erally thought that liver blood flow is reduced in cirrhosis, a recent review of the literature on highly extracted drugs[4] suggests that blood flow is often unchanged and that hepatic extraction and intrinsic clearance are reduced. In patients with reduced flow, intrinsic clearance was reduced to an even greater extent, suggesting that the clearance effect is the more important factor.

Highly extracted drugs are also subject to considerable presystemic (or first-pass) elimination during their passage from the gut to the systemic circulation in portal venous blood. Thus, reduced hepatic extraction and any extrahepatic shunting of blood in the mesenteric vein[5] will greatly increase the bioavailability of such drugs after oral administration.

Although the effects of liver disease on drug disposition can now be rationalized and quantified, several problems remain: not all drugs seem to be affected, even when the same biochemical pathway is apparently involved; even in liver disease, the drug-metabolizing enzymes can be induced by other drugs, leading to relatively normal clearance; and defects in drug metabolism correlate poorly with routine liver-function tests, except perhaps with reduced serum albumin and prolonged prothrombin time, which may reflect poor protein synthesis, including the metabolizing enzymes.[6] Until some of these problems are resolved and a good predictive test developed, the clinician must be guided by a knowledge that drug disposition may be altered in such patients. Although such aids as plasma-level monitoring may be helpful, there is no substitute for adjusting drug dosage according to the patient's response, for the effectiveness of any given drug concentration may also be altered, as a result of altered receptor sensitivity.

Vanderbilt University
Nashville, TN 37232 DAVID G. SHAND, PH.D., M.B.

REFERENCES

1. Wilkinson GR, Schenker S: The effects of liver disease on drug disposition in man. Biochem Pharmacol 25:2675-2681, 1976
2. Wilkinson GR, Shand DG: A physiological approach to hepatic drug clearance. Clin Pharmacol Ther 18:377-390, 1975
3. Branch RA, James J, Read AE: A study of factors influencing drug disposition in chronic liver disease, using the model drug (+)-propranolol. Br J Clin Pharmacol 3:243-249, 1976
4. Branch RA, Shand DG: Propranolol in chronic liver disease, a physiological approach. Clin Pharmacokinet 1:264-279, 1976
5. Gugler R, Lain P, Azarnoff DL: Effect of portacaval shunt on the disposition of drugs with and without first-pass effect. J Pharmacol Exp Ther 195:416-423, 1975
6. Branch RA, Herbert CM, Read AE: Determinants of serum antipyrine half-lives in patients with liver disease. Gut 14:569-573, 1973

HEPATITIS B VIRUS AND ANTIGEN-ANTIBODY COMPLEX DISEASES

INFECTION with the hepatitis B virus (HBV) can induce a variety of responses in human beings. Physicians generally think first of acute hepatitis, a disease characterized by a relatively long incubation period, the appearance in the blood, during the prodromal and acute phases, of the surface antigen of the hepatitis B virus (HB_s Ag) and the clinical symptoms and signs of malaise, nausea, vomiting, fever, right-upper-quadrant tenderness and jaundice. The disease, in 90 per cent of the cases, is self-limited with disappearance of HB_s Ag and clinical recovery occurring from four to six weeks after onset. Such patients, in whom antibody to HB_s Ag (anti-HB_s) usually develops during the convalescent period, are protected from further infection with hepatitis B virus. This pattern of response was frequently observed in human volunteers experimentally infected with contaminated serum[1,2] but occurs less commonly in response to "natural" infection.

A spectrum of responses occurs after natural infection, including (1) asymptomatic infection with little or no liver damage, transient production of HB_s Ag and the development of protective titers of anti-HB_s; (2) asymptomatic infection with little or no liver damage, persistent production of HB_s Ag, minimal synthesis of anti-HB_s and minimal or no cellular immune response to HB_s Ag (these persons are the "chronic carriers" of HBV); (3) acute hepatitis (described above); (4) chronic hepatitis (including chronic persistent and chronic aggressive), which may develop from acute hepatitis or may have an insidious onset — postnecrotic cirrhosis and (probably) primary hepatocellular carcinoma may occur as sequelae. In HBV-related chronic hepatitis, HB_s Ag is usually found in the patient's blood, but cellular and humoral immune responses to the virus are also detectable.[3,4] Persons with any of these four responses usually develop antibody to the core of the virus, anti-HB_c. Since the reports of Gocke et al.[5] and Trepo and Thivolet,[6] associating hepatitis B infection with polyarteritis nodosa, it has become increasingly clear that there is a fifth category of response. These patients have both persistent production of hepatitis B viral antigens and antibody to the surface (and probably core) antigens. Antigen-antibody complexes develop that bind and activate complement, producing tissue damage primarily in the vascular system. In addition to polyarteritis, HBV infection has been associated with cases of glomerulonephritis,[7] polymyalgia rheumatica,[8] infantile papular acrodermatitis (Gianotti's disease)[9] and essential mixed cryoglobulinemia.[4,10] It is likely that HBV antigen-antibody complexes are responsible for the vasculitis observed in each of these pathologic processes.

The report by Levo et al. in this week's issue of the *Journal* lends strong support to this thesis. In a study of mixed cryoglobulinemia of previously unknown cause they found HB_s Ag or anti-HB_s (or both) in the cryoprecipitates of 14 of 19 patients. Furthermore, they observed HBV-like particles in four cryoprecipitates examined by electron microscopy. Although most of these patients had hepatomegaly, liver disease was not an important feature of their illness. Their major complaints were rash (purpura), arthralgia and weakness — symptoms related to vasculitis. Rapidly progressive glomerulonephritis was the most serious aspect of their disease. In addition to

complement components and HB_s Ag or anti-HB_s of IgG or IgM class, all the cryoprecipitates contained rheumatoid factor, IgM (or less commonly Ig's of other classes) antibodies directed against antigenic determinants on the Fc portion of the constant region of IgG heavy chains.

During the prodrome of acute hepatitis B, arthralgias and sometimes frank arthritis frequently develop. Cryoprecipitates containing complement components, HB_s Ag and anti-HB_s have been isolated from the serum of such patients, and similar cryoprecipitates, but without complement, have been found in patients with acute hepatitis B without arthritis.[11] Rheumatoid factor commonly occurs in the course of both B and non-B hepatitis. Thus, the various HBV-associated immune-complex diseases may represent an abnormal persistence of the usual host responses seen in acute hepatitis. The different manifestations of immune-complex disease may be dependent on whether HB_s Ag is in excess, as in polyarteritis and Gianotti's disease, or whether anti-HB_s is in excess, as in mixed cryoglobulinemia and polymyalgia rheumatica. The presence or absence of rheumatoid factor could further influence the site and extent of tissue damage. Patients with polymyalgia rheumatica do not have rheumatoid factor and do not have arthritis.

It is possible that rheumatoid arthritis also occurs as a result of the persistence of "normal" host responses to a common virus or viruses. In fact, one third of the 21 patients with rheumatoid arthritis studied by Levo et al. had anti-HB_s in their serum, a frequency not substantially different from the 12 of 25 anti-HB_s-positive serums found among the patients with mixed cryoglobulinemia. It would be interesting to know whether they also had immune complexes containing HBV antigens.

The great clinicians used to say, "Know syphilis and you know medicine." Later, as tertiary syphilis became rare, diabetes mellitus was substituted. Soon, with the identification of the diverse manifestations of infection with HBV, physicians may tell their students, "Know hepatitis B and you know medicine."

The Institute for Cancer Research
Philadelphia, PA 19111 W. THOMAS LONDON, M.D.

REFERENCES

1. Giles JP, McCollum RW, Berndtson LW Jr, et al: Viral hepatitis: relation of Australia/SH antigen to the Willowbrook MS-2 strain. N Engl J Med 281:119-122, 1969
2. Barker LF, Shulman R, Murray R, et al: Transmission of serum hepatitis. JAMA 211:1509-1512, 1970
3. Yeung Laiwah AAC, Chandhuri AKR, Anderson JR: Lymphocytic transformation and leukocyte migration-inhibition by Australia antigen. Clin Exp Immunol 15:27-34, 1973
4. McIntosh RM, Koss MN, Gocke DJ: The nature and incidence of cryoproteins in hepatitis B antigen (HbsAg) positive patients. Q J Med 45(177):23-38, 1976
5. Gocke DJ, Hsu K, Morgan C, et al: Association between polyarteritis and Australia antigen. Lancet 2:1149-1153, 1970
6. Trepo C, Thivolet J: Hepatitis associated antigen and periarteritis nodosa (PAN). Vox Sang 19:410-411, 1970
7. Combes B, Stastny P, Shorey J, et al: Glomerulonephritis with deposition of Australia antigen-antibody complexes in glomerular basement membrane. Lancet 2:234-237, 1971
8. Bacon PA, Doherty SM, Zuckerman AJ: Hepatitis-B antibody in polymyalgia rheumatica. Lancet 2:476-478, 1975
9. Gianotti F: Papular acrodermatitis of childhood: an Australia antigen disease. Arch Dis Child 48:794-799, 1973
10. Realdi G, Alberti A, Rigoli A, et al: Immune-complexes and Australia antigen in cryoglobulinemic sera. Z Immunitaetsforsch 147:114-126, 1974
11. Wands JR, Mann E, Alpert E, et al: The pathogenesis of arthritis associated with acute hepatitis-B surface antigen-positive hepatitis. J Clin Invest 55:930-936, 1975

ATAXIA IN FAMILIES FROM THE AZORES

THE hereditary ataxias are obscure degenerative diseases of the nervous system. Motor structures of the pons, spinal cord, and cerebellum are principally affected. Most patients begin to have symptoms in early adult life, although childhood illness, chiefly Friedreich's ataxia, does occur. Understanding of these conditions has not progressed very far since the main varieties were described 70 to 100 years ago. Classification has never been very satisfactory; many intermediate cases occur. The clinical features of the illness may vary considerably as progression occurs, and the pathologist can show only the final results of the process.

The two methods of description, clinical and pathological, employed separately or together, do not appear to be able to untangle the puzzle. On the other hand, genetic aspects of these diseases have never received much attention, many authors having noted that the same clinicopathological entity can be the product of recessive, dominant or sporadic (nongenetic) background. In this issue of the *Journal* (page 1505) a special feature of dominant inheritance, traceability through many generations, is brought to bear on the problem. An effort is made to "lump" rather than to "split."

Three prior papers in the literature describe a hereditary ataxia in families descended from emigrants from the Azores Islands. Now, Romanul et al. report on another family from the Azores and present two more autopsy reports, thereby paying their respects to the traditional approach. Careful examination of the clinical and pathological data from all four families allows the strong suspicion that they represent variations of one and the same genetic illness.

Two families of the four originate in the island of Saint Michael, and these two are from the town of Bretanha on that island. All emigrated in the middle of the 19th century. None of the families bear the same name. Expressing itself clearly as a dominant gene, the disease has spread widely through the descendants. Because many of them remained part of an ethnically based and cohesive community, the families are much more easily traced than is common in American society. In this year of "Roots," that seems appropriate.

The expression of the gene seems to have produced a bewildering variety of neurologic syndromes. This