

PROGRESS IN HEPATOLOGY

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CHRONIC ACTIVE LIVER DISEASE REEXAMINED: PROGNOSIS HOPEFUL

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The concept of chronic active liver disease (CALD) was proposed 5 years ago to encompass several conditions of unknown etiology characterized by continuous or recurrent hepatic inflammation with cell necrosis.¹ CALD was considered to be incurable and usually to progress to cirrhosis, liver failure, or both. Concern was expressed (a) that uniform diagnostic criteria and specific therapeutic regimens were neither applied nor available; and (b) that an insouciant approach to clinical manifestations, coupled with unvalidated presumptions of etiology, had endowed disorders, not always objectively distinguishable from each other, with a plethora of descriptive or eponymous labels. An orderly approach was urged, beginning with standardized criteria which would allow the natural history of CALD to be defined and examined from the practical aspects of chronicity, activity, and responses to treatment.

Since then, numerous clinical, biochemical, and histological features have been defined which usefully typify the interrelated conditions comprising CALD and exclude other conditions earlier considered indistinguishable; associations between hepatitis B antigen (HB Ag) and all the component disorders of CALD have provided the first integrating concept with regard to possible etiologies; and valuable information concerning treatment has at last been garnered from properly designed trials. These and other areas of progress

will be reviewed, emphasizing (a) the characteristics and differential diagnosis of CALD; (b) current viewpoints concerning etiology; and (c) therapeutic indications and responses.

What is CALD?

CALD (table 1) comprises disorders with clinical, biochemical, immunochemical, and histological features which differ mainly in degree, often have similar responses to treatment, and are not etiologically distinct. The more extensive the hepatic inflammation, the greater the changes in liver function or immunoserological tests; the worse the prognosis, the more urgent the need for treatment. The liver diseases include chronic active ("aggressive") hepatitis; subacute hepatitis ("subacute hepatic necrosis") with bridging or multilobular necrosis; and an inactive phase of hepatitis, which occurs spontaneously or is induced by therapy. Each may be associated with cirrhosis, and, as the typical histological patterns are not then always evident, cirrhosis with active or inactive hepatitis more conveniently describes such instances. This terminology approximates popular usage, preserves descriptive morphological labels of demonstrated clinical importance and retains from an extensive selection (a recent tally² identified 47 options) only conditions with the scientific credentials—particularly differences in prognosis and treatment—to be considered independent entities.

Diagnosis

Differentiation between the conditions comprising CALD may be surmised from the clinical features, supported by changes

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TABLE 1. Classification and common features of chronic active liver disease

Disease activity	Clinical features of disease	Changes in liver function tests	Immunoserological abnormalities	Histological characteristics	Prognosis
<i>Inactive phase</i> Inactive hepatitis	None or nonspecific	SGOT* < $\times 2$ Others normal	None	Portal inflammation $\pm$ minimal piecemeal necrosis.	Good without treatment
Inactive hepatitis with cirrhosis	$\pm$ Residual evidence of earlier activity	SGOT < $\times 2$ Others normal	None	Cirrhosis with minimal or absent inflammation and necrosis.	Immediately good without treatment; later?
<i>Indeterminate phase</i>	Equivocal	SGOT $\times 2$ - $\times 10$	Perhaps	Portal inflammation; mild piecemeal necrosis.	May be good, requires observation.
<i>Active phases</i> Chronic active hepatitis*	Frequent	SGOT > $\times 3$ Others often abnormal	Frequent	Portal inflammation; moderate or severe piecemeal necrosis.	Cautiously optimistic; often needs treatment.
Subacute hepatitis*	Severe	Usually general and striking	Frequent	Bridging or multilobular necrosis with inflammatory changes.	Guarded (good or poor): requires treatment.
Active hepatitis with cirrhosis	Frequent	SGOT > $\times 3$ Others often abnormal	Frequent	Cirrhosis, cell necrosis and inflammatory changes.	Fair only, even with treatment.

* SGOT, serum glutamic oxaloacetic transaminase.
* or chronic aggressive hepatitis.
* or subacute hepatic necrosis.

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in liver function tests, but reliably determined only by liver biopsy.^{3, 4} Expert interpretation is often essential since the morphological features exemplify interrelationships which differ mainly with regard to the extent and degree of inflammation and cell necrosis. Chronic active (aggressive) hepatitis⁵ features portal tract inflammation with moderate or severe piecemeal necrosis of liver cells extending outwards from the limiting plate. More extensive inflammatory changes characterize subacute hepatitis,^{4, 6} and necrosis may span the lobule between portal or hepatic veins (bridging necrosis), or cause more diffuse destruction, with collapse of adjacent lobules (multilobular necrosis). Inactive hepatitis is mainly limited to the portal areas and comprises round cell infiltration, Kupffer cell proliferation, and mild or absent piecemeal necrosis.^{4, 7} These findings are identical with those also typifying chronic persistent hepatitis.⁵ In all these conditions, patchy lobular changes with "acute viral" characteristics⁸ may be identified in one-half the instances,⁴ and cirrhosis, if present, is usually of the macro- or micromacronodular variety. Sampling and observer errors are trivial in detecting the presence, degree, and type of hepatitis in CALD; but blind biopsy may overlook the presence of cirrhosis, particularly when macronodular, in up to 50% of instances,⁹ and peritoneoscopy or other techniques may then be indicated to establish a complete diagnosis.

Chronicity and Activity

The poor prognosis earlier accorded CALD must be abandoned after the development of better or successful treatments.^{7, 10, 11} But variable diagnostic criteria and differing types or schedules of therapy, together with the uneven caliber and duration of follow-up, still preclude definitive revisions of natural history. The decisive potential of treatment is exemplified by a series in which more than one-third of the patients assigned to less effective therapies died within 6 months, whereas progressive remission of all clinical, biochemical, and morphological features of the disease were the rule in those

allocated to the better regimens.⁷ However, spontaneous remission, even of severe disease, occurs in 20% of instances. Prognosis appears worse with regard to early death and later complications with subacute hepatitis,^{6, 7} especially when multilobular necrosis is present,⁷ or with cirrhosis and active hepatitis.¹² By contrast, it is uncertain if chronic active hepatitis is inevitably aggressive and associated with an ominous outlook.^{4, 12} Cook et al.¹⁰ found that 18 of 49 patients died during a period of 6 years, and that cirrhosis had developed in all 10 available for autopsy; but whether this outcome is attributable to chronic active hepatitis rather than fluctuations in disease activity,³ with episodes of subacute hepatitis,⁴ is uncertain. These and other factors determining the course of CALD, including remission, relapse, and treatment failure, are more fully considered later in this paper in relation to therapy.

Chronicity of active liver disease can now be predicted from the morphological features on biopsy. The changes of chronic active or subacute hepatitis signify the probability of a prolonged course and chronicity is presumed irreversible when cirrhosis is demonstrated. The features of chronic active (aggressive) hepatitis described by the European group⁵ have been substantiated as reliable indicators of continuing disease by the behavior of patients selected by these criteria.^{7, 10, 11} The great majority had continuing disease activity throughout the period of observation, sometimes despite treatment and with progress to cirrhosis and a fatal outcome. The finding of subacute hepatic necrosis (comprising both bridging and multilobular necrosis associated with subacute hepatitis) as described by Boyer and Klatskin⁶ also portends continuing disease, with or without cirrhosis, in those who survive.^{4, 7} Of 42 such patients in their study, which was confined to those developing subacute hepatitis as an early sequel to acute viral hepatitis, 50% developed cirrhosis, chronic active hepatitis, or both during a follow-up period of 4 years. The Mayo study, comprising patients who developed subacute hepatitis at different stages of the course of CALD, reported these lesions in 16 of 35 survivors¹²; fur-

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ns.⁷ However, even of severe distances. Prognosis led to early death with subacute hepatitis in multilobular necrosis with cirrhosis and contrast, it is uncertain that hepatitis is inevitably followed with an ominous prognosis. We found that 18 of a period of 6 years, developed in all 10 but whether this led to chronic active hepatitis in dissections of subacute hepatitis. These and other course of CALD, response, and treatment fully considered relation to therapy. Liver disease can be morphological changes of chronic hepatitis signify the course and chronicity when cirrhosis or features of chronic hepatitis described by have been substantiated by continuing patients selected by the great majority activity throughout, sometimes delay progress to cirrhosis. The finding of (comprising both necrosis associated with hepatitis) as described also portends consequences without cirrhosis, 42 such patients confined to those with hepatitis as an early hepatitis, 50% developed hepatitis, and period of 4 years. Long patients who hepatitis at different CALD, reported survivors¹²; fur-

thermore, cirrhosis had already developed in the majority who died with multilobular necrosis.⁷ Biochemical criteria can also gauge the likelihood of disease chronicity. The 10-week elevations of serum glutamic oxaloacetic transaminase (SGOT) and γ -globulin continuing without improvement, and cited by Geall and his associates,¹ proved effective when applied in practice.⁷ Also, in evaluating large series of patients with acute hepatitis reported in the literature, all but five of 370 instances of self-limited disease would have been excluded by using these criteria.¹³

Activity of CALD can also be assessed by histological and biochemical methods. Morphological features of activity are reflected by the extent of hepatic cell necrosis, together with the degree of associated round cell infiltration and Kupffer cell proliferation. The most sensitive biochemical indicators of these changes are the degrees of elevation of serum transaminases and γ -globulin.^{7, 10, 11} Preliminary evidence suggests that serum bile acid concentrations are also valuable, and, in addition, discern instances of activity not revealed by standard histological and biochemical techniques.¹⁴ Geall and associates¹ predicted that 50% of patients with $\times 10$ elevation of SGOT, or $\times 5$ of SGOT and $\times 2$ of γ -globulin, who failed to improve after 10 weeks or more, would have disease of such activity that death would occur within 3 years. When applied prospectively, more than one-third of such patients died within 6 months unless adequately treated.⁷ Less extreme abnormalities of liver function tests are consistent with the presence of CALD,^{10, 11} and sometimes little or no abnormality may be detected, especially when the disease is approaching remission,^{7, 12} or is difficult to differentiate from persistent hepatitis.

Newer Clinical Associations of CALD

Findings from two large series of patients with CALD have been published in the last 5 years.^{3, 15} These reemphasize the frequency of systemic features, associations between CALD and diseases of other organs considered to have an immunopathological basis, the varying patterns of abnor-

malities of liver function and immunoserological tests, and the diverse morphological features of the condition. The similarity of chronic active hepatitis in the pediatric age group to the adult form of the disease has also been depicted,¹⁶ and occasional associations between CALD and fibrosing alveolitis,¹⁷ thyrotoxicosis,¹⁸ or eosinophilia with Coombs positive hemolytic anemia¹⁹ have been recorded. Resemblances between CALD and primary biliary cirrhosis or cryoglobulinemia have practical importance. Cooksley and his colleagues²⁰ described clinical, biochemical, or immunochemical features of cholestasis consistent with the diagnosis of primary biliary cirrhosis in 14 of 30 patients whose course and biopsy features were those of CALD. The correct interpretation of dysglobulinemias in CALD can also be obscure. Jori and Buonanno²¹ describe relationships between chronic (active or persistent) hepatitis, or cirrhosis and cryoglobulinemia. In patients whose purpura, arthralgia, and hepatosplenomegaly were attributed to cryoglobulinemia, overt signs of liver disease were usually inapparent, whereas, in others, evidence of liver disease was more prominent. The authors suggest that the cryoglobulin-associated syndrome may lead to liver involvement, but the alternative that CALD is associated with synthesis of abnormal plasma immunoglobulins, some of which reversibly precipitate on cooling, also merits consideration. Zawadzki and Edwards²² in fact document dysimmunoglobulinemia in 20 cases of chronic hepatobiliary disease, find transformation of polyclonal to monoclonal gammopathy in two instances, and cite evidence that prolonged paraproteinemia associated with liver disease may ultimately lead to overt myeloma. Abnormal protein metabolism in CALD also accounts for the other numerous immunoserological phenomena which are discussed later. Some recent additions to the list include false-positive tests for serum carcinoembryonic antigen,²³⁻²⁵ Salmonella agglutinins,²⁵ and antimitochondrial antibody.^{26, 27}

Patients with chronic hepatitis (including CALD) and HB Ag may present newly recognized syndromes. The development of

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periarteritis nodosa under such circumstances was considered by Gocke et al.²⁸ to represent tissue damage caused by circulating immune complexes of antigen, homologous IgM antibody, and complement components. This explanation was not supported by the density gradient experiments of others using sera from patients with periarteritis or HB Ag.²⁹ The pathogenesis of the association between membranous glomerulonephritis and chronic persistent hepatitis with HB Ag, described by Combes and his colleagues,³⁰ also invokes immune complex deposition. Immunofluorescent staining of kidney tissues suggested that deposits of IgG, C-3, and antigen may cause the glomerular damage.

What Isn't CALD? Differential Diagnosis

The majority or all of the findings characterizing CALD may be mimicked by related conditions (unresolved or relapsing acute hepatitis and chronic persistent hepatitis), as well as by certain unrelated conditions (primary biliary cirrhosis, Wilson's disease, or hepatitis due to certain drugs).

Difficult clinical distinctions between CALD and unresolved or relapsing acute hepatitis usually require tissue examination. Scrutiny of the limiting plate area is essential, since portal and lobular changes may be similar in all these conditions. Acute viral hepatitis rarely continues for 10 weeks without improvement,¹³ whereas relapse, accompanied by deterioration in clinical and biochemical findings, is characterized by a limited course and followed by improvement. Should this not occur, the possibility of subacute hepatitis⁴ is pertinent.

Differentiating chronic persistent hepatitis from CALD can be particularly difficult. The natural history of chronic persistent hepatitis is not fully documented—no information is available to determine whether the disease continues through life, is self-limited, or is subject to fluctuations in activity. Furthermore, the clinical, biochemical, and morphological features of

chronic persistent and mild chronic active hepatitis resemble each other, and sharp criteria separating the conditions are lacking. Chronic persistent hepatitis is typically benign and nonprogressive and requires no treatment. Symptoms are non-specific or absent. Objective abnormalities comprise occasional enlargement or tenderness of the liver, associated with elevation of serum transaminase.³¹ Becker et al.³¹ will accept concentrations of serum aspartate transaminase of up to $\times 20$ as consistent with the diagnosis, provided that other tests are normal and that the liver biopsy shows only inflammatory round cell infiltrate in the portal tract ("triaditis") with minimal or absent piecemeal necrosis. Patients with mild chronic active hepatitis have very similar features, and, indeed, findings may be identical when they are in remission.⁷ One well documented study showed that 5 of 30 patients originally classified as having chronic persistent hepatitis progressed to chronic active hepatitis during a follow-up which exceeded 2 years.³² By contrast, another study of 63 patients with severe CALD contained 2 patients with florid clinical manifestations and widespread abnormalities of liver function tests whose initial biopsies were interpreted as chronic persistent hepatitis—although each later developed characteristic morphological features of chronic active hepatitis.⁷ Given these uncertainties, and the slight sampling error of liver biopsy,⁹ all patients considered to have chronic persistent hepatitis should be followed for 1 year.³¹ Longer supervision is recommended for those who continue to have prominent symptoms. SGOT exceeding $\times 5$ normal, abnormalities of other liver function tests, positive immunoserological tests (including elevated serum γ -globulin concentrations), or the presence of identifiable piecemeal necrosis on biopsy.¹²

Certain conditions now accepted as having different etiologies may nevertheless feature elevations of serum transaminases and γ -globulin, positive immunoserology, and patterns of necrosis on biopsy which are identical with those found in CALD.

The diagnosis of primary biliary cirrhosis

under such circumstances and sex (especially third decade), presence of hyperlipidemia. Diagnosis is not necessarily facilitated by antimitochondrial antibodies, although this may occur in some cases. Confirmation depends on characteristic bile duct proliferative cholangitis, which they have developed only in rare instances. Conventional doses of azathioprine without azathioprine are much more consistent with CALD than CALD.

Similarities between CALD and CALD have been noted by Sternlieb and Scheinman in patients, ages 12 to 20, with clinical, biochemical, and histological features consistent with CALD. A careful history and physical examination, including liver biopsy, serum ceruloplasmin, and urinary copper excretion, and mandatory screening tests for Wilson's disease.

Changes resembling subacute hepatitis have been shown to be induced by drugs oxyphenisatin. More recently, isoniazid has been implicated as a cause of liver disease with bridging or massive necrosis. Evidence of possible drug-induced liver disease identified in 120 cases in the United States.¹ Isoniazid appears frequently in the sample, of 21 consecutive cases. Goldstein and his colleagues reported that 9 were associated with laxatives containing phenolphthalein. Cases could have occurred with methyl dopa. In subacute hepatitis, however, several investigators have found a toxic etiology, presumably a sensitivity reaction, by skin tests. Improvement occurred after withdrawal of the drugs. Whether this is a true additional therapeutic

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and/or cirrhosis, whereas they are seldom identified in acute uncomplicated hepatitis and absent in healthy "carriers" of HB Ag. Differences in ratios between the small spherical and rod-shaped bodies also associated with HB Ag are less striking.⁴⁵ Once CALD with HB Ag is established, the disease runs a more serious course in untreated patients with anticomplementary assays,⁴⁶ although no strong evidence exists that deposition of immune complexes causes the hepatic (as opposed to extrahepatic) damage in CALD. Both the spectrum of CALD and the proportion of cases attributable to viral infection would be greatly expanded if the Milan antigen⁴⁷ was confirmed as a valid marker for the virus of type A hepatitis, since Doniach⁴⁸ identified this material in the sera of 16 to 36% of patients with chronic active hepatitis, primary biliary cirrhosis, or cryptogenic cirrhosis.

The proposal that host rather than external factors determine the course (chronicity or otherwise) of hepatitis with HB Ag originates from clinical observations. These, summarized by Sherlock,³⁸ comprise inability to correlate the variable severity and course of hepatitis with differences in virulence of the virus or quantities of the antigen in the serum, and the fact that infants or patients with impaired cellular immunity (for example, chronic renal disease, leprosy, lymphoma) more often have subclinical or mild chronic hepatitis than severe acute or subacute disease. In preliminary studies, hypotheses are being tested that chronicity is specifically determined by abnormalities of host immunity mediated by T cells. Dudley and his colleagues⁴⁹ suggest that T lymphocytes normally induce proliferation of specifically sensitized cells which recognize the antigen when it is extruded to the surface of infected hepatocytes, and then, perhaps through mediators, destroy both the liver cell and the infective agents (thus causing acute self-limited hepatitis). Impairments of T cell function might lead to variable amounts of hepatic damage and permit antigen continuously to proliferate within liver cells. Preliminary and circumstantial evidence of reduced cell-mediated

immunity in patients who carry HB Ag (with or without chronic hepatitis) includes the failure of HB Ag sera to induce blast transformation of lymphocytes,⁴⁹ inhibit leukocyte migration,⁵⁰ or impair lymphocyte transformation induced by phytohemagglutinin⁵¹ in such instances. Normal responses are preserved in individuals with acute B-type hepatitis. On the other hand, Bolin and others⁵² employed dinitrochlorobenzene skin sensitization as an indicator of cell-mediated immunity, and found intact responses in carriers of HB Ag.

The belief that CALD sometimes represents an "autoimmune" process invokes a different mechanism and is perpetuated by titles such as "autoallergic," "autoimmune," or "lupoid" hepatitis, although it has not gained universal acceptance. The postulate demands that primary host mechanisms be directed against tissue constituents of the host in the absence of any triggering external agent,⁵³ as may occur in Addisonian pernicious anemia or Hashimoto's thyroiditis. The process arises *de novo*, perhaps as a forbidden clone. Several variably nonspecific but unexplained similarities between CALD and conditions considered to have an immunopathic basis support the hypothesis. Such common "immune markers" include the frequent coexistence with CALD of inflammatory diseases of unknown etiology involving other organ systems (ulcerative colitis, thyroiditis, sclerodermatomyositis, etc.); elevations of serum γ -globulin concentrations, together with all immunoglobulin fractions; positive serological tests for numerous non-organ specific antibodies; the presence of plasma cells on liver biopsy; and the possibly immunosuppressive role of adrenocorticotropin and corticosteroids, with or without azathioprine, in the therapy of CALD. The major objections to an autoimmune basis for CALD comprise the failure to demonstrate organ- (liver) specific antigens and antibodies; the fact that the majority of the immune markers cited do not specify the type of liver disease, but may be present in a variety of hepatobiliary disorders; and evidence that such markers can also occur in CALD associated with HB Ag, or in chronic hepatitis induced

by drugs, and the response to external^{54, 55} Popper and others⁵⁶ have noted inconsistencies between viral etiologies in identical features. The virion complexed with membrane proteins is not customary for other viruses. It may include pre-hepatic liver cell; or specimens may be in antigen particle.

The events is envisaged as a selective immunologic response against the virus and the cells damaged by the virus. The search for autoantibodies in preliminary work of Popper and others⁵⁷ describes isolation from the sera of an IgG type of antibody in experimental conditions only by liver specimens.

An extensive but inconclusive search for etiological significance of serum non-organ specific (mitochondrial, alpha-fetoprotein, etc.), immunoglobulin, and hematosus cell markers in diseases or HB Ag. It is suggested that HLA antigens and antibodies are mutually exclusive. A stance later more believed that patients with lower titers of specific antibodies than others. Bulk studies of a small series showed lack of overlap of antibodies in lupus erythematosus might account for the lack of CALD.⁵⁸ L. J. Popper and others⁵⁹ that lupoid hepatitis with HB Ag.^{54, 55} A prospective study of identical pre-established patients (age and sex), biochemical and histological differences with, or without, erythematosus test of a positive test and severe

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HB Ag includes induce blast tes,⁴⁹ inhibit pair lympho- by phyto- nces. Normal dividuals with e other hand, dinitrochloro- an indicator and found in- HB Ag. etimes repre- ess invokes a erpetuated by ;," "autoim- s, although it eptance. The rimary host ist tissue con- bsence of any may occur in mia or Ha- cess arises de clone. Several plained simi- l conditions, thic basis, common the frequent inflammatory gy involving re colitis, thy- is, etc.); ele- n concentra- munoglobulin tests for nu- tibodies; the liver biopsy; opressive role orticosteroids, , in the ther- jections to an comprise the (liver) spe- the fact that markers cited r disease, but of hepatobili- e that such LD associated atitis induced

by drugs, and therefore can arise in response to external (viral or toxic) agents.⁵⁵ ^{54, 55} Popper and McKay,⁵⁶ acknowledging inconsistencies between autoimmune and viral etiologies in patients with otherwise identical features, offer compromise solutions. The virion in the liver cell may be complexed with more host protein than is customary for other viruses; the viral coat may include pre-existing structures of the liver cell; or specific host protein components may be incorporated into the B antigen particle. One or more of these events is envisaged as exciting an aggressive immunological reaction directed both against the virus and against host hepatocytes damaged by it. Nevertheless, the search for autoantibodies continues. Preliminary work of potential pertinence describes isolation from patients with CALD of an IgG type globulin, which, under experimental conditions, is fully absorbed only by liver specific protein.⁵⁷

An extensive literature attests to the inconclusive searches for correlations of etiological significance between CALD and serum non-organ specific antibodies (anti-mitochondrial, antinuclear, smooth muscle), immunoglobulin fractions, lupus erythematosus cell tests, autoimmune diseases or HB Ag. For example, it was once suggested that HB Ag and smooth muscle antibody are mutually exclusive in CALD, a stance later modified by Wright,⁵⁸ who believed that patients with HB Ag had lower titers of smooth muscle antibody than others. Bulkley and her colleagues,⁵⁹ studying a small series, speculated that the lack of overlap observed between positive lupus erythematosus cell and HB Ag tests might account for differences in the behavior of CALD.⁵⁹ Later studies have shown that lupoid hepatitis can be associated with HB Ag.^{54, 55} Indeed, a comprehensive prospective study of patients selected by identical pre-established criteria for CALD showed no major clinical (including age and sex), biochemical, immunochemical, or histological differences between 30 patients with, or 58 without, a positive lupus erythematosus test, other than the association of a positive test with evidence of more active and severe disease. Responses to

treatment were identical in the two groups.⁵⁵

In studying 94 patients with "chronic idiopathic liver disease," Finlayson et al.⁶⁰ reported significantly more autoantibodies to nuclei, smooth muscle, and mitochondria in patients without HB Ag. Similar findings in CALD⁶¹ included greater elevations of IgG in HB Ag-negative individuals. In both series, the overlap of results was too great to support contentions of entirely different etiologies. The possibility that clinical as well as serological findings may yield clues to etiology deserves emphasis. In evaluating extensive immunological data from 128 consecutive patients with severe CALD chosen by pre-established criteria,⁷ the only significant difference involving HB Ag was absence of this marker in all of 26 patients who had associated inflammatory diseases of an autoimmune type and the corresponding absence of associated inflammatory disorders in all of 20 patients with HB Ag.¹²

Abnormalities of the complement system were originally implicated in pathogenesis of the arthritis with acute hepatitis by Alpert and his colleagues,⁶² and later evaluated as causes of other extrahepatic manifestations in chronic hepatitis. Measurements of total hemolytic complement, C-3 and C-4, in 110 patients with chronic liver diseases indicated that low complement levels are associated with impaired liver synthetic function rather than related to the activity of the liver disease⁶³ or to the postulated etiology, as reflected by HB Ag or circulating non-organ specific antibodies. On the other hand, Grob and associates⁶⁴ found decreased concentrations of B₁A (a constituent of C-3) in more than one-half of 31 patients with chronic active or chronic persistent hepatitis and variable results in acute hepatitis. Patients with HB Ag more often had decreased levels of B₁A than others. No correlations were discovered between immunoglobulins G and M and B₁A. The reduction of B₁A in liver disease might be due to the formation of immune complexes, decreased synthesis, increased catabolism, or the formation of anticomplementary serum complements. Since B₁A concentrations are also reduced

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in some autoimmune diseases, the authors speculate that low levels after acute hepatitis may herald the intervention of autoimmune processes and a chronic course. Another determinant of chronic disease, in this instance of postulated genetic origin, could be the twice normal incidence of histocompatibility antigens (HL-A1 and A8) in CALD. These have also been presented as immunopathic markers, signifying an abnormal response to autoantigens and a predisposition to autoimmune hepatitis.⁶⁵

A critical summary of this literature leads to the conclusion that, with the important exception of HB Ag, neither individual immunological tests, nor their permutations, yet reliably indicate etiology, diagnosis, or prognosis in CALD.^{27, 66} Rather, such tests mainly reflect disease activity, since all revert to normal when CALD is effectively treated.^{7, 33} Increased production of normal or abnormal proteins is probably responsible and immunoglobulin G synthesis has been measured in CALD, found to be increased, and shown to return toward normal during treatment with prednisone.⁶⁷ What "turns on" the production of various globulins in chronic liver disease is unknown. A theory recently advanced by Thomas and others⁶⁸ holds that the magnitude of hyperglobulinemia and immune response may be determined by the relative distribution of antigens between the liver and spleen. They demonstrated that, in experimental cirrhosis, gut-derived antigens contribute to globulin production since they are not efficiently trapped in the liver and are consequently dispersed to antibody-producing tissues, such as the spleen.

Further clarification of etiologies of CALD is most likely to follow investigations directed (a) toward identification of additional external mechanisms (whether viral or otherwise) initiating the process; (b) toward host factors determining immunological responsiveness and chronicity; and (c) characterization of mechanisms whereby viral or toxic agents produce necrosis and inflammation of liver cells and then cause diverse clinical and serological abnormalities. To these ends, the develop-

ment of suitable animal models for CALD is desirable, and the selection of clinical material more precisely defined than has usually been the case will be essential.

Treatment of CALD

For more than a decade, corticosteroids, adrenocorticotropin, and azathioprine, or its metabolic product, 6-mercaptopurine, were employed empirically in numerous, nonstandardized and uncontrolled treatment schedules, propagating findings which could not be interpreted in relation to therapeutic indications, benefit-risk ratio, and effects on long term prognosis in CALD.¹ Similar descriptions have lately recorded experiences with penicillamine, cyclophosphamide, or chloroquin. By contrast, the results of acceptably designed therapeutic trials in CALD, published in the past 2 years, dramatize improvements in management of the disease and promise a potential for more advances. Remission can be secured in a large proportion of instances, and there are even indications that the ultimate goal of cure may sometimes be attainable.

Three controlled studies of CALD deserve scrutiny. In London, Cook and his colleagues¹⁰ reduced mortality with variable doses of prednisolone (usually approximating 10 mg daily of prednisone). Treatment did not uniformly improve liver function tests and effects on hepatic histology were not sought. The Mayo study employed higher doses of medications, different schedules, and additional methods. These included double blind evaluation of responses, strict criteria for beginning and discontinuing therapy, and regular recording of data which included hepatic histology.⁷ Maintenance schedules with prednisone (20 mg daily), or a combination of smaller daily doses of prednisone (10 mg) with azathioprine (50 mg), were significantly more effective than azathioprine (100 mg daily) alone or placebo. Prednisone, or the combination, not only increased survival, but resulted in remission of jaundice, ascites, and other clinical features. Biochemical, immunochemical, and histological indicators of activity usu-

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ally later underwent contrast, most patients alive or placebo deteriorated from hepatic failure of the start of therapy. Murray-Lyon and his colleagues¹⁰ found that the probability of survival with CALD receiving a course of prednisone, 15 mg daily, was greater than for those randomly assigned (75 mg daily). Improvements in liver function tests were seen with prednisone, but alterations in histology were not investigated. These studies. Careful effects were undertaken attributable to drugs, the benefits of effective selection differed. Colleagues¹⁰ enrolled 44 patients on basis of histological evidence of active hepatitis. The Mayo study included chronic active hepatitis, cirrhosis, and at least ties of serum aspartate aminotransferase and γ -globulin concentration according to the Mayo criteria for severe disease, since grade of liver function tests at admission, and indication of hepatitis or cirrhosis confirmed.

Selection of

Do all patients with CALD benefit? Risks to be balanced include the likelihood of relapse in 10% of patients after treatment,^{7, 10} and the ease subject to spontaneous remission in those patients who will respond, cannot yet be predicted. There is no evidence of etiologic of CALD responses,^{7, 12, 55} although features definitely affect prognosis, and providing confirmation of CALD by biopsy is feasible, the criteria for therapy are: (a) the levels of SGOT and γ -g-

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mine chronicity of disease are reviewed, and the importance of autoimmune mechanisms as causes of CALD is questioned. Recent advances in treatment show that effective therapy can induce remission in some instances of CALD and that ultimate cure may be feasible. By contrast, other findings in CALD are cited as indicating a poorer prognosis with the development of cirrhosis, liver failure, or both, despite treatment. It is to be concluded that encouraging theoretical and practical advances have occurred, since until recently, CALD was considered to be of unknown etiology, and the majority of patients were believed unlikely to survive.

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CHRONIC IN PERSPECTIVE

During the past few years, the field of chronic liver disease has been expanding exceedingly fast. It is implicitly¹⁻³ or "what is chronic" by Summerskill previously,⁴ he "what is chronic" Having neatly colored labels in an attempt to leave us with an is, at least in my somewhat disputable clearly written, or interpreted as CO problem. The term "disease" is used to pass a variety of labels to share certain pathological, and Whether a search among the various liver diseases productive in terminology, prevention, uncertain. My cor detract from the gantly controlled ducted by the Mayo question the wisdom disorders under a time.

A major goal of inflammatory liver disease is the determination of etiological and genetic mechanisms. The management of these disorders the epidemiology of been given adequate

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