vention Trial, funded by the National Heart, Lung, and Blood Institute. The Cleveland Clinic Lipid Research Clinic and four other clinical centers will evaluate the effects of cholesterol-lowering and antithrombosis therapy on the rate of stenosis and patency of aortocoronary saphenous vein grafts. The trial, to involve 1,200 patients, will compare high- with low-dose lovastatin therapy, and low-dose anticoagulation with placebo.

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INTERFERON FOR CHRONIC HEPATITIS

Until recently, the treatment of chronic viral hepatitis was entirely supportive, with no practical therapy that could be directed against the underlying hepatic infection. The recent promise shown by interferons against some cases of chronic viral hepatitis signals a new era in the treatment of this disorder.

RATIONALE FOR THERAPY

Interferons are approved by the Food and Drug Administration for use in hairy-cell leukemia and approval is being sought for their use in chronic hepatitis C. Interferons are glycoproteins whose production in the body is stimulated by a variety of viruses, including those that cause hepatitis. Liver biopsies from patients with chronic active hepatitis demonstrate focal clusters of alpha interferon-containing mononuclear cells and fibroblasts, and interferon may be briefly detected in the serum within a few weeks of exposure to hepatitis B.

Chronic hepatitis develops when the infection fails to clear, possibly because of a deficiency in interferon production. Accordingly, the administration of exogenous interferon may result in improvement.

CHRONIC HEPATITIS B

Although hepatitis B usually resolves spontaneously, there is enthusiasm now for immunoregulatory therapy, especially interferon. It is unknown whether one preparation is better than another, what the optimal dosage and duration of therapy may be, and whether the promising short-term benefits of interferon will be sustained long after treatment is stopped.

A promising regimen employs pretreatment with prednisone, 60 mg per day, for 2 weeks, and then tapered by 20 mg every 2 weeks. This is followed by the administration of alpha interferon, 5 million units daily for 3 months. This regimen resulted in a 44% clearance of viral B replication and improved liver histology; in 50% of patients, liver enzymes remained normal after treatment was stopped. The hepatitis B surface antigen (HBsAg) usually remains positive during and after therapy, but markers of viral replication, including the hepatitis B e antigen (HBeAg), hepatitis B virus DNA, and DNA polymerase may disappear.

A recent multicenter randomized trial confirmed the benefits of alpha interferon and suggested that pretreatment with prednisone was not statistically significantly better than the use of interferon alone. Many investigators use longer treatment periods, from 6 to 9 months.

It is not unusual for clinical hepatitis to flare during interferon treatment. Such a flare could have serious consequences for the patient with advanced cirrhosis because of the lack of hepatic reserve, and treatment probably should be withheld from these patients.

Unfortunately, only a minority of patients with chronic hepatitis B will benefit from interferon therapy. Those less likely to respond include males, patients who are HIV positive, individuals of Chinese descent, and patients with childhood onset of disease. Patients with high levels of viral replication also respond less often.

CHRONIC HEPATITIS C

Interferons show promise for some patients with hepatitis C. The dosages are usually lower than those used for hepatitis B. In one multicenter, 26-week study, 180 patients with chronic hepatitis C were randomized to receive 1 million units three times a week, 3 million units three times a week, or no treatment. The pretreatment SGPT averaged 175 U/L and this value fell to a mean of 95 U/L at a dose-dependent response rate. At the end of the trial, 46% of the high-dose group and 28% of the low-dose group had normal or near-normal SGPT levels. Among those who responded to treatment, nearly one

half had a relapse after cessation of therapy. Only 8% in the control group showed a "response."

Serologic and tissue markers for antigens associated with hepatitis C have not yet been developed, so it is difficult to diagnose hepatitis C with certainty. An antibody directed against one or more antigens from the C virus will soon be released for general use. Until then, the diagnosis of hepatitis C remains presumptive, based on exposure to blood or blood products. It is a mistake to assume that all cases of chronic hepatitis without B markers represent hepatitis C. The diagnosis should be considered only in patients with suitable epidemiologic risk factors (and those who test positive for the C antibody when this test becomes available).

SIDE EFFECTS

Side effects are frequent with interferon. Most are not serious and are reversible with dosage reduction or cessation of therapy. Flulike symptoms, including muscle and joint aches, fatigue, nausea, and malaise, develop in most patients and usually abate after a week or two. Leukopenia may occur and, if unrecognized, can be serious in the event of bacterial superinfection. This is rare at the dosage used for treatment of hepatitis. Depression may be severe, and is most likely to be troublesome in patients with a history of depression. Diarrhea may occur in one third of treated patients and mild alopecia in nearly one fourth. Hypo- and hyperthyroidism have recently been described in hepatitis patients treated with interferon. Whether this is caused by the drug or is merely a coincidence is unknown.

UNRESOLVED ISSUES

Opinion is divided regarding the wisdom of widescale use of these drugs outside of a research setting. Interferons are expensive and their administration is cumbersome. Although the drug should not be withheld if it appears to be indicated, it is probably best to refer these patients for treatment under research protocols. If none exist, it is justifiable to make this treatment option available to the patient, although interferon therapy is best monitored by a gastroenterologist or a hepatologist.

The dosage and duration of therapy are unsettled. Studies that use higher dosages have higher success rates, and longer courses of therapy appear to be superior to shorter ones. Retreatment schedules for those who relapse after therapy are just now being settled. Although retreatment appears to be successful, its duration and cost remain sources of concern. The long-term benefits also are unknown. It will be many years before we know whether interferon therapy is associated with fewer complications, including cirrhosis, decompensated cirrhosis, hepatoma, and death or need for transplantation.

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MILESTONES IN THE TREATMENT OF BREAST CANCER

Today's treatment of breast cancer reflects our improved understanding of tumor biology. The principles of treatment have evolved from the "Halstedian" concept of tumor growth to consideration of breast cancer as a systemic disease at its onset. Accordingly, we treat the regional as well as the systemic disease, with new appreciation for the value of adjuvant chemotherapy.

Early detection of any malignancy, including breast cancer, has a positive effect on survival. Periodic breast self-examination (BSE) is associated with a lower probability of positive axillary nodes at the time of diagnosis (47% *v* 63%), lower probability of distant metastases (2.7% *v* 14.6%), smaller tumors (2.5 cm *v* 3.3 cm), and improved 5-year survival (75% *v* 57%). The survival advantage remains even after we account for "lead-time bias," whereby early clinical detection of cancer can give the appearance of improved survival.

Mammography detects smaller cancers (32% less than 1 cm, Breast Cancer Detection Demonstration Project [BCDDP]), which have a lower probability of positive axillary nodes (20%, BCDDP); this translates into lower mortality (30% in the breast screening project of the Health Insurance Plan of Greater New York).

These data led the American Cancer Society to recommend the following for breast cancer screening: monthly BSE after age 20; examination by a physician every 3 years between ages 20 and 40 and every year after age 40; baseline mammography between ages 35 and 39; and screening mammography every 1 to 2 years