Liver

MEDICAL GRAND ROUNDS

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# CHRONIC ACTIVE "AUTOIMMUNE" HEPATITIS

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## HISTORICAL PERSPECTIVE

The first clinical description of what, in retrospect, was probably chronic active "autoimmune" or "lupoid" hepatitis was provided by Waldenstrom in 1950. In 1956 the sometimes impressive endocrine, specifically Cushings, features that may dominate the clinical presentation of this disorder was described by Kunkel and his associates. They described 26 young women with chronic liver disease among whom coarse nodular cirrhosis with hypergammaglobulinemia provided the backdrop for a clinical picture marked by a combination of amenorrhea, hirsutism, obesity, acne, pigmented abdominal striae, Cushingoid facies and arthritis.

The first indication that chronic liver disease might have an immunologic association was provided by Joske and King who described a patient in 1955 who they believed had a chronic form of viral hepatitis and whose blood, on multiple occasions demonstrated the then rather new phenomenon of LE-cells. Among seven other patients with presumed chronic viral hepatitis one more was found to have LE cells. The authors concluded that there were three possible explanations for the observed association:

1) the patients were suffering from both chronic viral hepatitis and SLE
2) the primary disease was SLE with predominant hepatic manifestations
3) the LE cell phenomenon was in some fashion the result of primary chronic hepatitis.

Thirty years later we have excluded the first possibility (not one taken seriously by the authors) and remain divided about the truth of the latter two.

The 1960s saw the development of a widespread interest in the subject. The phenomenology of CAH was recorded in a number of papers describing series of as many as 80 patients. The attention of much of the scientific community has remained fixed on immunologic processes and mechanisms in the ensuing years, but the interest of hepatologists was diverted comprehensively by the discoveries beginning in the late 1960s of serologic markers for the hepatitis viruses. These markers have led to the elucidation of much new information and knowledge concerning chronic viral hepatitis, but in the intervening years little new has been discovered concerning chronic "autoimmune" hepatitis. Indeed it is not even clear, in retrospect, how much of what was learned and written in the 1960s is true. The doubt derives from the recognition that many of the patients described originally as having chronic "lupoid" hepatitis were actually suffering from chronic viral hepatitis or had a drug-induced disease. It is time that clinical interest in this group of patients was rekindled.

1. *Schaffner F. Autoimmune chronic active hepatitis: three decades of progress. Progress in Liver Disease, Vol VIII:485, 1986.*
2. *Joske RA, et al. The "LE-cell" phenomenon in active chronic viral hepatitis. Lancet (ii):477, 1955.*
3. *Bearn AG, et al. The problem of chronic liver disease in young women. Amer J Med 21:3, 1956.*
4. *MacKay IR, et al. Lupoid hepatitis. Lancet (iii):1323, 1956.*
5. *MacKay IR, et al. Lupoid hepatitis and the hepatic lesions of systemic lupus erythematous. Lancet (i):65, 1959.*

## DEFINITION

The initial reports and descriptions of patients with chronic active hepatitis avoided the question of a definition for the disease. Definitions that were attempted simply identified the major manifestations (clinical and serologic) and excluded other known causes of liver disease. Thus, Mackay in 1961 identified five markers of autoimmunity in defining this disease. They were hypergammaglobulinemia, circulating autoantibodies, lymphoid infiltration of the liver, steroid responsiveness and association with other "autoimmune" processes. Some or all of these markers in the setting of a patient with a progressive form of liver disease which could not be accounted for by another known cause of liver injury warranted the application of the term chronic active "autoimmune" or "lupoid" hepatitis.

No better definition exists today. This is still a disease defined by clinical and serological manifestations none of which is specific. It is not surprising then that there is a substantial variation in which patients are included under this categorization at different centers. Nor is it surprising that within any series of patients carrying this diagnosis a very wide variability in clinical expression may be found. Indeed, it is probable that this loosely defined entity houses a number of essentially different disease processes.

1. *MacKay IR, et al. Autoimmunity in liver disease. Progress in Liver Disease, Grune & Stratton, Vol I:39, 1961.*

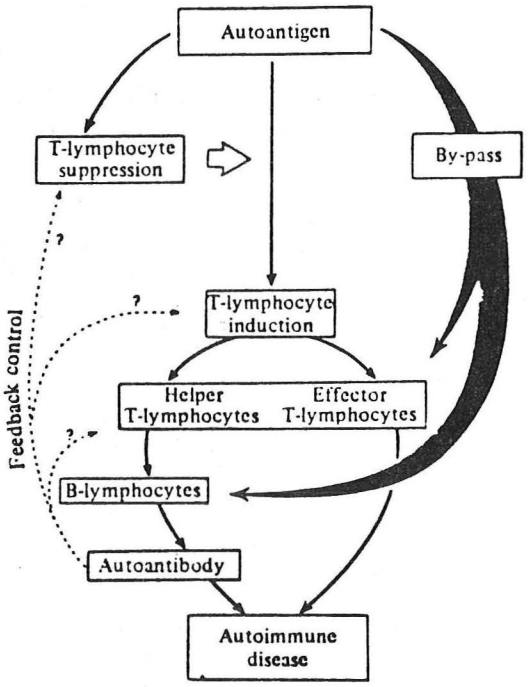
## ETIOLOGY

By definition, this form of chronic liver disease is understood to be an

"autoimmune" disorder. Autoimmunity is the state where immune reactions are generated against a "self" antigen.

In the normal state there are present in blood both T and B cells which have the capacity to recognize a variety of "self" antigens and promote an autoimmune reaction directed against them. The production of these cells is controlled by a separate population of suppressor T cells. Normal persons have also been shown to have low levels of circulating tissue-specific autoantibodies. It is believed that these antibodies may serve a role in a feedback loop which helps to limit the expression of the effector lymphocytes by promoting the suppressor cells. This system may go awry and result in autoimmune disease if there is:

1) promotion of the induction of the effector cells. It is argued that this may be under genetic control and account for the disproportionate frequency of HLA Types B8-DRW3 among patients with this disorder
2) inhibition of the specific suppressor cells
3) breakdown of the "feedback" control exerted by the cirulating auto-antibodies.




Schematic view of pathogenesis of autoimmunity. From McFarlane Clin. Science 1984.

The system may be bypassed by exogenous agents and/or drugs if they:

1) directly stimulate the induction of the effector T lymphocytes or autoreactive B lymphocytes

2) bear antigens which cross-react with cell surface "self" antigens
3) modify the surface antigens such that their "self" nature is obscured and they appear "foreign" to immunocompetent lymphocytes.

There remains substantial controversy over the mechanism of cell destruction in autoimmune diseases. The options appear to be:

1) direct effector T lymphocyte cytotoxicity
2) antibody dependent cellular cytotoxicity involving the interaction of the surface antigen with an autoantibody and subsequently the action of killer (k) cells
3) complement activated cytolysis occurring in response to an immune complex formed by the surface antigen and its autoantibody.

With specific respect to the liver and autoimmune attack, two candidate "self" antigens have been proposed:

Liver specific membrane lipoprotein (LPS) is found in what remains a crude extract of hepatocyte membranes. Antibodies to LPS are present in the sera of patients with acute viral hepatitis and many other forms of liver disease. The frequency of their occurrence seems to correlate more with the activity of the liver disease rather than its etiology. For this reason the autoantibodies might reflect the consequence of liver injury rather than be the case of its origin.

Liver membrane antigen (LMA) This is a liver specific, species cross reactive antigen found on the surface of fresh rabbit hepatocytes. Antibodies directed against this antigen have been found in the sera of patients with CAH, PBC, and cryptogenic cirrhosis (25% to 40%) and with very low frequency in patients with other liver diseases. It is not clear what, if any, relationship there is between LPS and LMA.

It is very probable that neither of these is the antigen functioning as the "self" antigen in chronic active "autoimmune" hepatitis.


1. *Nouri-Aria KT, et al. Effect of corticosteroids on suppressor cell activity in "autoimmune" and viral chronic active hepatitis. N Engl J Med 307:1301, 1982.*
2. *Galbraith RM, et al. Histocompatability antigens in active chronic hepatitis and primary biliary cirrhosis. Brit Med J 3:604, 1974.*
3. *MacKay IR, et al. HCA associations with autoimmune type chronic active hepatitis: Identification of B8-DRW3 haplotype by family studies. Gastroenterology 79:95, 1980.*
4. *McFarlane IG. Autoimmunity in liver disease. Clin Science 67:569, 1984.*

## CLINICAL FEATURES

### LIVER DISEASE

The liver disease in patients with chronic active "autoimmune" hepatitis is substantial almost by definition. However, it may not be the most clinically overt manifestation of the disorder and may indeed be silent until very late in the course of the disease. Involvement of organ systems outside the liver may cause recurrent problems to the patient and occupy center stage for most of the course of the illness until the complications of cirrhosis become apparent and then, too often, dominate the terminal period of the patient's life. On the other hand, the liver disease may be dramatic and may indeed be the only clinical manifestation of what apparently ends up being a one organ system disorder. The spectrum of hepatic involvement may lie anywhere between these two poles.

#### The acute and recurrent hepatitis presentation

Some patients present with what seems like a straightforward episode of acute (presumed viral) hepatitis. They have symptoms of malaise, fatigue, various GI complaints, dark urine and icterus. When these episodes are accompanied by arthralgias or even frank arthritis and skin rashes the possibility that they have a viral etiology remains tenable because of the well known association of acute hepatitis B and serum-sickness accompaniments. At times these episodes are accompanied by striking fever. This is very unusual in viral hepatitis unless the episode is fulminant and the presence of fever should raise serious questions about the etiology or severity of the hepatitis. Usually the chemical profile of such patients is quite typical for someone with acute viral hepatitis. The serum bilirubin is varyingly elevated depending on the severity of the acute process and the presence or absence of an associated hemolytic anemia. The serum alkaline phosphatase activity is elevated but not remarkably so and the serum activity of aspartate aminotransferace (AST) is usually greater than 500 u/ml. The prothrombin time is normal unless the acute injury is very severe and the serum albumin is usually preserved. There is generally a marked increase, polyclonally, in the gamma globulin fraction. Values of more than 3 g/dl are quite common.

Most of these acute episodes are self-limited. With bed rest (+/- hospitalization) there is resolution of symptoms and a return towards normal of the liver tests. Patients seem well on the way to recovery when, characteristically, there is a recrudescence of symptoms and of the chemical hallmarks of hepatitis. Untreated, this sequence may be repeated on a number of occasions. Each episode

may vary in severity and be spaced weeks or months apart. In the intervals it is unusual for the liver tests to return entirely to normal. Occasionally one or other of these episodes will be very severe and the patient will present a picture of acute hepatic failure and massive hepatic necrosis. In other patients the episodes of acute hepatitis will merge and run a subacute course with the gradual development of signs of chronic liver disease with portal hypertension, hypoalbuminemia, prolonged protime, peripheral edema, splenomegaly, and ascites. Ultimately the complications of chronic liver disease will dominate the picture and the patient may die with hepatic coma, variceal hemorrhage, intractable ascites and/or the hepatorenal syndrome within a matter of months from the onset of an apparently straightforward episode of acute hepatitis.

Patients who present with this "hepatitic" picture tend to be very responsive to therapy with corticosteroids so that this gloomy course and outcome is is less usual than before. More commonly, complete and often dramatic resolution of the acute episode is achieved with high dose steroids and maintained as the dose is tapered for chronic use. Relapses are very common, however, whenever steroid therapy is discontinued.

CASE REPORT W.W.:

1976 - 28 year old Black woman
Polyarthritis and jaundice
Maculopapular rash - face and arms
Splenomegaly
Coombes + hemolytic anemia (HT 19%)
Bil 6.2 mg%, Alk Ph 239, SGOT 500
ANA 1:1280, LE Prep +, Lupus Band Test -
SMA -, AMA -, Anti DNA Ab -
HBsAg -, Ceruloplasmin - Normal
Gamma globulin 3.9 g%
Dramatic response to steroids

1978 - D/C Steroids 2 weeks
Rash and jaundice
Bil 16 mg%, SGOT 1030, CPK 7, HT 31%
Liver Biopsy = CAH with bridging necrosis

1979 - D/C Steroids 1 month
Arthritis, rash, jaundice
Rapid response to steroids

July, 1979 - Cough and SOB (DLCO 28%)
Interstitial pulmonary fibrosis

1980 - Off steroids
Bil 3.6, SGOT 1900

1981 - Asymptomatic
Rx - 30 mg Prednisolone
LFTs normal

1986 - Probation Department requests records

*W.W. exemplifies the acute hepatitic presentation, the reason for the confusion with SLE (she qualifies for this diagnosis by the ARA criteria), the dramatic steroid responsiveness, the rapid relapse when treatment is stopped, the histologic progression of the disease, the association with other "autoimmune" processes (in this case interstitial pulmonary fibrosis) and the potential for long-term survival even if management is at times less than ideal.*

The occult hepatic presentation

It is more common for patients with chronic active "autoimmune" hepatitis to be unaware that they have any liver dysfunction and to come to medical attention because of the presence of extrahepatic associated disorders. If there are no other accompaniments the liver disease will be found only by serendipity (e.g. routine liver tests or an insurance examination) or will not be identified until cirrhosis is established and the complications of chronic liver disease become apparent. At this stage the patient's prognosis may be established by these irreversible complications and even successful interruption of further disease activity may not materially influence the patient's prognosis.

CASE REPORT B.H.:

23 year old Black woman
Abnormal LFTs found by serendipity
Isolated increase in SGOT (100-200 u/ml)
Biopsy = Chronic active hepatitis with bridging
ANA 1:320, SMA 3+, HBsAg -
AMA -, Anti DNA Ab -
Rx - Steroids - Normal LFTs
Lost to follow up after 9 months

CASE REPORT M.H.:

1977 - 76 year old Black man
Melena and varices

Jan '78 - U.G.I. hemorrhage
Encephalopathy
Emergency P-C shunt

April '78 - Liver biopsy = Chronic Active Hepatitis
ANA 1:5120 RA + SMA +
g glob 3.5 g%
Cryoglobulins +
Bil 1.3 Alk Ph 990 AST 110 Protine - normal

*B.H. illustrates the variation of clinical expression of the disease compared to W.W. She was asymptomatic, appeared to have no organ involvement apart from the liver disease which was substantial by biopsy despite minimal chemical disturbance. There was serologic evidence of autoimmune dysfunction and the disease responded promptly to steroids. She might well develop extrahepatic manifestation in the future, but otherwise would presumably not have come to medical attention until cirrhosis had become established and its complications manifest. This was the case with M.H. who presented with variceal hemorrhage.*

EXTRAHEPATIC MANIFESTATIONS

The frequency with which patients with chronic active "autoimmune" hepatitis manifest involvement of other organ systems is difficult to gauge insofar as the diagnosis is in part defined by such involvement. The relative frequency of specific organ involvement is more defined. It is apparent that skin rashes, polyarthritis and ulcerative colitis are the commonest associations and that cerebritis and renal involvement are uncommon. A very broad array of inflammatory lesions have been documented in patients with chronic hepatitis and few organ systems have been spared involvement.

Arthritis This is usually a non-deforming, non-erosive acute polyarthritis involving the hands, knees, wrists, and ankles. The incidence of overt joint involvement varies from 20% to 30%. Complaints of joint pain and stiffness without objective evidence of effusion are even more common. The episodes of polyarthritis are often associated with fever and maculopapular skin reactions. These episodes tend to coincide with recrudescences of hepatic disease activity. A very occasional patient will have a chronic deforming arthritis which mimics rheumatoid arthritis. These patients generally have associated ulcerative colitis as do the rare patient whose joint manifestations are those of ankylosing spondylitis.

Skin lesions A variety of different cutaneous manifestations have been described in these patients. The classic malar rash of SLE does occur but is unusual. Maculopapular rashes on other areas of the body are described. Occasional patients have had erythema nodosum and a rare patient has been described with chronic indolent ulcers around the ankles, palpable purpura, alopecia, photosensitivity or pigmentation. Acne may be a prominent feature in young woman with a Cushingoid presentation and occurs with high frequency in patients receiving steroid therapy. Perhaps as many as 20% of untreated patients will manifest skin involvement. The maculopapular eruptions tend to be associated with exacerbation of liver disease activity.

CASE REPORT W.L.:

1974 - 34 year old Black woman
Acute hepatitis

1977 - Polyarthritis
Discoid lupus rash, alopecia
Raynaud's phenomenon

1979 - Bil 0.7 Alk ph 118 AST 116
g globulin 5.0 g% ANA + RA +

1981 - Liver biopsy = Active P.N. Cirrhosis
ANA + Coombes + Lupus band test +
SMA - AMA - anti DNA Ab -
RX - steroids - no effect on LFTs

*W.L. demonstrates the presentation with skin and joint manifestations that are evocative of SLE. This is enhanced by the serologic abnormalities and the positive lupus band test.*

Ulcerative colitis (UC) Approximately 10% to 20% of patients with chronic "autoimmune" hepatitis are afflicted also with ulcerative colitis. There tends to be no correlation between the activity of the UC and the activity of the liver disease. In some patients the liver disease precedes clinical evidence of ulcerative colitis, while in other patients the liver disease develops long after the onset of the bowel disorder. Generally the liver disease in these patients is occult and declares itself only when cirrhosis is already established or is discovered by the coincidental finding of abnormal laboratory tests during an episode of diarrhea. In patients where colectomy became necessary because of the complications of UC no ameliorating effect was noted on the liver disease.

CASE REPORT D.F.:

1972 - 15 year old White man
Asymptomatic
Abnormal LFTs
Intermittent steroids

1978 - Diarrhea, edema, ascites
Splenomegaly
Proteinuria (1.75 g/day) 20-30 RBC
Ulcerative colitis

1978 - Bil 0.5 mg%, Alk Ph 163, SGOT 73
Alb 2.6%, Cr 0.9 mg%, HT 28%
ANA 1:80, LE -, SMA -, AMA -, RA -
Liver Biopsy: Active PNC

1979 - Leveen Shunt
Lots of P.O. problems
Died of sepsis and bleeding

*D.F. demonstrates that UC may develop long after the onset of the liver disease, that without effective therapy asymptomatic liver disease may progress to a terminal condition, that renal disease may occur in these patients and that none of the seologic markers may be present in an individual patient whose clinical lesions bespeak an immunologic process.*

Pulmonary disease Pleurisy is described in a few patients in each series of patients reported in the literature. This may be manifest as episodes of pleuritic chest pain with an audible rub in a patient with no other pulmonary symptoms, signs, or radiologic findings. Alternatively, it may present as a pleural effusion (perhaps accompanied by a pericardial effusion) the fluid from which has exudative characteristics.

More ominous for long-term survival is the development of interstitial pulmonary fibrosis. This usually becomes manifest by the development of symptoms of shortness of breath and non-productive cough years after the onset of the liver disease. It may develop and progress despite therapy with corticosteroids which has effectively suppressed the evidence of hepatic activity. Pulmonary function tests reflect restrictive lung disease. A reticulo-nodular infiltrate which is most prominent in the lower lobes appears on chest X-ray and lung biopsy findings of interstitial fibrosis and mononuclear inflammation are demonstrable.

Another ominous pulmonary phenomenon is the development of pulmonary hypertension. This appears to be a primary process and not the consequence of recurrent pulmonary emboli. Its long-term consequence includes severe right sided heart failure. The pulmonary parenchyma remains normal in these patients and the lesions appear to be confined to the small pulmonary arterial vessels.

CASE REPORT D.C.:

Aug '81 - 53 year old Black woman
Malaise, arthritis, jaundice
Clinical resolution

Oct '81 - Arthritis (hands), Raynaud's, jaundice
Bil 24 mg%, Alk ph 256, SGOT 2500
CPK 52, HBsAg -
11 days later: Bil 4.8, SGOT 133

Nov '81 - Jaundice, Bil 12.0, SGOT 900
ANA 1:2560, SMA -, AMA -, Anti DNA Ab -
11 days later: Bil 4.8, SGOT 465
Liver Biopsy: Acute "Plasma Cell" Hepatitis

Dec '81 - SGOT 1000
Rx - steroids: Rapid complete resolution
Diabetes but normal LFTs

April '84 - Cough, SOB
CXR - Reticulonodular infiltrate
CPK 1000
Lung Bx - Interstitial fibrosis, inflammation
Rx - 60 mg qd Prednisolone

March '85 - PFTs worse
Steroids tapered
Normal LFTs

Oct '85 - Died, infections and seizures
Autopsy refused

*D.C. exemplifies the classic recurrent acute hepatitic presentation, the plasma cell inflammation, the steroid responsiveness, the association with probable myositis and progressive interstitial pulmonary disease and the fact that even when the liver disease responds to Rx an associated mortality remains.*

Renal disease Most patients with chronic "autoimmune" hepatitis have normal renal function. There are a small number of such patients, however, who do have a nephropathy. There appears to be two distinct renal lesions:

a) some patients have membraneous or membrano proliferative glomerulonephritis. They present with evidence of nephrotic syndrome or with chronic renal insufficiency which is usually mild.

b) some patients present with polydipsia, polyuria muscle weakness accompanied by nausea and vomiting. These patients have renal tubular acidosis and are found at autopsy to have an interstitial nephritis occasionally with calcinosis.

Cerebral disease Evidence of cerebritis is uncommon in this population but occasional patients are described with seizure disorders or with psychotic episodes that strongly suggest a direct cause and effect relationship.

Muscle disease The early series did not describe patients with polymyositis but, more recently, occasional case reports have been published in which this has been a major manifestation. Our own experience supports the association. At times the only evidence of the muscle involvement may be an asymptomatic increase in the serum activities of muscle enzymes such as CPK or aldolase. In other patients the myositis dominates the clinical picture with marked weakness (especially proximally) with aches and stiffness and muscle tenderness. The patient may complain of red urine from the myoglobinuria. Control of the muscle disease may be much more difficult to achieve than control of the accompanying liver disease.

Hematologic disorders Coombes positive hemolytic anemia is a well documented accompaniment of chronic "autoimmune" hepatitis as is an immunologically mediated thrombocytopenia. Leukopenia, anemia, and thrombocytopenia are frequently present in these patients but the concurrence of multiple factors may contribute to their presence and it is often difficult to ascribe an immunologic basis to these hematologic abnormalities. Thus, the iron deficiency associated with ulcerative colitis and the hypersplenism associated with cirrhosis and congestive splenomegaly account for most instances of a selective or pan reduction in the formed elements of the blood.

Thyroid disorders There is sometimes a past history of hyperthyroidism partic-

ularly in the older patients. Established Hashimoto's thyroiditis has been described in an occasional patient in most reported series.

Endocrine abnormalities A striking but unusual presentation of chronic "autoimmune" hepatitis is seen in occasional young women who are evaluated for what appears to be Cushing's syndrome. They complain of amenorrhea, hirsutism, acne, truncal obesity and purple abdominal striae. The metabolism of endogenous corticosteroids is impaired by liver disease and this presumably contributes to the production of these findings in a population of patients particularly predisposed by age and sex to manifest them. There is no evidence that steroids are produced excessively or inappropriately in these patients.

Iatrogenic Cushing's syndrome is readily produced in patients with chronic liver disease so that there is a high incidence of the cosmetic features as well as the more sinister findings of proximal myopathy, osteoporosis, diabetes and hypertension. Even low doses of corticosteroids may provoke substantial evidence of this complication of therapy in these predisposed patients.

Other organ involvement Uveitis, keratoconjunctivitis sicca, percarditis, and myocarditis with conduction defects have all been described as isolated accompaniments of chronic active "autoimmune" hepatitis.


1. *Read AE, et al. Active 'juvenile' cirrhosis considered as part of a systemic disease and the effect of corticosteroid therapy. GUT 4:378, 1963.*
2. *Reynolds TB, et al. Lupoid hepatitis. Ann Int Med 61:650, 1964.*
3. *Mistilis SP, et al. Natural history of active chronic hepatitis clinical features, course, diagnostic criteria, morbidity, mortality and survival. Australian Ann Med 17:214, 1968.*
4. *MacLachlan MJ, et al. Chronic active ("lupoid") hepatitis. A clinical, serological and pathological study of 20 patients. Ann Int Med 62:425, 1965.*
5. *Cohen N, et al. Concurrent "active juvenile cirrhosis" and "primary pulmonary hypertension". Amer J Med 39:127, 1965.*
6. *Dordal E, et al. Hepatic lesions in chronic inflammatory bowel disease. Clinical correlations with liver biopsy diagnosis in 103 patients. Gastroenterology 32:239, 1967.*
7. *Silva H, et al. Renal involvement in active "juvenile" cirrhosis. J Clin Pathol 18:157, 1965.*

8. *Popp JW, et al. Cutaneous vasculitis associated with acute and chronic hepatitis. Arch Int Med 141:623, 1981.*
9. *Bradley JD, et al. Chronic active hepatitis associated with polymyositis. J Rheumatol 12:368, 1985.*
10. *Bloom JN, et al. Uveitis complicating autoimmune chronic active hepatitis. Amer J Dis Child 137:1175, 1983.*

## PATHOLOGY

Chronic hepatitis has similar pathologic features independent of etiology. There is an "active" component which is defined by the presence of cell necrosis and inflammation and a "chronic" component which is defined by the repair processes employed by the liver in response to the acute injury.

The necrosis is found throughout the lobule of the liver and varies in severity from scattered foci of single cell "drop out" to submassive necrosis with panlobular necrosis where every cell in the lobule is destroyed. The severity of the "hepatitis" correlates generally with the clinical severity of the disease "activity". Early in the course of the disease the biopsy may show only this "hepatitis" feature and be indistinguishable from the lesion seen in patients with acute viral hepatitis. The necrosis may appear as eosinophilic necrosis leading to the formation of Councilman bodies and/or as balloon necrosis with large swollen degenerating cells. These tend to be particularly prominent centrilobularly. The most common morphologic manifestation of parenchymal necrosis is "cell drop out" which refers to the replacement of necrotic cells by an accumulation of inflammatory cells and macrophages. These foci may be very small and represent single cell loss or they may consist of large confluent areas which may link vascular structures (portal tracts and central veins) and constitute "bridges" of necrosis. Much emphasis has been given in the past to the destruction of the layer of cells abutting the portal triads. The loss of this "limiting plate" has been given an undue significance in diagnosis and prognosis. It is true that in patients with progressive forms of chronic hepatitis the portal tracts are enlarged and there is destruction of the immediately adjacent parenchyma. The continued loss of individual periportal cells results in an irregular outline to the portal tract/parenchymal interface. An impression is created that the portal tracts are

expanding by the progressive outward erosion of the cells at this junction. The term "piecemeal necrosis" was coined to describe this pattern. The terms "loss of the limiting plate" and "piecemeal necrosis" became synonymous unfortunately with the diagnosis of chronic active hepatitis. The implication of an inevitably progressive course also became linked to this pathologic feature. In reality, the destruction of the limiting plate is a nonspecific event which, per se, has no implications as to etiology or prognosis. Is is very common in patients with acute viral hepatitis and some of the very best examples of this pathologic finding are to be found in patients with alcoholic liver disease and extrahepatic biliary obstruction.

The inflammatory response in chronic hepatitis is mononuclear in type. Lymphocytes and plasma cells are concentrated in the portal triads and in the foci of cell necrosis. At times the plasma cell infiltrate is particularly striking. This accounts for one of the many names applied to patients with chronic active "autoimmune" hepatitis in the early years; to wit, plasma cell hepatitis. Lymph follicles may form in the portal tracts and occasionally there may be an inflammatory destruction of small bile ductules. None of these findings, however, are specific for the autoimmune variant of chronic hepatitis. Heavy plasma cell infiltrates, duct lesions and lymph follicles may all be found on occasion in patients with chronic viral hepatitis as well.

The second pathologic component is that which reflects the hepatic repair processes. When liver cells are destroyed two consequences may follow. The liver may regenerate and replace the damaged cells with new parenchyma or it may, in part, repair the injury by the deposition of collagen. The degree to which the latter occurs and the rate at which it occurs determines the long-term prognosis of patients with chronic hepatitis no matter what the cause. Thus, when regeneration is the entire repair response there is no progressive loss of hepatic mass despite continued activity, the liver disease is benign, the patient's prognosis is excellent, and specific therapy is not warranted. This is the situation with chronic persistent hepatitis. The degree to which fibrosis forms part of the repair process is independent of the severity of the acute process (except perhaps in an inverse way) but is influenced by etiology. Thus, patients with chronic "autoimmune" hepatitis virtually always have, as a part of their pathology and their natural history, the progressive deposition of fibrous tissue. This is not so with chronic viral hepatitis where the majority of patients heal by regeneration alone, but it is true for those patients with chronic alcoholic hepatitis where fibrogenesis also appears to be a constant.

The fibrous tissue is deposited in the expanded portal tracts and may form bands as well which course through the hepatic substance. These are presumed to represent areas of previous submassive hepatic necrosis. They may link the vascular structures or be independent of these. Ultimately, the surviving parenchyma between these bands regenerates and forms nodules which vary greatly in size. Some are usually quite large and are readily visible to the naked eye. The presence of bands of fibrosis and nodular regeneration defines the presence of cirrhosis. This coarsely nodular pattern is varyingly called "macronodular" or "post necrotic" cirrhosis.

The four patterns of chronic hepatitis that can be identified by the nature and extent of the repair processes are:

Chronic persistent hepatitis - regeneration is the sole mechanism of repair. If the disease becomes more active (i.e. increase in necrosis and inflammation) the term "chronic lobular hepatitis" is employed. The significance remains unchanged because the repair process is still by regeneration.

Chronic active hepatitis - portal tract fibrosis is present but the fibrous tissue appears to be confined to the expanded portal tracts.

Chronic active hepatitis with bridging - as above, but with bands of fibrous tissue linking vascular structures.

Post necrotic cirrhosis - bands of fibrous tissue and coarse nodular regeneration.

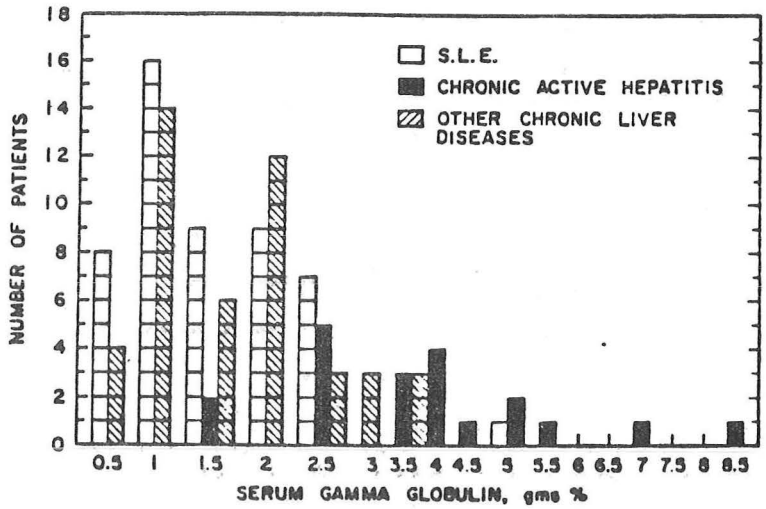
The prognostic significance of each of these pathologic patterns differs depending on etiology. Thus, patients with chronic active "autoimmune" hepatitis have a progressive disease that (untreated) will lead to cirrhosis no matter what the biopsy shows at any given time. Patients with chronic viral hepatitis have a predictably benign course if the biopsy pattern is that of chronic persistent hepatitis and a predictably progressive course if the biopsy shows bridging. The prognosis in patients with chronic active hepatitis without "bridging"is quite unpredictable when the etiology is viral. In some patients the disease will progress further with time but many (? most) patients do not show deterioration towards cirrhosis despite continued activity for years.


1. *De Groote J, et al. A classification of chronic hepatitis. Lancet (ii):626, 1968.*
2. *Boyer JL. Chronic hepatitis - a perspective on classification and determinant of prognosis. Gastroenterology 70:1161, 1976.*
3. *Scheuer PJ. Changing views on chronic hepatitis. Histopathology 10:1, 1986.*

## SEROLOGIC MARKERS

Hypergammaglobulinemia This was the first marker described in patients with chronic hepatitis that suggested an "immune" association. It is obviously not a specific finding and is not universal. It is, however, very common and the levels of gammaglobulin may be strikingly high (e.g. 6 to 7 gm%). The increase is polyclonal and the subclass most affected is IgG.

SERUM GAMMA GLOBULIN LEVELS IN PATIENTS WITH CHRONIC ACTIVE HEPATITIS, SYSTEMIC LUPUS ERYTHEMATOSUS AND OTHER FORMS OF CHRONIC LIVER DISEASES




From MacLachlan, et al. Ann Int Med, 1965.

LE cells The LE cell phenomenon was described before there was widespread recognition that it represented an insensitive measure of certain antinuclear antibodies. There is subjectivity to the reading of the slides and the determination of what is and what is not a positive finding. It is not surprising then that the frequency of a positive test in patients with chronic "autoimmune" hepatitis is quite low and quite inconstant from time to time. The presence or absence of this phenomenon is not associated with any particular component of clinical expression, pathologic finding, therapeutic responsiveness, or prognostic consequence. It was the demonstration that the presence of LE cells in patients with chronic hepatitis represented a "nonentity" that contributed to the aversion hepatologists have since had for the term "lupoid" hepatitis.

Antinuclear Antibodies (ANA) The presence of ANA contributes to the definition of chronic active "autoimmune" hepatitis so it is not surprising perhaps that this test is positive in a majority of patients with the disorder. Most series record positive tests for ANA in 50% to 90% of the patients reported. The titer of ANA may be very very high and the pattern of nuclear staining is usually speckled or diffuse. There has been little attempt to define specific antibodies within the broad range of ANAs in this patient population. The one exception to this is the virtual absence of reports of antibody directed against double-stranded DNA in patients with "autoimmune" hepatitis when specific assays using crithidia luciliae were employed. Earlier reports using very nonspecific substances reported a high frequency of anti DNA antibodies in patients with chronic hepatitis. In retrospect, these antibodies were directed against single stranded DNA, histones and other nuclear antigens.

The reason for the appearance of ANA in these patients is not known. They are not believed to be important in the initiation or propagation of tissue injury and are generally considered to be paraphenomena of the process. Some patients with multisystemic disease do not display these antibodies. The presence of ANA is not, therefore, a sine qua non for the diagnosis of chronic active "autoimmune" hepatitis.

Anti-Smooth Muscle Antibody (SMA) The presence of circulating antibody to a constituent (probably actin) found in species-nonspecific smooth muscle cells is probably the single most characteristic feature of chronic active "autoimmune" hepatitis. This antibody was first identified in 1966 and since then it has been evaluated principally within the confines of patients with various liver diseases. It is present in low titer in many patients with a wide variety of hepatic diseases. It's presence in titers exceeding 1:80 is unusual, however, in patients who do not have "autoimmune" hepatitis, primary biliary cirrhosis, or cryptogenic cirrhosis. Again, this antibody is considered to be a paraphenomenon rather than an integrally important pathogenetic marker in patients with chronic hepatitis. There have been only a few studies assessing the presence of SMA in other collagen vascular disorders. None of the small numbers of patients with SLE, for example, who were investigated by this assay had antibodies detected. The frequency with which the antibody is detected in patients with chronic active "autoimmune" hepatitis is very variable. Some series describe the finding in more than 60% of patients. Our experience, which is probably in accord with the majority of centers, is that this antibody occurs in only 20% to 30% of patients who qualify for the diagnosis.

Anti-Mitochondrial Antibody (AMA) Circulating antibody directed against an antigen on the inner membrane of species and organ nonspecific mitochondria is most commonly associated with the diagnosis of primary biliary cirrhosis. Indeed, greater than 90% of people with this disorder test positively for this antibody. A smaller proportion of patients (perhaps 20% to 30%) who have chronic active "autoimmune" hepatitis also have a positive test for AMA. This antibody is not considered to be pathogenetically important for either disease.

Antibodies to LPS and LMA Tests for these antibodies are not commercially available. They have been considered to be potentially important in the autoimmune process in patients with chronic hepatitis. Antibodies to LPS have been shown to be present in many different liver diseases, to correlate with evidence of disease activity and (at least from one center) to be useful in predicting the occurrence of relapse when corticosteroid therapy has been withdrawn. It is unlikely, however, that utility of these assays will become widespread.

Other markers A proportion of patients with chronic active "autoimmune" hepatitis have positive Rheumatoid factor, positive Coombes test, depressed levels of complement, components and/or demonstrable circulating immune complexes. These findings are not specific for autoimmune hepatitis obviously, but their presence lends credence to the concept of an autoimmune process being responsible for the liver disease present in such patients.


1. *Eddleston ALWF. Immunology of chronic active hepatitis. Quart J Med 55:191, 1985.*
2. *Kunkel HG, et al. Extreme hypergammaglobulinemia in young women with liver disease of unknown etiology. J Clin Invest 30:654, 1951.*
3. *Soloway RD, et al. "Lupoid" hepatitis, a nonentity in the spectrum of chronic active liver disease. Gastroenterology 63:458, 1972.*
4. *Johnson GD, et al. Antibody to smooth muscle in patients with liver disease. Lancet (ii):878, 1965.*
5. *Whittingham S, et al. Smooth muscle autoantibody in "autoimmune" hepatitis. Gastroenterology 51:499, 1966.*
6. *Sontheimer RD, et al. An immunofluorescence assay for double stranded ANA antibodies using the crithidia luciliae kinetoplast as a double stranded DNA substrate. J Lab Clin Med 91:550, 1978.*

7. *Jain S, et al. Double stranded DNA-binding capacity of serum in acute and chronic liver disease. Clin Exp Immunol 26:35, 1976.*
8. *McFarlane IG, et al. Antibodies to liver-specific protein predict outcome of treatment withdrawal in autoimmune chronic active hepatitis. Lancet (ii):954, 1984.*
9. *Thomas HC, et al. Immune complexes in acute and chronic liver disease. Clin Exp Immunol 31:150, 1978.*

## DIFFERENTIAL DIAGNOSIS

There are two levels of differential diagnostic difficulty. One is in distinguishing chronic active "autoimmune" hepatitis from other forms of chronic liver disease. The other is in distinguishing it from other (if other they be) autoimmune diseases such as systemic lupus erythematsus (SLE).

### Chronic viral hepatitis

The clinical, chemical, radiographic and histologic features of the hepatic disease seen in chronic active "autoimmune" hepatitis may be indistinguishable from those seen in chronic viral hepatitis. In such instances distinction between them depends on the presence of extrahepatic manifestations, the presence of autoantibodies, or the presence of serologic markers of hepatitis B infection. There does appear to be a major difference in the natural history of these two causes of chronic hepatitis. Chronic active "autoimmune" hepatitis virtually always results in progressive damage to the liver and leads to cirrhosis unless treated effectively. Chronic viral hepatitis is most often a benign and nonprogressive disease although a proportion of affected patients do develop cirrhosis and its sequelae.

### Chronic drug induced hepatitis

Revision of some of the early series of chronic active "autoimmune" hepatitis identified a subset of patients whose disease was actually caused by the administration of certain drugs. The two agents that were commonly identified were "over the counter" laxative preparations containing oxphenisitan (subsequently withdrawn from the market) and alpha methyl dopa (aldomet). The liver disease caused by these drugs was not distinguishably different from that occurring without a drug association. There was a high incidence of circulating autoantibodies, hypergammaglobulinemia, lymphocytic infiltration in the liver and steroid

responsiveness. Withdrawal of the offending agent resulted in abatement of clinical and chemical activity and, in effect, long-term resolution of the disease. It is likely that other drugs may be responsible for some cases of what are presumed to be instances of chronic active "autoimmune" hepatitis.

Primary biliary cirrhosis

In its characteristic form, this disorder causes no diagnostic confusion with "lupoid" hepatitis. A middle-aged woman who complains of persistent pruritus without skin disease, who may have keratoconjunctivitis sicca, hyperpigmentation, steatorrhea, or xanthomatosis and whose liver tests are remarkable for an extremely high serum alkaline phosphatase activity does not conjure up the diagnosis of chronic hepatitis. A high titer in serum of antimitochondrial antibody and a biopsy showing the characteristic interlobular necrotising cholangitic lesion is likewise quite diagnostic. There are patients, however, where distinction between PBC and CAH is not clear-cut. Some patients with chronic "autoimmune" hepatitis have a distinctly "cholestatic" flavor to their acute "hepatitic" episodes, approximately 30% of patients with primary biliary cirrhosis have a positive ANA test and a minority have circulating smooth muscle antibodies. On the other hand, approximately 30% of patients with chronic "autoimmune" hepatitis have antimitochondrial antibodies in their sera. Some extrahepatic manifestations (particularly skin, lung, and renal disease) may be seen in patients with PBC. A percutaneous needle biopsy of the liver may fail to disclose the characteristic ductular lesion of PBC. In such case the histologic abnormalities may resemble very closely the pattern seen in chronic active hepatitis. Somewhat atypical but nonetheless quite definite ductular lesions have been described in patients with chronic hepatitis. Indeed, at times, one just cannot determine whether a given patient has a cholestatic form of chronic active "autoimmune" hepatitis or an atypical form of PBC.

Wilson's disease

Acute on chronic liver injury of unidentified cause in a young person should raise the diagnostic question of Wilson's disease. The concurrence of acute hemolysis enhances this possibility. Though rare, this disease is eminently treatable. Appropriate evaluation of copper metabolism will allow the proper diagnosis to be made.

Cryptogenic cirrhosis

There exists a group of patients, usually middle aged women, who present

with evidence of acute hepatitis and are found already to have established post necrotic cirrhosis. Alternatively they come to medical attention because of the complications of cirrhosis but without much evidence of acute disease past or present. These women have no toxin, drug, or hepatitis virus exposure, do not drink alcohol, and cannot be shown to have any known cause for hepatic dysfunction. They are, therefore, declared to have "cryptogenic" cirrhosis. There is an immunologic flavor to such patients. They have a frequency of low titer ANA levels, of positive RA latex tests and weakly positive SMA or AMA tests. They do not, however have florid evidence of autoimmune disease. Some of these patients probably have chronic non A/non B viral hepatitis. The determination of definitive criteria that separates such patients from those with chronic active "autoimmune" hepatitis has never been made. It is indeed impossible to say what are the minimal criteria necessary to establish this latter diagnosis. In the absence of such there will continue to be confusion as to who should be counted as having chronic active "autoimmune" hepatitis and who should be designated as "cryptogenic" cirrhosis.

Systemic Lupus Erythematous (SLE)

To the extent that both chronic "autoimmune" hepatitis and SLE are multisystemic diseases of autoimmune origin and to the extent that they respond to the same therapeutic agents there may be little point in trying to distinguish between them. It is remarkable, however, that such a clear distinction has been implied by the literature pertaining to these two disorders that the question of their being essentially the same disorder has seldom been raised since the authors of the early case reports of chronic active hepatitis coined the sobriquet "lupoid" hepatitis. It has been an accepted tenet that significant liver disease does not occur in patients with SLE and therefore any patient presenting with a lupus-like syndrome and predominant liver disease must have chronic active "autoimmune" hepatitis. There is no doubt that the majority of patients with chronic active "autoimmune" hepatitis manifestly do not have SLE as it is defined. This definition is, however, a very loose one. The 1982 classification of the American Rheumatologic Association requires any 4 of the following 11 criteria occurring serially or simultaneously in a patient to warrant the diagnosis of SLE:

. malar rash
. discoid rash
. photosensitivity
. oral ulcers

. non-erosive arthritis
. serositis (pleuritis or pericarditis)
. renal disorder (proteinuria or cellular castes)
. neurologic disorder (seizures or psychosis)
. hematologic disorder (hemolytic anemia, leukopenia, thrombocytopenia)
. immunologic disorder (LE prep, anti DNA ab)
. antinuclear antibody

It is clear that some patients with manifestations of major liver involvement do satisfy these requirements for the diagnosis of SLE. Clinical criteria alone do not the distinction make. Renal and neurologic involvement are not common manifestations of chronic active "autoimmune" hepatitis. Nonetheless, every large series of patients described has a finite incidence of both accompaniments.

There is some evidence, however, that the two groups of patients may be separable by serologic means. Obviously both groups of patients may have positive ANA and LE preps. Approximately 50% of patients with SLE have anti DNA antibodies. Only a rare patient with chronic active hepatitis has been shown to have these antibodies when the crythidia assay has been employed. The deposition of immunoglobulins at the dermal-epidermal junction found in approximately half the patients with SLE has been observed in 10% to 15% of patients with presumed chronic "autoimmune" hepatitis. On the other hand, the serologic manifestations so prevalent in chronic active "autoimmune" hepatitis (anti-smooth muscle Ab and antimitochondrial Ab) seldom have been looked for in patients with SLE.

**Incidence of smooth muscle immunofluorescence in various diseases**

| Disease groups | No. tested | Percentage positive |
|---|---|---|
| Liver disorders | | |
| Active chronic hepatitis | 39 | 67 |
| Primary biliary cirrhosis | 40 | 50 |
| Cryptogenic cirrhosis | 32 | 28 |
| Alcoholic cirrhosis | 13 | 0 |
| Extrahepatic obstruction | 20 | 0 |
| Infective hepatitis | 12 | 8 |
| Systemic lupus erythematosus | 10 | 0 |
| Other collagenoses | 28 | 4 |
| Rheumatoid arthritis | 32 | 16 |
| Thyrotoxicosis | 40 | 3 |
| Lymphoid thyroiditis | 31 | 3 |
| Mixed hospital patients | 228 | 3 |

From Doniach et al, Clin. Exp. Immunol. 1966, 1:237

**Incidence of non-organ-specific 'M' immunofluorescence in 799 patients with various conditions, excluding liver diseases**

| Disease groups | No. tested | Percentage positive |
|---|---|---|
| Systemic lupus erythematosus | 17 | 29 |
| Other collagenoses | 44 | 16 |
| Rheumatoid arthritis | 71 | 10 |
| Lymphoid thyroiditis (Hashimoto and primary myxoedema) | 78 | 3 |
| Thyrotoxicosis (Graves' disease) | 123 | 1 |
| Mixed hospital patients | 466 | 2 |

From Doniach et al, Clin. Exp. Immunol. 1966, 1:237

Domiach, et al. found positive tests for antimitochondrial antibody in 5 of 17 patients with SLE. Goudee, et al. on the other hand tested 18 patients with SLE and found none with antimitochondrial antibodies; while Whittingham, et al. failed to see any positive reactions for anti-smooth muscle antibodies in 42 patients with SLE. This was supported by Johnson, et al. in 16 patients.

The summary of these studies would suggest that anti DNA antibodies rarely if ever occur in patients with chronic active hepatitis and smooth muscle antibodies are not seen in patients with SLE despite a high incidence in patients with autoimmune liver disease. There seems to be serologic reasons, therefore, to believe these two diseases are essentially distinct. Nonetheless, I believe that the term chronic active "autoimmune" hepatitis encompasses patients with a variety of disease processes. I have no intrinsic difficulty in believing that a disease such as SLE that is capable of causing dysfunction in almost every organ system in the body could also cause injury to the liver. It is probable, therefore, that occasional patients deservedly qualify for both diagnoses. Until a more precise understanding of the pathogenesis of these disorders is available it is reasonable to accept the notion that while the prototype of each disease is distinguishably different, an area of overlap exists where either diagnosis may be justifiably applied to a single patient.

CASE REPORT R.R.:

1970 - 18 year old Black man
Ulcerative colitis
Polyarthritis
ANA, RA latex Negative

1971 - Ulcerative colitis
Palpable purpura (leukocytoclastic angiitis)
Hepatomegaly and high AlK ph
Biopsy = Chronic active hepatitis

1972 - Ulcerative colitis
Idiopathic thrombocytopenic purpura
Rx - Steroids

1976 - Persistent abnormal LFTs
ANA 1:2560, SMA +, AMA -

1977 - Perirectal abscess

1979 - Chest wall abscess
Pleural effusion
Pericardial effusion
Decreased $C_3$, $C_4$, $C_{H50}$
Anti DNA Ab -

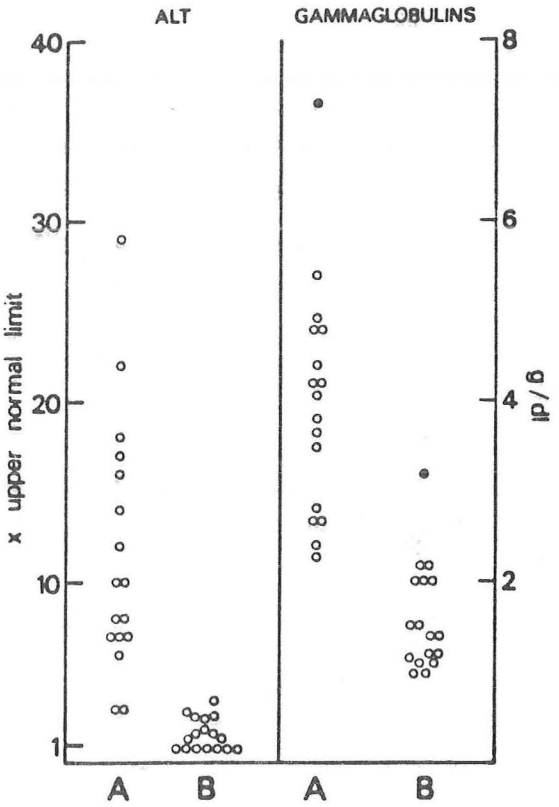
1987 - Stable on 15 mg qd Prednisolone

*R.R. exemplifies the diagnostic confusion with SLE. He merits this diagnosis by virtue of polyarthritis, angiitis, ITP, ANA, and serositis. On the other hand, the association with ulcerative colitis and substantial liver disease legitimately qualifies him for the diagnosis of chronic active "autoimmune" hepatitis. He also demonstrates that with effective management long-term survivial is possible if non-responsive associations don't develop, the therapy doesn't prove fatal, and the progress of the liver disease is halted before it causes portal hypertension.*

1. *Goldstein GB, et al. Drug-induced active chronic hepatitis. Dig Dis 18:177, 1973.*
2. *Reynolds TB, et al. Chronic active and lupoid hepatitis caused by a laxative oxyphenisatin. N Engl J Med 285:813, 1971.*
3. *Goudie, et al. Serological and histological diagnosis of primary biliary cirrhosis. J Clin Pathol 19:527, 1966.*
4. *Doniach D, et al. Tissue antibodies in primary biliary cirrhosis, active chronic (lupoid) hepatitis, cryptogenic cirrhosis and other liver diseases and their clinical implications. Clin Exp Immunol 1:237, 1966.*
5. *Sternlieb IS, et al. Chronic hepatitis as a first manifestation of Wilson's disease. Ann Int Med 76:59, 1972.*
6. *Gurian LE, et al. The immunologic diagnosis of chronic active "autoimmune" hepatitis: distinction from systemic lupus erythematous. Hepatology 5:397, 1985.*
7. *Tan EM, et al. The 1982 revised criteria for the classification of systemic lupus erythematous. Arthritis & Rheumatism 25:1271, 1982.*

## TREATMENT

The cornerstone of specific therapy for chronic active "autoimmune" hepatitis is the use of corticosteroids. Most of the acute inflammatory manifestations of the disorder, be they in the liver or in the extra hepatic organs, will respond to high dose therapy with prednisolone. It is unusual to require more than 60 mg per day to achieve remission for any of the manifestations.

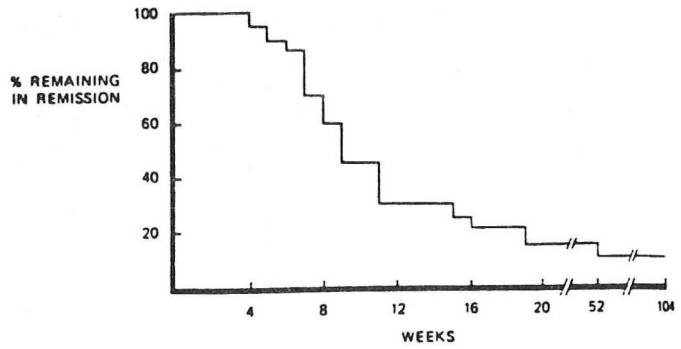



Response of children with CAH to Rx.
From Maggiore, et al. J. Ped. 1984.

Generally the remission can be maintained as the dose is tapered. Ideally one would like to achieve a maintenance dose of no more than 15 mg per day given as alternate day therapy while full remission is retained. More commonly, evidence of low grade activity of the disease (e.g. a slight increase in AST activity) appears before the dose of steroids can be reduced this far. Evidence of disease activity may recur with doses of prednisolone as high as 40 mg per day. This is especially likely with some extrahepatic manifestations (e.g. myositis). When effective control of disease activity cannot be maintained without using doses of prednisolone that are unacceptably high, azathioprine has been added to the regimen in an attempt to sustain remission with lower doses of steroids. This use of azathioprine has not been studied very well, but it has been the experience of most hepatologists that this maneuver is sometimes successful. One center showed

a rather high relapse rate when Imuran was discontinued in patients maintained in remission by double therapy. It is important to reduce the steroid dose as low as possible because of the serious consequences of iatrogenic Cushing's syndrome and the sensitivity these patients show to its development. One has to accept less than complete remission of disease activity at times in the interests of achieving a dose of prednisolone low enough to minimize long-term drug induced complications. This is a dilemma because any evidence of hepatic activity, no matter how mild, may be associated with predominantly collagenous repair and progression of the disease. Nonetheless, one usually has to accept the possibility of disease progression secondary to incomplete suppression of activity over the certainty of serious side effects secondary to long-term high dose therapy with steroids. If there is no evidence of a response to steroids the drug should not be continued. This is particularly likely to happen in patients with an occult form of liver disease where the only manifestation of disease activity that is available for recurrent assessment is a low grade elevation of AST activity. In some patients the disease may have progressed to a point where the use of steroids is not even considered worthwhile. Such patients usually present with major complications associated with established cirrhosis and it is apparent that their prognosis is already sealed by the established chronic process and no longer influenced by whatever disease activity may be present.

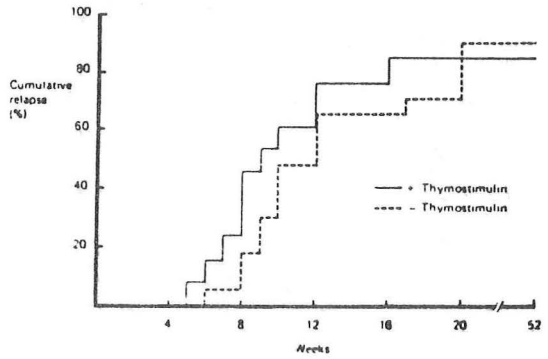
If remission is achieved and can be maintained with a low dose of prednisolone (+/- azathioprine) therapy should be continued long-term perhaps indefinitely. Attempts to "wean" the patient off steroids in 6 or 12 months are associated with a very high rate of relapse. It is true that the disease in some patients appears to "burn itself out" over time, but in most patients this does not seem to happen in the short term.




Effect of withdrawing steroids in CAH.
from Hegarty, et al. Hepatology 1983.

Other modalities of therapy are either experimental, have a very limited use, or have been ineffective. Thus, liver transplantation has been used for patients with end stage disease but the number of patients with "autoimmune" hepatitis transplanted have been too small to determine whether or not they have special problems related to the procedure.

Antimalarial agents such as chloroquine, immunostinulation with BCG, levamisole, or thymostimulin and anabolic steroid therapy have all been tried without success.




Relapse of CAH after withdrawal of Rx.
From Hegarty, et al. Lancet 1984.

Penicillamine therapy appears to have a positive effect on disease activity but its high incidence of side effects makes it a non-useful therapy. Hepatoprotective compounds such as silymarin and + cyanidol -3 are used in Europe but have not been evaluated seriously and are not available in the USA.

The value of cyclosporin in this disorder is at present anecdotal, but encouraging. Formal evaluation of this therapy has yet to be undertaken. It may provide an alternative for those patients who are either non-responsive to steroids or who suffer severe side effects from its use.

Most of the "inflammatory" components of the associated disorders are steroid responsive, but the modulation of steroid dose may have to be determined by the activity of disease in organs other than the liver. Some associations, such as the interstitial pulmonary fibrosis and the renal lesions appear to be uninfluenced by therapy.

1. *Cook GC, et al. Controlled prospective trial of corticosteroid therapy in active chronic hepatitis. Quart J Med 40:159, 1971.*
2. *Hegarty JE, et al. Relapse following treatment withdrawal in patients with autoimmune chronic active hepatitis. Hepatology 3:685, 1983.*
3. *Stellon AJ, et al. Randomized controlled trial of azathioprine withdrawal in autoimmune chronic active hepatitis. Lancet (i):668, 1985.*
4. *Williams R, et al. Current results with orthotopic liver grafting in Cambridge/King's College Hospital series. Brit Med J 290:49, 1985.*
5. *Stern RB, et al. Controlled trial of synthetic D-penicillamine and prednisone in maintenance therapy for active chronic hepatitis. GUT 18:19, 1977.*
6. *Mistillis SP, et al. Cyclosporin, a new treatment for autoimmune chronic active hepatitis. Med J Aust 143:463, 1985.*
7. *Lam KL, et al. Isoprinosone in classical acute viral hepatitis. Dig Dis 23:893, 1978.*

## NATURAL HISTORY AND PROGNOSIS

Chronic active "autoimmune" hepatitis is basically a bad disease. It is a progressive disease if untreated. The liver disease will usually progress to cirrhosis within 2 years of onset unless the course is effectively interdicted by therapy. Patients die with this disorder. Some die of liver failure or the complications of chronic liver disease (varciceal hemorrhage, ascites, infections). Others die of the associated manifestations or their complications (hemolytic anemia, pulmonary hypertension, ulcerative colitis). Some die of the therapy used to control the disease or the complications attendant or the resultant immunosuppression. There are no recent data available to define the outlook for this group of patients. The original descriptions suggested that 30% to 40% of patients would die within 5 years of the diagnosis being made. Considering the confusion of the diagnosis then and the non-universality of specific therapy this figure is probably unduly pessimistic. Patients who have an acute hepatitic presentation are likely to be very responsive to steriods and are less likely to die from the effects of liver disease. They do have a finite mortality associated with the effects of steroid therapy and from associations that are not steroid responsive. Those patients with an occult hepatic presentation may already have established their doom by the time they are identified. Cirrhosis carries with it its own mortality even when the initiating cause can be effectively controlled.