Cryptogenic Versus Autoimmune Chronic Hepatitis: To Split or To Lump?

In this issue of the Proceedings (pages 23 to 30), Czaja, Hay, and Rakela offer a retrospective assessment of the experience with chronic active hepatitis at the Mayo Clinic. They dispute the accepted notion that the prognosis for patients with chronic active hepatitis with autoimmune features is different from that for patients with idiopathic cryptogenic chronic active hepatitis. If they are right, it will certainly not be the first time in the history of medicine that today's facts have become tomorrow's fallacies. As another thinker, Alonzo Clark, once stated, "The medical errors of one century constitute the popular faith of the next." Do Czaja and his group offer enough evidence to overturn our prior beliefs about these two types of hepatitis?

Chronic hepatitis was first described by Waldenström in 1950. He reported the histories of seven young women with a syndrome of hypergammaglobulinemia, plasma cell infiltration of the hepatic parenchyma, and cirrhosis. His observations were confirmed in 1951 by Kunkel and associates. Thereafter, Saint and colleagues applied the term "active chronic hepatitis" to this condition in both male and female patients. Bearn and co-workers described systemic features such as fatigue, fever, arthralgias, acne, and striae in patients with this new condition. The term "lupoid hepatitis" was used by Mackay and coauthors in their report of a group of patients who had a positive antinuclear antibody or lupus erythematosus cell test together with hypergammaglobulinemia, fibrosis, and active hepatic necrosis. Subsequently, however, Whittingham and collaborators reported data indicating that lupoid hepatitis was distinct from systemic lupus erythematosus. They suggested instead the term "autoimmune hepatitis" to encompass patients with hepatitis who had autoimmune or immunoserologic features.

In evaluating Czaja and colleagues' most recent addition to the literature on hepatitis, one must remember that the conclusions were based on a retrospective analysis. For assessment of prognosis, it might seem that the results would be reliable regardless of whether the analysis was prospective or retrospective. In this situation, that may not be the case. The patients under consideration had been assigned to a variety of treatment groups—some may have received corticosteroids only, and others may have received corticosteroids in conjunction with azathioprine. One might presume that various treatments or nontreatments would not influence long-term conclusions about prognosis. In fact, how can we be certain? If large numbers of patients had been present in each group, and if each group had been analyzed separately, then the reliability of these conclusions might be more definite. Instead, patients were classified into autoimmune (112 patients) or idiopathic cryptogenic chronic active hepatitis (26 patients) categories without consideration of the treatments that were administered. Nevertheless, this broad analysis did not identify major differences between the two categories. Thus, we can be relatively comfortable with the conclusions although not 100% certain of their reliability.

Another limitation that may influence acceptance of the findings is that all patients in the report had "severe" chronic active hepatitis. Thus, the conclusions are based solely on patients with severe chronic active hepatitis and may not pertain to patients with lesser degrees of disease activity. Indeed, when my colleagues and I evaluated our experience with patients with chronic active hepatitis, we found that less than 10% of the patients seen each year would fulfill the Mayo Clinic criteria for inclusion in...
this study of severe disease. On the basis of this finding, a purist might conclude that autoimmune disease is associated with the same prognosis as idiopathic cryptogenic disease for only a minority of patients; we do not yet have a data base with which to extend such a conclusion to more than 90% of the patients commonly seen.

Furthermore, diseases of many different causes may be classified together within the category of idiopathic cryptogenic chronic active hepatitis. Some of these diseases may have viral causes; others may have toxic, drug, or other causes. What percentage of these patients actually have viral-induced chronic active hepatitis C remains uncertain. If Czaja and associates had been able to subdivide the group with cryptogenic chronic active hepatitis into those who had hepatitis C and those who did not, and then had compared those two groups with the autoimmune disease group (with the assumption that none of the patients with autoimmune disease had evidence of hepatitis C infection), would the conclusions have been the same? Because two hepatitis C tests have become available, such comparisons should soon be possible. One of these tests has been reported in the literature.

In assessment of cryptogenic versus autoimmune hepatitis, many similarities are evident between the groups at the time of initial manifestation. In the current study by Czaja and associates, almost 20% of those patients with cryptogenic disease already had cirrhosis, as did 35% of those with autoimmune disease. The implications of this observation, however, are difficult, if not impossible, to determine. The patients were neither randomly selected nor consecutive. In fact, the patients were highly selected, in that they had been referred to a tertiary-care center. This high degree of selectivity makes it difficult to extrapolate observations about these patients to the general community of patients with severe chronic active hepatitis. In addition, the diagnosis of cirrhosis was based on a percutaneous needle biopsy. Czaja and colleagues clearly point out that although needle biopsy is a reliable means of assessing inflammation, it is not a reliable diagnostic tool for cirrhosis, a fact that was emphasized in a prior Mayo Clinic study. An obvious question arises: Did the patients with autoimmune chronic active hepatitis in the early course of their disease (before referral to the Mayo Clinic) have a rapidly progressive condition, such that more of them already had cirrhosis at the time of initial examination, whereas others had cirrhosis that was undetectable? Could these patients have had hepatitis that rapidly progressed to a late stage before being referred to the Mayo Clinic and thus were no longer distinguishable from those with cryptogenic disease? The fact that these patients had a long duration of symptoms before referral is comforting but not totally assuring, in that many patients with early chronic active hepatitis may be symptom-free.

Despite these concerns, Czaja and associates present the best available data to resolve the issue and make a convincing case. Moreover, this important article serves to dispel the widely promulgated concept that idiopathic chronic active hepatitis without immunoserologic markers does not merit treatment with corticosteroids or azathioprine. The data on which this dictum was based are open to criticism. Nevertheless, the limited data dealing with hepatitis B serologic responses in the presence of corticosteroid treatment have served as the basis for extending this dogma to preclude corticosteroid treatment in all patients with chronic active hepatitis without immunoserologic abnormalities. Czaja and co-workers show that patients with severe idiopathic cryptogenic chronic active hepatitis without viral markers do indeed respond to corticosteroids or corticosteroids and azathioprine often enough to warrant use of this treatment. Furthermore, they point out that this type of treatment is not harmful to these patients. Whether the medical community will accept this message is debatable. The belief that viral-induced chronic active hepatitis should not be treated with corticosteroids, and the extension of this concept to encompass non-autoimmune chronic active hepatitis,
has been widely accepted. Although not based on carefully developed data, the standard of practice has been established. Whether this important study can alter widely accepted "propaganda" to the contrary is uncertain.

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REFERENCES