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CHRONIC HEPATITIS - 1980

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CONTENTS

Chronic hepatitis has been described as "among the most confused and confusing areas in medicine" (1). Chronic hepatitis "defined in its broadest sense as an unresolving inflammatory lesion of the liver initiated by viral, drug or unknown factors" (2), consists of a number of similar diseases distinguished from one another by clinical, etiologic and histological features. The various forms of chronic hepatitis differ in their prognosis and their need for - and response to therapy.

Although the confusion persists, review of the literature and prolonged observation of such patients does lead to the impression (illusion?) of movement toward better understanding of this interesting group of diseases.

I. CLASSIFICATION OF CHRONIC HEPATITIS

Rigid criteria for the diagnosis of chronic hepatitis have not been established but many authors would probably accept continued elevation of the serum transaminase - AST (SGOT) or ALT (SGPT) - to levels exceeding twice the upper limit of normal as the minimal definition of "hepatitis" and persistence of this abnormality for six months or more as the criterion of chronicity. Symptoms and physical abnormalities are often present but are not essential for the diagnosis. Implicit in the diagnosis of chronic hepatitis is the exclusion of other well-defined forms of chronic hepatic disease such as alcoholic liver disease, primary biliary cirrhosis, hemochromatosis, etc. which are distinguished by their characteristic historical, clinical, biochemical and/or histological features.

Table I is a suggested classification of chronic hepatitis based on the current literature.

TABLE 1. A Classification of Chronic Hepatitis

I. Chronic persistent hepatitis (CPH)

II. Chronic lobular hepatitis (CLH)

III. Chronic active hepatitis (CAH) or chronic active liver disease (CALD)

- A. Autoimmune ("lupoid") hepatitis
- B. Chronic active type B hepatitis
- C. Chronic active non-A, non-B hepatitis
- D. Drug-induced CAH
- E. Idiopathic CAH

The diagnosis of each of these types of chronic hepatitis requires knowledge of laboratory data and liver histology; the history and physical examination provide valuable contributory information.

A. CHRONIC PERSISTENT HEPATITIS (CPH)

This most "benign" form of chronic hepatitis is typically an asymptomatic condition characterized by the minimal criteria of CH - a persistent transaminase elevation, and compatible histologic changes in a patient with a normal physical examination. The other liver tests are usually normal but a few CPH patients have displayed a persistent mild elevation of the serum unconjugated bilirubin level.

Liver biopsy shows preservation of the lobular architecture; the portal tracts are of normal size or moderately enlarged, containing a "chronic" inflammatory infiltrate consisting mainly of lymphocytes. For the most part, the limiting plate (the outermost layer of hepatocytes in the lobule, abutting the portal tracts) is intact. Small collections of inflammatory cells or foci of liver cell necrosis may be present in the lobule, but these changes tend to be minimal. Fibrosis is absent or trivial.

It is important to recognize that, not infrequently, the histologic differentiation of "severe" CPH and the milder lesions of CAH may not be possible with confidence.

The histological changes in CPH are non-specific and final diagnosis by the pathologist requires knowledge of the patient's history. The same liver biopsy changes may occur in patients with extrahepatic disease, notably ulcerative colitis and Crohn's disease and, knowing this, the pathologist's diagnosis would be "non-specific" or "reactive" hepatitis, or "portal triaditis."

CPH may be caused by most of the same etiologic factors producing CAH, as discussed below; these include hepatitis B virus, non-A, non-B viruses, drugs and unknown factors. It is not clear that there is an "autoimmune" variety of CPH, but conceivably chronic lobular hepatitis comes close to representing such an entity.

B. CHRONIC LOBULAR HEPATITIS (CLH)

In 1971, Popper and Schaffner (3) described a new histiologic type of chronic hepatitis, chronic lobular hepatitis, characterized by;

1. Focal necrosis of single - or small groups of hepatocytes throughout the hepatic lobule,

2. Lobular infiltration with mononuclear cells,

3. Kupffer cell hyperplasia throughout the lobule and

4. Lymphocytic portal tract inflammation.

For the diagnosis of CLH, these liver biopsy changes must be observed in the setting of prolonged transaminase elevations since, without historical information, the pathologist could not distinguish this lesion from that seen in some patients with acute viral hepatitis.

Popper and Schaffner did not define the clinical syndrome accompanying the CLH lesion, and some authors have regarded CLH as falling within the clinical and histologic category of chronic persistent hepatitis. However, Wilkinson et. al. (4) have recently reported the clinical course of five patients selected for study because their liver biopsies showed CLH. In all five patients the clinical onset was indistinguishable from that of ordinary acute hepatitis. In two of the patients the transaminases remained persistently elevated and the disease did, indeed, behave like chronic persistent hepatitis. But in the other three, a succession of relapses separated by periods of complete biochemical and histologic remission occurred, quite unlike the course of other forms of chronic hepatitis. The remissions lasted from several months to five years. During the relapses clinical manifestations resembled those of acute viral hepatitis with AST (SGOT) ranging from 844 to 2800 i.u., much higher than expected during exacerbations of chronic persistent or chronic active hepatitis.

All five patients were HBsAg-negative, but either antinuclear antibody, antimitochondrial antibody or smooth muscle autoantibody or a combination of these were present in the serum of all of the patients.

The prognosis of CLH appears to be good if the experience of this small group of patients is representative; three of the patients have been followed for three, five and eight years with repeated liver biopsies and none have shown progression toward cirrhosis.

In a review of Wilkinson's study (5), Benhamou states that he also has observed patients with CLH whose course was characterized by the pattern of complete remissions and relapses with very high serum transaminase values. The relative rarity of this form of chronic hepatitis was emphasized.

The presence of autoantibodies in Wilkinson's five patients raises the question of whether CLH is not a variant of autoimmune CH, however, Wilkinson et. al. favor the hypothesis that CLH could result from a chronic viral infection in which the agent undergoes cyclical reactivation, perhaps analogous to a herpes virus infection.

C. CHRONIC ACTIVE HEPATITIS (CAH)

This category comprises a group of chronic liver diseases of different etiologies which have in common certain clinical and laboratory features and which share the same spectrum of histological changes in the liver biopsy.

Mayo Clinic investigators (6) have divided the histological changes of CAH into four patterns which (modifying their terminology somewhat) are:

1. "Simple" chronic active hepatitis.

As in chronic persistent hepatitis, there is portal tract infiltration with lymphocytes, and in some cases, plasma cells. The portal tracts are expanded to a greater degree than seen in CPH, and part of this expansion is the result of irregular destruction of the hepatocytes of the limiting plate bordering the portal tracts; this is referred to as "piecemeal necrosis" or by the essentially synonymous term "erosion of the limiting plate." There may also be foci of hepatocellular necrosis within the lobule. The inflammatory infiltrate often penetrates from the portal tracts into the lobules, forming septa. Fibrosis develops in the portal tract and extends into these septa.

2. Chronic active hepatitis with bridging necrosis (CAH-BN)

In addition to the changes of simple CAH, this more severe pattern of injury involves more extensive hepatocellular necrosis producing parenchymal collapse between adjacent portal tracts or between portal tracts and central veins creating necrosis and inflammatory "bridges." Whether or not bridging necrosis is an extension of piecemeal necrosis is a matter of dispute (2, 7).

3. Chronic active hepatitis with multilobular necrosis (CAH-MN)

This form of injury appears to represent an extension of bridging hepatic necrosis in which entire lobules are obliterated and broad bands of stromal collapse are observed.

4. Chronic active hepatitis with cirrhoris ("Active cirrhosis, CAH-C).

At this stage of CAH, cirrhosis, characterized by regenerative nodules of hepatocytes separated by bands of fibrous tissue is seen in a liver in which the inflammatory cell infiltrate and hepatocyte necrosis characterizing the lesser forms of CAH are still evident.

Because of the reluctance of some pathologists and clinicians to include cirrhosis within the category of CAH, the Mayo group has proposed the term "chronic active liver disease" (CALD) to encompass all four of the histologic stages described. The term CALD seems to be gaining in popularity. There is some disagreement (even within the Mayo Clinic staff) regarding whether chronic persistent hepatitis should be included within the definition of CALD; most authors prefer to exclude CPH from this category.

1. Autoimmune chronic active hepatitis

Autoimmune hepatitis was the first specific variety of CAH to be clearly defined (8, 9). Indeed, the earlier literature often dealt with this disease as though it was the only form of CAH.

Because it shares certain clinical and serologic features with systemic lupus erythematosus (SLE), this disease has often been referred to as "lupoid" hepatitis, among many other terms. The SLE-like features include a strong female preponderance, recurrent fever, non-deforming migratory arthritis, rashes, pleurisy and pericarditis; a positive antinuclear antibody (ANA) test is found in nearly all of these patients, and, indeed, is commonly regarded as an essential criterion for the diagnosis. Other serologic abnormalities include positive tests for rheumatoid factor, anti-smooth muscle autoantibody (SMA) and anti-mitochondrial antibody (AMA). Biologic false-positive tests for syphilis are also common.

Autoimmune hepatitis is generally regarded as only lupus-like and not a variety of SLE complicated by liver disease. The development of such liver disease in patients with a well-established diagnosis of SLE is unusual. Clinical nephritis rarely complicates autoimmune hepatitis and the characteristic pathologic changes of SLE, particularly in the kidney and spleen, are not often found at autopsy in autoimmune hepatitis patients.

The age distribution of autoimmune hepatitis is bimodal, most often affecting females in the age ranges of 10 to 25 and 40 to 60 years.

In addition to the "lupoid" features mentioned, during exacerbations these patients may be quite debilitated by malaise,

anorexia and fatigue. On the average, these symptoms are more prominent in autoimmune hepatitis patients than in patients with other types of CAH, who are more likely to be asymptomatic.

As in all forms of CAH, in the absence of therapy, the serum transaminase levels are chronically elevated, usually in the range of 100 to 300 i.u. Bilirubinemia and jaundice are seen during severe exacerbations or with advanced disease. The most prominent laboratory feature of autoimmune CAH, apart from the serologic abnormalities, is the marked hyperglobulinemia; levels up 6-8 grams/dl are often found in these patients. The HBsAg test is almost always negative, and this form of CAH does not develop as a consequence of post-transfusion hepatitis.

While the initiating factor(s) is unknown, genetic factors seem to be important in the pathogenesis of autoimmune CAH. Studies of patients' blood relatives reveals an increased prevalence in these families of positive ANA and SMA tests, hyperglobulinemia (10), and of other "autoimmune" diseases including SLE, rheumatoid arthritis, Sjogren's syndrome, iridocyclitis and pernicious anemia (11).

Mackay and Morris (12) first demonstrated the increased prevalence of HLA determinants A1, B8 and Dw3 in patients with autoimmune hepatitis and this has subsequently been confirmed by several other (but not all) groups. The prevalence of HLA-B8 is also increased with several other diseases including Graves' disease, Addison's disease, myasthenia gravis, Sjögrens syndrome and dermatitis herpetiformis/celiac disease (13). The association of HLA-B8 with SLE is a weak one, but HLA-DRw3 is more strongly associated (14). HLA-DRw3 is known to be in linkage dysequillibrium with HLA-B8 and is also associated with autoimmune hepatitis.

It has been proposed that patients with autoimmune CAH are genetically predisposed to develop an abnormally aggressive immune response to liver damage by unknown factors (viral?, toxic?) leading to persistent and progressive liver cell destruction. As discussed in the next section, this liver injury may be mediated by an antibody-dependent mechanism of cellular cytotoxicity (ADCC).

2. Chronic active type B hepatitis.

Chronic infection with hepatitis B virus (HBV) is the cause of about half of the cases of CAH seen in this country. The observation that this virus produces chronic active hepatitis in some patients, benign chronic persistent hepatitis in others and no disease at all in certain others ("healthy" carriers) is

believed to reflect differing host immune responses to the virus rather than infection with HBV strains of differing virulence.

In roughly half of cases, type B chronic active hepatitis develops insidiously and, since these patients are often minimally symptomatic or completely free of symptoms, the disease may be discovered only during routine examinations or at the time of blood donation.

In the remaining patients, CAH-B follows the incomplete resolution of acute type B hepatitis (AVH-B). Among patients with AVH-B who are sufficiently ill to seek medical attention, about 10% will fail to become HBsAg-negative within a three to four month period. The majority of these patients will develop some form of chronic hepatitis; two-thirds of them develop CPH and the other one third progress to CAH-B (15). It is unusual for the healthy carrier state (normal liver tests and near normal liver biopsy) to follow acute type B hepatitis, i.e. healthy HBsAg carriers usually lack a history of clinically apparent acute type B hepatitis.

3. Chronic active non-A, non-B hepatitis

When the specific serologic diagnosis of type A hepatitis became possible a few years ago, it was learned that none of the cases of HBsAg-negative post-transfusion hepatitis (currently 90% of post-transfusion hepatitis cases) were attributable to hepatitis A virus infection. Certain evidence suggests that these infections may be produced by at least two different non-A, non-B hepatitis viruses. At least one - and quite possibly both of these agents are capable of causing CAH, as well as CPH.

The limited information currently available suggests that the risk of acute non-A, non-B hepatitis progressing to chronic hepatitis (20-40%) is greater than for acute type B hepatitis (10%) (16, 17, 18, 19). However, the figure for non-A, non-B hepatitis is derived from experience with post-transfusion hepatitis patients, and the same infection in younger, basically healthier persons in whom non-transfusional hepatitis develops may not carry so high a risk of progression to chronic hepatitis.

Recent reports of the tentative identification of a "type C" hepatitis virus (20) may lead to specific assays for this virus.

There is no evidence that hepatitis A virus causes chronic hepatitis.

4. Drug-induced chronic active hepatitis

A great number of drugs produce liver injury in a small percentage of patients, by hypersensitivity, direct toxicity or unknown mechanisms. Most drug-induced hepatitis is of sufficient severity to lead to recognition of the liver injury in its acute stages.

A small number of drugs, perhaps because of their ability to produce rather low-grade, "silent" hepatic damage, produce a form of CAH which by clinical and liver biopsy criteria is indistinguishable from the other types of CAH. The diagnosis is made when liver tests become normal shortly after removal of the drug and promptly re-escalate on re-exposure to the same - or a related agent. Such a drug challenge may provoke a severe reaction in patients who have had "hepatitic" - as distinguished from cholestatic hepatotoxicity, and should be done cautiously and avoided if not essential to the diagnosis. The development of "allergic" phenomena including fever, arthralgias, rashes and eosinophilia also suggests the possibility of drug hepatotoxicity.

There do not appear to be any clearly documented cases of drug-related CAH which have remained active for more than six months after withdrawal of the drug (21), although several patients have been reported with chlorpromazine-induced cholestatic hepatitis which remained active and progressed to a biliary cirrhosis-like syndrome despite withdrawal of the drug (22).

One of the best documented causes of drug-induced CAH is *oxyphenisatin*, formerly a component of several over-the-counter laxatives, now removed from the market.

Isoniazid causes mild, asymptomatic liver injury not requiring discontinuation of the drug in 10-20% of patients (21). Black et.al. (23) reported 114 patients who developed overt hepatitis while receiving INH; in three the clinical features and liver biopsy were like other forms of CAH, and a fourth patient had developed cirrhosis.

Alpha-methyldopa also produces asymptomatic elevation of the serum transaminases (5% of patients) which generally subsides despite continued administration of the drug. In Toghill's series of 20 patients with significant methyldopa-induced liver injury, two had clinical and histological features of CAH (24).

There have been several reports of patients developing chronic hepatitis after prolonged *nitrofurantoin* therapy (25, 26, 27, 28). All 20 patients described to date have been women,

but since most chronic users of the drug are women, the significance of this is uncertain.

Two possible cases of CAH-like liver injury caused by *acetaminophen* have been described (29, 30). Seaman (31) reported a patient with *aspirin*-related hepatoxicity whose liver biopsy findings were considered consistent with CAH. Isolated instances of CAH have also been attributed to *sulfonamides* (32), *dantrolene* (a muscle relaxant) (33) and *propylthiouracil* (34).

It is of interest that several patients with drug-related CAH, particularly those with oxyphenisatin - and nitrofurantoin-induced disease, have had abnormal serologic tests as found in patients with autoimmune CAH, i.e. positive LE cell -, ANA - and SMA tests (21, 26).

5. Idiopathic chronic active hepatitis

Patients not assignable to the groups described above are left to this category. It is encouraging that, with time, this group becomes a progressively smaller fraction of all chronic hepatitis cases. It is suspected that many, if not most, of these cases will eventually be shown to have a viral etiology.

In the Dallas VAMC GI/Liver Clinic about 20 CAH patients are followed at any one time. In a recent survey of current cases, 12 (60%) had type B CAH and the remaining cases were divided between non-A, non-B CAH (developing after blood transfusion) and idiopathic CAH. In view of the high female to male ratio characteristic of autoimmune CAH, it is not surprising that such patients are not seen at the VA Medical Center, but this disease is also uncommon in the Parkland Hospital. Such patients are being seen by local private physicians, however.

II. PATHOGENESIS OF CHRONIC HEPATITIS

Much evidence suggests that the liver injury in chronic - as well as acute hepatitis is mediated by immunologic mechanisms. Evidence for humoral immunity has been obtained by the study of autoantibodies occurring in autoimmune CAH and of antibodies against hepatitis B viral antigens in both acute and chronic hepatitis. Some data support an immune complex mechanism of liver injury. Cellular immune reactions have been shown against antigens of hepatitis B virus and of hepatocyte plasma membranes. Diminished suppressor T cell activity, in some cases paralleling the degree of hepatitis activity, has been reported in CAH patients.

A great number of data concerning the immunopathogenesis of CAH have been published during the past decade. Because many studies have involved methodology of uncertain relevance to *in vivo* human conditions, have lacked appropriate controls, and have proven irreproducible, this has become what is probably the "muddiest" area in the study of chronic hepatitis.

Currently, the most popular hypothesis offered to explain the liver injury of CAH, particularly of the autoimmune type, invokes an antibody-dependent cellular cytotoxicity (ADCC) mechanism. It is proposed that, in response to liver injury by viruses, drugs or other unknown factors, certain antigens which are specific to the liver cell membrane become immunogenic. Antibodies developing against these antigens become affixed to them at the hepatocyte membrane and serve as targets for cytolytic (K-cell) lymphocytes.

A "chain of evidence" has been developed in support of the ADDC hypothesis;

1. Liver specific membrane antigens (at least two) have been identified (35).

2. Antibodies directed against these hepatocyte membrane antigens have been identified in the serum of patients with (autoimmune) chronic hepatitis and their frequency and titer were shown to parallel the severity of liver injury (36). (Figs. 1 and 2).

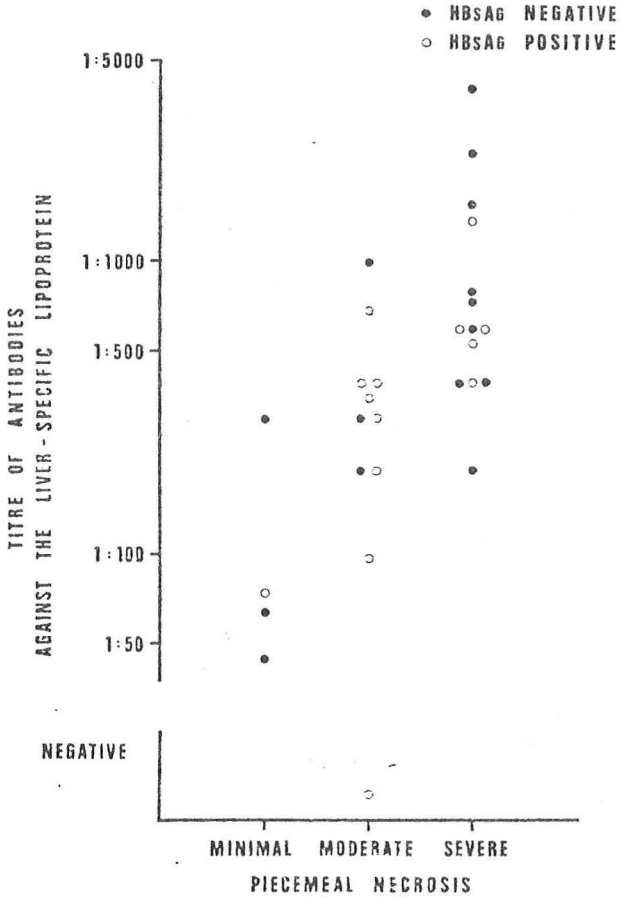

Figure 2. Antibody Titer in Relation to Severity of Piecemeal Necrosis in 29 Patients with Chronic Active Hepatitis (36).

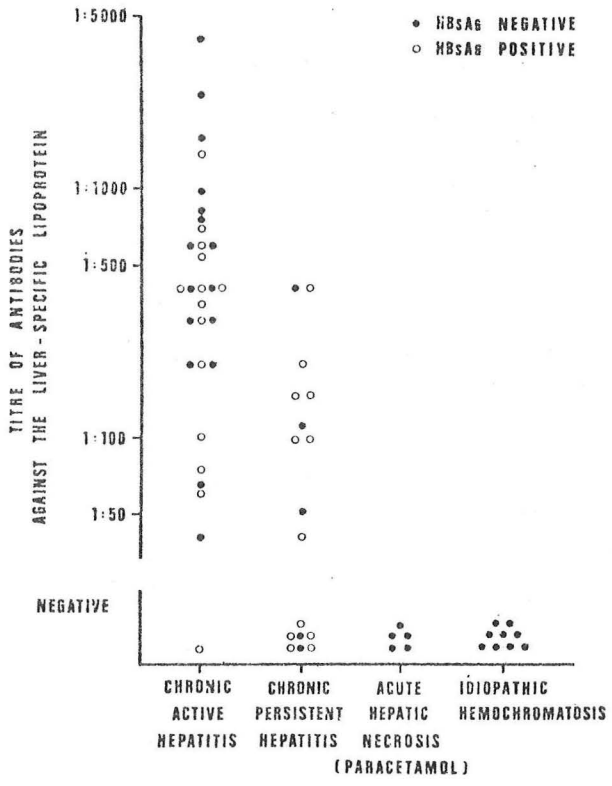

Figure 1. Antibody Titers in 30 Patients with Chronic Active Hepatitis, 17 with Chronic Persistent Hepatitis, Five with Fulminant Hepatic Failure Induced by Acetaminophen (Paracetamol) and Nine with Idiopathic Hemochromatosis (36).

3. By immunofluorescence, IgG (presumably antibody directed against the hepatocyte membrane antigens) has been demonstrated on membranes of liver cells from CAH patients. The IgG was distributed in a "linear" pattern over the entire membrane in patients with autoimmune CAH (cf. Goodpasture's syndrome) and in focal clumps in patients with type B CAH (as in immune-complex nephritis). The latter immunofluorescence pattern may be the result, not of the presence of anti-membrane antibody, but of fixation of circulating HBsAg anti-HBs complexes to Fc or C3 receptors on the hepatocyte membrane (37).

4. K-cell containing lymphocyte preparations from CAH patients have shown *in vitro* cytolytic activity against autologous liver cells (38) as well as against a variety of other human and animal liver cell targets.

Despite the persuasiveness of this collection of evidence, it is difficult to reconcile ADCC or, indeed, any other antibody mediated mechanism of liver cell injury with the recognition that both acute - and chronic active hepatitis are known to develop in patients with agammaglobulinemia, who are incapable of antibody production (39).

As with any disease suspected of involving an "autoimmune" mechanism of pathogenesis, various data support the possibility that the serologic abnormalities found in chronic hepatitis patients are merely secondary epiphenomena developing in genetically predisposed persons in response to liver cell injury.

III. DIFFERENTIAL DIAGNOSIS OF CHRONIC HEPATITIS

Three important chronic liver diseases may, on occasion, be confused with chronic active hepatitis.

Least common but perhaps most important is *Wilson's disease* (hepatolenticular degeneration). Correct diagnosis is imperative because specific therapy (penicillamine and other copper-chelating agents) is available and because, in the absence of appropriate therapy, the disease has crippling and lethal consequences.

Sternlieb and Scheinberg (40) first reported Wilson's disease presenting in young adults as a syndrome with the clinical and liver biopsy features of CAH. They estimated that in about 5% of Wilson's disease patients the disease is first manifested in this way.

LaRusso (41) measured 24-hour urinary copper excretion, hepatic copper concentration and serum ceruloplasmin in 54 patients with CAH.

The 24-hour urinary copper excretion was increased in about 50% of the patients, and was significantly higher during disease activity than during remission; it was in the Wilson's disease range in 10% of cases. Hepatic copper concentration was also increased in the majority of patients, and sometimes overlapped values reported in Wilson's disease. By contrast, serum ceruloplasmin levels were elevated in nearly half of these CAH patients and were never below the normal range. It was concluded that the serum ceruloplasmin test is the most reliable (and fortunately, least expensive) routine test to differentiate CAH and Wilson's disease. Slit-lamp examination for occult Kayser-Fleischer rings is also a simple and inexpensive test for Wilson's disease. It is recommended that these two tests be done on all persons below age 30 presenting with CAH.

Sherlock's group studied 17 patients with Wilson's disease presenting as CAH (42) (Figs 3 and 4). Neurological dysfunction was evident in only three and Kayser-Fleischer rings in 9. The serum ceruloplasmin was within the normal range in three of these patients with severe hepatic failure. Cirrhosis was present on initial biopsy in 15 of the 17 patients. Despite D-penicillamine therapy, four patients died within three weeks of diagnosis from fulminant hepatic failure associated with hemolysis, and an additional five patients died within two years. A sustained improvement was observed in eight patients.

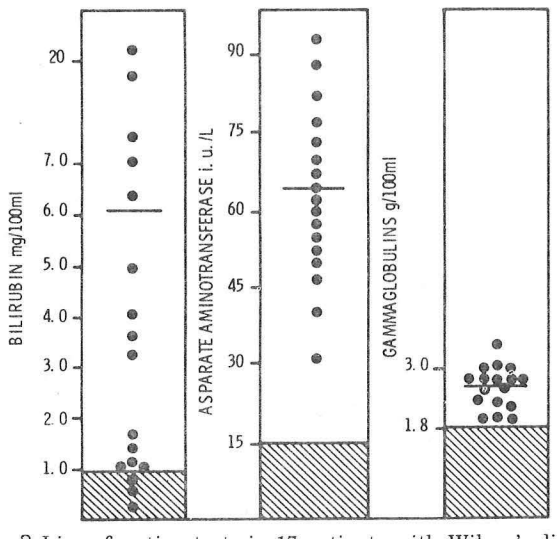

FIG. 3. Liver function tests in 17 patients with Wilson's disease at the time of presentation as chronic active hepatitis. *Horizontal lines* indicate mean values. Normal ranges are denoted by *hatching* (serum bilirubin, 0.2 to 0.8 mg dl^{-1}; aspartate aminotransferase, 4 to 15 IU liters $^{-1}$; γ-globulins, 0.7 to 1.8 g dl^{-1}). (42)

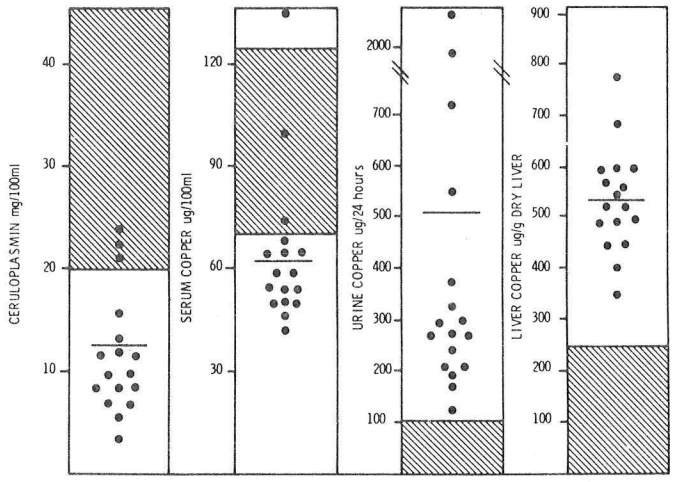

FIG. 4. Copper studies in 17 patients with Wilson's disease presenting as chronic active hepatitis. *Horizontal lines* indicate mean values. *Hatched areas* represent the normal ranges for serum ceruloplasmin (20 to 45 mg dl^{-1}) and serum copper (69 to 125 μg dl^{-1}) and delineates the levels above which urine copper (greater than 100 μg per 24 hr) and liver copper concentration (greater than 250 μg per g dry weight) are compatible with the diagnosis of Wilson's disease (42)

Sherlock's group advised that, although corticosteroids have no long-term usefulness in the treatment of Wilson's disease, they may be indicated together with D-penicillamine in cases presenting with this severe CAH-like syndrome. The hope is that, by stabilizing lysosomes the corticosteroids may prevent hepatic necrosis which has been attributed in Wilson's disease to lysosomal damage by copper leading to release of injurious acid hydrolases.

Primary biliary cirrhosis (PBC) is usually diagnosed by the presence of a combination of slowly worsening "obstructive" liver tests and a positive anti-mitochondrial antibody test in a patient (usually a middle-aged woman) shown to have a patent extrahepatic biliary tract (by ERCP, exploratory laparotomy, etc) and characteristic liver biopsy findings.

On occasion, these features are not sufficiently distinctive to allow the exclusion of chronic active hepatitis particularly of the autoimmune type in these female patients. In a Mayo Clinic series of 125 patients with chronic active liver disease, 15 (12%) presented with morphological features of the liver biopsy consistent with the diagnosis of both CAH and PBC (43). From their experience they concluded the two conditions could be distinguished by the response to corticosteroid therapy; those who ultimately developed more convincing evidence of PBC failed to respond.

The diagnosis of *alcoholic liver disease* is usually made easily when a liver biopsy is available. However, Goldberg described ten alcoholic patients with histological features on liver biopsy more consistent with chronic active or chronic persistent hepatitis than with alcoholic hepatitis (44). The disease became inactive clinically and histologically in two of these patients who markedly reduced their alcohol consumption. The possibility that these patients had non-alcoholic chronic liver disease cannot be excluded, however.

IV. TREATMENT OF CHRONIC ACTIVE HEPATITIS

Although CAH has been treated with a variety of different agents including penicillamine, chlorambucil, cyclophosphamide (45), transfer factor (46) and interferon (47), much evidence suggests that corticosteroids, possibly combined with azathioprine, are the current drugs of choice.

Convincing evidence that corticosteroids benefit at least some CAH patients has been provided by four different controlled studies (48, 49 50, 51) and is suggested in other studies (52, 53, 54).

Some of these studies also indicated that azathioprine, either alone (53, 54) or in combination with prednisone (50, 54) also produced improvement in some patients.

Cook, Mulligan and Sherlock (48) carried out the first controlled study, in which corticosteroids were used to treat 22 patients while a comparable, concurrent control group received no therapy (not a blinded study; no placebo-treated group included). Treated patients initially received 15 mg/day of prednisolone. This was progressively reduced to the smallest dose capable of maintaining a therapeutic effect - in most cases between 5 and 10 mg/day.

By the time the study was terminated, mortality was significantly higher in the control group (15 of 27; 56%) than in the corticosteroid treated group (3 of 22; 14%, $p > 0.005$).

In a study of 334 unselected cirrhotic patients in Copenhagen, half were treated with corticosteroids while the remainder served as controls (51). When the data were analyzed at the completion of the study only the subgroup of non-alcoholic females (without ascites) showed significant benefit from treatment. The majority of these patients were believed to have CAH, primarily of the autoimmune type.

Murray-Lyon et. al.compared prednisone 15 mg/day to azathioprine 75 mgs/day for treatment of 22 and 25 CAH patients, respectively (49). One prednisone-treated and six azathioprine-treated patients died ($p < 0.05$). The major deficiency of this study is the lack of a concurrent untreated control group; the data were compared to those from a historical control group.

The most elaborate and carefully designed study of CAH therapy has been conducted over the past decade at the Mayo Clinic (50, 55, 6). Five different treatment regimens were compared; (1) Prednisone 20 mg/day (Pred), (2) Azathioprine 100 mg/day (Az), (3) A combination of prednisone (10 mg/day) and azathioprine (50 mg/day (Comb), (4) A group receiving alternate day, single-dose prednisone therapy "titrated" to optimally suppress the serum transamine level (Pred-titrad) and (5) a placebo-treated control group.

Early in the study it was concluded that azathioprine alone was ineffective and therefore this treatment arm was discontinued; the Az data were combined with those of the placebo group in subsequent analyses. Later the placebo group was also discontinued. The Pred-titrad arm of the study was added even later. Therefore, not all treatment groups could be compared with concurrent controls.

TABLE II

Comparison of Treatment Programs for CALD: Mayo Clinic Study

Treatment	No. of patients	Remission: Clinical & biochemical	Remission: Histological	Remission: Later relapse	Remission: Sustained remission	Treatment failure: Death	Treatment failure: Other
Combination of prednisone (10 mg) and azathioprine (50 mg) daily	30	24	17	8	9	2	4
Prednisone, 20 mg daily	30	24	18	10	8	3	3
Prednisone, QOD - "titrated"	31	23	6	0	6	2	4
Control group	29	10	7	2	5	12	6

Data Comparisons	Differences*
Histological remission: Comb vs. Pred-titrad	p = 0.005
Sustained remission off therapy: Comb vs Pred-titrad	(p = 0.20) N.S.
Sustained remission: all treatment groups vs. control group	(p = 0.28) N.S.
Treatment failures: all treatment groups vs. control group	p = 0.002
Deaths:	
Comb vs Pred	(p = 0.50) N.S.
Comb vs Pred-titrad	(p = 0.23) N.S.
All treatment groups vs.control group	p = 0.0002

* Calculated by Fisher's exact test; 2-tailed p values

It was concluded that (1) three types of therapy, Pred, Comb and Pred-titrad were more effective than the azathioprine/placebo control drugs in producing biochemical and histological remission and reducing mortality (Table II); (2) among the three effective modes of therapy, Comb was optimal because drug-related complications were less frequent than with the Pred regimen and histological remission occurred more often than with Pred-titrad therapy. When histological relapse after withdrawal of therapy is considered, however, the advantage of Comb over Pred-titrad is less apparent; (3) the histological pattern of the initial liver biopsy influences the outcome of the disease (6). Cirrhosis developed more often in patients whose biopsies showed CAH with bridging necrosis (CAH-BN) or CAH with multilobular necrosis (CAH-MN) than in those with simple CAH ($p = 0.022$), (Table III)

Table III. Development of cirrhosis according to the morphology of the initial liver biopsy and form of treatment received (Mayo Clinic Study)

Treatment	Morphology of Initial Liver Biopsy			
	CPH	Simple CAH	CAH-BN*	CAH-MN **
Pred and Comb				
No. of patients	1	4	8	9
No. developing cirrhosis	0	0	1	3
Placebo and Azathioprine				
No. of patients	2	6	6	5
No. developing cirrhosis	0	1	3	4

* CAH-BN; CAH with bridging necrosis

** CAH-MN; CAH with multilobular necrosis

Similarly, mortality was less in patients with CPH or simple CAH than in those with the more serious patterns of liver injury ($p = 0.035$; one tailed) (Table IV).

Table IV. Mortality from chronic hepatitis according to the morphology of the initial liver biopsy and the form of treatment received (Mayo Clinic Study)

Treatment	Morphology of Initial Liver Biopsy				
	CPH	Simple CAH	CAH-BN	CAH-MN	CAH-C*
Pred and Comb					
No. of patients	2	5	9	9	7
No. of deaths	0	0	0	1	1
Placebo and azathioprine					
No. of patients	2	6	6	5	12
No. of deaths	0	0	1	5	6

* CAH-C; CAH with cirrhosis

These controlled trials were evaluated by Wright et. al. (56). They proposed a list of criteria for the optimal therapeutic trial of this type and assessed the degree to which each of the three major studies met these criteria (Table V). According to their standards, the Mayo study was clearly the best designed.

TABLE V. *Performance of chronic active hepatitis (CAH) studies according to proposed basic requirements for a controlled trial* (56)

Parameters	Hospital		
	Royal Free	King's College	Mayo Clinic
Definition of disease	(48)	(49)	
Precision of definition	N	P	Y
Limit of required abnormalities	N	Y	Y
Definition of patients			
Base line characteristics	Y	P	Y
Reasons for exclusion	Y	Y	Y
Numbers so excluded	N	N	N
Preselected therapeutic specifications			
Dose (initial and maintenance)	Y	Y	Y
Reasons for drug modification	P	Y	Y
Treatment duration	P	N	Y
Patients randomized	Y	Y	Y
Placebo	N	N	Y
Double blind evaluation	N	P	Y
Follow-up evaluation			
Frequency	Y	Y	Y
Adherence to schedule	N	N	N
Drug compliance	N	N	N
Precalculation of sample size	N	N	N
Description of end points	N	N	Y

[a] Abbreviations are: N, does not meet criteria; P, partially meets criteria; Y, meets criteria.

None of these studies were known to include more than a small percentage of patients with type B-CAH and their conclusions cannot be applied with confidence to this important form of CAH. A major objection to the Mayo study is that its admission criteria (SGOT greater than ten times normal or SGOT greater than five times normal with gamma globulin levels over twice normal, for a period exceeding ten weeks) would exclude a majority of patients with clinically significant CAH being treated in many clinics.

Wright et. al. (56) concluded from their review of these studies that the only patients with CAH in whom it has been established that benefit from corticosteroid therapy outweighs its potential toxicity are those who have severe histological abnormalities, are HBsAg-negative and are symptomatic. The natural history of patients with HBsAg-negative CAH who have milder histological abnormalities (simple CAH) remains uncertain, but the Mayo data suggest a relatively benign prognosis for such patients. Treatment efficacy for HBsAg-positive patients is also uncertain.

There appears to be ample justification for a major multi-center study designed to answer these questions.

A recommended treatment program for chronic active hepatitis

Patients who should be considered for treatment include primarily those with histological and biochemical evidence of severe chronic active hepatitis, the liver biopsy showing bridging - or multilobular necrosis or active cirrhosis. This is based on the evidence that the risk of progression to severe liver disease is considerably greater for these patients than for those with either CPH or simple CAH (6). In addition, treatment appears justified even in those patients with simple CAH if, over a prolonged period of observation, and with repeated liver biopsy, there is evidence of progression of the liver disease as indicated by rising serum bilirubin and globulins, lengthening prothrombin time, falling albumin, significantly increasing fibrosis on liver biopsy, deterioration of the liver-spleen scan pattern etc. If, on the basis of the above considerations, uncertainty remains concerning the need for treatment, the presence of symptoms provides additional justification for therapy.

Although most patients with CPH or simple CAH do not require treatment, they should be re-evaluated every three to six months by physical examination and laboratory tests. The liver biopsy should be repeated if the liver tests become worse or, in the case of simple CAH, after a year or two to rule out clinically occult progression to a more severe form of CAH.

Drug therapy is clearly contraindicated in any patient in whom the risk of steroid/azathioprine therapy exceeds the estimated risk of the liver disease. This includes some patients who are elderly, diabetic, or suffer from illnesses which significantly reduce their life expectancy. When such conditions exist, liver biopsy is justified only to exclude conditions other than chronic hepatitis in a patient having some evidence for another type of liver disease (granulomatous, alcoholic, toxic, neoplastic, etc.).

We do not regard type B-CAH as a contraindication to therapy.

A suggested approach to the treatment of CAH with corticosteroids and azathioprine

Patients considered candidates for therapy have been managed in our clinic according to the following sequential program.

A. Therapy is initiated with prednisone (or prednisolone) 40 to 60 mg, depending on the patient's size, given as a single dose every other morning. While relatively few patients respond to this regimen, it appears to be safer than daily steroid therapy as is widely reported in the literature; the only significant side effect we have noted is activation of latent diabetes. Initial therapy with a QOD schedule also has the advantage of a lesser risk of steroid withdrawal problems in patients who abruptly discontinue the drug and stop attending the clinic.

B. If QOD steroid therapy has not shown significant benefit after approximately three months, the second phase of this program is the use of a daily dose of 15-20 mg. of prednisone t.i.d. If this proves effective (which is unusual in patients with CAH of other than the autoimmune type), the dose is progressively reduced by 10-15 mg per week, until a level of about 20 mg daily is reached. At this point, some clinicians would more slowly reduce the daily dose to the minimal level providing satisfactory transaminase suppression (i.e. SGOT values of 100 i.u. or less). Being unconvinced that the alternate day, "titrated" steroid regimen is less effective than daily steroid administration, we prefer to change the patient back to the alternate day schedule at this point. As an example, for a patient whose transaminase level is adequately suppressed on 20 mg per day, the dose would be changed to perhaps 50 mg QOD. That dose would then be reduced to the lowest effective level.

C. If the patient fails to respond to the high-dose steroid regimen after two to three weeks of treatment, azathioprine (50 mg, 1 tablet-daily) is added, and the steroid dose is progressively reduced as described above. While some authors (54) have used azathioprine in a dose of 2 mg/Kg body weight (about 150 mg/day for the average male), we have been reluctant to use this potentially hepatotoxic drug in doses above 100 mg/day, but concede the possibility that the larger doses may be acceptably safe.

D. The final, and surely the most debatable stage of this treatment program concerns the management of those patients who fail to respond satisfactorily to the previously described regimens. In such patients, we have sometimes elected to continue treatment for prolonged periods with prednisone (10 mg) and azathioprine (50-100 mg), both given daily. This approach is based on the unconfirmed assumption that, if these diseases are ultimately self-limiting (as appears true in at least some cases) and, in some patients, they eventually become spontaneously inactive, one may be able to hasten the onset of inactivity and perhaps reduce the severity of the permanent liver injury present at that time by use of such maintenance therapy.

   Obviously, in such a situation, treatment on such uncertain grounds should be discontinued at the first sign of any consequential drug side-effects.

In view of the tendency for relapses of disease activity after cessation of treatment as demonstrated in the Mayo studies, we prefer to discontinue therapy very gradually once the patient appears to have reached remission. In general, treatment is continued until the serum transaminase level has remained within the normal range on at least three consecutive monthly determinations. At that time, the current steroid dose (typically in the range of 20 mg QOD) is reduced by 2.5 mg at a time every 2-4 weeks, checking the serum transaminase level before reduction. Our experience has been that if, in the course of such dose reduction, the transaminase rises (usually to twice normal or less) the drug dose should be held at the current level (not increased) and the test repeated 1-2 weeks later; it will often have returned to the normal range on retesting, and the dose reduction process can resume.

Regardless of the status of the chronic hepatitis, therapy should be stopped whenever drug side-effects develop or other considerations lead to the conclusion that continued treatment carries more risk than the untreated disease.

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