

drug seems to interfere with the maturation of selected classes of thymocytes.⁸ In addition, there is evidence that the mechanisms of GVHD may in fact be normal physiologic processes in the induction and maintenance of self-tolerance.⁴

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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: Dr. Schmidt and colleagues present data that by and large confirm our results. Their letter does not tell us, however, whether cyclosporine was given as a continuous infusion or as a “bolus infusion,” or the point at which GVHD developed — i.e., cyclosporine levels are expressed relative to the development of GVHD, not relative to transplantation. The latter would be of interest, since cyclosporine levels, even in the patients in whom GVHD developed, tended to be higher than in our study. For the same reason, it would be of interest to know whether patients were conditioned with chemotherapy alone or chemotherapy combined with irradiation, since gastrointestinal toxicity and recovery might differ, thus leading to differences in absorption and possibly hepatic metabolism.^{1,2}

Dr. Glazier's letter addressed questions that go beyond the scope of our study. We agree that the literature on the effect of cyclosporine on self-tolerance is quite convincing in the rat model,^{3,4} although the results in mice have been controversial.^{5,6} Nevertheless, recent data obtained in a mouse model show convincingly that cyclosporine inhibits the differentiation of thymocytes into mature CD4+8- or CD4-8+ T-cell-receptor $\alpha\beta$ + T cells and interferes with the deletion of cells expressing self-reactive T-cell-receptor specificities.⁷ Under certain conditions these changes could be responsible for undesired self-reactivity and the development of pseudo-GVHD even after transplantation of syngeneic or autologous marrow.^{3,4,8} We should emphasize, however, that recipients of autologous and syngeneic transplants generally do not receive cyclosporine after transplantation. However, considering such a mechanism, the statement of Schmidt and colleagues that “despite this immunosuppression,” GVHD developed in 18 patients could perhaps have read “because of this immunosuppression. . . .”^{9,10} As stated by Dr. Glazier, the mechanism appears to be rather complex, in the light of the involvement of the thymus, the conditioning regimen, and the age of the recipient.^{5,11} Randomized studies comparing methotrexate and cyclosporine have generally shown no differences in the incidence of GVHD.¹² Conceivably, what is gained with cyclosporine with regard to alloaggression is lost to autoimmunity,^{9,10,13} leading some investigators to conclude that there may not be a therapeutic window for cyclosporine.¹⁴ It would seem possible, then, that the addition of a short course of methotrexate to cyclosporine, which

has resulted in a clear reduction in the incidence of GVHD,^{15,16} is effective because methotrexate interferes with autoreactivity.

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ABNORMAL T-CELL SUBSETS IN NORMAL PERSONS

To the Editor: Abnormalities in the display of distinctive differentiation markers (CD4 or CD8) on T-cell subsets have been shown to correlate with the progression of human immunodeficiency virus (HIV)-related disease. In California, the measurement of T-cell subsets is being used by the insurance industry to screen the general population before the issuance of life or disability insurance, to avoid insuring apparently healthy persons with occult HIV infection. The use of this indirect test has produced a group of healthy persons who are unable to obtain life or disability insurance. At the University of California at Los Angeles School of Medicine, the reference ranges for the number of CD4 cells (430 to 1367 per cubic millimeter), the number of CD8 cells (205 to 717 per cubic millimeter), and the ratio of CD4 to CD8 (1.00 to 3.15) were established as the 5th to 95th percentile of a large cohort of normal healthy persons, with the result that 5 percent of healthy persons

were arbitrarily defined as having low and therefore abnormal values. This has provoked needless anxiety and consternation among persons so labeled and has challenged their physicians, who have been asked to prove that these stigmatized persons are not harboring occult HIV.

We propose the use of the following protocol to establish with reasonable certainty that a person with an abnormal result on a T-cell-subset determination is not infected with HIV: (1) a history documenting the absence of HIV infection-related symptoms and risk factors for the acquisition of HIV, and a physical examination showing no positive findings for HIV-related disease and (2) an enzyme-linked immunosorbent assay (ELISA) giving negative results for the HIV antibody (cost, \$7 to \$26). If this evaluation provides no evidence of HIV infection, the workup should be considered complete. Further testing will only waste money without notably altering the odds of establishing the presence of HIV infection. A negative history, physical examination result, and HIV ELISA should be adequate to assure both patients and insurance companies that the odds of HIV infection are less than 1 in 100,000 on the basis of current estimates of the incidence of HIV infection in the United States and the sensitivity and specificity of commercial HIV ELISAs.

Further laboratory testing should be pursued only in the setting of definite risk factors or physical findings suggestive of HIV infection and a negative HIV ELISA. To document the ability to produce antibody, the following measurements should be obtained: (3a) quantitation of immunoglobulin levels (cost, \$50 to \$70) or the IgG level (cost, \$15 to \$25), to show that the person has normal levels of immunoglobulin, and (3b) levels of antigen-specific antibody, such as antitetanus IgG levels before and after booster immunization (cost, \$30 to \$65). The ability to produce antigen-specific antibody greatly lowers the risk of a false negative HIV ELISA.

If the patient does have an abnormality in the ability to produce antibody or has risk factors and a negative HIV ELISA, a (4) polymerase chain reaction for HIV (cost, \$130 to \$150) should be performed. This technique will document the presence of HIV-specific nucleic acid, with extremely high sensitivity. Although this test should be the "gold standard" for the detection of occult HIV, a potential problem is that the sensitivity and specificity of this test are not well established at some commercial laboratories.

We believe that the following tests to rule out occult HIV infections should not be ordered outside of research settings, because of their high cost or low sensitivity and specificity: the determination of free serum HIV p24 levels (cost, \$50 to \$100), Western blot testing or HIVAGN testing in the setting of a negative HIV ELISA (cost, \$40 to \$90), or HIV viral coculture with normal phytohemagglutinin lymphocyte blasts and subsequent measurements of p24 production or reverse transcriptase activity (cost, \$200 to \$400). In the absence of a history of a specific infection or illness or major abnormalities on a physical examination, it is not worthwhile to attempt to find a specific cause for the abnormality of T-cell subsets. If an abnormal ratio of CD4 to CD8 is found that is secondary to non-HIV viral infection, then a repeated T-cell subset determination (cost, \$75 to \$260) performed 6 to 12 months later should show that the ratio has returned to normal. In a subgroup of patients, the low T-cell numbers or ratios appear to be stable findings (unpublished data). A uniform approach to this problem throughout the medical community will help alleviate patients' anxiety and reduce the concern of the insurance industry about this relatively common problem.

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HYPOGLYCEMIA IN HYPERTENSIVE DIABETIC PATIENTS TREATED WITH SULFONYLUREAS, BIGUANIDES, AND CAPTOPRIL

To the Editor: The need for early antihypertensive intervention in non-insulin-dependent diabetes (NIDDM) is becoming more and more accepted.¹ In contrast to all other hypotensive agents, angiotensin-converting enzyme inhibitors exert a marginal beneficial effect on metabolic control in NIDDM^{2,3} that apparently does not

increase the incidence of hypoglycemia in combination with sulfonylureas. The only anecdotal report of hypoglycemic episodes⁴ has not been confirmed by other investigators. We have seen two cases of unexpected hypoglycemia that developed when captopril was added to a regimen of sulfonylureas and biguanides for NIDDM.

A 49-year-old woman with a 14-year history of diabetes, a 4-year history of hypertension, a body-mass index of 30.8, a hemoglobin A_{1c} level of 12.7 percent, albuminuria (10 mg per gram of creatinine), Grade I diabetic retinopathy, and Grade II hypertensive retinopathy was given captopril (50 mg per day) because of hypertension. She had been receiving a fixed combination of glyburide (glibenclamide; 10.5 mg per day) and metformin (1700 mg per day), which resulted in stable but poor metabolic control. She had never had any hypoglycemic reactions, but 24 hours after receiving captopril, she had hypoglycemic symptoms and a blood glucose level of 2.2 mmol per liter, which continued for three consecutive days despite a reduction in the doses of the oral antidiabetic agents.

A 59-year-old man with a 13-year history of diabetes, a 5-year history of hypertension, a body-mass index of 29.7, a hemoglobin A_{1c} level of 10.6 percent, albuminuria (86 mg per gram of creatinine), Grade I diabetic retinopathy, and Grade II hypertensive retinopathy received the same therapy for diabetes. The metabolic control was poor, with glucose concentrations constantly above 13 mmol per liter. Forty-eight hours after receiving captopril, the patient had a blood glucose nadir of 2.9 mmol per liter and hypoglycemic symptoms. Oral antidiabetic treatment had to be stopped.

These observations may indicate an additive synergistic hypoglycemic effect due to the combination of three drugs with the capacity to lower blood glucose levels. Although glyburide is known to stimulate insulin secretion and to improve insulin action after the binding capacity has been reached,⁵ metformin increases muscular glucose use⁶ and blocks hepatic gluconeogenesis.⁷ Angiotensin-converting enzyme inhibitors increase the muscular glucose disposal rate,³ an effect that may be mediated by kinins, which also have been shown to decrease hepatic glucose output.⁸ Thus, when angiotensin-converting enzyme inhibitors are given together with biguanides and sulfonylureas, different hypoglycemic mechanisms may act together and potentiate the effects of each drug.

On the basis of our observations, we think that physicians should be aware of this potential additive effect and should consider close monitoring of blood glucose levels and early reductions in doses of oral antidiabetic agents.

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HLA AND IgA NEPHRITIS REVISITED 10 YEARS LATER: HLA-B35 ANTIGEN AS A PROGNOSTIC FACTOR

To the Editor: In 1978 in the *Journal*, we reported that the frequency of HLA-B35 antigen was increased among 43 patients with idiopathic mesangial IgA glomerulonephritis, as compared with 105