CASE REPORT AND DISCUSSION: CHRONIC ACTIVE HEPATITIS

FREDERICK FRASER*
Halifax, Nova Scotia

INTRODUCTION:

In 1950, Waldenström reported a series of cases of chronic hepatitis in young women. This generated considerable interest in the disease. Subsequent reports have demonstrated that while it is much more prevalent in the young, it is not confined to them and that cases have been reported from all age groups.

Chronic active hepatitis is a syndrome of unknown etiology, characterized by a progressive necrosis of liver parenchyma resulting in chronic hyperbilirubinemia and elevation of transaminases. Hypergammaglobulinemia is always found. The disease uniformly progresses to cirrhosis, liver failure and death. About 25% of cases follow what appears to be an acute attack of viral hepatitis. The remaining cases have no such antecedent history, becoming clinically recognizable at the stage of liver failure. The role of anicteric hepatitis as a predecessor of chronic active hepatitis is suspected but not proven. The prognosis is poor, most patients dying within 3-5 years from the onset of symptoms.

MacKay and his colleagues (1) reported finding L.E. cells in some patients with chronic active hepatitis. He has named this entity lupoid hepatitis, making its diagnosis dependent on the presence of L. E. cells. This phenomenon suggests that autoimmunity plays a role in the etiology. Many aspects of this disease are similar to ones found in autoimmune processes.

There are many problems presented by this disease. What part does viral hepatitis play in the etiology? Is there an autoimmune process perpetuating virus-induced damage? Does the L. E. cell phenomenon separate the patients into two distinct groups? Finally, how best does one treat this illness? The following case may illustrate some of these points.

*Fourth year medicine, Dalhousie University.

CASE REPORT:

A 16 year old white male presented to the Victoria General Hospital in October 1967 complaining of jaundice for the last 15 months. His illness began in August 1966 with the appearance of scleral icterus, preceded for 3 days by dark urine and pale stools. He was diagnosed at this time as having infectious hepatitis. The onset is remarkable for the absence of the usual prodromal symptoms of anorexia, nausea, fatigue, fever, and malaise. He gave no history of contact with hepatitis, nor of receiving parenteral administrations, nor hepatotoxic drugs. His right hand was stiff for one day and his right breast was swollen, both at the time of onset of scleral icterus.

During the next year, he was admitted to another hospital on two occasions, regular liver function tests were performed, and he remained in bed, with no improvement in his condition. During this time his sclerae remained icteric, his urine was dark and his stools were normal in color. He noticed no decrease in his appetite. During the winter of 1967, he had a papular rash on his trunk, lasting for 3 days. Off and on during this period, he experienced dull pain in his right upper quadrant. Pruritis was present for several weeks.

His mother died 10 years ago from hepatic failure after a short illness suggestive of acute viral hepatitis. She was operated on because obstructive jaundice was suspected but no obstruction was found. At autopsy, a pathological diagnosis of acute yellow atrophy was made.

On examination, this patient was a healthy looking 16 year old boy. His sclerae were icteric. He had an acneform rash on his face and upper thorax. A few spider nevi were found on each upper limb, one on his right foot and one on his right hip. He had bluish striae on both buttocks. There was palpable breast tissue on the right. Liver and

spleen were just palpable below the costal margins.

On admission, the following values were obtained for liver function tests:

Total protein	7.7 G%
Albumin	3.7 G%
Globulin	4.0 G%
Alkaline phosphatase	47.8 U
Total bilirubin	4.3 mg%
Thymol turbidity	30.6 U
SGOT	870 U/ml
SGPT	450 U/ml
Prothrombin time	50%

This biochemical picture had been present since the beginning of the clinical illness in August 1966.

Two weeks after admission, a liver biopsy was performed. The histology was consistent with chronic active hepatitis with early post-necrotic cirrhosis.

On November 14: The patient was started on 15 mg. of prednisone q 6h, for two weeks, to be gradually reduced during the next two weeks, until it was stopped. On November 28, azathioprin (Imuran) was started, 2 mg/kg/day.

Several side effects of steroid therapy were seen. There was a sense of well-being and an increased appetite. Weight gain of several pounds was noted. The patient's acne at first improved but later became worse. He also developed a moon-faced appearance.

Towards the end of his hospital course, the striae and spider nevi had all but disappeared. His liver and spleen were no longer palpable. His liver function tests on discharge were as follows:

Total protein	5.5 G%
Albumin	3.4 G%
Globulin	2.1 G%
Alkaline phosphatase	16.4 U
Total bilirubin	1.6 mg%
SGOT	110 U/ml
SGPT	67 U/ml
Prothrombin time	100%

DISCUSSION:

Several aspects of this case are worthy of discussion; firstly, the onset. According to the history, the onset was noteworthy for the lack of any signs or symptoms except scleral icterus. It is also interesting that his mother died 10 years previously after a short illness suggestive of viral hepatitis. It is possible that our patient's illness began at this time with a subclinical or anicteric attack of viral hepatitis. This presumably progressed to chronic active hepatitis, resulting in cirrhosis which did not become clinical until August, 1966, when he first noticed jaundice. His liver function studies reveal the typical picture of low grade jaundice, liver cell necrosis as evidenced by elevated transaminases, hepatic cholestasis (alkaline phosphatase up to 50), and hypergammaglobulinemia.

The etiology of chronic hepatitis is thought to be an autoimmune process. MacKay (2) cites three possibilities for the mechanism: (1) Viral damage causes liver cell necrosis, and the immune reaction in response to antigens of the virus. This, he states, is untenable because autoantibodies to antigens of nuclei, cytoplasm, and smooth muscle can be demonstrated. (2) The immune reaction is to antigens liberated from degraded liver cells, but is entirely a consequence of continuing liver cell injury caused by a persisting virus in the liver. This will not be proved or disproved until a method of isolating the virus is developed. It is not typical of viral illnesses, in general, that the agent persists for an extended time in the host's tissues. (3) The immune reaction is to antigens of liver cells and this constitutes a damaging autoimmune process which causes further release of liver cell antigens; this in turn causes perpetuation of the immune reaction and continuing liver cell necrosis with activity of the hepatitis. MacKay favors the third and says that "this continuing cycle of liver cell necrosis-immune reaction is presumed to lead to increasing fibrosis with loss of normal liver architecture and to culminate in coarsely nodular cirrhosis". He notes five phenomena or "markers" which are consistently present in any autoimmune disease: 1. hypergammaglobulinemia, 2. presence of circulating autoantibodies including L.E. factors, 3. lymphoid infiltration (of the liver in this case), 4. therapeutic response to cortisone, 5. association with other lesions thought to be of autoimmune origin. With regard to the last, in every series of chronic hepatitis, (4) there is always a higher incidence of so-called autoimmune disorders found to be associated with the liver disease. These include rashes, arthralgia, ulcerative colitis, thrombocytopenia, kidney disease, hemolytic disease, etc. Our patient did not have any serious associated condition but did have arthralgia for a short time during the early part of his disease. He also gave a history of a rash.

With regard to lupoid hepatitis and the L.E. cell phenomenon, Isselbacher (4), in a series of 33 cases in young people, could find no evidence for separating any of these cases into a separate entity. MacKay (5) has a series of 22 cases of lupoid hepatitis which he uses to demonstrate the differences between lupoid hepatitis and other types of chronic liver disease. These differences seem to be a matter of degree except for the L.E. cell phenomenon. Hepatic histology is identical in lupoid and chronic active hepatitis.

The treatment of chronic active hepatitis is a matter deserving attention. This disease has been a uniformly fatal one; even the treated cases as a rule do not survive very long. There are, in every series, however, a few cases who have either remitted or survived for a long time. The average survival is about 3-5 years after the onset of symptoms. These patients die in hepatic failure, the end result of the progressive cirrhosis. Treatment has centered around suppression of the postulated autoimmune process with corticosteroids. Success with these agents has not been great, however.

In our case, after administering prednisone, 60 mg/day, the process was brought to a halt as evidenced by a reduction in bilirubin level, reversal of the A/G ratio, lowering of transaminase levels to practically normal, and reduction in alkaline phosphatase. Clinical improvement was witnessed by a reduction in hepatosplenomegaly. Histological proof of improvement was obtained by liver biopsy.

Another recent development in therapy is the use of antimetabolites. Transaminase levels are lowered by 6-mercaptopurine but bilirubin tends to rise, presumably due to the direct hepatotoxic effect of 6-MP. The rationale behind the use of these agents is to suppress the effect on lymphoid cells by interference with nucleic acid synthesis. They may limit proliferation of pathogenic forbidden clones of lymphoid cells. In our case, we used azathioprin (Imuran) 2 mg/kg/day in an effort to suppress the damaging process. We did not detect any hepatotoxic side effects. The patient was discharged from hospital after two months showing marked clinical, biochemical, and histological improvement in his condition. He was to be maintained on 2 mg/kg/day of azathioprin.

In summary, a case of chronic active hepatitis has been presented in an effort to illustrate two points. Firstly, we have put forward the idea that perhaps this boy's illness was a sequel of anicteric viral hepatitis which he contracted at the time of his mother's illness, ten years prior to the appearance of his own clinical picture. Secondly, we feel that we were successful, at least for a time, in treating our patient with a short course of prednisone and adding to this on a long term basis, an antimetabolite, namely azathioprin.

References

(1) Mackay, I. R., Taft, L. I., & Cowling, D. C. (1956) *Lupoid Hepatitis.* Lancet ii, 1323.

(2) Mackay, I. R., et al (1963). *The Course and Treatment of Lupoid Hepatitis.* Gastroenterology 45: 4-13.

(3) Sherlock, S. (1963), p-351. Oxford - Blackwell, Scientific Publications.

(4) Willcox, R. G. & Isselbacher, K. J. (1961). *Chronic Liver Disease in Young People. Clinical Features and Course in Thirty-three Patients.* Amer. J. Med. 30, 185.

(5) Mackay, I. R., G Wood, I. J. (1962). *Lupoi Hepatitis: A Comparison of 22 Cases Withd Other Types of Chronic Liver Disease.* Quart. J. Med 31, 485.

A recent survey was said to prove that the people we Americans most admire are our politicians and doctors. I don't believe it. They're simply the people we're most afraid of. And with the most reason.

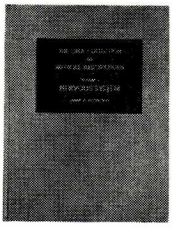
–McLaughlin

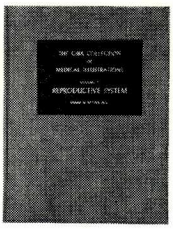
A non-profit service
to the medical
profession . . .

THE CIBA COLLECTION OF MEDICAL ILLUSTRATIONS

■ Life-like illustrations by Frank H. Netter, M.D., the internationally famous medical illustrator ■ Concise, explanatory text by recognized authorities ■ Full-color plates of anatomy and pathology ■ Cross-referenced index to each volume ■ Hard-bound, covered in green buckram, stamped in gold ■ Valuable as visual aids when explaining medical problems to patients, as a teaching aid, or as an aid to medical students.

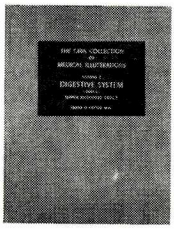
VOLUME 1—NERVOUS SYSTEM
In 5 sections **plus** a bound-in Supplement on the hypothalamus, 122 plates.
Sold at cost—**$10.00**
Supplement separately—$1.00

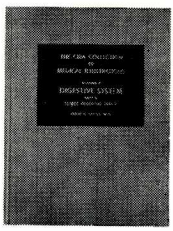




VOLUME 2—REPRODUCTIVE SYSTEM—In 14 sections, 233 plates.
Sold at cost—**$13.00**

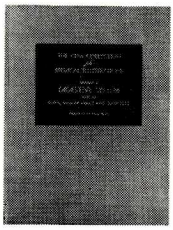
VOLUME 3—PART I, DIGESTIVE SYSTEM: UPPER DIGESTIVE TRACT
In 7 sections, 172 plates.
Sold at cost—**$15.00**

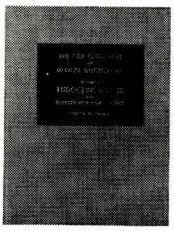




VOLUME 3—PART II, DIGESTIVE SYSTEM: LOWER DIGESTIVE TRACT
In 7 sections, 200 plates.
Sold at cost—**$15.00**

VOLUME 3—PART III, DIGESTIVE SYSTEM: LIVER, BILIARY TRACT AND PANCREAS
In 5 sections, 133 plates **plus** a bound-in Supplement on New Aspects of Structure, Metabolism, Diagnostic and Surgical Procedures Associated with Certain Liver Diseases, 21 plates.
Sold at cost—**$12.00**
Supplement separately—$2.00





VOLUME 4—ENDOCRINE SYSTEM AND SELECTED METABOLIC DISEASES
In 10 sections, 222 plates.
Sold at cost—**$22.00**

8099

Detailed information and order forms may be obtained from CIBA Company Limited, Dorval, Quebec