Liver
Hepatitis

MEDICAL GRAND ROUNDS

December 6, 1973

Chronic Hepatitis

CLASSIFICATION

ETIOLOGY AND PATHOGENESIS

THERAPY AND PROGNOSIS

The term "chronic hepatitis" refers to a group of liver diseases characterized primarily by persisting or recurrent liver cell injury (hepatitis) continuing over a period of several months to years. Primary biliary cirrhosis and conditions of well defined non-viral etiology such as alcoholic liver disease, hemochromatosis and Wilson's disease are arbitrarily excluded. Chronicity has been defined mainly as a continuation of hepatitic activity significantly beyond the usual duration of acute viral hepatitis and figures ranging from 10 weeks to 6 months or more are used by different authors. The category of chronic hepatitis encompasses diseases of both benign and lethal prospect, of acute and insidious onset and of known (hepatitis B virus, certain toxins) postulated ("autoimmunity") or completely unknown etiology.

CLASSIFICATION

TABLE I

CHRONIC HEPATITIS

I Chronic persistent hepatitis (CPH)
- A *HBAg - positive
- B HBAg - negative
- C (toxic?)

II Chronic active hepatitis (CAH)
(Chronic aggressive hepatitis (CAgH);
Chronic active liver disease (CALD))
- A Chronic active viral hepatitis (HBAg-Pos)
- B Chronic active lupoid hepatitis (autoimmune hepatitis)
  1. Idiopathic
  2. Toxic (same as IIC-1)
- C Chronic active toxic hepatitis
  1. Lupoid
  2. Non-lupoid
- D Chronic active cryptogenic hepatitis

* HBAg - Hepatitis B antigen; the Committee on Viral Hepatitis (Division of Medical Sciences, National Academy of Sciences-National Research Council) has recommended use of this term in place of "Australia antigen", "Hepatitis-associated antigen" and synonymous terms (1). Identification of HBAg in serum is considered indicative of the presence of hepatitis B virus.

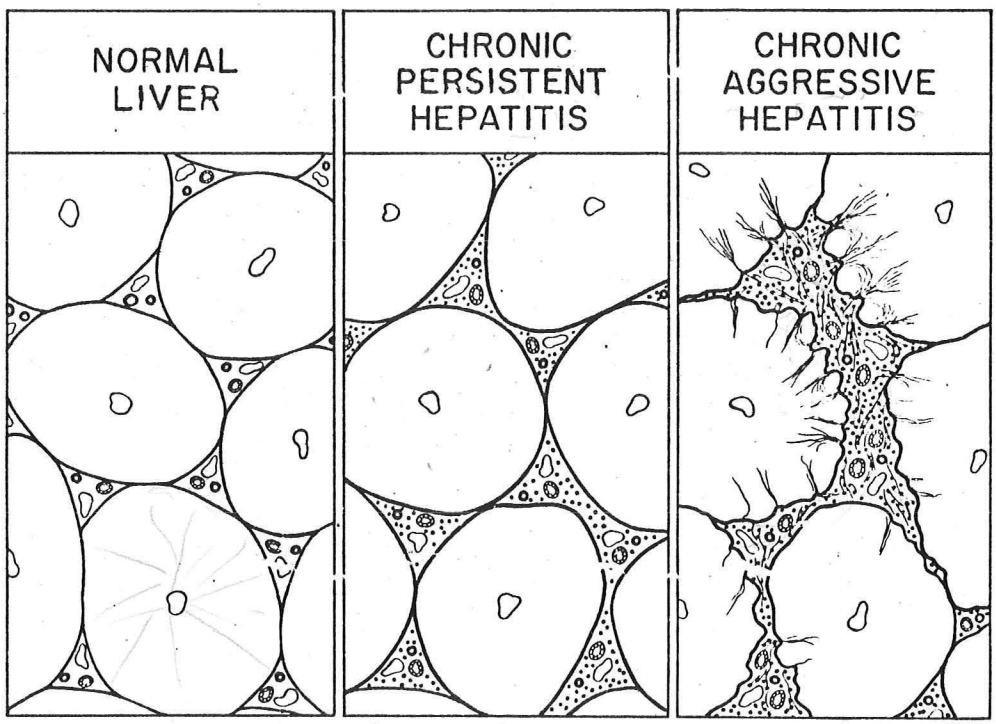


Fig. 1

CLASSIFICATION OF CHRONIC HEPATITIS

The literature concerning chronic hepatitis is littered with partially synonymous terms (nearly 50 by a recent count (2)) applied to various facets of this disease complex, and both reflecting and further contributing to the confusion about these diseases. Against this background, the histologic classification of chronic hepatitis developed by DeGroote's committee of pathologists has been a welcome step toward a consistent nomenclature (3). This group suggested that, on the basis of liver biopsy changes, chronic hepatitis could be divided into two main categories which they designated "chronic persistent hepatitis" and "chronic aggressive hepatitis". The histologic patterns on which this distinction is made are illustrated in Fig. 1 and were described as follows:

1. Chronic persistent hepatitis

   Chronic inflammatory infiltration, mostly portal, with preserved lobular arthitecture and little or no fibrosis. Piecemeal necrosis is absent or slight. Features of acute hepatitis may be superimposed.

2. Chronic aggressive hepatitis

   Chronic inflammatory infiltration involving portal tracts and extending into the parenchyma, with piecemeal necrosis and formation of intralobular septa. Architecture is disturbed but (in the absence of cirrhosis) there is no nodular regeneration. Features of acute hepatitis may be superimposed. Activity, as shown by piecemeal necrosis and inflammation varies from moderate (type A) to severe (type B).

It was recognized that a number of different clinical forms of chronic hepatitis were associated with each of these two patterns of liver injury. However, the clinical syndromes, classified according to liver histology, form two distinct groups of differing severity, therapeutic significance and prognosis and are designated "chronic persistent hepatitis" (CPH; note that this term applies to both a clinical syndrome and a specific liver biopsy pattern) and "chronic active hepatitis" (CAH)(Table I).

Why chronic hepatitis is a clinically mild and ultimately benign condition in some patients and a disease progressing to cirrhosis and death in others is unknown. Even in those cases where the etiology is apparently known - the HBAg positive patients (infected with hepatitis B virus) - no basis for the development of two different patterns of disease is evident; HBAg is found about as often in CPH as in CAH, and with the same HBAg-subtype distribution, i.e. subtype ad found more commonly than ay (4). Both CPH and CAH may develop either insidiously or as a continuation of acute viral hepatitis.

I. Chronic Persistent Hepatitis

The clinical syndrome of CPH was first clearly described by Gallagher and Goulston in 1962 (5) and a number of additional cases have been reported by Becker and others since then (6,7). Seven of Becker's cases began insidiously while the remaining 13, and all five of Gallagher's patients, began as acute viral hepatitis which then failed to subside completely. Patients with CPH are minimally symptomatic and the only evidence of disease in most is a persistently elevated serum transaminase level, usually in the range of 50-200 Karmen Units. Jaundice rarely, if ever, occurs and the physical examination is normal except for mild hepatomegaly in some patients. Serial biopsies usually reveal the changes of CPH described by DeGroote et al. (3)(see above) and tend to show progressive improvement. Eventually, after one to 10 or more years, there may be complete clinical, biochemical and histological resolution, although HBAg persists in some patients (9). However, Redeker states that he has not seen resolution of cases continuing for more than a year (7). Progression of CPH to CAH is rare, but since this has been reported (8,9) it is probably advisable to check the liver function tests periodically and to repeat the liver biopsy at least once even if the disease remains unchanged, but especially if there is clinical or laboratory evidence of deterioration.

Combined data from several published series indicated that HBAg was present in 86 out of 226 (38%) of patients with CPH (9-17). As discussed below the "autoantibodies" commonly present in CAH (antinuclear antibody, smooth muscle autoantibody, anti-mitochondrial antibody) are absent, or present only in low titer in CPH patients. (Tables II and III; Fig. 4)

TABLE II
"AUTOANTIBODIES" IN CHRONIC PERSISTENT- AND CHRONIC ACTIVE HEPATITIS
(Vischer (14))

	Number of patients	Anti-nuclear antibody	Smooth muscle autoantibody > 1:40	Anti-Mito. antibody
Chronic Persistent Hepatitis	12	1	1	0
Chronic Active Hepatitis	85	20	11	9

TABLE III
"AUTOANTIBODIES" IN CHRONIC PERSISTENT- AND CHRONIC ACTIVE HEPATITIS
(Dudley (26))

	Number of patients	Anti-nuclear antibody	Smooth muscle autoantibody > 1:40	Anti-Mito. antibody
Chronic Persistent Hepatitis	27	0	1	0
Chronic Active Hepatitis	73	22	23	6

TABLE IV

HBAg IN CHRONIC ACTIVE HEPATITIS

Author	Ref. No.	No. of HBAg-pos. cases	Total cases
Fox	(10)	0	32
Wright	(27)	6	24
Bulkley	(28)	7	31
Gitrick	(29)	3	31
Hadziyannis	(30)	5	15
Kuboth	(11)	33	94
Mathews	(31)	2	53
Prince	(32)	11	42
Reinicke	(13)	0	12
Velasco	(33)	0	13
Vischer	(14)	19	85
Kaplan	(12)	1	34
Berg	(15)	10	49
Haas	(34)	19	65
Redeker	(7)	20	73
Bianchi	(17)	30	59
		167	712

23% HBAg-positive

II. Chronic Active Hepatitis

This term encompasses a group of diseases which have certain features in common;

(a) The pattern of chronic aggressive hepatitis (CAgH) on liver biopsy, as defined by DeGroote et al. (3). In addition to CAgH other features may be noted including the presence of partial lobular necrosis and parenchymal collapse leading to portal-portal and portal-central vein "bridging" (a pattern called subacute hepatic necrosis (21) or subacute hepatitis with bridging (18)) and in other instances complete necrosis of entire liver lobules (subacute hepatitis with multilobular necrosis). Still others have a combination of CAgH and cirrhosis sometimes referred to as active postnecrotic necrosis (18).

(b) A tendency to progress to cirrhosis with complications of fluid retention, hemorrhage from esophageal varices, sepsis and hepatic encephalopathy.

(c) A clinical state of chronic debilitation of variable severity, sometimes showing a dramatic and sustained improvement during treatment with corticosteroids and other immunosuppressive drugs.

Redeker has suggested four categories of chronic active hepatitis (7) which, for the most part, are mutually exclusive (Table I);

A. Chronic Active Viral Hepatitis; HBAg-positive cases of CAH.

B. Chronic Active Lupoid Hepatitis; patients with consistently positive antinuclear antibody tests as well as other "autoantibody" tests, also called "autoimmune" hepatitis (19).

C. Chronic Active Toxic Hepatitis; those cases of CAH apparently caused by a toxic or hypersensitivity reaction to drugs.

D. Chronic Active Cryptogenic Hepatitis; all CAH patients not included in the first three categories.

The viral and cryptogenic types of CAH, and less often the lupoid type, may begin with what appears to be acute viral hepatitis. Boyer and Klatskin have shown that among 52 acute hepatitis patients with the pattern of subacute hepatic necrosis on liver biopsy (described above) 7 patients (13%) developed CAH. Among all patients with acute viral hepatitis, however, progression to chronic liver disease is quite rare (22,23). Boyer suggests that only hepatitis B ("serum hepatitis" in the past; now HBAg-positive hepatitis) developes into CAH (24) and this has also been Redeker's experience (7). On the other hand, Gocke studied 5 patients who developed CAH following acute hepatitis and all were HBAg-negative when tested by the (relatively insensitive) agar gel diffusion test (25).

A. Chronic Active Viral Hepatitis

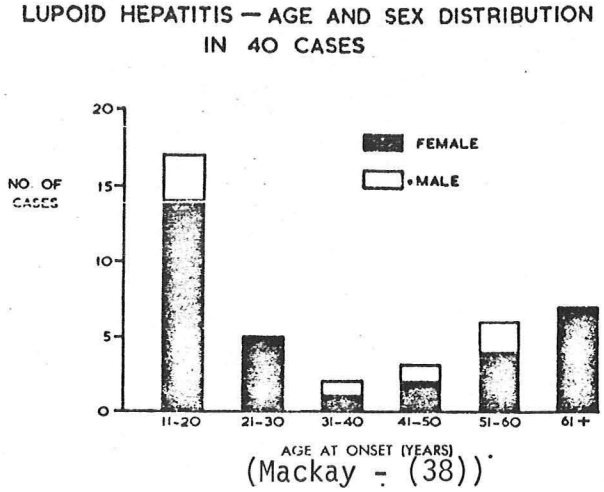
As shown in Table IV, hepatitis B antigen is present in the serum of approximately 1/4 of CAH patients, but varies widely among different series.

To some extent this may reflect different sensitivities of the HBAg assays used. This consideration may be more important for CAH than for acute viral hepatitis, since HBAg titers are generally much lower in chronic hepatitis and, indeed, the HBAg test may fluctuate between positive and negative in cases (7,27). However, geographical factors are probably more important, with higher proportions of HBAg-positive cases in continental Europe and the United States and low frequencies in Great Britain and Australia. Of 130 case records gathered from three centers in Australia, only 4 were HBAg-positive (35). Wright found 6 of 23 cases positive while working in New Haven (28), but only 1 of 20 (an infant born to an HBAg-positive mother) after moving to Oxford, England (36).

Nielsen's study in Copenhagen suggests that the persistance of a positive HBAg test after the acute phase of viral hepatitis indicates the likelihood that CAH has developed (37). In a prospective study of 112 HBAg patients, HBAg remained in the serum for longer than 13 weeks in 11 patients, 8 of whom were drug addicts. Liver biopsy was performed in 10 of these 11 patients and chronic aggressive hepatitis was found in 8, and CPH in the other 2. In a control group of 24 transiently HBAg-positive hepatitis patients and 23 consistently HBAg-negative hepatitis patients, 3 of 47 developed chronic aggressive hepatitis and another 3 developed CPH. This remarkably high frequency of CAH after acute hepatitis was not found by Redeker in Los Angeles whose patients also include a large percent of drug addicts (7). Of 134 patients with acute hepatitis B, 6 remained HBAg-positive. One had recovered in all other respects and could be regarded as a healthy HBAg carrier. The other 5 were found to have "unresolved hepatitis", a term Redeker considers synomynous with chronic persistent hepatitis.

B. Chronic Active Lupoid Hepatitis

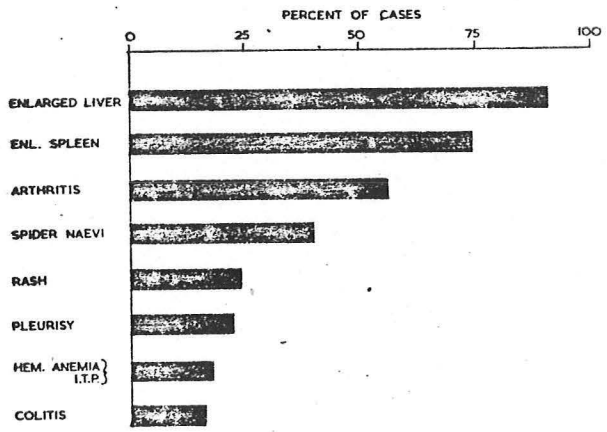
Joske in 1955 (39) and Bearn in 1956 (40) first reported the presence of positive LE cell tests in young women with chronic active hepatitis. Mackay first applied the term "lupoid" hepatitis to these patients who in addition to being young women with positive LE cell tests manifested other features of systemic lupus erythematosus (SLE) including arthritis and arthralgias, rashes



(Mackay - (38))

Fig. 2

Lupoid Hepatitis - frequency of various clinical features



(Mackay - (38))

Fig. 3

pleurisy, intermittent fever, hypergammaglobulinemia, biologic false-positive serologic tests for syphilis, and positive antinuclear antibody (ANA) tests. (The ANA test has replaced the LE cell test as a primary indicator of lupoid hepatitis (19).) It is not surprising that some writers have considered lupoid hepatitis to be a form of SLE with liver involvement predominating (41,42), but most consider the two conditions to be separate and distinct entities (43-46). The frequency of liver disease among patients with well documented SLE has been very low (46-48) and the characteristic pathologic changes of SLE, particularly in the kidney and spleen, are found only rarely in patients with lupoid hepatitis (49,50). Patients with SLE have been observed to develop acute viral hepatitis and recover uneventfully (42,43).

Support for the separate nature of lupoid hepatitis and SLE is given by the results of smooth muscle autoantibody (SMA) studies. This antibody, apprently directed against actomyosin proteins of smooth muscle (non-species and non-organ specific) is frequently found in the serum of patients wtih various acute and chronic liver diseases and is present in high titer in lupoid hepatitis (Tables II, III, VII and VIII; Fig. 4). Johnson (52) found SMA in 8 of 10 lupoid hepatitis patients but in none of 16 SLE patients; Whittingham (53) found this antibody in 36 of 44 cases of lupoid hepatitis and in none of 42 SLE patients (Table V).

TABLE V

SMOOTH MUSCLE ANTIBODY (SMA) AND ANTINUCLEAR ANTIBODY (ANA) IN LIVER DISEASE AND SYSTEMIC LUPUS ERYTHEMATOSUS
(Modified from Whittingham et al. (53))

	of Cases	ANA Positive	SMA Positive	Both ANA and SMA Positive
Liver Disease				
Autoimmune (Lupoid) Hepatitis	44	39	36	33
Non-Lupoid Active Chronic Hepatitis	9	0	0	0
Primary Biliary Cirrhosis	6	4	0	0
Acute Hepatitis	6	0	0	0
Alcoholic Liver Disease	11	1	0	0
Hemochromatosis	9	0	0	0
Systemic Lupus Erythematosus	42	42	0	0

Since HBAg testing has become available, a number of reports have appeared describing features which distinguish lupoid hepatitis from HBAg-positive, chronic active viral hepatitis (7,14-16,28,31,54-58). These distinguishing characteristics are listed in Table VI.

TABLE VI
DISTINGUISHING FEATURES OF CHRONIC ACTIVE VIRAL HEPATITIS AND -LUPOID HEPATITIC

	Chronic Active Viral Hepatitis	Chronic Active Lupoid Hepatitis
HBAg	Positive	Negative
Sex	Male > female	Female >> male
Age	Adults of all ages	Bimodal - 10 to 25 years - over 45 years
Onset	Acute; often as acute viral hepatitis	Insidious
Systemic manifestations (acne, arthritis,amenorrhea)	Uncommon	Frequent
Associated "autoimmune" diseases (ulcerative colitis, thyroiditis, Sjögren's syndrome, rheumatoid arthritis)	Rare	Increased incidence
Elevated serum globulins	Less Common	Frequent
"Autoantibodies" (SMA, ANA, AMA, LE cells)	Absent, or present in low titer	Frequently positive

Others have been unable to identify these separate forms of chronic active hepatitis (17,59) and Soloway et al. (Mayo Clinic) has called lupoid hepatitis a "non-entity" (60); this group studied 88 CAH patients - 30 with positive LE cell tests and 58 with negative tests and found no difference in sex ratio, age, associated "autoimmune" disease, systemic manifestations of liver disease, response to therapy or presence of smooth muscle autoantibodies, or of HBAg. Remarkably, neither did they find a significant difference in the incidence of positive antinuclear antibody tests, which were present in less than half of the patients in either group. The question arises whether the LE cell test as performed in this study is really valid, in view of the bizarre ANA data, and whether different results would have been obtained if the patients were divided according to a positive or negative ANA test, as has been done in most other recent studies.

TABLE VII

"AUTOANTIBODIES" IN HBAg-POSITIVE AND HBAg-NEGATIVE CHRONIC ACTIVE HEPATITIS (Vischer (14))

	Number of patients	Anti-nuclear antibody	Smooth muscle autoantibody > 1:40	Anti-mitochondrial antibody
HBAg Positive	19	1	0	0
HBAg Negative	66	18	11	9

TABLE VIII

"AUTOANTIBODIES" IN HBAg-POSITIVE AND HABg-NEGATIVE CHRONIC ACTIVE HEPATITIS (Dudley (26))

	Number of patients	Anti-nuclear antibody	Smooth muscle autoantibody > 1:40	Anti-mitochondrial antibody
HBAg Positive	34	0	1	0
HBAg-Negative	39	22	22	6

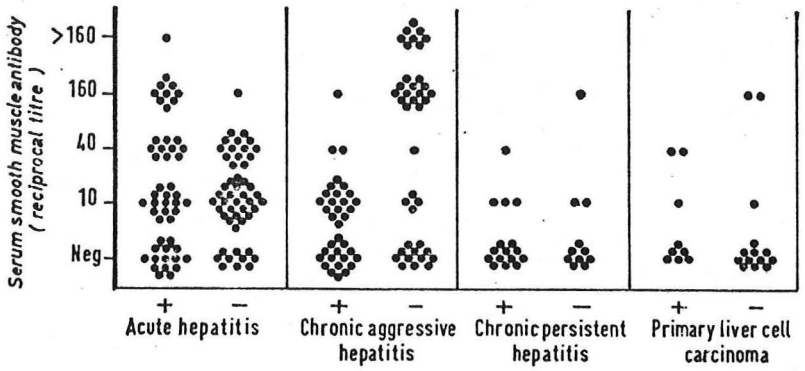


Fig 4 *Smooth muscle antibody titres in HAA-positive (+) and -negative (−) patients with both acute and chronic liver disease.* (Dudley (26))

C. Chronic Active Toxic Hepatitis

Drugs capable of producing liver injury by a direct toxic effect can be identified in experimental animal studies and therefore are not likely to be put on the market. Most drug-related liver injury is presumed to be due to a hypersensitivity reaction, usually manifested as either a benign cholestatic syndrome (such as "Thorazine® jaundice") or an acute and sometimes severe hepatocellular injury (halothane; Iproniazide). In 1964 Reynolds described a form of chronic aggressive hepatitis apparently due to a prolonged ingestion of a laxative product containing oxyphenisatin (61) and several other cases have been reported since then (62-69). Some of these patients have had positive LE cell tests and ANA tests, and being HBAg-negative, would otherwise be considered fairly typical cases of chronic active lupoid hepatitis (63). It is not certain what percentage of CAH cases are caused by oxyphenisatin; Gjone found 5 cases among 70 patients in Scandinavia, all of whom showed progressive improvement when the drug was discontinued (69); Mistilis' group in Australia actually identified 9 oxyphenisatin related cases among 21 consecutive CAH patients seen in 1971-1972 (68). This group had reported extensive studies on 82 patients with CAH in 1970 (70); they were able to contact 29 of these patients more recently and none admitted use of oxyphenisatin-containing laxatives (or alpha-methyldopa; see below). In contrast neither oxyphenisatin nor alpha-methyldopa had been taken by 130 consecutive CAH patients treated at the Mayo Clinic (72).

Reynolds (61) believed oxyphenisatin liver injury was due to a hypersensitivity reaction since administration of the agent to patients with other types of CAH caused no change in liver function tests. However, Mistilis (68) suggested that the drug is actually a direct toxin which must accumulate in the liver over a period of time before reaching a threshhold of injury. He related the high prevalence of this type of CAH in Sydney to the availability of laxatives containing 10 mg/tablet of oxyphenisatin, as compared to 3 mg (formerly) contained in Dialose-plus®, the most commonly used preparation in this country.

It has been suggested that dioctyl-sodium sulfosuccinate (DSS), an additional component of many oxyphenisatin-containing compounds, is also hepatotoxic (71), but some cases of CAH have been caused by preparations containing only oxyphenisatin, and no reports of liver injury due to other DSS-containing preparations are known.

In the same series of 21 CAH patients discussed above (68) 5 additional cases were apparently caused by alpha-methyldopa hypersensitivity and similar cases were reported by Hoyumpa (73).

D. Chronic Active Cryptogenic Hepatitis

This is a "waste basket" category including cases not assignable to other classes of CAH. As knowledge of chronic hepatitis increases, this group should become progressively smaller. For example, most oxyphenisatin-associated cases (those without lupoid feature) would have been placed in this category until recently.

Chronic Active Hepatitis and Cirrhosis

Whether cirrhosis eventually developes in all cases of chronic active hepatitis is uncertain (82). Mistilis found cirrhosis in 1/3 of his cases at the time of diagnosis and states that it was present in most patients by two

years after onset of illness (83). It has been Redeker's experience that HBAg-positive cases of CAH which began as active hepatitis progressed to cirrhosis within 12 to 18 months (7). Data from the Mayo Clinic study of chronic hepatitis indicate that patients with the histologic lesion of "subacute hepatic necrosis" (21) progressed to cirrhosis more often than patients with CAgH without bridging necrosis (18) and this led Summerskill to speculate that cirrhosis may develop in these patients as a consequence of repeated episodes of submassive necrosis and lobular collapse, rather than the persistent erosive effects of piecemeal necrosis characterizing CAgH (72).

"Cryptogenic cirrhosis", typically of a postnecrotic pattern, is the term applied to cirrhosis discovered in patients without previous history of alcoholism, clinical hepatitis or exposure to liver toxins. Increasingly, cryptogenic cirrhosis is coming to be regarded as the end stage of previously silent CAH (84-88) and the same "autoimmune" serologic markers may be present in these patients as in chronic active lupoid hepatitis, while others are HBAg-positive (87). Klatskin described several patients with anicteric hepatitis, who were observed on serial liver biopsy to develop cirrhosis (90). The liver biopsy may show chronic aggressive hepatitis in addition to the nodular regeneration and scarring in patients with "active post-necrotic cirrhosis" and it is reasonable to treat these patients in the same manner as other CAH patients (60).

Differential Diagnosis of Chronic Active Hepatitis

Two other types of chronic liver disease show chronic aggressive hepatitis on liver biopsy;

1) Primary biliary cirrhosis (PBC); this chronic obstructive form of liver disease results from progressive destruction of the smaller intrahepatic biliary ducts, a chronic cholangitis (74). The hepatocellular injury and eventual cirrhosis appear to be a reaction to the biliary obstruction, just as prolonged extrahepatic biliary obstruction leads to "secondary" biliary cirrhosis. Apart from CAgH, there are several histologic features considered "characteristic" of PBC (reduced numbers of interlobular bile ducts, "pseudoductules", portal tract granulomas) and ductular injury apparently due to "aggressive" lymphocytes has been considered a pathognomic lesion of PBC (72). However, Poulssen and Christoffersen have described such ductular injury in liver biopsies from otherwise typical CAH patients (75). HBAg is rarely found in PBC (15) but the "autoimmune" markers of lupoid hepatitis (smooth muscle autoantibody, antinuclear antibody) are often noted, and anti-mitochondrial antibody (AMA) in high titer is present in most PBC patients (76). Cases are reported with features of both CAH and PBC (77,78).

2) Hepatolenticular degeneration (Wilson's disease) Sternlieb and Scheinberg recently reported cases of apparently typical CAH with CAgH on liver biopsy in 7 patients who were later shown to have Wilson's disease (79). Hepatic tissue copper content exceeding 250 µg/g dry weight in patients without high grade biliary obstruction is considered an important diagnostic feature of Wilson's disease and was found in these patients. However, Bensen found liver copper concentrations of 480 and 625 µg/g in 2 patients with typical lupoid hepatitis

without obstructive jaundice in whom no other evidence of Wilson's disease could be detected (80). These patients improved on penicillamine therapy, but penicillamine may have other beneficial effects in chronic liver disease in addition to those attributable to copper chelation (81).

PATHOGENESIS OF CHRONIC ACTIVE HEPATITIS

Certain evidence indicates that hepatocellular injury in CAH is in some way related to immunologic mechanisms directed against antigens in the liver; the liver is heavily infiltrated with lymphocytes and in some cases with plasma cells, various non-organ specific autoantibodies may be detected (smooth muscle autoantibody, antinuclear antibody, anti-mitochondrial antibody) and there is an increased frequency in these patients of other diseases suspected of having an autoimmune basis such as ulcerative cholitis, Hashimoto's thyroiditis, and Sjögren's syndrome (70). Mackay and Morris demonstrated a significantly increased prevalence of HL-A1 and HL-A8 antigens among CAH patients (as previously observed in SLE patients) and suggested a genetic basis for the immunologic disturbance (92). In some cases persistent infection with hepatitis B virus appears to be the initiating factor of chronic hepatitis. It has been observed that the greatest amounts of HBAg detectable in liver biopsy tissue by immunofluorescent staining techniques are found in HBAg carriers - patients with minimal liver cell damage, while much less HBAg is identified in liver tissue from HBAg-positive CAH patients (93). This suggests that rather than a direct effect of the virus on the liver dell, cellular injury results from immunologic responses directed against the virus but secondarily producing tissue damage.

The evidence regarding the role of humoral and cellular immunity in chronic hepatitis is summarized below.

Antibody-mediated liver injury

The autoantibodies present in some CAH patients (SMA, ANA, AMA) are not likely to be involved directly in any liver cell injuries since they are non-organ specific and cause no apparent damage when found in other tissues. It is commonly believed that these antibodies represent an incidental secondary response to liver damage.

In 16 of 85 CAH patients, Meyer zum Büschenfelde identified circulating antibodies with affinity for liver tissue and which could be completely absorbed only by liver tissue (94). Such antibodies were not found in the serum of patients with acute hepatitis, alcoholic cirrhosis, post-necrotic cirrhosis or of blood donors. Subsequently, this investigator identified two "liver specific antigens" against which these antibodies are directed (LP1 is a lipoprotein distinct from serum lipoprotein and believed to be of membrane origin; LP2 is a water soluble cytoplasmic protein). When these protein antigens were fluoresceinated and applied to liver biopsy tissue from CAH patients certain cells were stained which apparently were specifically sensitized to (making antibody against?) the liver specific proteins. In further studies he was able to produce a chronic hepatitis in rabbits with a histologic pattern of CAgH by repeated immunization with LP1 + 2. No hepatitis resulted when rabbit liver specific protein was injected into these animals, but in tissue

from the rabbits with CAH caused by human LP, immunofluorescent staining identified cells sensitized to rabbit LP. Thus it appeared that the human LP, because of incomplete immunologic identity with rabbit LP, provoked an immune response in the rabbit against its own liver specific proteins in addition to human LP. If this mechanism were to apply to the pathogenesis of human CAH, the provocative antigen might be a liver specific protein modified by the effect of drugs or viruses.

Nowoslawski identified depsoits of IgG, IgM and HBAg in liver of autopsied patients with HBAg-positive CAH. Faint immunofluorescent staining for complement was also observed in some specimens. However, similar deposits were noted in several other tissues, including spleen, kidney and blood vessels (95). Hadziyannis failed to identify gamma globulin or β_1C in biopsies from any of 9 HBAg-positive chronic hepatitis patients, though positive immunofluorescent staining for HBAg was observed in each case (96). Similarly, Svec could find neither bound immunoglobulins nor complement in the liver of lupoid hepatitis patients (97). Paronetto et al., in human liver tissue culture studies showed that although CAH patients serum (with fresh serum added as a complement source) contained antibodies which bound to the cultured cells, these antibodies were devoid of cytotoxic properties (98).

Antibodies may produce tissue injury indirectly by forming noxious complexes with circulating antigen which then initiate destructive mechanisms wherever they are deposited. HBAg-containing immune complexes have been implicated in the pathogenesis of polyarteritis nodosa (100) and glomerulonephritis (101) but Prince and Trepo (102) found no relationship between levels of circulating immune complexes and the manifestations of CAH, and the immune complex mechanism has not been convincingly implicated in the development of chronic liver disease.

The report of chronic hepatitis in agamma-globulinemic patients (99) raises further uncertainty about the importance of antibodies in the genesis of CAH.

Serum complement levels are commonly depressed in chronic hepatitis patients whether the β_1A/β_1C component (41,103-105) or total hemolytic complement ($C'H_{50}$)(106,107) are measured. Pagaltsos found lower $C'H_{50}$ levels in CAH patients than in patients with equally severe alcoholic liver disease, hemochromatosis and cryptogenic cirrhosis, and considered this evidence for increased C' consumption in CAH rather than reduced synthesis (107). Other reports, however, favor reduced synthesis as the mechanism of hypocomplementemia in CAH. Potter found normal $C'H_{50}$ and C'3 levels in CAH patients without cirrhosis, but reduced levels in those with cirrhosis (108). Finlayson observed that $C'H_{50}$, C'3 and C'4 levels in 110 patients with "chronic liver disease of unknown etiology" were reduced in proportion to the severity of hepatic disease, but that $C'1_q$, the one complement component not synthesized in the liver, was normal in the 11 cases tested (109). Petz studied the plasma disappearance rate of ^{125}I-labeled C'3 and calculated the C'3 synthesis rate in 3 patients with Laennec's cirrhosis and a group of normal subjects. He found markedly reduced C'3 synthetic rates in 2 of the cirrhotic patients (110). Nevertheless, increased complement consumption, as in immune complex formation, has not been specifically excluded in chronic hepatitis patients.

Cellular-immune mechanisms of liver injury

Transient and mild chronic hepatitis has been produced in rats and mice by injecting spleen cells from other animals of the same inbred species which had been "sensitized" by inocculation with heterologous liver extract (111,112). Smith observed migration inhibition of CAH patients' leukocytes exposed to fetal liver antigens (113); the degree of inhibition correlated with the severity of illness. Similar observations were made by Chen who exposed CAH patients' lymphocytes to homogenates of the same patient's liver (114). He also found that the supernatant medium from the lymphocyte-liver culture stimulated collagen synthesis as indicated by increased incorporation of tritiated proline into hydroxyproline.

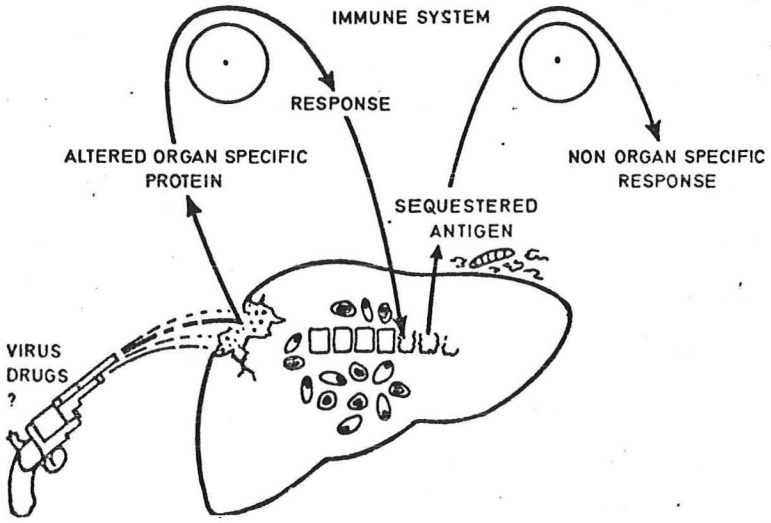


Fig. 5: Williams' concept of the pathogenesis of chronic active (lupoid) hepatitis (91)

Williams et al. offer the following concept of the role of cellular immune responses in "auto-immune" liver disease (Fig. 5); they invisage an exogenous stimulus, such as a drug or virus, damaging the liver and releasing or altering a liver specific protein (94), most likely a cell surface antigen. This process stimulates a genetically predisposed immune system to attack the liver. They feel that the damage produced is mediated by lymphocytes sensitized to the liver specific antigen(s). The disrupted liver cells release sequestered antigens, such as nuclear fragments and mitochondria, which secondarily stimulate the immune system to produce excess amounts of the various autoantibodies which are recognized as markers of the underlying autoimmune process (91).

With regard to chronic active viral (HBAg-positive) hepatitis particularly, Dudley offered the following hypothesis; that in patients with a normal functioning cellular immune system, liver cells infected with HBAg are destroyed and the virus is eliminated. If all liver cells are infected fatal fulminant hepatitis results, but if some cells are uninvolved, acute viral hepatitis occurs after which the patient becomes HBAg negative and recovers. If the cellular immune response to the hepatitis virus is inadequate because of the absence of a specific T-cell (thymus-derived lymphocyte) response to the viral antigen then little or no liver damage will occur and the virus will continue to proliferate

with production of HBAg. Such a patient would be an apparently healthy carrier of HBAg. However, when T-cell function is impaired in some way an intermediate course may be followed; some liver necrosis will occur due to cellular immune response, but the response will not be sufficient to react with all infected cells in order to eliminate the viral infection. This will result in a continuing process of liver cell damage (CAH) and persistent viral proliferation reflected in a chronically positive HBAg test. The degree of immunologic reactivity will determine the severity of hepatitis produced and also whether the resultant liver disease can be classified as chronic aggressive or chronic persistant hepatitis (115).

THERAPY AND PROGNOSIS

Chronic active hepatitis is a serious disease. In 1963 Mackay stated that "....Most (CAH patients) will die, usually of hepatic failure, within 3 years of diagnosis" (116). In the same year Read reported a study of 81 CAH patients among which 27 had died with a mean survival time of 3½ years after apparent onset (117). Page et al. reported a 12 year survival of 30% in a group of treated juvenile CAH patients (118) and in a similar but untreated group Willcox noted less than 20% ten year survival (118). In 1972 Mackay gave an updated assessment of prognosis in treated CAH patients, stating that for 25-30% of patients the prognosis is good, with a sustained remission after withdrawal of drugs; in roughly half of CAH patients, sustained remission will depend on a continuous or intermittent course of suppressive drugs, possibly for an indefinite period of years - "although survival time is undertain, at least 10 years could be suggested"; in the remaining quarter of cases the disease seems to progress despite therapy and death occurs in 3 to 5 years from liver failure and/or an adverse effect of treatment (85).

Corticosteroid Therapy in CAH

Corticosteroids have been used to treat CAH since the late 1950s. (44,120-122). Results in individual cases were often dramatic (Fig. 6). However, Sherlock's group in one of the first systematic studies of steroid therapy in chronic hepatitis, using an earlier group of 38 untreated patients as a control series, found that survival of 43 patients was not improved by this treatment. The authors concluded that corticosteroid therapy was indicated primarily for its symptomatic effect - "in those who feel ill, as such patients seem to be living more useful and happier lives while receiving steroids" (117).

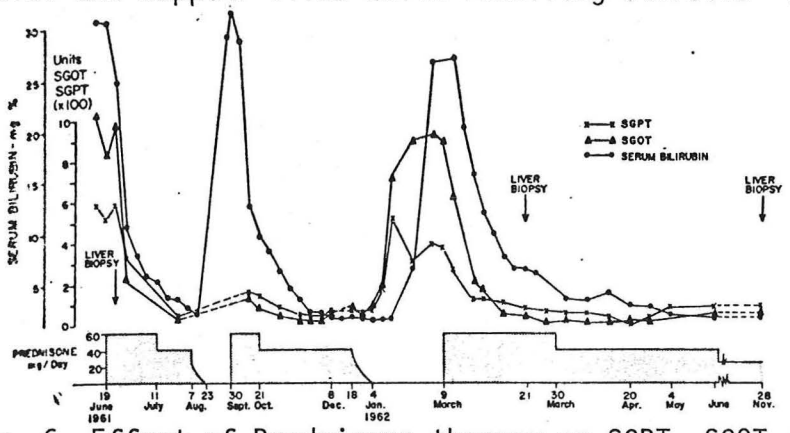


Fig. 6 Effect of Prednisone therapy on SGPT, SGOT and bilirubin in a patient with CAH (Mistilis (122))

Much more optimistic results were observed recently in a second study by Sherlock's group, this time using concurrently studied control subjects (123). The steroid treated patients showed a high significant survival advantage over the controls as shown in Table IX. In addition, at the time the study was completed, the treated patients were in a better state of health with 15 of 18 having a normal work capacity as compared to 7 of the 14 control subjects.

TABLE IX
TRIAL OF PREDNISOLONE THERAPY IN CHRONIC ACTIVE HEPATITIS
(Cook, G. C. et al. (123))

Group	Total number of patients	Death due to liver failure	Death due to other causes	Total deaths
Corticosteroid	22	3	0	3
Control	27	13	2	15
Significance		$p < 0.05$		$p < 0.01$

In an uncontrolled study, Mistilis also showed improved survival of patients treated with steroid, with or without added 6MP or azathioprine (20) (Fig. 7).

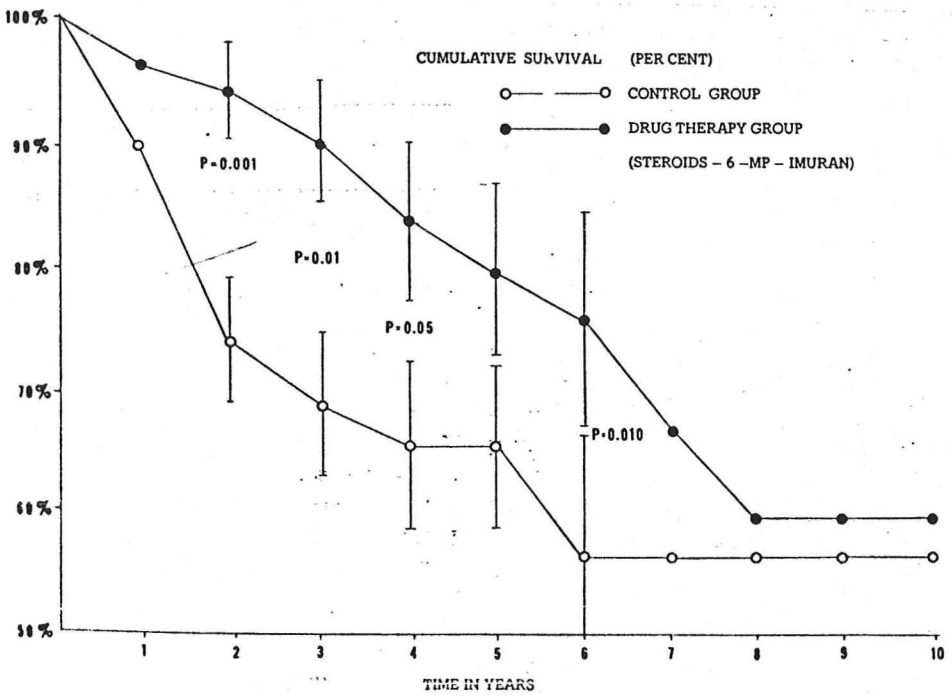


Fig. 7 Survival of treated CAH patients and untreated controls (Mistilis (129))

The prospective study of the Copenhagen Study Group for Liver Diseases also apparently demonstrated the effectiveness of corticosteroids in CAH, though through an oblique approach (124). They treated half of a group of 334 unselected cirrhotic patients with corticosteroids (unless contraindicated) and observed the other half as controls. A large proportion of the males but only a few of the females were alcoholics. The results are shown in Figs. 8-11. When the data were analyzed at the completion of the study, only the females without ascites (most with "liver disease of unknown etiology") showed significantly improved survival with steroid therapy. The statistical illegitimacy of this approach is recognized, however,

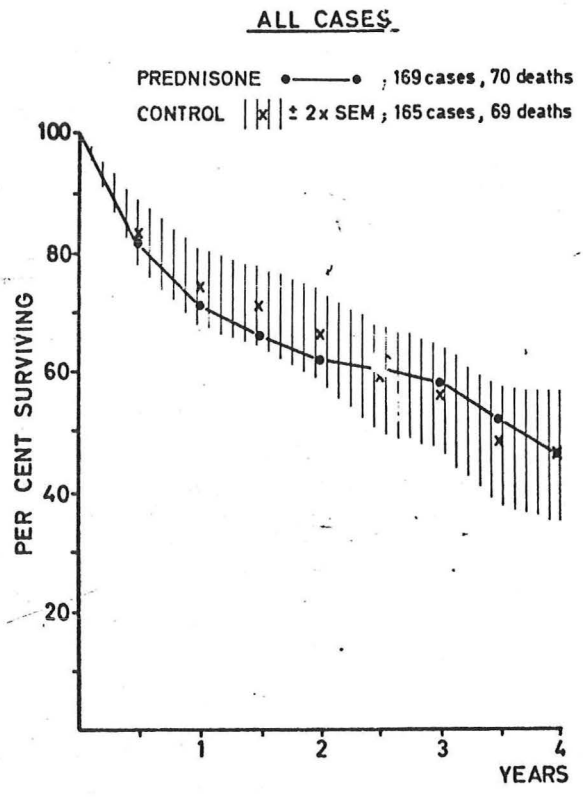


Fig. 8 Copenhagen Study overall survival (124)

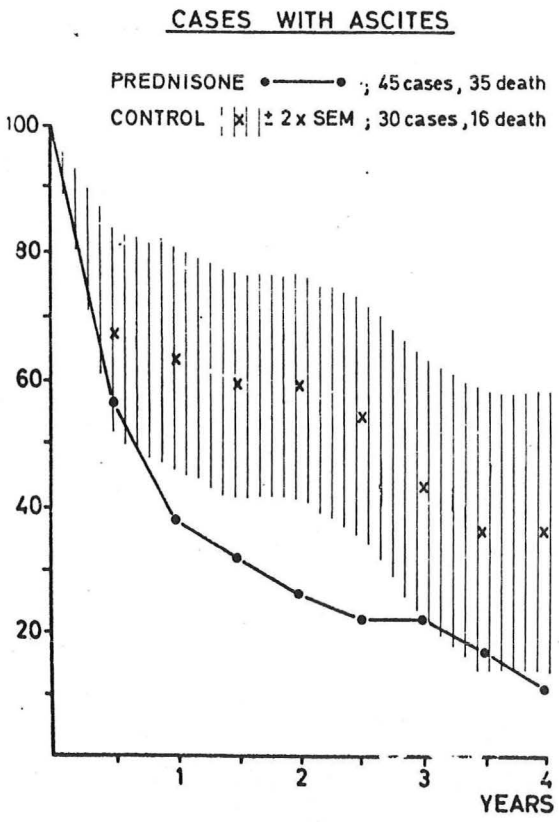


Fig. 9 Survival of patients with ascites (124)

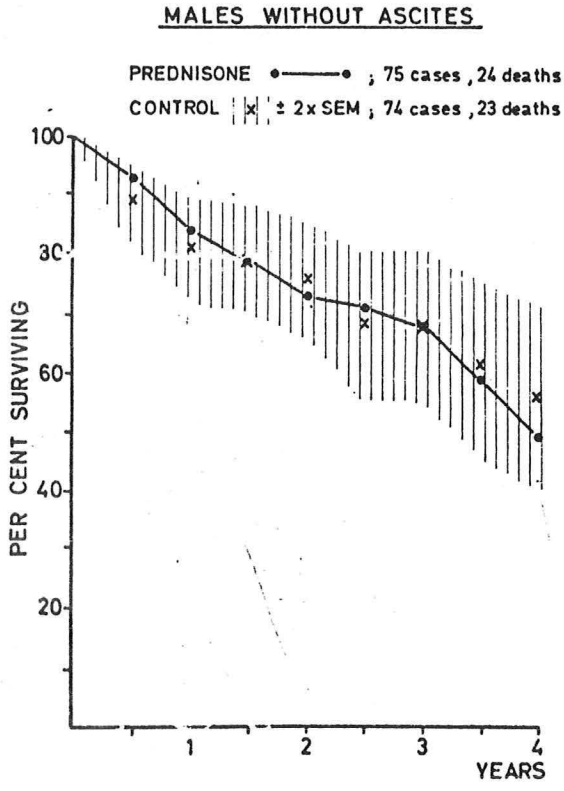


Fig. 10 Survival of male patients without ascites (124)

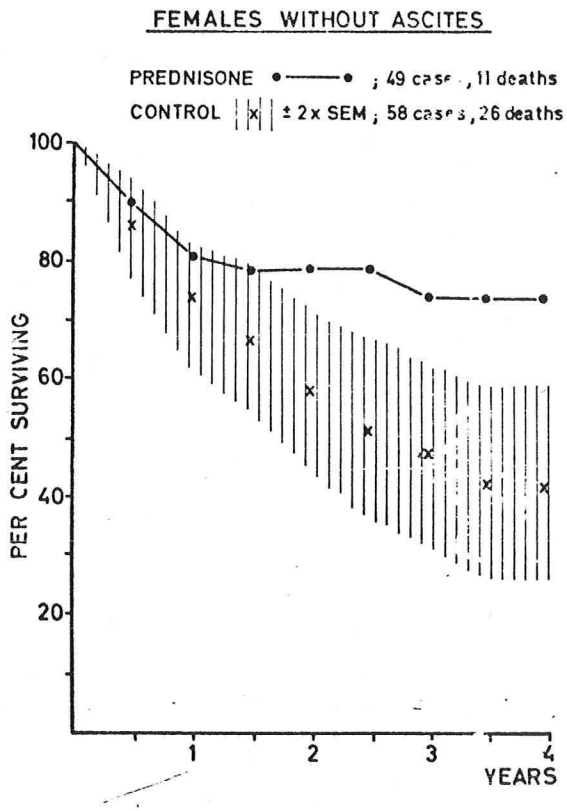


Fig. 11 Survival of female patients without ascites (124)

Antimetabolite therapy of chronic hepatitis

In 1960 Damesheck and Schwartz found that in a patient with autoimmune hemolytic anemia and lupoid hepatitis the liver function tests improved during treatment of the anemia with Thioguanine, a drug related to 6-mercaptopurine (6MP) (125). Subsequently antimetabolites-originally 6 MP and later azathioprine (Imuran®)-have been used to treat a number of CAH patients with apparent benefit (126-128).

A significant problem in the use of these antimetabolites for treatment of liver disease is their apparent hepatotoxicity (130). In earlier studies Mistilis' group reported alarming toxic reactions to these agents even at the reduced dose of 1.5 mg/kg/day (as compared with 2.5 mg/kg/day then used to prevent renal transplant rejection) (129). These effects were noted within 3 weeks of therapy in almost all cases and included anorexia, nausea, abdominal pain, leukopenia, thrombocytopenia, jaundice and hepatic precoma. Mistilis now initiates azathioprine therapy with a dose of 25 mg daily and rarely exceeds 75 mg per day, i.e. approximately 1 mg per kg per day in an adult. It may be difficult to distinguish azathioprine hepatotoxic reactions from spontaneous exacerbation of CAH (60).

Mackay concluded from his studies that azathioprine and corticosteroids are equally effective in treatment of CAH (131) while Murray-Lyon et al. found prednisone superior to azathioprine (132). The Mayo Clinic group has recently completed the only controlled study of azathioprine - a prospective evaluation of CAH patients treated with azathioprine alone.as compared with other groups treated with prednisone, prednisone plus azathioprine (each in reduced doses) or placebo (60). Fairly early in the study it was apparent that azathioprine (100 mg/day) was ineffective when used alone. Prednisone (20 mg/daily) on the other hand was clearly more effective than placebo in all respects, leading to improved life expectance, resolution to normal of clinical, biochemical and immunochemical abnormalities, and histological resolution from chronic aggressive hepatitis to a non-specific (CPH) liver biopsy pattern. Despite its lack of effect when used alone azathioprine (50 mg/day) combined with prednisone (10 mg/day) was as effective as the higher dose of prednisone alone (Figs. 12 and 13). The possibility that either drug alone in these doses might also be effective was not studied. Powell and Axelsen investigated the possibility that the apparent potentiation of prednisone by azathioprine is due to an azathioprine-induced reduction of prednisone binding by serum proteins, making the steroid more available to tissues; no such effect was observed (133).

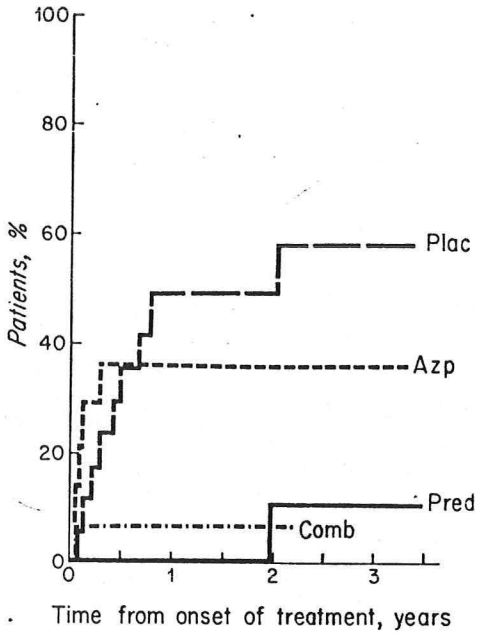


Fig. 12 Treatment failure - Mayo Clinic Study (60)

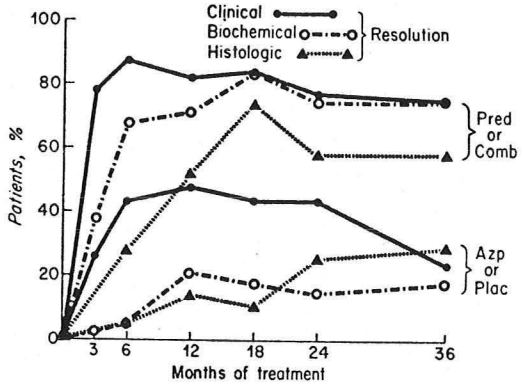


Fig. 13 Resolution of chronic active liver disease - Mayo Clinic Study (60)

Murray-Lyon (132) comments that one explanation for the poor results with azathioprine therapy in CAH is that immunosuppressive activity of the drug depends on production of an active metabolite(s) in the liver (134). Serum immunosuppressive reactivity of azathioprine is greatly reduced in patients with advanced liver disease (135-137). It is conceivable that steroids render azathioprine more effective in CAH by improving metabolic activation of the latter drug.

Many of the apparent beneficial effects of corticosteroid therapy in CAH patients could also be explained as relatively non-specific steroid effects. These include the increased sense of well being, reduced fatigability and improved appetite, decline of serum bilirubin levels (145) and accelerated albumin synthesis (146,147). For these reasons, as well as because of its direct relationship to liver cell necrosis, the serum transaminase test is generally considered most specific indicator of CAH "activity". Changes in transaminase values with treatment are also more quickly apparent than other clinical or biochemical changes.

Use of corticosteroids in doses sufficient to completely suppress chronic hepatic activity is commonly associated with minor side effects such as acne, facial mooning and other fat redistributions and offers a distinct risk of major complications including osteoporosis, sepsis, and possibly GI bleeding (63,123). Alternate-day steroid therapy (single dose at 8:00 a.m. QOD) has been shown to reduce side effects (141,142) while minimizing pituitary-adrenal suppression (143). Although there have been no systematic studies of its effectiveness in this disease, alternate day steroid therapy of chronic hepatitis appears to be common practice. It has been pointed out that the advantages of this regimen depend on nearly complete catabolism of each dose within less time than 48 hours (144). Prednisone, the drug most commonly used in treating chronic hepatitis, used in a dose of 50 mg QOD suppresses the adrenal cortex for roughly 30-36 hours and longer acting steroids such as dexamethasone in sufficient dose produce continuous suppression when given on alternate days (144). Prednisone must be converted to prednisolone by hydroxylation in the liver before it is therapeutically active, ordinarily a very rapid process. However, in liver disease this conversion is slowed (133 and Fig. 14) and conceivably with larger QOD doses of prednisone adrenal "release" may fail to occur in patients with CAH. For this reason prednisolone would appear the drug of choice for QOD steroid therapy of chronic hepatitis.

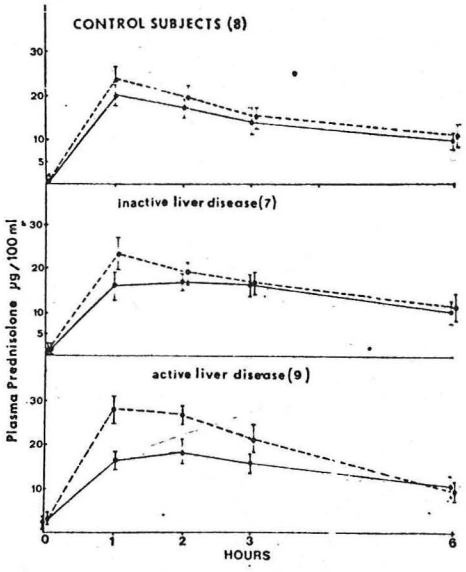


Fig.14 *Plasma prednisolone levels (mean values ± 1 SE) after the oral administration of 20 mg prednisolone (○ - - - ○) and after 20 mg prednisone (●—●) in eight control subjects and 16 patients with chronic liver disease. In the group with active chronic liver disease the levels are significantly higher after prednisolone than after prednisone at one and two hours (t = 3·6 and 2·6; P < 0·01 and < 0·05 respectively).* (Powell (133))

Case summaries of selected CAH patients treated locally are given in the following pages.

Case I: Active Postnecrotic (Cryptogenic) Cirrhosis

In 1965 this 13-year-old black girl was noted to have "yellow eyes" during a routine eye examination but she felt well and did not seek medical advice. In January 1967 she was hospitalized at the Childrens Medical Center in Dallas for pneumonia at which time abnormal liver function tests were found. A liver biopsy (reviewed at the Armed Forces Institute of Pathology) showed "postnecrotic collapse, scarring and active chronic inflammation; early cirrhosis". After subsidence of the pneumonia the serum bilirubin was 5.3 mg. % and SGOT 250 units. Prednisone therapy was begun with daily doses of 30-80 mg. In May 1967 while she was taking 80 mg. per day of prednisone the SGOT had fallen to 40 units. On reduction of the daily steroid dose and then conversion to an alternate day regimen the transaminase values fluctuated between 70 and 110 units and the serum bilirubin between 0.7 and 1.8 mg. %. On January 23, 1968 the SGOT was 100 units and bilirubin 1.6 mg. %; the prednisone dose was reduced to 15 mg. QOD. On February 20, 1968 the SGOT had increased to 600 units and the bilirubin to 4.5 mg. %. At that time prednisone was increased to 40 mg. QOD and 6-Mercaptopurine was begun in a dose of 75 mg. per day. By April the SGOT had declined to 94 units and the bilirubin to 3.0 mg. %. The 6-MP was stopped and prednisone continued in doses of 20-40 mg. QOD.

In November 1969 she began vomiting blood and was admitted to the Parkland Hospital for the first time. Bleeding stopped after transfusion with 4 units of whole blood, and esophageal varices were observed by endoscopy. However, it could not be determined whether bleeding was from the varices or due to aspirin-induced gastric erosions. On that admission two LE preps and ANA, latex fixation and VDRL tests were negative. Serum protein electrophoresis showed albumin of 2.32, gamma globulin 3.41 and total protein 6.8 gm. %. Subsequent HBAg tests were consistently negative.

Thereafter the patient was treated in the Parkland Hospital Liver Clinic with 50-60 mg. QOD prednisone. She was essentially asymptomatic on this regimen but because evidence of hepatitic activity persisted (SGOT 100-170), azathioprine (Imuran®) was added in a dose of 25 mg. per day in June 1971.

By August 1973 her medication had been reduced to 20 mg. QOD of prednisone and 25 mg. QOD (non-steroid days) of Imuran. She continued to feel well but the SGOT test remained abnormal in the range of 80-300 units.

On September 10, 1973 she was readmitted to PMH with recurrent upper GI hemorrhage, presumed to be variceal bleeding, and she died in hepatic failure two days later. Permission for autopsy was denied.

Comment; severe chronic active liver disease in a young woman with hyperglobulinemia and a negative HBAg test suggest the "autoimmune" type of chronic hepatitis, but none of the serologic markers of this disease such as positive LE preps, ANA, latex fixation and BFP-syphilis tests, were positive.

Case II: Chronic Persistent Hepatitis -- HBAg Positive

This 26-year-old WF hematology technician first became ill in September 1970 with arthralgias of the elbows, knees and ankles but with minimal digital stiffness. She consulted a private physician who found that her LE prep, ANA and latex fixation tests were negative but the SGOT was 400 Karmen units. A liver biopsy was reported to show increased lymphocytes in the portal areas and in the sinusoids, but no necrosis.

After a brief course of butazolidine the joint pains disappeared and have not recurred. Her hepatitis was treated with daily prednisone in unknown doses. She stopped the drug after several months because of facial "mooning". At no time did the SGOT fall below 100 units. Steroid therapy was resumed and discontinued several times largely according to rather vague symptomatic indications -- mainly fatiguability.

There was no past history of other "lupoid" features such as rashes, pleurisy, pericarditis, pneumonitis, unexplained fevers or anemia. There was no family history of arthritis or liver disease.

When first seen at Parkland Hospital in October 1972, her physical examination was completely normal. Specifically, there was no jaundice, spider angiomas, hepatomegaly or splenomegaly, nor was there evidence of arthritis. Her SGOT was 128 units, alkaline phosphatase 4.5 Bodansky units and bilirubin 0.4 mg. %; by electrophoresis the total protein was 7.1 gm. %, albumin 4.3 gm. and gamma globulin 1.4 gm. The HBAg test was positive and found to be of subtype ad. Liver biopsy showed a lymphocytic portal infiltrate, with minimal fibrosis and without piecemeal necrosis of the periportal lobular parenchyma. The biopsy was interpreted as showing chronic persistent hepatitis, and for this reason further steroid therapy has been withheld without apparent clinical deterioration. Repeat liver biopsy within the next year is planned.

Comment; HBAg antigen of subtype ad has been identified in the serum of patients with uncomplicated acute hepatitis, in asymptomatic chronic HBAg carriers (some of whom have normal liver biopsies) and patients with chronic aggressive hepatitis (see Case 3) as well as chronic persistent hepatitis as in this case. Clearly non-viral factors are of great importance in determining the outcome of hepatitis B virus infections.

Case III: Chronic Active Viral (HBAg positive) Hepatitis

This 23-year-old white female was jaundiced (physiologic?) shortly after birth and her mother is said to have had hepatitis at that time. However, the patient was in good health until late 1968 when she developed unusual fatiguability while in the last year of nursing school. Infectious mononucleosis was suspected but several "Mono-spot" and heterophile tests were negative. No liver function tests were done. In July 1969 she developed anorexia, nausea, vomiting and increased lethargy and her SGOT was found to be 250 units. The liver edge was

felt 2 cm below the costal margin and the spleen was palpable. She was believed to have anicteric hepatitis. With bedrest the SGOT fell somewhat but remained abnormal. Slides of a liver biopsy done in October 1969 were sent to Dr. Gerald Klatskin who interpreted them as "suggestive of mildly active post-necrotic cirrhosis", however, noted that the specimen was too small for definitive diagnosis. On treatment with prednisone (50 mg/da) the SGOT levels dropped to near normal. When the dose was reduced over several months, the SGOT again rose to 150, whereupon azathioprine (100 mg/day) was added. The effect of this treatment on the liver function tests is not reported, but the drug was stopped when the WBC count fell to 800 per mm^3. A repeat liver biopsy in July 1971 again yielded a fragmented specimen with evidence of "aggressive" inflammation and cirrhosis. At this time HBAg was first tested, and found positive. Several LE cell tests were negative. The SGOT was 202, albumin 4.4 gm, globulin 2.5 gm and total serum bilirubin 0.9 mg/100 ml. The DRL was negative.

On referral to PMH in December 1971 she complained of continued easy fatiguability and depression but denied joint pains or other "lupoid" symptoms. Physical examination revealed a few large spider angiomas on the hands and arms, liver edge palpable 2 cm and spleen 4 cm below the costal margin. Laboratory tests included SGOT 300, bilirubin 0.4, alkaline phosphatase 14.5 KA units, SPEP - total protein 7.0 gm, albumin 4.6 gm and gamma globulin 1.0 gm. (Total serum globulins and gamma globulin have been normal on each of several determinations since 1969.) HBAg was found to be subtype ad.

Since the SGOT had risen significantly since she stopped taking prednisone several months earlier this drug was resumed in a dose of 40 mg QOD. Over the next few months the SGOT gradually fell from 330 to 100 units. In March 1972 she developed mild polyuria and polydipsia and was found to have glucosuria and an elevated fasting blood sugar. For this reason azathioprine (25 mg/day) was started and the dose of prednisone was reduced to 35 mg QOD with subsidence of the glucosuria. The SGOT has fluctuated between 60 and 200 units since that time and symptoms of moderate fatiguability persist. Larger doses of azathioprine (50 mg/day) have had no significant effect on the transaminase levels. Because of a slowly declining platelet count, Imuran was discontinued in July 1973. The platelet count remained low (60-100,000/mm^3), probably due to hypersplenism. Since there was no deterioration of the clinical status or laboratory tests while off azathioprine, the drug has not been restarted.

Comment: Conceivably this patient's liver disease could have begun with perinatal HBAg infection, though she was well until age 20. Her mother's serum, obtained in 1972, was negative for anti-HBAg antibody (tested by RIA) suggesting (but not proving) that she has not had hepatitis B in the past.

Although chronic active liver disease among young females is characteristically of the "lupoid" type, this patient lacked lupoid symptoms and was HBAg-positive with negative LE cell tests and normal gamma globulin levels. She is considered a case of chronic active viral hepatitis.

Case IV: Chronic Active (Lupoid?) Hepatitis following Acute Viral Hepatitis

This 32-year-old white male developed features of typical acute viral hepatitis in March 1969 with complete clinical resolution after an illness of approximately 6 weeks. Laboratory data from this time are not available. He remained well until October 1969 when he had a "relapse" of hepatitis with symptoms like those of the original attack but milder. Following this he failed to recover his normal energy and appetite and lost 20 lbs. over the next several months. In July 1970 because of progressive worsening of these symptoms he was admitted to a local hospital for evaluation. Total serum bilirubin was 4.0 mg %, SGOT 200, SGPT 180, ceph. floc. 4+ at 24 hrs., total serum protein 7.3 gms. % and the serum protein electrophoresis was reported to be "essentially normal". He was started on prednisone 15 mg t.i.d. with marked symptomatic improvement and complete correction of the abnormal liver function tests. The steroid dose was gradually reduced to 1 tablet daily and finally discontinued early in 1971. In April 1971 he again became jaundiced with a serum bilirubin of 8 mg %. Prednisone was resumed in a daily dose of 5 mg but jaundice and fatiguability persisted. For this reason a liver biopsy was done in August 1971 and was reported to show "nodular cirrhosis". He was then referred to PMH for further evaluation. He admitted having mild stiffness of the fingers, elbows and right temporo-mandibular joint, but no other "lupoid" symptoms. The family history was negative for liver or connected tissue diseases. On examination he was mildly jaundiced, had diffuse steroid acne over the chest and shoulders, and the spleen tip was palpable. The liver was not enlarged and there was no ascites, edema, palmar erythema or spider angiomas. Anti-nuclear antibody was positive (2+, diffuse) and the RA latex test was negative. HBAg was negative. Liver function tests are shown in the following table. Prednisone was increased to 60 mg QOD (a.m.) and maintained at this level for the next 10 months with no complications except the appearance of a slight "buffalo hump". He has been completely asymptomatic since approximately 6 weeks after beginning alternate day steroid therapy. Since July 1972 the dose has gradually been reduced to the present 10 mg QOD without clear evidence of clinical or biochemical relapse.

Comment; Corticosteroid therapy of chronic hepatitis is usually begun with divided daily doses of the drug. This patient responded well to prednisone taken on alternate days from the outset. The rather high dose, remarkably well tolerated, was maintained for almost a year in hope of achieving maximal suppression of hepatitis activity for as long as possible. He has now been on a moderate dose (20 mg QOD) for 5 months with no evidence of resurgent disease. If he remains well, the present dose (10 mg QOD) will be continued for at least another year, dictated largely by intuition.

	1971				1972						1973			
	8/28	9/21	10/23	12/16	3/24	4/25	6/15	7/25	9/13	11/21	2/1	6/6	7/6	9/24
Bilirubin (Total)	4.2	2.1	1.5	1.2	1.1	1.3	1.4				1.5		1.2	
Alk. Phos. (Nl.20-82)	250	161	90	87	111	100	100				100		98	
SGOT (Nl.10-55)	500	103	55	48	71	52	50	27 (40)	27 (40)	20 (40)	50	25	62	20 (40)
Albumin	3.6	4.2	3.5	3.9	5.0	4.2	4.7				4.2		4.1	
Globulin	4.0	3.6	2.9	3.1	2.8	2.9	2.1				2.2		2.7	
Prednisone Dose	60 QOD →							50 QOD →	40 QOD →		30 QOD →	20 QOD →	15 QOD →	10 QOD

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