therapy frequently causes a major reduction in serum testosterone levels and that this effect appears to be mediated by suppression of the secretion of gonadotrophin-releasing hormone (GnRH) by the hypothalamus.

Methods

We studied 16 men with chronic obstructive pulmonary disease (mean age, 67 ± 4 [SD] years) who had been taking either prednisone or methylprednisolone for at least 1 month and who had been on a stable dosage of glucocorticoid for at least 1 week. No patient had any physical signs or history of hypothalamic, pituitary, or gonadal disease preceding the start of glucocorticoid therapy. Eight patients were being treated on a daily basis, and 8 patients were receiving doses on alternate days.

Eleven age-matched (mean age, 64 ± 5 years) and disease-matched patients not receiving glucocorticoid therapy were selected as controls. The forced expiratory volume in 1 second in the patients receiving steroids (1.1 ± 0.4 L) was not significantly different from that in the control group (1.3 ± 1.0 L).

All patients were receiving multiple medications, which invariably included a theophylline preparation and a beta-adrenergic agonist. No patient receiving a gonadal steroid preparation was included. The average number of medications taken, other than glucocorticoids, was five in both groups. Because morbid obesity reduces serum testosterone levels by altering protein binding (7), patients whose weight was greater than

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terone level was analyzed with Pearson's correlation coefficient. For the purpose of this analysis, we assumed that the relative potencies of prednisone and methylprednisolone were, on a weight basis, equal. The average daily glucocorticoid dosage in patients given alternate-day treatment was defined as one half of the total glucocorticoid dose taken every 2 days. Data are presented as means ± SD. The protocol was approved by the Human Subjects Review Committee at the University of California, Davis, School of Medicine.

Results

TESTOSTERONE LEVELS

As shown in Figure 1A, the mean total level of serum testosterone in the control group was 449 ± 111 ng/dL. Only 1 of these 11 men had a testosterone level below 300 ng/dL. In contrast, the mean level in the patients taking glucocorticoid was significantly lower, 211 ± 92 ng/dL ($p < 0.0001$). Of these 16 patients, only 2 had testosterone levels above 300 ng/dL.

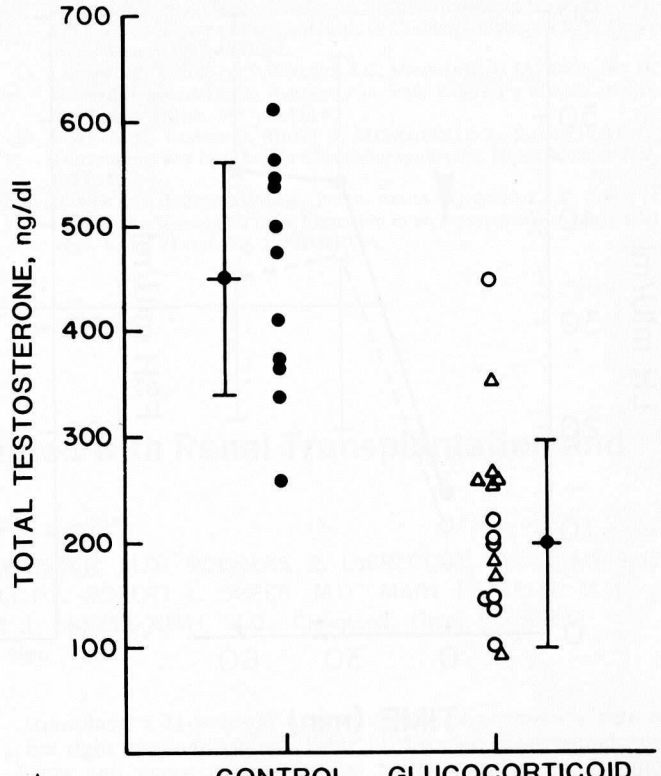
The mean testosterone level in the patients who were receiving a fixed dose of glucocorticoid each day (mean, 24 mg/d) was 195 ± 108 ng/dL, which was not significantly different from the level of 226 ± 78 ng/dL in the patients who were receiving alternate-day treatments (mean dose of 23 mg alternating with 3 mg every other day). However, as indicated in Figure 1B, the average

daily dosage of prednisone or methylprednisolone was inversely related to the testosterone level ($r = -0.78$). The mean serum testosterone level in patients receiving a "low" dose of corticosteroid (15 mg/d or less), 270 ± 89 ng/dL, was significantly reduced when compared to that of the control patients ($p < 0.01$) and was significantly greater ($p < 0.01$) than the mean testosterone level of 137 ± 68 ng/dL in patients taking more than 15 mg/d of prednisone or methylprednisolone.

The percentage of total testosterone not bound to protein was assayed in 13 glucocorticoid-treated patients and in 10 control patients. Our findings showed no significant difference between the two groups: 1.8 ± 0.6% unbound testosterone in the glucocorticoid-treated patients and 1.5 ± 0.5% in the control patients.

LUTEINIZING AND FOLLICLE-STIMULATING HORMONE LEVELS

In six patients treated with glucocorticoid and in six control patients, basal and GnRH-stimulated luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels were measured (Figure 2). Basal LH (14 ± 2 mIU/mL) and FSH levels (19 ± 5 mIU/mL) in the control group were not significantly different from the basal LH (11 ± 4 mIU/mL) and FSH levels (12 ± 7 mIU/mL) in the glucocorticoid-treated group, despite



potentiated the effect we observed of chronic glucocorticoid therapy on the serum testosterone level.

Previous reports have shown that glucocorticoids produce a direct suppressive effect on gonadal steroid secretion (1, 2, 4, 5). If this mechanism were the only one responsible for the reduction in the serum testosterone levels that we observed, baseline gonadotrophin levels should have been elevated. The finding of normal FSH and LH levels indicates that glucocorticoid therapy suppresses the secretion of LH and FSH by the pituitary gland, although it does not exclude a coexistent suppression of testicular function. When synthetic GnRH was administered and the LH and FSH secretory responses monitored, no significant differences between glucocorticoid-treated patients and eugonadal control patients were found, indicating an intact pituitary response. Although these data do not exclude a more subtle direct inhibition of pituitary gonadotrophin secretion in glucocorticoid-treated men, as has been reported in glucocorticoid-treated women (6), they clearly indicate that glucocorticoid therapy exerts a suppressive influence on the secretion of GnRH by the hypothalamus.

Our findings may have some important clinical ramifications. For example, in glucocorticoid-treated men with chronic lung disease, the frequent occurrence of impotency in glucocorticoid-treated men may be a useful adjunct to prevent and treat glucocorticoid-associated osteoporosis. Regardless of the biologic effects of glucocorticoid-induced suppression of the serum testosterone level, clinicians should be aware of this phenomenon and recognize it as one of the causes of a low serum testosterone level.

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Hepatic Veno-occlusive Disease Associated with Renal Transplantation and Azathioprine Therapy

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Four patients with renal transplants developed hepatic veno-occlusive disease after immunosuppressive therapy with azathioprine. Severe progressive portal hypertension developed in all patients, with the clinical presentation varying from a mild viral-like syndrome to rapidly fulminant liver failure and death. The disease was associated with cytomegalovirus infection but not with the dose of azathioprine, the type or duration of transplant, or the type of underlying kidney disease. In view of the high mortality rate associated with veno-occlusive disease (a combined 55% in our four patients and in five reported in the literature) and wide spectrum of clinical presentation in patients with renal transplants, a high index of suspicion is required and aggressive intervention indicated.

HEPATIC VENO-OCCLUSIVE DISEASE is a nonthrombotic obliterative process of the central or sublobular hepatic veins (1) that is characterized by ascites, hepatomegaly, and a varied clinical outcome. Worldwide, the hepatotoxic pyrrolizidine alkaloids that occur naturally in plants are its most frequent cause (2-7). However, in the United States, chemotherapy (8-10) and irradiation (11, 12), especially in patients who have had bone marrow transplants (13-17), appear to be the commonest causes.

We describe hepatic veno-occlusive disease in four patients with renal transplants who were treated with azathioprine. We also have reviewed the literature and emphasize the importance of recognizing this potentially fatal disease in a continuously enlarging pool of patients.

Case Histories

PATIENT 1

After 9 years of being maintained on daily treatments with azathioprine (125 mg) and prednisone (10 mg) for her renal transplant, a 31-year-old woman developed nonspecific pain in her right upper abdomen (Table 1). Esophagogastroduodenoscopy and upper gastrointestinal barium studies had normal findings, but an abdominal ultrasound revealed diffuse hepatic parenchymal abnormalities and an enlarged portal vein. A computed tomographic (CT) scan of the abdomen showed hepatosplenomegaly, and a liver-spleen radionuclide scan revealed diffuse parenchymal disease with increased bone marrow activity. The hepatic veins and inferior vena cava were patent on both the ultrasound and CT scan. Serum aminotransferase levels were elevated twofold, but the serum bilirubin and alkaline phosphatase levels were normal. Cytomegalovirus titers were positive (1:256), but serologic tests for hepatitis A, hepatitis B, and Epstein-Barr virus were negative. Autoantibodies (antinuclear, antismooth muscle, and antimitochondrial) were also absent. Liver biopsy results were consistent with veno-occlusive disease (Table 2).

Azathioprine therapy was discontinued for 6 months but was reinitiated at 25 mg/d because of renal allograft rejection. Fifteen months after an episode of hematemesis, an upper endoscopic examination showed esophageal varices for the first time. Repeat liver biopsy studies showed the histologic changes of veno-occlusive disease similar to those on the first biopsy but less severe. Cyclophosphamide (100 mg/d) was substituted for azathioprine, and the patient has done well for 30 months.

PATIENT 2

After renal transplantation, a 53-year-old man received daily immunosuppressive treatments with azathioprine (150 mg) and prednisone (20 mg) (Table 1). Six months later, fatigue, jaundice, and ascites developed. Liver function tests revealed total and direct bilirubin levels of 11.8 and 9.2 mg/dL, respectively, an aspartate aminotransferase level of 116 U/L (laboratory normal, 31), and an alkaline phosphatase level of 456 U/L (normal, <200). Serologic tests for hepatitis A and B were negative, but a test for cytomegalovirus was positive at a titer of 1:10. Abdominal ultrasound and CT scanning showed hepatomegaly and ascites. Cyclophosphamide (125 mg/d) was substituted for azathioprine. After 4 months without improvement, a liver biopsy was done and showed histopathologic findings consistent with veno-occlusive disease (Table 2). An endoscopic retrograde cholangiogram was normal, as was a venogram of the large hepatic veins and inferior vena cava. The patient died 2 months later of progressive hepatic failure.

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