International Symposium on Problems of Chronic Hepatitis Montecatini Terme, 1975

CHRONIC HEPATITIS

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Chronic Hepatitis

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Preface

The fact that renowned hepatologists from all over the world have readily accepted to participate in this International Symposium as chairmen or speakers, shows the great interest in this topic, which has become the object of widespread and detailed study only relatively recently. Only in the 50s did the concept that chronic hepatitis was an autonomous nosological entity begin to make its way: autonomous in relation to cirrhosis, even if some cases actually develop into liver cirrhosis later; and also autonomous in relation to acute hepatitis, especially protracted viral hepatitis, particularly studied immediately after the war. This autonomy derives from anatomo-clinical features which are by now well outlined so that in most cases diagnosis is not difficult. There is still, however, a certain amount of doubt when ascertaining the degree of 'activity' of the disease and its seriousness.

The interest in the subject today therefore does not lie in its nosological aspect, which is by now clarified, also according to the recent classification established in Acapulco. Although the main subject of our Symposium is chronic active hepatitis, other forms will have to be taken into consideration as a necessary means of comparison. These forms are included, in a broad sense, in the term chronic hepatitis, above all the persistent form, described by BOCK in 1957, and then chronic alcoholic hepatitis, drug-induced chronic hepatitis and so on.

The reason for choosing this particular subject is on one hand the ever-increasing incidence of this 'active' form, on the other, the fact that the problem of its etiopathogenesis, of its morphological, functional and above all immunological and therapeutical aspects has still to be clarified. Since the disease can present an extremely different prognosis case by case, the urgent questions we have to answer today is what factors play a determinant role in

its development, and if and how it can be modified by suitable treatment. We should ask ourselves what factors promote or determine chronicity in acute hepatitis. I should just like to mention that the Australia antigen has often been reported in the blood of patients with chronic active hepatitis. (We ourselves found that the relatives of at least 12 patients out of the 180 studied after a certain time developed an acute liver disease, with or without jaundice, or else active or persistent, HB_sAg-positive chronic hepatitis.)

Why the antigen, and therefore the virus, should persist is not quite clear. It may depend on abnormal immunological reactivity, and precisely on a decrease in cell immunity. In this connection, I should point out that according to our own experience, besides that of the School of Sherlock, cortisone treatment carried out during the acute stage of viral hepatitis promotes chronicity, probably lowering immunological defense.

However, the etiopathogenetic problem of chronic hepatitis certainly cannot be reduced to the simple persistence of the virus, which in many cases even has to be demonstrated. On the other hand, the persistence of the virus does not mean *sic et simpliciter* that the latter maintains its pathogenetic activity (e.g. as in the cases of 'healthy carriers').

A number of predisposing conditions should also be taken into consideration: alcoholism, protein denutrition due to various exogenous and endogenous causes, and even concomitant chronic diseases, such as diabetes and siderochromatosis, or chronic infections, as tuberculosis and malaria. Genetic predisposition also seems probable and cases of acute hepatitis developing into chronic forms and finally into cirrhosis have sometimes been observed in later generations. However, rather than dealing with the etiopathogenesis of chronic hepatitis, I should like to point out the ever-increasing incidence of this disease, and therefore its social importance, and to propose a prophylaxis, based on the factors which I mentioned above as promoting the disease. Although the kind of prophylaxis which we could term primary is far from easy, a secondary prophylaxis should be carried out through early diagnosis and early treatment of the disease.

There is unanimous agreement on the problems of rest and diet for these patients, but the actual therapeutic value of the various drugs, particularly cortisone and immunosuppressive drugs, must still be ascertained.

I hope that the various contributions presented in this Symposium by highly qualified researchers and the reciprocal exchange of ideas ensuing may shed more light on concepts which are merely outlined and may reduce the extent areas of doubt.

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Introduction to the Problem of Chronic Hepatitis

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An international conference focusing on a specific disease with rising incidence serves several purposes. One is, to take stock of the information available. A second is, to develop new viewpoints and approaches by discussion among investigators of different disciplines concerned with the disease. A third would be, to interest in the disease biological investigators who represent techniques not yet fully applied to the problems.

The charge of this conference is to find agreement on the state of the art in chronic hepatitis. The first and probably most difficult problem is definition and nomenclature. With the term 'chronic hepatitis', we speak of forms in which we incriminate the hepatitis virus or do not know the etiology, but assume it could be viral hepatitis and exclude those forms with established etiologic factors like alcohol abuse, metabolic disorders, exemplified by Wilson's disease or iron overload, drug-induced lesions, or hepatitis induced by bacteria, fungi or viruses different from the elusive hepatitis virus.

Another question concerns the term 'chronic', which may either be used descriptively, often morphologically, or may refer to duration. A gradual consensus seems to call chronic hepatitis any liver disease of viral hepatitic, presumably viral hepatitic or cryptogenic nature lasting longer than 6 months. However, we may agree not to include prolonged acute hepatitis which lasts longer than 6 months but eventually subsides. A further question is posed by the word 'hepatitis', that means the role of inflammation. In acute hepatitis, viral, but also alcoholic, and chemical-induced, the inflammation is of little functional importance in that the functional deficit is caused by an alteration of the hepatocytes. Inflammation is almost always a reaction to liver cell injury, indicating that this injury is severe enough to elicit an inflammation. We might call the inflammation a morphologic liver function

test, a symptom rather than the basis of the disease [1]. By contrast, in chronic hepatitis, the inflammation, including its macrophagic, immunologic and fibroblastic component, is a key element determining the evolution of the disease. We might therefore eventually agree that the knowledge of its evolution, acquired by morphologic and functional procedures, may guide us in the management. However, we still have few clinical parameters to reliably ascertain its degree at the bedside. Discrepancy amongst clinical, laboratory, and histologic features is rather common in chronic hepatitis, and a special problem as to management represents a case with impressive histologic features of chronic active hepatitis in the absence of clinical and laboratory manifestations. We need prospective studies to appreciate the prognostic implications.

The second problem is the pathogenesis, especially the mechanism by which the hepatitis virus leads to liver injury. This includes immunologic hepatic injury, its role in initiation and perpetuation of liver disease, as well as the pathogenesis of hepatic fibrosis, to which a recent international conference was devoted [2]. Since we know more about pathogenesis than about etiology, the former may be more useful in classification.

The third major problem are the implications. One is acute hepatic failure as result of extensive hepatic necrosis, which is rare in chronic hepatitis before cirrhosis sets in. When massive necrosis develops in the stage of chronic hepatitis, the possibility of a second etiologic factor, for instance, infection with another type of hepatitis virus, arises. We are further concerned about sustained morbidity, i.e. interference with the quality of life. Most dreaded is the transition to cirrhosis with all its known consequences, especially interference with hepatic circulation predisposing to hepatic failure, to portal hypertension, to infections – to list only a few. The step between chronic hepatitis, which is reversible, and the irreversible stage of cirrhosis is still mysterious. We define it as the 'committed precursor stage' which separates the phase in which full morphologic restitution is possible, from the condition which either leaves a permanent scar stage or progresses to a life-threatening disorder. The identification of this stage, identifying the person at risk, depending possibly on genetic factors, is one of the main charges of this conference.

In the last year, three events took place which might influence our discussion. The first was a conference devoted to Nomenclature, Diagnostic Criteria and Diagnostic Methodology for Diseases of the Liver and Biliary Tract sponsored by the John E. Fogarty International Center for Advanced Studies in the Health Sciences, National Institutes of Health, USA, and

the International Association for the Study of the Liver. A book as result of this international cooperation is soon to appear. While many of us may not agree with everything accepted, this classification will assist in communication even if it might exert a restraining influence in many aspects. In chronic liver disease, this classification is greatly based on the work of a group of pathologists interested in liver disease who under the sponsorship of the European Association for the Study of the Liver met yearly [3–5]. Most of its members are present here. The second dramatic event are studies on the chemical nature of the collagen in chronic liver disease [6, 7]. We learned, for instance, that in the cirrhotic nodule both in man and in experimental animals a type of collagen is found which differs from the four forms established in various organs [7, 8]. Since new formation of collagen is the key process in the disfiguration of the liver characterizing cirrhosis, the forms of collagen specific for this disease may offer diagnostic tools to monitor its development and possibly, even more important, permit a specific antifibroblastic therapy.

The most exciting development in an old disease is the rapidly increasing knowledge of the anatomy and immunology of the hepatitis virus. While this field was stagnant for decades, the discovery of the Australia antigen by BLUMBERG has led recently to almost explosive accumulation of new information. Significant information became available in the short span of several weeks between two recent conferences devoted to the subject, one in Milan and the other a few weeks later in Washington [9]. One development concerns clinical diagnosis of type A hepatitis. Several years ago, evidence was presented [10] that this type of hepatitis, already transferred to human volunteers, can be transmitted to marmosets, a small South American monkey. Quite recently, this has been also accomplished in the chimpanzee [11], in whom histologically typical hepatitis was found coinciding with shedding of virus. These studies acquired major significance when it was shown that virus aggregates cannot only be identified by complex immunoelectron microscopy, but that infection can be demonstrated by a much simpler immune adherence test using infected marmoset livers [12, 13]. Hepatitis A may only be of limited interest here because there is only little evidence that it causes chronic hepatitis, as a matter of fact, in blood-transfusion-induced hepatitis, many cases seem to be caused by neither type A nor type B hepatitis, and therefore other types of etiologic agents, either putative type C or D hepatitis or some other agent, may be responsible.

In hepatitis B, the progress was even more impressive, particularly since nature and configuration of the DNA, of the polymerase, of core (c) and surface (s) antigens are now being understood on the basis of correlated

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physical/chemical and immunologic studies [9]. Secondly, the tissue localization of the c and s antigens by light microscopy, fluorescence microscopy and electron microscopy are now far advanced. One can now demonstrate the s component in paraffin sections prepared from blocks on file for as long as 50 years [14]. The expectation can be expressed that these studies correlated with the investigations of the respective antibodies, polymerases and γ-globulins in the serum may permit to trace the evolution of chronic hepatitis and to finally understand the pathogenesis at least in the type B, which may be a model for other types. Moreover, a vaccine for type B hepatitis may indeed be soon commercially available.

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Pathology of Chronic Hepatitis

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Table I presents as introduction a classification of chronic hepatitis which is in principle based on the above-mentioned deliberations of the hepatopathologists and of the Conference on Nomenclature, Diagnostic Criteria and Diagnostic Methodology of Liver and Biliary Tract Diseases. The two entities listed on top are not really chronic hepatitis but enter into the differential diagnosis. Their main characteristic is the almost invariable healing, while the two main groups listed below represent the basic framework of chronic hepatitis. The presence of bridging necrosis, linking central and portal canals, also called subacute hepatic necrosis, and massive or submassive necrosis involving several lobules, is the most telling sign as to transition to cirrhosis. The persistence of inflammation in such location, possibly stimulated by surviving cells, is probably the main factor in sustaining progression of the process. In chronic persisting hepatitis residual intralobular inflammation is frequent.

The HB_sAg carrier stage presents a specific problem in that it may be associated exceptionally with chronic active hepatitis, frequently with chronic persisting hepatitis, and often with essentially normal liver [1–4]. In the latter two groups, a type of hepatocyte is common which is characterized by a diffuse finely granular appearance of the whole cytoplasm or a greater part of it [5]. In the latter instance, these areas look almost like inclusions [6]. These 'ground-glass hepatocytes' have been previously described in persons receiving large amounts of drugs leading to induction of the microsomal biotransformation system in the smooth endoplasmic reticulum, and indeed this reticulum was found in excess in these 'induction cells' [7], as it is also found in the ground-glass cells of the HB_sAg carriers, in which these cells sometimes form almost nodular aggregates. Electron microscopy reveals in

Table I. Chronic hepatitis

Pathologic designation	Picture	Clinical designation	Outcome
Prolonged	nonspecific changes	'transaminitis' in bouts	heals
Slowly resolving lobular	spotty necrosis	unresolved	usually subsides with some scarring
Portal	portal inflammation	persistent	stationary (except with IgG and during regression)
Periportal aggressive lobular with extensive necrosis	piecemeal necrosis		some tendency ↓
	spotty with bridging or multilobular necrosis	chronic active	to cirrhosis ↑
		a *conspicuous immune* reactions (lupoid)	
		b conspicuous[1]	greater tendency
		c almost silent[1]	

1 Often hepatitis-B-antigen-positive.

the endoplasmic reticulum circular and tubular structures [8–10], and on immunoelectron microscopy the surface component of hepatitis B antigen can be localized in the endoplasmic reticulum. The cytoplasm of these cells, moreover, reacts with anti-HB_sAg on immunofluorescence. The ground-glass cells, thus recognizable in HE sections, are even better visualized with either the orcein or the aldehyde fuchsin variety of the Shikata stain [11]. Their presence is also useful in indicating a chronic condition. There is another type of carrier, particularly patients with immunosuppression either from spontaneous disease, like leukemia and lymphoma, or as result of therapy, in which the c component of the hepatitis B antigen is demonstrated within the nucleus by immunofluorescence technique and particles comparable to the core of the antigen are found in the nucleus by electron microscopy and identified by immunoelectron microscopy, as particularly was shown by HUANG *et al.* [8] in patients with renal transplants. There are, exceptionally, healthy carriers which only have c particles in the nucleus [12]. The morphologic evidence is in keeping with the concept that c particles are formed in the nucleus and receive their surface cover in the cytoplasm. In very early viral hepatitis, that means the prenecrotic stage, the membranes of the hepatocytes

contain much s component [13] and the same is seen in infected chimpanzees [14]. In necrotizing acute hepatitis, very little if any of the components is demonstrable (much s is found in Kupffer cells), and GUDAT and BIANCHI [15] suggest that the balance of the more hepatocytic distribution of c and s in the chronic active hepatitis reflects the progression. The distribution of these components thus may indicate the nature of the hepatocytic injury, and possibly the destruction of hepatocytes with antigenic material in the membrane makes for the acute hepatitis, and the continued presence, for progression into the chronic disease. It remains to be decided whether the cell containing the virus is simply eliminated [15] or whether persistence or expression of the virus is inhibited by immunosuppression [13]. This may also clarify the mechanism and the consequences of the centrocellular localization of the antigen in carriers and in persistent hepatitis.

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