Chronic Hepatitis Associated with Drug Abuse: 
Significance of Hepatitis B Virus

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One hundred and seventy-seven former heroin addicts, consisting of 85 who were newly admitted to a
methadone maintenance program and 92 who had received methadone for a mean period of 30 months, were
prospectively studied for up to 2 years in order to determine: (1) the effect of heroin withdrawal on the
hepatic abnormalities, and (2) the incidence of HBsAg, anti-HBs, and anti-HBc as indices of the frequency
of hepatitis B virus infection. Our study indicates that (1) hepatic abnormalities persist when heroin is
discontinued and are not temporally related to drug and/or needle usage, and (2) that 71% of subjects had
either HBsAg or anti-HBs; anti-HBc was tested for in 16 patients and was present in 100%, although 9 of the
16 were both HBsAg- and anti-HBs-negative. This study suggests that hepatitis B is largely responsible for
the liver dysfunction. It is proposed that an abnormality in immune function, induced by heroin, is
responsible for the high incidence of chronic hepatitis. Attention is drawn to the similarity between former
drug addicts and hemophiliacs, since both develop chronic hepatitis in spite of anti-HBs in the serum.

INTRODUCTION

Abnormal liver function tests have been found in up to 83% of asymptomatic drug
addicts entering a detoxification program [1,2]. The cause of these abnormalities has
not been determined, although a direct toxic effect of the drug [3], contamination of
the drug with other toxic agents [4], concomitant use of alcohol [1] and viral hepatitis
[5,6] have all been suggested etiologies. Although most studies [2,7] have shown a low
incidence of HBs-antigenemia in these patients, recent studies employing sensitive
assays for both HBsAg and anti-HBs [2,8] have shown a high incidence of prior
infection with hepatitis B virus (HBV).

In view of the uncertainty regarding the etiology of hepatitis in drug users, the
present study was designed to assess: (1) the effect of heroin withdrawal on the
hepatic abnormalities, since their persistence would exclude a lesion temporally
related to injection of the drug and/or contaminants, and (2) the prevalence of HBV
infection as determined by the incidence of HBsAg, anti-HBs, and anti-HBc.

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Patients

Two groups of patients were studied. Eighty-five patients were newly admitted to a methadone program and had not received methadone prior to the study (Group A). Ninety-two patients (Group B) had received methadone for periods of 2 months to 6 years (mean duration of 30 months) before the study. None of the patients showed evidence of alcoholic liver disease. Twenty percent had intakes of alcohol which varied between 3 and 6 ounces daily. None admitted to an intake of alcohol in excess of 6 ounces. The dosage of methadone was similar in both groups (mean 35 mg/day). The ages of the patients ranged from 21 to 59 years, mean 29 years.

Methods

Serum GOT, alkaline phosphatase, and bilirubin were measured on entry to the study and were followed serially at intervals of three months in Group A patients and six months in Group B patients. Testing for hepatitis B surface antigen was done by radioimmunoassay (RIA) (Austria II, Abbott Laboratories, No. Chicago, IL). Initial anti-HBs testing was done by agar gel diffusion (AGD) and counter immunoelectrophoresis (CEP). Subsequent testing during follow-up was done by passive hemagglutination (Electronucleonics Laboratories, Bethesda, MD). Anti-HBc testing was done by radioimmunoassay (courtesy of Dr. V. McAuliffe) in 16 patients who were all in Group B and who had been on heroin for a mean (± SD) period of 8.6 (± 5.3) years, followed by methadone for a mean (± SD) period of 4.4 (± 2.2) years. These 16 patients were selected at random.

Results

On initial testing, SGOT elevations were found in 65% of newly admitted patients and in 76% of patients already maintained on methadone. The abnormalities were minor, and the mean value for newly admitted patients was the same as that for patients already on therapy (Table 1). Two of the newly admitted patients had acute viral hepatitis on entry to the study and were excluded from the group analysis. There was no significant difference between serum alkaline phosphatase and bilirubin levels for the two groups of patients (Table 1).

| TABLE 1 |
| --- |
| Liver Function Tests on Entry to Study |

| Table Entry | Newly admitted | On therapy | Normal |
|---|---|---|---|
| Number of patients | 85 | 92 | — |
| Male:Female | 61:24 | 78:14 | — |
| SGOT abnormalities | | | |
| Number of elevated levels | 55(65%) | 70(76%) | |
| Mean level (± SEM) | 64 ± 9 | 64 ± 6 | 15-35 units |
| Bilirubin abnormalities | | | |
| Number with elevated levels | 1 | 0 | <1.50 mg/100 mm |
| Mean level (± SEM) | 0.41 ± .07 | 0.34 ± .02 | |
| Alkaline phosphatase abnormalities | | | |
| Number with elevated levels | 1 | 7 | |
| Mean level (± SEM) | 47 ± 2 | 55 ± 3 | 10-70 IU |
| HBsAg-positive in serum | 6 | 3 | — |
Serial evaluation of SGOT levels in newly admitted patients showed no significant change in mean levels after patients had been on methadone for up to 2 years. Serial follow-up of long-term methadone maintenance patients similarly showed no significant change in SGOT levels. Seventy-three percent of patients with initially normal SGOT levels in Group A had elevations on subsequent testing, as did 64% of patients from Group B. Thus, 67% of patients with normal SGOT levels initially had elevations during subsequent testing.

The overall incidence of HBsAg was 6%. There was no significant difference in the incidence of HBs-antigenemia in patients who had not taken methadone and those already on therapy. Only one patient had demonstrable anti-HBs when testing was done by AGD or CEP; however, when subsequent testing was done by passive hemagglutination, 44 of 68 (65%) were found to have anti-HBs, irrespective of liver function test abnormality or of duration of methadone therapy. Anti-HBc was done in 16 patients of whom 9 were both HBsAg- and anti-HBs-negative; all 16 patients had anti-HBc present. Table 2 shows the duration of heroin use and methadone therapy in the 16 patients tested for anti-HBc.

Of the 9 patients who had no detectable anti-HBs, 7 had abnormal SGOT values (mean 69 ± 40). Of the 7 patients who did have detectable anti-HBs, 5 had abnormal SGOT values (52 ± 28). Thus, there was no significant difference in the frequency of SGOT abnormalities in patients with and without anti-HBs. This analysis holds true for the larger group of patients in whom anti-HBc was sought, as well.

DISCUSSION

This study confirms the previously reported high incidence of SGOT abnormalities in a randomly selected population of asymptomatic drug users. Furthermore, the frequency with which initially normal SGOT levels became abnormal suggests that the incidence of SGOT abnormalities may approach 100% if samples are tested with sufficient scatter in time. The persistence of the SGOT abnormalities after 2 years of

| Subject | Age | Sex | Years on heroin | Years on methadone | SGOTa | Anti-HBs b | Anti-HBc c |
|---------|-----|-----|-----------------|--------------------|-------|------------|-----------|
| MB      | 31  | F   | 7               | 4                  | 17    | 8          | +         |
| FH      | 29  | M   | 2               | 6                  | 51    | 8          | +         |
| LB      | 30  | M   | 10              | Newly admitted     | 71    | 32         | +         |
| KR      | 23  | F   | 6               | 3                  | 96    | 128        | +         |
| LJ      | 28  | M   | 12              | 3                  | 38    | 32         | +         |
| AE      | 28  | F   | 3               | 7                  | 64    | 128        | +         |
| CJ      | 51  | M   | 19              | 6                  | 24    | 32         | +         |
| BF      | 29  | M   | 6               | 6                  | 32    | 0          | +         |
| LD      | 29  | F   | 6               | 3                  | 131   | 0          | +         |
| RB      | 37  | M   | 7               | 1.5                | 48    | 0          | +         |
| ES      | 47  | M   | 22              | 7                  | 51    | 0          | +         |
| WW      | 25  | M   | 7               | 1                  | 32    | 0          | +         |
| JW      | 34  | F   | 9               | 3                  | 79    | 0          | +         |
| RM      | 35  | M   | 4               | 5                  | 74    | 0          | +         |
| CR      | 29  | M   | 9               | 2                  | 136   | 0          | +         |
| DE      | 28  | F   | 8               | 8                  | 39    | 0          | +         |

aSGOT in karmen units/ml, normal 35; b titer of anti-HBs by PHA; c radioimmunoassay, courtesy of Dr. V. McAuliffe
follow-up, in some cases after 7 years of heroin abstinence, is in keeping with the observations of others [9,10], but in contrast to the findings in one study [11], although the authors of that study point out differences in their addict population from that generally encountered. Chronic liver dysfunction, temporally unrelated to heroin and/or needle use, thus results in these patients. There is little evidence that heroin itself induces changes in liver function, or that contaminants are important in the pathogenesis of the liver disease [12,13]; similarly, alcohol has generally not been a significant factor in the causation of the liver disease in these patients. Although alcohol consumption is frequently high in drug addicts, liver histology has generally shown the features of chronic hepatitis (compatible with unresolved viral hepatitis) [2,14]. The most likely lesion that accounts for the transaminase abnormalities is thus viral hepatitis, giving rise to chronic (unresolved) hepatitis.

The incidence of HBsAg and anti-HBs was 71%, well in keeping with the experience of others. However, when anti-HBc was sought in 16 patients, 9 of whom were HBsAg- and anti-HBs-negative, it was positive in all. This information is of major interest since it indicates that in a randomly selected group of 9 patients, 7 of whom had abnormal SGOT levels and none of whom had detectable HBsAg or anti-HBs, there was evidence for HBV infection in 100%. Indeed, anti-HBc has been shown to be a more sensitive indicator of HBV infection than the other serological markers [15] and it has been suggested that it correlates well with viral replication in the hepatocyte. The presence of anti-HBc in these patients thus may indicate that viral replication is occurring in the liver cells. This provides further evidence that the HBV is responsible for the liver disease in these patients. If, indeed, the hepatic abnormalities are related to HBV infection, the frequency of unresolved hepatitis after this infection would be 7 to 8 times greater than the incidence in the general population, where it is estimated at 10% [16]. Furthermore, it is unusual to lose HBsAg and then develop chronic hepatitis; Redeker [16] studied 429 patients with acute icteric type B hepatitis and found that all the patients who developed chronic hepatitis remained HBsAg-positive. In no instance was the loss of HBsAg followed by chronic hepatitis. The situation in the drug addict is clearly different and may be similar to the situation in hemophiliacs, where chronic hepatitis has been described, despite clearance of HBsAg and the presence in the serum of anti-HBs [17]. It is thus possible that former drug addicts and hemophiliacs represent a unique population, in that they develop chronic hepatitis despite the presence of excess anti-HBs, long considered a protective or neutralizing antibody. This may be related to the fact that both groups are exposed to frequent transfusions, with the possible risk of constant re-infection. Naturally, this risk is more significant in the drug addicts, but even hemophiliacs could be exposed, since blood containing anti-HBc, in the absence of HBsAg, has been shown to be infectious [18]. Routine blood screening would thus not detect viral particles. The possibility of non-A, non-B hepatitis is a real one, particularly in view of its parenteral transmissibility and potential for causing chronic hepatitis, but in the absence of a serological marker, this remains pure conjecture.

A second explanation for this anomaly, of persistent hepatitis in drug addicts, could be related to altered immune regulation. It is well established that heroin addicts have an abnormally high incidence of auto-antibodies, false positive syphilis serology, and hyperglobulinemia [19,20]; in addition, T cell function has been shown to be impaired [21]. We have studied suppressor T cell function in heroin addicts and have shown a defect when assessed by concanavalin A blast formation [22]. It may then be proposed that, during active heroin use, effector T cell function is impaired
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(as shown by Brown et al. [21]), resulting in incomplete clearance of virus antigen from the liver. A suppressor T cell defect allows for inappropriately high levels of immunoglobulin and auto-antibody production. With withdrawal of the heroin, the suppressor T cell defect abates, allowing for normal immunoregulation, with gradual reduction in the levels of immunoglobulin and auto-antibodies, as has been observed when heroin addicts stop their drug abuse [23]. It is conceivable that the abnormalities in immune function described in heroin addicts are unrelated to the persistence of the hepatitis and that this persistence is merely a result of continuous, low-dose infection by HBV. However, there is mounting evidence that the nature of the immune response is all-important in the pathogenesis of the liver injury associated with HBV infection [24,25], especially since the HBV appears not to be a cytopathic virus in its own right [26,27].

It is thus apparent that the nature of the hepatitis in former drug addicts is a complex one; the lesion is chronic, persisting for years after discontinuance of heroin, and appears to be related to HBV infection. There appears to be a similarity between the immunological behavior, in terms of hepatitis serology, between hemophiliacs and former drug addicts, a similarity which was not previously mentioned. It is possible that study and comparison of the immune response in these two groups, dissimilar as they may be in this respect, will result in better understanding of the nature and mechanisms of chronic (unresolved) hepatitis, type B.

REFERENCES

1. Stimmel B, Vernace S, Schaffner F: Hepatic dysfunction in heroin addicts. The role of alcohol. JAMA 222:811, 1972
2. Seeff LB, Kiernan T, Zimmerman HJ, et al: Hepatic disease in asymptomatic parenteral narcotic drug abusers. A VA collaborative study. Am J Med Sci 270:41, 1975
3. Marks V, Chappel P: Hepatic dysfunction in heroin and cocaine users. Br J Addict 62:189, 1967
4. Rosenblate HJ: Nonviral hepatitis in drug addicts. Arch Path 95:18, 1973
5. Cherubin EC, Hargrove LR, Prince AM: The serum hepatitis related antigen in illicit drug users. Am J Epidem 91:510, 1970
6. Sutnick A, Cerda JJ, Toskes PP, et al: Australia antigen and viral hepatitis in drug abusers. Arch Int Med 127:939, 1971
7. Szmuness W, Prince AM: HAA in drug addicts. Lancet 2:433, 1971
8. Stimmel B, Vernace S, Schaffner F: Hepatitis B surface antigen and antibody. A prospective study in asymptomatic drug abusers. JAMA 234:113S5, 1975
9. Cherubin CE, Kane S, Weinberger DR, et al: Persistence of transaminase abnormalities in former drug addicts. Ann Int Med 76:385, 1972
10. Kreek MJ, Doses L, Kane S, et al: Long-term methadone maintenance therapy: effects on liver function. Ann Int Med 77:998, 1972
11. Cherubin CE, Rosenthal WS, Stenger RE, et al: Chronic liver disease in asymptomatic drug addicts. Ann Int Med 76:391, 1972
12. Brooks FP, Deneau GA, Potter PB Jr, et al: Liver function tests in morphine addicted and in non-addicted Rhesus monkeys. Gastroenterology 44:287, 1963
13. Sapira J, Jasinski D, Gorodetzky CW: Liver disease in narcotic addicts. II. Role of the needle. Clin Pharmacol Ther 9:720, 1968
14. Iretorn HJC, Gust ID, Moon WJ, et al: The covert liver diseases of drug addicts. Aust N Z J Med 4:444, 1974
15. Hoofnagle JH, Gerety RJ, Ni Ly, et al: Antibody to hepatitis B core antigen: a sensitive indicator of persistent viral replication. New Eng J Med 290:1336, 1974
16. Redeker AG: Viral hepatitis: Clinical aspects. Am J Med Sci 270:9, 1975
17. Spero JA, Lewis JH, Van Thiel DH, et al: Asymptomatic structural liver disease in hemophilia. New Eng J Med 298:1373, 1978
18. Hoofnagle JH, Seef LB, Bales ZB, et al: Type B hepatitis after transfusion with blood containing antibody to hepatitis B core antigen. New Eng J Med 298:1379, 1978
19. Husby G, Pierce PE, Williams RC: Smooth muscle antibody in heroin addicts. Ann Int Med 83:801, 1975
20. Boak RA, Carpenter CM, Miller JN: Biologic false positive reactions for syphilis among narcotic addicts. A report on the incidence of BFP reactions as measured by TPI test. JAMA 175:326, 1961
21. Brown SM, Stimmel B, Taub RN, et al: Immunologic dysfunction in heroin addicts. Arch Int Med 134:1001, 1974
22. Desaules M, Miller DJ, Kleber HD, et al: Effect of heroin on immunoregulation. In preparation
23. Cushman P, Grieco MH: Hyperimmunoglobulinemia associated with narcotic addiction. Effects of methadone maintenance treatment. Am J Med 54:320, 1973
24. Edington TS, Chisari FV: Immunological aspects of hepatitis B virus infection. Am J Med Sci 270:213, 1975
25. Dudley FJ, Fox RA, Sherlock S: Cellular immunity and hepatitis-associated Australia antigen in liver disease. Lancet 1:723, 1972
26. Brighton WD, Taylor PE, Zuckerman AJ: Changes induced by hepatitis serum in cultured liver cells. Nature (New Biol) 232:57, 1971
27. Zuckerman AJ: Laboratory investigations into the aetiology of human viral hepatitis. Br Med Bull 28:134, 1972