do not appear to change significantly in overall activity, as judged by measurement of soluble CD8 levels (*Fig. 4*). However, it is possible that there is increased activity of the suppressor subunit of the CD8-positive cells and decreased activity of the cytotoxic subunit. This gives further support to the hypothesis that soluble IL-2 receptors may be released mainly by CD4-positive cells, B cells and natural killer cells, which have been shown to be activated by recombinant IL-2 during major surgery[48].

The present results confirm that the H_2-receptor antagonist ranitidine may inhibit different aspects of postoperative immunosuppression and improve some postoperative immune reactions[23–28], but it is unclear at present how histamine may participate in trauma-induced immunosuppression. Major operations may induce complement activation, specifically of the C3a and C5a subclasses, and endotoxin release, which may subsequently lead to enhanced release of histamine by mast cells and basophils[49–51]. Histamine may be an important regulator of immune function, as immunoactive cells express histamine receptors on their surface[52]. Histamine is an immunostimulant in physiological concentrations, acting mostly on H_1 but also on H_2 receptors[52]. Increased concentrations, as seen during the early postoperative period and in the septic response[51,53], are followed by preferential binding to H_2 receptors; this may lead to suppression[52] in several parts of the immune system, for example by reducing lymphocyte blastogenesis, lymphokine production, antibody formation, natural killer cell activity and granulocyte chemotaxis[52,54,55], and by activating suppressor CD8-positive cells[56].

The mechanism by which ranitidine improves postoperative immune function[23–28] is not yet known in detail, but blockade of H_2 receptors expressed on helper T lymphocytes may lead to improved IL-2 production[54]. Furthermore, H_2 receptor blockade on the CD8-positive suppressor subsets may result in decreased production of suppressor active peptides, subsequently helping IL-2 and other immunoactive mediators to normalize postoperative immune function[57,58]. Thus, ranitidine may have potential clinical value in the prevention of postoperative infectious complications and dissemination of malignancy[59,60]. However, no dose–response study in humans is available at present, although normal doses used to treat ulcers have been effective in the authors' studies; results from current clinical placebo-controlled randomized studies are awaited to confirm or invalidate these hypotheses[59].

It is concluded that soluble IL-2 receptors may be shed significantly from cells other than CD8-positive cells during postoperative immunosuppression and that the high levels seen in different disease states may arise from 'spill-over' when the 55-kDa subunit is overexpressed following decreased IL-2 production. IL-2 receptor release may not, therefore, participate directly in trauma-induced immunosuppression, but may be secondary to IL-2 regulation of its own biological responses[42].

Acknowledgements

The authors thank Dr F. Moesgaard of Hvidovre University Hospital for help with statistical evaluation.

This study was supported by grants from the Gerda and Aage Haensch Foundation and the Mimi and Victor Larsen Foundation.

References

1 Antrum RM, Solomkin JS. Monocyte dysfunction in severe trauma: evidence for the role of C5a in deactivation. *Surgery* 1986; **100**: 29–37.
2 Christou NV, Mannick JA, West MA, Kasper DL. Lymphocyte macrophage interactions in the response to surgical infections. *Arch Surg* 1987; **122**: 239–51.
3 Ogle CK, Johnson C, Guo XL, Ogle JD, Solomkin JS, Alexander JW. Production and release of C3 by cultured monocytes/macrophages isolated from burned, trauma, and septic patients. *J Trauma* 1989; **29**: 189–94.
4 Tanaka H, Ogura H, Yokota J, Sugimoto H, Yoshioka T, Sugimoto T. Acceleration of superoxide production from leukocytes in trauma patients. *Ann Surg* 1991; **214**: 187–92.
5 Athlin L, Holmberg SB, Hafström L. Macrophage function and surgery. A clinical review with special reference to phagocytosis. *Eur J Surg* 1991; **157**: 163–70.
6 Moesgaard F, Lykkegard-Nielsen M. Preoperative cell-mediated immunity and duration of antibiotic prophylaxis in relation to postoperative infectious complications. A controlled trial in biliary, gastroduodenal and colorectal surgery. *Acta Chirurgica Scandinavica* 1989; **155**: 281–6.
7 Wakefield CH, Carey PD, Foulds S, Monson JRT, Guillou PJ. Polymorphonuclear leukocyte activation. An early marker of the postsurgical sepsis response. *Arch Surg* 1993; **128**: 390–5.
8 Wakefield CH, Carey PD, Foulds S, Monson JRT, Guillou PJ. Changes in major histocompatibility complex class II expression in monocytes and T cells of patients developing infection after surgery. *Br J Surg* 1993; **80**: 205–9.
9 Schnaper HW, Aune TM, Roby RK. A role for histamine type II (H_2) receptor binding in production of the lymphokine, soluble immune response suppressor (SIRS). *J Immunol* 1987; **139**: 1185–90.
10 Ozkan AN, Hoyt DB, Tompkins S, Ninnemann JL, Sullivan JJ. Immunosuppressive effects of a trauma-induced suppressor active peptide. *J Trauma* 1988; **28**: 589–92.
11 Halpern MT. Human nonspecific suppressive lymphokines. *J Clin Immunol* 1991; **11**: 1–12.
12 Akiyoshi T, Koba F, Arinaga S, Miyazaki S, Wada T, Tsuji H. Impaired production of interleukin-2 after surgery. *Clin Exp Immunol* 1985; **59**: 45–9.
13 Rodrick ML, Wood JJ, O'Mahony JB *et al.* Mechanisms of immunosuppression associated with severe non-thermal traumatic injuries in man: production of interleukin-1 and 2. *J Clin Immunol* 1986; **6**: 310–18.
14 Smith KA. Capitalising on the therapeutic potential of interleukin 2. In: Borden EC, ed. *Therapeutic Strategies in Oncology.* London: Mediscript, 1990: 9–29.
15 Fernandez-Botran R. Soluble cytokine receptors: their role in immunoregulation. *FASEB J* 1991; **5**: 2567–74.

16 Zerler B. The soluble interleukin-2 receptor as a marker for human neoplasia and immune status. *Cancer Cells* 1991; **3**: 471–9.
17 Jacques Y, Le Mauff B, Boeffard F, Godard A, Soulillou JP. A soluble interleukin 2 receptor produced by a normal alloreactive human T cell clone binds interleukin 2 with low affinity. *J Immunol* 1987; **139**: 2308–16.
18 Teodorczyk-Injeyan JA, McRitchie DI, Peters WJ, Lalani S, Girotti MJ. Expression and secretion of IL-2 receptor in trauma patients. *Ann Surg* 1990; **212**: 202–8.
19 Barral-Netto M, Barral A, Santos SB *et al.* Soluble IL-2 receptors as an agent of serum-mediated suppression in human visceral leishmaniasis. *J Immunol* 1991; **147**: 281–4.
20 Swain SL. T-cell subsets and the recognition of MHC class. *Immunol Rev* 1983; **74**: 129–42.
21 Tomkinson B, Brown MC, Ip SH, Carrabis S, Sullivan JL. Soluble CD8 during T cell activation. *J Immunol* 1989; **142**: 2230–6.
22 Nishanian P, Hofmann B, Wang Y, Jackson AL, Detets R, Fahey JL. Serum soluble CD8 molecule is a marker of CD8 T-cell activation in HIV-1 disease. *AIDS* 1991; **5**: 805–12.
23 Nielsen HJ, Moesgaard F, Kehlet H. Ranitidine for prevention of postoperative suppression of delayed hypersensitivity. *Am J Surg* 1989; **157**: 291–4.
24 Nielsen HJ, Hammer JH, Moesgaard F, Kehlet H. Ranitidine prevents postoperative transfusion-induced depression of delayed hypersensitivity. *Surgery* 1989; **105**: 711–17.
25 Nielsen HJ, Pedersen BK, Moesgaard F, Haahr PM, Kehlet H. Ranitidine improves postoperative depression in natural killer cell activity and delayed hypersensitivity. *Acta Chirurgica Scandinavica* 1989; **155**: 377–82.
26 Nielsen HJ, Witt K, Moesgaard F, Kehlet H. Ranitidine improves delayed hypersensitivity in patients with sepsis. *Acta Chirurgica Scandinavica* 1989; **155**: 445–9.
27 Nielsen HJ, Hammer JH, Moesgaard F, Heron I, Kehlet H. Ranitidine improves post-operative suppression of antibody response to preoperative vaccination. *Surgery* 1992; **111**: 69–73.
28 Nielsen HJ, Nielsen H, Jensen S, Moesgaard F. Ranitidine improves postoperative monocyte and neutrophil function. *Arch Surg* 1994; **129**: 309–15.
29 Rubin LA, Kurman CC, Fritz ME *et al.* Soluble interleukin-2 receptors are released from activated human lymphoid cells *in vitro*. *J Immunol* 1985; **135**: 3172–5.
30 Rubin LA, Kurman CC, Biddison WE, Goldman ND, Nelson DL. A monoclonal antibody 7G7/B6 binds to an epitope on the human interleukin-2 (IL-2) receptor that is distinct from that recognized by IL-2 or anti-Tac. *Hybridoma* 1985; **4**: 91–102.
31 Nielsen HJ, Hammer JH, Moesgaard F, Kehlet H. Comparison of the effects of SAG-M and whole-blood transfusions on postoperative suppression of delayed hypersensitivity. *Can J Surg* 1991; **34**: 146–50.
32 Jensen LS, Andersen AJ, Christiansen PM *et al.* Postoperative infection and natural killer cell function following blood transfusion in patients undergoing elective colorectal surgery. *Br J Surg* 1992; **79**: 513–16.
33 Cole WH, Humphrey L. Need for immunologic stimulators during immunosuppression produced by major cancer surgery. *Ann Surg* 1985; **202**: 9–20.
34 Wood JJ, Rodrick ML, O'Mahony JB *et al.* Inadequate interleukin 2 production. A fundamental immunological deficiency in patients with major burns. *Ann Surg* 1984; **200**: 311–20.
35 Monson JR, Ramsden CW, Giullou PJ. Decreased interleukin-2 production in patients with gastrointestinal cancer. *Br J Surg* 1986; **73**: 483–6.
36 Smith KA. Lowest dose interleukin-2 immunotherapy. *Blood* 1993; **81**: 1414–23.
37 Robb RJ, Kutny RM. Structure–function relationships for the IL-2 receptor system. IV. Analysis of the sequence and ligand-binding properties of soluble Tac protein. *J Immunol* 1987; **139**: 855–62.
38 Pizzolo G, Chilosi M, Semenzato G. The soluble interleukin-2 receptor in haematological disorders. *Br J Haematol* 1987; **67**: 377–80.
39 Symons JA, Wood NC, Di Giovine FS, Duff GW. Soluble IL-2 receptor in rheumatoid arthritis. Correlation with disease activity, IL-1 and IL-2 inhibition. *J Immunol* 1988; **141**: 2612–18.
40 Honda M, Kitamura K, Matsuda K *et al.* Soluble IL-2 receptor in AIDS. Correlation of its serum level with the classification of HIV-induced diseases and its characterization. *J Immunol* 1989; **142**: 4248–55.
41 Rubin LA, Jay G, Nelson DL. The released interleukin 2 receptor binds interleukin 2 efficiently. *J Immunol* 1986; **137**: 3841–4.
42 Smith KA, Cantrell DA. Interleukin-2 regulates its own receptors. *Proc Natl Acad Sci U S A* 1985; **82**: 864–8.
43 Fujimoto J, Stewart SJ, Levy R. Immunochemical analysis of the released Leu-2 (T8) molecule. *J Exp Med* 1984; **160**: 116–24.
44 Fujimoto J, Levy S, Levy R. Spontaneous release of the Leu-2 (T8) molecule from human T cells. *J Exp Med* 1983; **158**: 752–66.
45 Pui CH, Ip SH, Thompson E *et al.* Increased serum CD8 antigen level in childhood Hodgkin's disease relates to advanced stage and poor treatment outcome. *Blood* 1989; **73**: 209–13.
46 Pui CH, Ip SH, Dodge RK *et al.* Serum levels of CD8 antigen in childhood lymphoid malignancies: a possible indicator of increased suppressor cell activity in poor-risk patients. *Blood* 1988; **72**: 1015–21.
47 Brown M, Carrabis S, Ip S, Kung P. Enzyme immunoassay for the quantification of cell-free human T-cell CD8-like molecule. *Federation Proceedings* 1987; **46**: 467 (Abstract).
48 Nichols PH, Ramsden CW, Ward U, Sedman PC, Primrose JN. Perioperative immunotherapy with recombinant interleukin 2 in patients undergoing surgery for colorectal cancer. *Cancer Res* 1992; **52**: 5765–9.
49 Frank MM, Fries LF. The role of complement in inflammation and phagocytosis. *Immunol Today* 1991; **12**: 322–6.
50 Glovsky MM, Hugli TE, Ishizaka T, Lichtenstein LM, Erickson BW. Anaphylatoxin-induced histamine release from human leukocytes. Studies of C3a leukocyte binding and histamine release. *J Clin Invest* 1979; **64**: 804–11.
51 Brackett DJ, Hamburger SA, Lerner MR *et al.* An assessment of plasma histamine concentrations during documented endotoxic shock. *Agents Actions* 1990; **31**: 263–74.
52 Beer DJ, Rocklin RE. Histamine modulation of lymphocyte biology: membrane receptors, signal transduction, and function. *Crit Rev Immunol* 1987; **7**: 55–91.
53 Sitter H, Lorenz W, Klotter HJ, Duda D, Buess G, Sattler J. Elevated plasma histamine concentration as a sensitive real-time parameter for distinct phases of surgical trauma: a tool for technology assessment. *Agents Actions* 1991; **33**: 203–7.
54 Dohlsten M, Sjögren HO, Carlsson R. Histamine inhibits interferon-gamma production via suppression of interleukin 2 synthesis. *Cell Immunol* 1986; **101**: 493–501.
55 Bury Th, Radermecker M. Role of histamine in the chemotactic deactivation of polymorphonuclear leukocytes following incubation with formylmethionyl peptides. *Int Arch Allergy Appl Immunol* 1992; **97**: 109–14.
56 Sansoni P, Silverman ED, Khan MM, Melmon KL, Engleman EG. Immunoregulatory T cells in man. Histamine-induced suppressor cells are derived from a Leu 2^+ ($T8^+$) subpopulation distinct from that which gives rise to cytotoxic T cells. *J Clin Invest* 1985; **75**: 650–6.
57 Gifford RR, Tilberg AF. Histamine type-2 receptor antagonist immune modulation. II. Cimetidine and ranitidine increase interleukin-2 production. *Surgery* 1987; **102**: 242–7.
58 Shibata M, Hoon D, Okun E, Morton D. Modulation of histamine type II receptors on $CD8^+$ T cells by interleukin-2 and cimetidine. *Int Arch Allergy Appl Immunol* 1992; **97**: 8–16.
59 Nielsen HJ, Hammer JH, Moesgaard F, Kehlet H. Possible role of histamine-2 receptor antagonists as adjuvant treatment in colorectal cancer. Clinical review. *Eur J Surg* 1991; **157**: 437–41.
60 van Zyl JM, Kriegler A, van der Walt BJ. Anti-oxidant properties of H_2-receptor antagonists. Effects on myeloperoxidase-catalysed reactions and hydroxyl radical generation in a ferrous–hydrogen peroxide system. *Biochem Pharmacol* 1993; **45**: 2389–97.