ANNALS OF SURGERY

Vol. 192 November 1980 No. 5

Intravenous Hyperalimentation

Effect on Delayed Cutaneous Hypersensitivity in Cancer Patients

JOHN M. DALY, M.D., STANLEY J. DUDRICK, M.D., EDWARD M. COPELAND, III, M.D.

Effects of nutritional repletion with intravenous hyperalimentation (IVH) on sequential skin test reactivity were evaluated in 160 malnourished cancer patients undergoing chemotherapy (76 patients), surgery (49 patients), radiation therapy (20 patients) and supportive care (15 patients). In the chemotherapy group, 45 patients had negative reactions initially, and 25 patients (55%) had at least one skin test convert to positive in an average period of 19 days of IVH. In the surgery group, 23 patients (46%) were initially positive and remained positive, 13 patients (24%) converted from negative to positive, and 13 patients (30%) remained negative or converted to negative. Postoperative complications occurred in 25% of positive reactors, compared with 69% ($p < 0.01$) of negative reactors. In the radiation therapy group, the skin tests of six patients (30%) remained positive, three patients (15%) converted from negative to positive and the skin tests of nine patients (45%) remained negative. In the supportive care group, the skin tests of 73% of the patients either remained positive or converted to positive with IVH within an average period of 11 days of treatment. Nutritional therapy with IVH was associated with restored skin test reactivity in 51% of malnourished cancer patients undergoing oncologic therapy. Radiation therapy was generally immunosuppressive despite adequate nutritional repletion. In surgical patients, positive skin test reactivity correlated directly with a favorable response to operative therapy.

Presented in part at The American College of Surgeons Clinical Congress Papers Session, Chicago, Illinois, October 23, 1979.

Reprint requests: John M. Daly, M.D., Department of Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, New York 10021.

Supported in part by an American College of Surgeons Schering Scholarship and an American Cancer Society Junior Faculty Clinical Fellowship (Dr. Daly), NIH grant CA-16672 and grants from McGaw and Abbott Laboratories.

Submitted for publication: January 28, 1980.

From The Departments of Surgery, The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute and The University of Texas Medical School at Houston, Texas Medical Center, Houston, Texas

PROGRESSIVE TUMOR GROWTH, hematologic dysfunction, malnutrition and depressed immune function form a common denominator leading to sepsis, organ failure and death in the cancer patient. Interruption of this vicious circle is best accomplished by surgical extirpation of the malignancy and/or inhibition of tumor growth by aggressive chemotherapy and radiation treatment. Often, however, oncologic therapy itself leads to, or is accompanied by, progressive complications such as malnutrition, impaired immunologic function and hematologic abnormalities requiring maximum supportive measures.[17,21]

Impairment of host immunocompetence has been shown to be related to several factors. Clinically, tumor histology and stage of the malignant disease and experimentally, tumor "bulk" have been demonstrated to affect immune function adversely.[11,16] In addition to the malignancy resulting in reduced immune function, anesthesia, operative treatment, radiation therapy and chemotherapy often depress host immunocompetence for prolonged periods.[12,19–22] Recently, malnutrition alone has also been demonstrated clinically and experimentally to result in depressed cell-mediated immunity. Several investigators have shown that immune function returns to normal fol-

0003-4932/80/1100/0587 $00.80 © J. B. Lippincott Company

lowing oral and intravenous nutritional repletion and weight gain.[2-6,9,10,17,20] Elucidation of the specific cause of impaired immunity in cancer patients is difficult because the primary disease, associated conditions such as malnutrition, and the treatment modalities used to eradicate the tumor all interact additively and adversely on the host's immune system.

Several investigators have shown that impairment of immunologic reactivity may have significant prognostic implications in patients with benign disease as well as in patients with cancer.[10,12,13,15] Christou and Meakins found a significant correlation between cell-mediated immunologic reactivity as measured by delayed cutaneous hypersensitivity and survival of medical and surgical patients in a general hospital.[1] Therefore, attempts to improve host immune function by nutritional repletion, tumor eradication and/or nonspecific immune stimulation seem justified in cancer patients. In an attempt to define further the contribution of malnutrition to the suppression of immune function, 160 cancer patients were sequentially evaluated to determine the effect of nutritional repletion with intravenous hyperalimentation (IVH) on established cell-mediated immunity.

Materials and Methods

Patient Selection

One hundred sixty patients with a variety of malignant diseases who were malnourished or whose treatment predictably would result in malnutrition were selected for study. Malnutrition was defined as the combination of any two of the three following criteria: A recent, unintentional weight loss of 10% or more, a serum albumin concentration below 3.5 g/dl or a negative reaction to a battery of five recall skin test antigens. The average patient received 45 kcal/kg and 1.5 g/kg/day* of amino acids along with required amounts of minerals and vitamins by constant intravenous infusion into the superior vena cava during treatment with chemotherapy and radiation therapy, before and/or after operation and as supportive care (nutritional support between courses of cancer therapy). Intravenous fat emulsion† (500 ml) was administered three times per week when needed to prevent essential fatty acid deficiencies. Catheter insertion, solution preparation, metabolic monitoring and sterile maintenance of the IVH delivery system were done according to strict protocol using standard techniques.[3] Patients were allowed oral intake compatible with their clinical condition and treatment program. Intravenous nutritional support was continued until adequate enteral nutrition (2000–2500 kcal/day) could be guaranteed for each patient.

Nutritional Assessment

Nutritional status was assessed prior to beginning IVH. Current body weight was measured, and body weight change (in pounds) was calculated by subtracting current body weight from body weight prior to diagnosis of cancer, or if the patient had a protracted course of oncologic therapy, by subtracting current body weight from maximum body weight within three months prior to admission. Total lymphocyte count was measured by multiplying the percentage of lymphocytes per 100 cell differential by the leukocyte count (cells/mm^3). Serum albumin concentration (g/dl) was determined by serum protein electrophoresis. Cell-mediated immunity was measured by determining delayed cutaneous hypersensitivity to a battery of five recall skin test antigens. One-tenth milliliter each of Varidase® (10 U Streptokinase—2.5 U Streptodornase, Lederle Laboratories, Pearl River, NY), mumps (2 U, Eli Lilly and Company, Indianapolis, IN), Dermatophytin (1:100, Hollister-Steir Laboratories, Spokane, WA), Dermatophytin-O® (1:100, Hollister-Steir Laboratories), and intermediate strength purified protein derivative (5 U, Ormont Drug and Chemical Company, Englewood, NJ) was injected intradermally into the volar aspect of the forearm of each patient prior to starting nutritional repletion and at seven- to 14-day intervals thereafter.[2] Skin tests were evaluated for erythema and induration 24 and 48 hours after injection. A skin test was considered positive if there was 10 × 10 mm of induration 48 hours after injection. Originally negative tests were interpreted as having converted to positive tests if there was at least 10 × 10 mm of induration and if there was a 100% increase in the diameter of induration compared with the negative reaction obtained during initial testing. Patients were considered to have converted from negative to positive reactors if all skin tests were negative initially and at least one test subsequently became positive. Patients were considered to have reverted to negative reactors if at least one skin test had been positive initially, and all tests reverted to negative during treatment. Responses to chemotherapy and radiation therapy were defined as at least a 50% reduction in identifiable tumor mass measured in two diameters and lasting 29 days or longer. In the group undergoing operative therapy, all complications of the surgical procedure, such as pneumonia, sepsis, wound infection or dehiscence, myocardial infarction, pulmonary embolus, or renal failure were tabulated.

* FreAmine, McGaw Laboratories, Santa Ana, CA.

† Intralipid (10%), Cutter Laboratories, CA.

Statistical analysis was performed using the Student's t-test for unpaired data and chi square analysis.

Treatment Categories

Chemotherapy

Seventy-six patients with a mean age of 44 ± 5 years received IVH for an average period of 28 ± 2 days (range: 10–77 days) and underwent chemotherapy as dictated by current institutional drug programs. Sixty-nine patients had metastatic carcinoma: lung—23 patients; gonadal—23 patients; breast—8 patients; gastrointestinal—8 patients; oropharyngeal—6 patients; and bladder—1 patient. Three patients had non-Hodgkin's lymphoma, three patients had metastatic sarcoma, and one patient had metastatic melanoma.

Surgery

Forty-nine patients with a mean age of 60 ± 2 years received IVH for an average period of 25 ± 3 days (range: 6–84 days) prior to and/or following their operative therapy. As shown in Table 1, five patients received IVH only preoperatively for an average period of 14 days; 13 patients received IVH only postoperatively for an average period of 24 days; and 31 patients received IVH for an average period of 27 days both pre- and postoperatively. Overall, 44% of the operative procedures were considered curative.

Radiation Therapy

Twenty patients with a mean age of 54 ± 5 years received radiation therapy (XRT) as primary treatment for their malignant diseases and nutritional repletion with IVH for an average period of 26 ± 3 days (range: 14–58 days). Seven patients had squamous cell carcinoma of the esophagus, four patients had adenocarcinoma or lymphoma of the stomach, three patients had bronchogenic carcinoma, of the lung, two patients had oropharyngeal carcinoma, and one patient each had adenocarcinoma of the pancreas, osteosarcoma of the ribs, Wilms' tumor of the kidney or metastatic carcinoma in the thoracic spine.

TABLE 1. *IVH in Surgery Patients*

Procedure	Pre-operative	Post-operative	Pre- and Post-operative
Neck dissection		1	
Closure pharyngeal fistula			1
Laryngopharyngectomy		1	2
Commando			1
Esophagectomy		3	
Esophagogastrectomy		2	2
Colon interposition	1		5
Total gastrectomy			1
Gastrojejunostomy			5
Pyloroplasty	1		
Exploratory laparotomy	3	1	6
Pancreaticoduodenectomy			1
Choledochojejunostomy		2	
Small bowel resection		1	1
Colectomy		1	1
Colostomy			1
Abdominoperineal resection			2
Cystectomy		1	1
Thoracotomy			1
Total	5	13	31

Numbers indicate number of patients.

TABLE 2. *Tumor Origin in Chemotherapy Patients*

	Remained Positive	Negative to Positive	Remained Negative	Positive to Negative
Lung	14	3	4	2
Gonad	8	10	4	1
Breast	2	3	3	
Gastrointestinal	1	2	3	2
Head and neck		2	3	1
Sarcoma		2	1	
Lymphoma		3		
Melanoma			1	
Bladder			1	

Supportive Care

Fifteen patients with a mean age of 59 ± 4 years received IVH for an average period of 18 ± 1 days (range: 8–28 days) in order to replenish them nutritionally between oncologic treatments prior to future therapy. Eight patients had oropharyngeal carcinoma, two patients had metastatic breast cancer, and one patient each had endometrial carcinoma, squamous carcinoma of the esophagus, leiomyosarcoma, intra-abdominal carcinomatosis and metastatic carcinoma of lung.

Results

Nutritional Status

A moderate to severe degree of malnutrition was present in this series of 160 patients. The mean body weight change prior to nutritional therapy for the entire patient group (160 patients) was −28 ± 3 lb, representing an average body weight loss of 18%. Mean serum albumin concentration at admission was 3.4 ± 0.04 g/dl, and the initial mean total lymphocyte count was 1160 ± 107 cells/mm^3 (normal: >1500 cells/mm^3). Prior to initiation of intravenous nutritional support, only 70 patients (44%) were skin test positive. These patients had lost an average weight of 21 ± 2 lb prior to IVH and had a serum albumin concentration of 3.8 ± 0.1 g/dl. In contrast, patients with negative skin tests had lost an average of 34 ± 2 lb prior to IVH ($p < 0.05$) and had a serum albumin concentration of 3.3 ± 0.1 g/dl ($p < 0.05$).

TABLE 3. *Tumor Response in Evaluable Chemotherapy Patients* (n = 62)

Remained Positive	Negative to Positive	Remained Negative	Positive to Negative
5/21 (24%)	11/21 (52%)	4/14 (28%)	0/6 (0%)
16/42 (38%)		4/20 (20%)	

Chemotherapy

Seventy-six patients received IVH for an average period of 28 days, gained an average of 7 lb, and had a mean rise in serum albumin concentration of 0.3 g/dl (Table 2). Total lymphocyte count was not valid for the chemotherapy patients after IVH and drug treatment because of discrepancies secondary to chemotherapy-induced leukopenia.

Thirty-one patients (41%) initially had positive skin tests and the skin tests of 25 patients remained so during treatment. Those patients whose skin tests converted to negative deteriorated during therapy, usually because of adverse reactions to chemotherapy.

Forty-five patients initially had negative skin tests (59%), and the skin tests of 25 patients (56%) converted to positive during an average period of 19 ± 2 days of IVH. Positive convertors received IVH for an average period of 30 ± 3 days, compared with 26 ± 4 days for those patients whose tests remained negative. Positive convertors gained an average of 8 ± 1 lb, compared with 6 ± 2 lb for negative reactors. Mean serum albumin concentration changes during IVH were similar in both groups. The heterogeneity of disease processes studied made statistical correlation meaningless. There were no significant differences in tumor response rates in patients whose skin tests remained negative, remained positive or converted from negative to positive. However, no patient who converted from positive to negative had a significant tumor response to chemotherapy (Table 3).

Surgery

Forty-nine patients received IVH for an average period of 25 days, gained an average of 7 lb, and had a mean increase in serum albumin concentration of 0.3 g/dl (Table 4). Increase in serum albumin concentration was significant in the group of patients whose skin tests converted from negative to positive, as was the mean increase in total lymphocyte count. Total lymphocyte count fell significantly in those patients whose skin tests converted to negative. Of the five surgical patients who received IVH preoperatively, three patients remained positive reactors, and two patients' reactions converted to positive. Of the thirteen patients who received IVH only postoperatively, five patients had negative skin test reactions initially and were begun on IVH between eight and 74 days (average: 35 days) *after* their operative procedures; these five patients' skin test reactions converted from negative to positive within an average period of 16 days of IVH. Of the 31 patients who received IVH both pre- and postoperatively, 14 patients remained positive reactors, six patients converted initial negative skin tests to positive reactions and ten patients remained negative reactors (Table 5).

There was a significant increase ($p < 0.05$) in the morbidity and mortality of those patients whose skin test reactions remained negative or converted from positive to negative compared with patients whose skin tests remained positive or converted from negative to positive. Overall, 36 patients either remained positive reactors or converted skin test reactions from negative to positive, and nine of these 36 patients (25%) had a significant postoperative complication (Table 6). However, IVH was begun after complications had occurred in two of these nine patients. In 13 patients, skin test reactions either remained negative or converted from positive to negative during IVH. Nine of these 13 patients (69%) had significant postoperative complications, and seven patients died usually due to pneumonia and sepsis.

Radiation Therapy

The 20 radiation therapy patients received IVH for an average period of 26 days, gained an average weight of 6 ± 2 lb, and had an increase in mean serum albumin concentration of 0.1 g/dl. Total lymphocyte count decreased slightly during radiation treatment. Nine pa-

TABLE 4. *Metabolic Response to IVH in Surgery Patients*

	Remained Positive	Negative to Positive	Remained Negative	Positive to Negative
Mean weight gain (lb)	6.3 ± 1.7	7.6 ± 2.8	7.5 ± 2.3	9.0 ± 4.1
Mean serum albumin before IVH (g/dl)	3.5 ± 0.1	3.5 ± 0.1	3.3 ± 0.1	3.1 ± 0.3
Mean serum albumin after IVH (g/dl)	3.5 ± 0.1	4.1 ± 0.1*	3.7 ± 0.2	3.5 ± 0.8
Total lymphocyte count before IVH (cells/mm^3)	917 ± 140	884 ± 49	780 ± 150	919 ± 420
Total lymphocyte count after IVH (cells/mm^3)	1500 ± 412	1220 ± 148*	830 ± 358	365 ± 85*

* $p < 0.05$.

TABLE 5. *Onset and Duration of IVH for Surgical Patients*

	No. Patients	Mean No. IVH Days	Remained Positive	Negative to Positive	Remained Negative	Positive to Negative
Preoperative	5	13.6	3	2	0	0
Postoperative	13	24.1	6	5	1	1
Pre- and postoperative	31	26.6	14	6	10	1

tients (45%) either remained skin test positive or converted from negative to positive during treatment with IVH; 11 patients (55%) either remained skin test negative or converted reactions from positive to negative. Only three of 12 patients (25%) converted initial negative skin test reactions to positive. There was no direct correlation between skin test reactivity and radiation treatment site (Table 7), amount of weight gain or change in serum albumin concentration. Significantly fewer radiation therapy patients (25%) converted their skin test reactivity from negative to positive compared with the other three treatment categories (average: 55%).

Supportive Care

Fifteen patients received IVH for an average period of 18 ± 2 days, gained an average body weight of 6 ± 2 lb, and had a mean increase in serum albumin concentration of 0.3 g/dl. Five of nine negative reactors (56%) converted their skin test reactivity to positive in an average period of 12 ± 2 days. These five patients received IVH for an average period of 17 days, gained an average weight of 6 lb, increased serum albumin levels an average of 0.3 g/dl, and increased mean total lymphocyte counts from 1350 to 1830 cells/mm^3.

Discussion

Impairment of host immune function has been demonstrated clinically to be related to 1) presence of a malignancy; 2) tumor histology[8,11]; 3) tumor stage[8,16]; 4) oncologic treatment such as operative therapy, radiation therapy and chemotherapy[19,21,22]; and 5) associated host conditions, particularly malnutrition.[2,3,9,10,15] Guiliano et al. and Orita et al. found that skin test reactivity to dinitrochlorobenzene was impaired in patients with lung and gastric cancer, respectively, and that impairment in delayed cutaneous hypersensitivity correlated with the stage of disease.[8,16] These investigators did not mention the longitudinal change in nutritional status of their patients. In our study, no significant correlation could be identified between skin test reactivity and tumor burden as estimated by stage of disease, site, and/or number of metastases. However, a correlation between nutritional status and skin test reactivity was apparent and has been documented previously.[7] Eighty-five per cent of our patients who initially had a positive reaction to at least one skin test continued to remain positive reactors throughout nutritional and oncologic treatment; 14.5% of the entire group converted their skin test reactions to negative. Fifty-six per cent of the patients (90/160) initially had negative reactions to the battery of five recall skin test antigens. Overall, 51% of these 90 patients converted at least one skin test to positive during an average period of 16 ± 2 days of nutritional repletion. Compared with major surgical procedures and chemotherapy, radiation therapy results in a more prolonged depression of cell-mediated immunity, which may be related to depressed lymphocyte levels and anatomical area treated.

Progressive tumor growth and oncologic treatment often result in severe malnutrition. Experimentally, Daly et al. have shown that nutritional deprivation depressed *in vivo* skin test reactivity and that nutritional repletion of malnourished tumor-bearing or non-tumor-bearing animals resulted in weight gain and return of immune function to normal.[5,6] Recently, Haffejee and Angorn studied 20 patients with unresectable carcinoma of the esophagus and found that nutritional repletion with reversal of negative nitrogen balance resulted in a significant increase in total lymphocyte count and per cent T-lymphocytes and significant increases in the mitogenic response to phytohemagglutinin.[9] In this group of patients, improvement in immune indices occurred without therapeutic reduction in tumor "bulk." Shizgal evaluated the relationship between immunocompetence and body composition in 60 patients receiving intravenous nutritional support.[20] Twenty-two patients had normal body composition and normal skin test reactivity both before and after IVH. Thirty-eight patients were either anergic or relatively anergic at the onset of IVH, and their body composition measurements were characteristic of malnutrition. Forty-five per cent of these patients (17/38) developed normal skin test re-

TABLE 6. *Surgery Patients: Morbidity and Mortality*

Skin Test Negative (n = 13)	Skin Test Positive (n = 36)
7 died (pneumonia and sepsis)	3 abscess
1 renal failure	3 pneumonia
1 wound dehiscence	1 died (pneumonia)
	1 fistula
	1 postoperative ileus

TABLE 7. *Radiation Therapy—Sites*

Remained Positive	Negative to Positive	Remained Negative	Positive to Negative
4 Mediastinum	2 Gastroesophageal junction	3 Stomach and pancreas	2 Mediastinum
1 Lung hilum	1 Mediastinum	2 Mediastinum	
1 Head and neck		1 Thoracic and lumbar vertebrae	
		1 Whole abdomen	
		1 Head and neck	
		1 Ribs	

activity while receiving IVH, and their body composition indices normalized.

Meakins et al., have recently demonstrated that operative therapy alone would reverse the anergic state if immune depression were secondary to such surgical disorders as undrained pyogenic abscess, intestinal obstruction and cholecystitis.[14] In our series of surgical patients, two patients converted skin tests from negative to positive preoperatively, five patients converted to positive reactors when IVH was started at least eight days after their operative therapy, and three of six patients in the pre- and postoperative group converted to positive reactors after exploratory surgery but without any reduction in tumor bulk or drainage of pyogenic abscesses. In these instances, correction of malnutrition rather than operative therapy seemed responsible for the return of delayed cutaneous hypersensitivity to normal.

Skin test reactivity, weight gain and improvement in serum albumin concentration are probably not ideal indices for evaluation of early improvement in nutritional status since weight gain may reflect expansion of the extracellular space, and albumin synthesis initially may not be manifested as a rise in serum albumin concentration. Similarly, continued skin test anergy probably has multifactorial origins such as tumor "bulk," metabolic stress or sepsis, previous degree of nutritional depletion and/or radiation therapy. Nevertheless, in our malnourished cancer patients, it is obvious that nutritional rehabilitation with IVH was probably responsible for, and at the very least, was associated with return of positive skin test reactivity.

References

1. Christou NV, Meakins JL. Neutrophil function in surgical patients: two inhibitors of granulocyte chemotaxis associated with sepsis. J Surg Res 1979; 26:355.
2. Copeland EM, MacFadyen BV, Dudrick SJ. Effect of intravenous hyperalimentation on established delayed hypersensitivity in the cancer patient. Ann Surg 1976; 184:60.
3. Copeland EM, Daly JM, Ota DM, Dudrick SJ. Nutrition, cancer, and intravenous hyperalimentation. Cancer 1979; 43:2108.
4. Craig F, Ota D, Corriere JN, et al. Effect of protein depletion on serum factors for lymphocyte transformation. Surg Forum (in press 1980).
5. Daly JM, Copeland EM, Dudrick SJ. Effects of intravenous nutrition on tumor growth and host immunocompetence in malnourished animals. Surgery 1978; 84:655.
6. Daly JM, Dudrick SJ, Copeland EM. Effects of protein depletion and repletion on cell-mediated immunity in experimental animals. Ann Surg 1978; 188:791.
7. Daly JM, Dudrick SJ, Copeland EM. Evaluation of nutritional indices as prognostic indicators in the cancer patient. Cancer 1979; 43:925.
8. Guiliano AB, Rangel D, Golub SH, et al. Serum-mediated immunosuppression in lung cancer. Cancer 1979; 43:917.
9. Haffejee AA, Angorn IB. Nutritional status and the nonspecific cellular and humeral immune response in esophageal carcinoma. Ann Surg 1979; 189:475.
10. Harvey KB, Bothe A, Blackburn GL. Nutritional assessment and patient outcome during oncological therapy. Cancer 1979; 43:2065.
11. Hilal EY, Wanebo HJ, Pinsky CM, et al. Immunologic evaluation and prognosis in patients with head and neck cancer. Am J Surg 1977; 134:469.
12. Hersh EN, Whitecar JP, McCredie KB, et al. Chemotherapy, immunocompetence, immunosuppression, and prognosis in acute leukemia. N Engl J Med 1971; 285:1212.
13. Johnson WC, Ulrich F, Meguid MM, et al. Role of delayed hypersensitivity in predicting postoperative morbidity and mortality. Am J Surg 1979; 137:536.
14. Meakins JL, Christou NV, Shizgal HM, MacLean LD. Therapeutic approaches to anergy in surgical patients. Ann Surg 1979; 190:286.
15. Mullen JL, Gertner MH, Buzby GP, et al. Implications of malnutrition in the surgical patient. Arch Surg 1979; 114:121.
16. Orita K, Miwa H, Fukuda H, et al. Preoperative cell-mediated immune status of gastric cancer patients. Cancer 1976; 38:2343.
17. Ota DM, Copeland EM, Corriere JN, Dudrick SJ. The effects of nutrition and treatment of cancer on host immunocompetence. Surg Gynecol Obstet 1979; 148:104.
18. Pietsch JB, Meakins JL, Gotto D, MacLean LD. Delayed hypersensitivity responses: the effect of surgery. J Surg Res 1977; 22:228.
19. Slade MS, Simmons RL, Yunis E, Greenberg LJ. Immunodepression after major surgery in normal patients. Surgery 1975; 78:363.
20. Shizgal HM. Nutrition, immunocompetence, body weight and body composition. Cancer Bull 1978; 30:84.
21. Silverman A, Alexander JC, Potvin C, Chretien PB. Effect of nonthymic irradiation on cellular immunocompetence. Surg Forum 1975; 26:345.
22. Tarpley JL, Potvin C, Chretien PB. Prolonged depression of cellular immunity in cured laryngopharangeal cancer patients treated with radiation therapy. Cancer 1975; 35:638.
23. Twomey PL, Catalona WJ, Chretien PB. Cellular immunity in cured cancer patients. Cancer 1974; 33:435.