

should be noted that the systemic administration of interleukin-2, a lymphoid product, has profound effects on cardiac function and causes marked decreases in systemic vascular resistance, increases in cardiac index, and a mild, reversible myocardial depression, as evidenced in a decreased left ventricular ejection fraction.¹⁻⁴ B cells can respond to interleukin-2 with proliferation, and it has been suggested that malignant B cells may be able to make interleukin-2.⁵ It is possible that the myeloma and the profound decreases in systemic vascular resistance in the patients studied were related to a common causation. Furthermore, it is possible that interleukin-2 itself is not the direct mediator of the effects observed with the pharmacologic administration of interleukin-2. Many cytokines are detectable in the serum after administration of interleukin-2, including gamma interferon, tumor necrosis factor, and interleukin-6.^{6,7} If similar patients are seen in the future, or if serum samples are available from these patients, they may be evaluated for the presence of such cytokines. The results of study in such patients may give important clues about the clinical manifestations of treatment with recombinant cytokines and their use in immunotherapy.⁸

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The above letters were referred to the authors of the article in question, who offer the following reply:

To the Editor: We appreciate the comments of Drs. Leporrier and Lotze. Their inquiries focus on what we believe are two of the most likely explanations for this syndrome — arteriovenous shunting and the production of an as-yet undetected humoral factor.

Autopsy data are now available for two of the reported cases. In the young man, the spleen weighed 225 g and was found to have an increased amount of fibrous tissue and an atrophic white pulp. Although the Billroth's cords were severely distended by the presence of large numbers of plasma cells, there was no evidence of active fistulae. The other patient with available data had a small, shrunken and fibrotic spleen weighing 105 g. The blood flow was not quantitated during life, but these organs showed no evidence of major arteriovenous shunts. The bone marrow — a much larger organ that was diffusely involved in all the patients — appears a more likely candidate.

Dr. Lotze's suggestions are intriguing, and parallel some of our own thoughts. We agree that measurements of selected cytokines should be obtained in these patients.

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SYSTEMIC REACTION TO THE ANTI-T-CELL MONOCLONAL ANTIBODY OKT3 IN RELATION TO SERUM LEVELS OF TUMOR NECROSIS FACTOR AND INTERFERON- α

To the Editor: One major side effect associated with the in vivo use of the murine monoclonal antibody OKT3 is the spontaneously reversible systemic clinical reaction that is invariably associated with the first one or two injections of the antibody.¹ The systemic reaction includes chills, headache, pyrexia, vomiting, diarrhea, and tachycardia. Pulmonary edema has been described in a few patients with fluid overload.¹ Since this group of symptoms closely resembles that induced by the injection of pure recombinant cytokines,^{2,3} we tested the hypothesis that the OKT3 syndrome could be related to a massive release of some of these highly biologically active mediators.

We studied 17 recipients of renal allografts who received OKT3 six to eight hours before transplantation surgery. Fourteen of the 17 received OKT3 (5 mg per day intravenously) together with steroids (0.25 mg per kilogram of body weight per day) and azathioprine (3 mg per kilogram per day). Methylprednisolone (1 g) was administered one to three hours before the first OKT3 injection. Steroids were not given to the other three patients, who received a haplo-identical graft from a family member. Blood samples were obtained before and one and four hours after the first, second, and third OKT3 injections. Tumor necrosis factor (TNF α), interleukin-1 β , interferon- α , interleukin-2, and interferon- γ were measured with specific radioimmunoassays.^{4,5}

The results showed that the first OKT3 injection, and only the first one, induced a sharp increase in circulating serum levels of TNF α and interferon- γ (Table 1). In the three patients in whom the use of steroids had been avoided, interleukin-2 was also detected in serum. In none of the patients was it possible to detect either serum interleukin-1 β or interferon- α . Peak levels of TNF α were reached one hour after the first injection. Interferon- γ and, when present, interleukin-2 reached maximal levels at four hours. By 15 to 20 hours after the first injection, serum levels of TNF α , interferon- γ , and interleukin-2 had returned to pretreatment values.

Two main, not mutually exclusive mechanisms could explain these results: T-cell opsonization and subsequent trapping or lympholysis (or both) of OKT3-coated cells; or the specific capacity of OKT3 to induce T-cell activation, just as it induces T-cell mitogenesis in vitro. The arguments against exclusive responsibility of the

opsonization-lympholysis mechanism are that other opsonizing anti-T-cell monoclonal antibodies do not provoke an OKT3-like clinical syndrome^{6,7} and that, as recently shown, exclusive in vivo endotoxin-mediated monocyte-macrophage activation induces systemic release of TNF α but not of interferon- γ .⁸ The presence of interferon- γ and interleukin-2, exclusively of T-cell origin, in the serum of OKT3-treated patients is compatible with the hypothesis of ongoing T-cell activation in vivo. The presence of high serum levels of TNF α , interferon- γ , and interleukin-2 correlates well with the duration of the clinical reaction that is self-limited after the first injection of OKT3. The highest levels of TNF α and interferon- γ were detected in the patients who did not receive corticoids before OKT3; corticoids are administered to decrease the intensity of the systemic reaction. These results provide a plausible explanation for a major side effect of a widely used immunosuppressive agent and allow the possibility of preventive procedures, notably the use of antibodies to neutralize the cytokines directly implicated in the reaction.

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URINARY INCONTINENCE AMONG ELDERLY PERSONS

To the Editor: In their study of urinary incontinence in persons over the age of 65 (Jan. 5 issue),* Resnick et al. report a high

*Resnick NM, Yalla SV, Laurino E. The pathophysiology of urinary incontinence among institutionalized elderly patients. *N Engl J Med* 1989; 320:1-7.

percentage of detrusor overactivity (61 percent). Only 21 percent of their patients had stress incontinence. In 1988, 399 women underwent urodynamic studies (conforming to the standards of the International Continence Society) in the Department of Gynecology and Obstetrics at the University Hospital of Innsbruck; 36 patients (9 percent) were more than 65 years of age (range, 65 to 81). O diagnoses in this group of elderly persons differ from the findings of Resnick et al.

Our predominant diagnosis was stress incontinence in 78 percent (28 patients), whereas only 14 percent had urge incontinence and percent had urgency. In 33 percent there were two coexisting diagnoses: stress incontinence combined with either urge incontinence (14 percent) or urgency (19 percent). Other urodynamic diagnoses were low urethral-closure pressure at rest (44 percent), good pressure-transmission ratio (33 percent), poor pressure-transmission ratio (67 percent), and urethral instability (25 percent). The compliance was entirely in the normal range. The diagnostic findings of our elderly patients differed from the results in the younger patients in only two respects. The younger patients more often had urethral instability (13 percent) or a combination of stress and urge incontinence (6 percent). In two thirds of the patients, gynecologic examination showed a vaginal descensus, and in one patient a prolapsed findings again similar to those in younger patients with incontinence.

Fifty percent of our elderly patients had undergone genitourinary surgery: dilation of the urethra (11 percent), anterior repair (3 percent), or a Marshall-Marchetti-Krantz operation (3 percent). Thus, our data do not confirm the findings of Resnick et al. concerning the prevalence of detrusor overactivity as a cause of incontinence in elderly women. In our experience, low urethral-closure pressure, which can be improved neither by vaginal repair nor abdominal-incontinence surgery, is the main cause of incontinence in elderly women.

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To the Editor: Determination of the pathophysiology of incontinence is the first step in the development of effective treatment. This important condition, which has considerable associated economic costs. However, I would like to add a note of caution: the light of the knowledge Resnick's study adds to our understanding of the pathophysiology of incontinence, the sensitivity and specificity of these investigations in producing clinical improvement with respect to continence need to be examined. The results should be compared, possibly, with those of clinical evaluation plus urometry, and with those of clinical bedside evaluation plus estimation of residual urine.

Those of us involved in the care of the elderly should await description of effective interventions before allowing frail elderly patients in nursing homes to be subjected to urodynamic investigation for established urinary incontinence that has been present sometimes for years.

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The above letters were referred to the authors of the article in question, who offer the following reply:

To the Editor: We thank the authors of both letters for their comments. The letter from Drs. Andler and Kölle illustrates the problems we tried to address. First, their data on 36 patients both supports and opposes the findings in case series reports previously¹ and adds to the small supply of available data. How would be difficult to extrapolate their findings for use in a community population, since their patients were probably 20 years younger, less impaired, not institutionalized, and drawn from a gynecologic referral practice. In fact, it was for this reason that