Advances in Hepatology

Transactions of the International Symposium of the International Association for the Study of the Liver

J. Vandenbroucke, J. De Groote
and L. O. Standaert

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of the International Association for the Study of the Liver
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Edited by

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Preface by

H. POPPER, President of the Association

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ADVANCES IN HEPATOLOGY

PREFACE

International meetings of small groups with interest focused on limited fields are becoming more attractive than large international Congresses. The small group permits informal and, thus, meaningful discussions without the ceremonious delivery of prepared dissertations. But it deprives larger groups of stimulation which might arise from listening to experts of foreign countries. This is particularly regrettable if the scientific neophyte becomes the victim of the restrictive policy. The International Association for the Study of Liver Diseases makes every effort to remain a small group of members acting, in effect, as representatives of their respective countries to develop a well balanced program of their biennial meetings. To serve as a stimulus of larger groups, one open session is held in conjunction with one of the major international congresses of Gastroenterology followed by a small conclave in a nearby town. The following proceedings record the open session following the Seventh International Congress of Gastroenterology in Brussels and a small meeting in the ancient and charming university town of Louvain. Both in the broad setting of Brussels' Congress Palace and in the intimate but modern hall in Louvain, the organizational talent, thoughtfulness, and gracious hospitality of Professors J. Vandenbroucke and J. De Groote were apparent. The program which they organized with advice from the honorary president of the Association, Professor Sheila Sherlock, and the most effective international secretary, Professor Adolf Martini, reflected the recent exciting thinking in the broad field of the normal and abnormal function and structure of the liver. The charm of the meetings is the interdisciplinary character, thus representing an experiment in medical communication. Our Belgian colleagues have now undertaken to crown their achievements in organizing the meeting most effectively by editing the proceedings and have, thus, increased the debt of gratitude which the Association owes them for all they did for us.

Hans Popper, M.D.
New York, U.S.A.

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CHRONIC HEPATITIS: THE SCOPE OF THE PROBLEM (1)

BY

S. SHERLOCK

Chronic Hepatitis is a very difficult condition to define. Different observers have quite varying viewpoints. In this symposium only the chronic hepatitis presumed to follow acute virus hepatitis will be discussed and such conditions as chronic amoebic hepatitis will be excluded. The exact relation to virus hepatitis is of course uncertain for the agent of this common virus infection has still not been conclusively identified. Many of the cases of chronic hepatitis do not even follow what might be termed a classical, clinical attack of the acute disease.

Acute virus hepatitis often lingers on. Biochemical tests show minor abnormalities and liver biopsy sections reveal portal zone cellularity. These usually subside within a few months. For the purposes of this paper, therefore, only the sequelae lasting longer than one year after the acute attack will be considered. This greatly reduces the number of cases to be described (TABLE I).

TABLE I

Chronic Sequelae of Virus Hepatitis

Post-hepatitis hyperbilirubinaemia (rare)

Post-necrotic cirrhosis (rare)

? Active chronic hepatitis (rare)
(active juvenile, lupoid, etc.)

Chronic (persistent) hepatitis (rare)

The commonest sequel is the post-hepatitis syndrome (SHERLOCK and WALSHE, 1946). This mainly psychological condition is commonest in those most likely to be introspective (nursing and medical

(1) Royal Free Hospital, London.

profession etc.), and usually subsides within a year or two of the acute episode, especially if reassurance is firm. *Post-hepatitis hyperbilirubinaemia* is, in the present experience, extremely rare. It seems to be particularly frequent in Germany and Sweden (HULT, 1950; KALK and WILDHIRT, 1955). In a recent series of 366 adolescent subjects with unconjugated hyperbilirubinaemia in the absence of overt haemolysis in only 7 could virus hepatitis be incriminated (LEVINE and KLATSKIN, 1964).

Post-hepatitis cirrhosis of post-necrotic type can develop after acute virus hepatitis but this is astonishingly rare (SHERLOCK, 1963). Follow-up studies of the various large epidemics of hepatitis have revealed very few, if any, cases of definite cirrhosis. Nevertheless the sequence has been followed too often to deny that it exists. The relation may be a direct one through acute to subacute and so to cirrhosis and death within a year in liver failure. Alternatively, the original acute condition may subside to a "latent well-compensated" cirrhosis only to emerge perhaps five to ten yers later, often as portal hypertension or ascites.

The condition of "*active chronic hepatitis*" must now be considered. This has many synonyms including "active juvenile cirrhosis", "plasma cell hepatitis", cirrhosis of young women", "cirrhosis of young people", "lupoid hepatitis", and so on ! It is predominantly a disease of young people especially women and can affect both sexes and all ages. It is characterised by continued jaundice, high serum transaminase and gamma-globulin values and by a hepatic histological picture of much activity with isolation of rosettes of liver cells, agressive fibrosis and infiltration with plasma cells and lymphocytes. The hepatic histological picture is a definite one except in the later stages where a non specific postnecrotic cirrhosis may be seen. Such a condition may be associated with disease of other systems, for instance, diabetes, ulcerative colitis arthralgias and others. It is believed to be related to disturbed immunity. In 23 of 81 such cases (28 %) a past history of acute hepatitis was elicited (READ et al., 1963). The high percentage may mean a real relation between the two diseases or may reflect random diagnosis of virus hepatitis in any young person who becomes jaundiced from whatever cause.

The condition of true *chronic hepatitis* must now be considered. This can be regarded as continued non-cirrhotic inflammation of the liver persisting more than one year after the acute attack. In

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a brief survey of personal cases only 12 such instances could be found (TABLE II). In only four was there a good contact history of hepatitis. The patients came largely from a high income bracket,

TABLE II

Chronic (persistent) hepatitis
(1 year)

No. of cases : 12 (M. 7 F. 5)
Contact history : 4
Occupations:

Physicians	3
Armed Forces	2
Impresario	1
Executive	1
Housewife	5
Working class	0

were members of the armed forces where medical follow-up is careful or were physicians who again might be anticipated to perform repeated liver function tests upon themselves. There were none from the lower income range. The patients complained only of vague malaise and sometimes upper abdominal discomfort and fat intolerance. Physical examination showed an enlarged, sometimes tender, liver of normal or firm consistency. The spleen was not palpable. Biochemical tests showed a serum bilirubin of greater than 1 mg/100 ml in only three of the twelve patients while the serum aspartate transaminase was raised in only 9 of the 12 patients and then only mildly. A slight increase in total serum globulin was common. Liver biopsy sections showed portal zone cellularity and fibrosis with focal spotty necrosis of liver cells surrounded by a cellular, predominantly mononuclear, reaction. The reticulin framework was characteristically normal. Such a histological picture might persist unchanged for years and this was so in 5 of the patients who remained still active 2-10 years from diagnosis (TABLE III). In 4 others, over a period of three years, the hepatic activity slowly subsided, and the end result was very minor portal zone scarring. These patients could be regarded as healed. In 3 of the patients however serial biopsies over a period of 2-6 years showed a progression towards cirrhosis, the portal septa encompassing groups of liver cells until a frank cirrhotic picture was produced. This is exceedingly rare.

TABLE III

Chronic (persistent) hepatitis)
(Liver biopsies : 29)

	Duration		
	No.	(Years)	Mean
Healed	4	1 — 3	1.8
Still Active	5	2 — 10	5.2
Cirrhosis	3	2 — 6	3.5

This type of chronic hepatitis can be regarded as analagous to that described as "chronic persistent hepatitis" (GALLAGHER and GOULSTON, 1962). This symposium will discuss chronic hepatitis in more detail. It will not be clearly seen in prospective until better tests for the virus are available. Limited information however should come from careful follow-ups of large epidemics of hepatitis especially if such studies are intensive and include, where possible, needle biopsy of the liver. Serial study of hepatic histology seems to be the only present method of elucidating the natural history of chronic hepatitis.

I wish to thank the IRWIN STRASBURGER Memorial Foundation for financial support.

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ON CHRONIC VIRAL HEPATITIS (1)

BY

S. YAMAGATA, I. KAITO AND K. WAKUI

In the past few decades, knowledge concerning viral hepatitis has increased as it is indicated by an ever increasing number of medical reports on the subject. Although this is encouraging to all of us who are interested in the problem, the reports have given rise to confusion. One such confusion can be seen in the understanding of the concept of chronic hepatitis. Widespread application of needle biopsy in the field of liver disease unfortunately further increased this confusion.

As it is shown in the Table 1, the clinical disappearance of jaundice does not indicate the subsidence of the pathological process in the liver. After the disappearance of jaundice, various liver function tests remained abnormal in 13 to 74 %.

Table 2 indicates that following the clinical course of an epidemic of infectious hepatitis which occured in a rural junior high-school, liver function tests of the students of the school were found abnormal regardless of the presence of subjective symptoms. However, after about six months, the rate of the incidence of abnormal liver function tests sharply decreased. Besides this finding, the condition of those abnormal patients became rather static and hard to cure.

In Table 3 the results of the same follow-up studies on 143 various viral hepatitis patients are demonstrated and showed that here again the incidence of abnormal liver function tests in this group of patients sharply decreased at about the six month period and then these abnormal cases became less responsive to reasonable medical treatment. It also should be noted here that the prognosis of serum hepatitis is worse than that of infectious hepatitis.

(1) From : Medical Department of Professor Dr. S. YAMAGATA, Tohoku University School of Medicine, Sendai, Japan.

TABLE I

Prognosis of Viral Hepatitis and Liver Function Tests

Liver Function Test		Positive in %			
		1st Week	2nd Week	3rd Week	After Disappearance of Icterus
		(64 cases)	(65 cases)	(87 cases)	(122 cases)
B.S.P. Test		100.0	75.0	72.0	74.0
Hippuric Acid Test		75.0	50.0	56.3	37.5
Cephaline Floccul. Test		83.3	55.0	48.5	43.7
Thymol Turbidity Test		65.0	54.7	50.3	39.2
Kunkel's Test		46.8	46.5	40.8	30.7
Diethyl Barbiturate Test		42.1	49.1	41.5	37.0
Sublimat Test		60.0	61.0	48.5	30.8
Takata or Manke's Test		44.3	32.1	36.6	20.0
Urinary	Qual.	35.7	46.1	54.2	31.3
Urobilinogen	Quant.	30.1	50.0	66.6	42.8
Cholesterol Ester Ratio		75.0	40.0	40.0	12.5
SGOT		100.0	94.8	68.6	24.4
SGPT		100.0	94.8	56.0	24.4

In Table 4, the prognosis judged by serial liver function tests were plotted against the age of each patient, and showed rather evident influence of advanced age on the prognosis.

Because these studies were done by repeated liver function tests, the reliability of the liver function tests for this sort of study should be investigated.

TABLE II

Epidemic Hepatitis
(Time required to return to normal Liver Function)

Time / group	Returned to Normal				Total
	Less than 3 M.	3 to 6 M.	6 to 8 M.	More than 8 M.	
Symptomatic with Icterus	18 33.3 %	24 44.4 %	4 7.3 %	8 14.8 %	54
without Icterus	9 52.9 %	6 35.4 %	0	2 11.7 %	17
Asymptomatic	18 64.3 %	5 17.9 %	2 7.1 %	3 10.7 %	28
Total	45 45.5 %	35 35.4 %	6 6.0 %	13 13.1 %	99 100 %
	80.9 %		19.1 %		

In order to obtain a uniform series of cases for investigation, only cases of viral hepatitis which demonstrated liver function abnormalities were selected. From these cases, those who underwent liver biopsy and simultaneous liver function tests were selected. From this selection 41 instances on 51 cases were thought to be worthwhile in studying the relationship between the liver function studies and histological findings of the liver obtained by needle biopsy.

The needle biopsy was done under the peritoneoscopic control and specimens were taken at least from two different portions of the liver. The histological specimens were sent to a pathologist and his opinion was trusted although before arriving at a conclusion he consulted with other pathologists.

In Table 5 the over-all results of the study are demonstrated. The histological findings are classified according to the severity into 5 degrees. This is then compared with the values found

TABLE III
Prognosis of Viral Hepatitis Judged by Liver Function Tests

Prognosis	Time Length	Infectious Hepatitis			Serum Hepatitis			
		No. of Cases	%		No. of Cases	%		
Returned to Normal within	2 months	32	35.2	68.1	12	23.1	59.6	( ) discharged and not followed
	2 to 3 months	30 (1)	32.9		19 (1)	36.5		
	3 to 4 months	12 (3)	13.2	20.9	18 (2)	15.5		
	4 to 5 months	4	4.4		2	3.8	17.2	
	5 to 6 months	3	3.3		1	1.9		
Abnormality present	6 to 12 months	4 (2)	4.4	11.0	6 (1)	11.6	19.2	( ) improved afterwards
	1 to 3 years	5	5.5		2	3.8		
	Over 3 years	1	1.1		2	3.8		
		91	100	100	52	100	100	

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