in capillary lumina. Fibrin/fibrinogen was detected by immunofluorescence within glomerular and peritubular capillaries.

Comment

The two patients were previously healthy young people who developed a 'flu-like illness during a minor epidemic of influenza A. Influenza A virus was implicated in case 1 by serological studies and in case 2 by isolation. In both there was clinical and laboratory evidence of intravascular coagulation. In the first case this produced acute renal failure while in the second a severe consumption coagulopathy produced defibrination, intrapulmonary haemorrhage, and death.

Infectious agents are known to produce intravascular coagulation (McKay and Margaretten, 1967; Dodsworth and Burns, 1971) but influenza A virus has not been implicated previously. Wilson and Smith (1972) reported a case of Goodpasture's syndrome after influenza A2 virus infection but made no mention of intravascular coagulation. The mechanisms whereby viruses induce intravascular coagulation are unknown, but may be related to haemagglutinating properties, haemolytic factors, direct endothelial cell damage, or antigen antibody reactions. In neither of the above cases were we able to detect viral antigen or any significant immunoglobulin deposition within renal tissue. Certain drugs may produce intravascular

coagulation in sensitized people but such a mechanism is improbable in these two patients.

The treatment of intravascular coagulation is controversial but the use of anticoagulants has been advocated (Lo *et al.*, 1971). Such drugs are not without hazard, and the first patient resolved satisfactorily without such agents. Anticoagulant therapy should possibly be reserved for those patients with a consumption coagulopathy severe enough to render them at risk from haemorrhage. Such therapy might have been of value in the second patient.

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References

- British Medical Journal*, 1972, 4, 251.
- Brown, L. J., Stalker, A. L., and Hall, J. (1969). *Microvascular Research*, 1, 295.
- Dodsworth, H., and Burns, A. (1971). *British Medical Journal*, 4, 466.
- Lo, S. S., Hitzig, W. M., and Frick, P. G. (1971). *Acta Haematologica*, 45, 1.
- McKay, D. G., and Margaretten, W. (1967). *Archives of Internal Medicine*, 120, 129.
- Wilson, C. B., and Smith, R. C. (1972). *Annals of Internal Medicine*, 76, 91.

Active Chronic Hepatitis after Chlorpromazine Ingestion

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Active chronic hepatitis, described by Waldenstrom (1950) and Mackay *et al.* (1956), was initially thought to be a complication of acute viral hepatitis. In about 25% of patients the condition seems to have been preceded by a classical attack of viral hepatitis (Sherlock, 1968). There is much evidence that active chronic hepatitis is an autoimmune disturbance at the stage of hepatic involvement. Thus, lupus erythematosus cells are found in 15% of patients, and many patients are found to have false-positive Wassermann reactions, positive R.A. latex tests, and antinuclear and smooth muscle antibodies are found in over 50% (Johnson *et al.*, 1965; Whittingham *et al.*, 1966). The diagnosis is confirmed by hepatic biopsy, which shows a persistent and often progressive chronic inflammatory reaction in the portal tracts with extension of the cellular exudate into the surrounding periportal tissue. Here the limiting plate of hepatocytes disappears, while small foci of peripheral hepatocyte necrosis (piecemeal necrosis) may be seen. The inflammatory infiltrate consists mainly of lymphocytes and plasma cells, and fibrosis is often conspicuous in the periportal areas and around proliferating bile ductules.

It seems probable that any factor which might cause hepatic damage may precipitate a self-perpetuating destructive process in the liver in the susceptible patient. The virus of viral hepatitis may be responsible in some instances, but other factors might be involved. It is possible that drug-induced hepatic damage may be one such factor. Active chronic hepatitis has recently been

reported after the prolonged ingestion of laxative preparations containing oxyphenisatin (Reynolds *et al.*, 1971). Histological changes of active chronic hepatitis have also been reported in two patients treated with methyl dopa (Morin *et al.*, 1964; Williams and Khan, 1967).

We report a patient who developed active chronic hepatitis after the ingestion of chlorpromazine.

Case Report

A 59-year-old joiner was admitted to hospital with a three-week history of pruritus, painless jaundice, pale stools, and dark urine. He had a long-standing history of peptic ulceration for which a partial gastrectomy had been performed eight years previously. Six weeks before admission he had had contact with a relative who was jaundiced but who was shortly thereafter found to have carcinoma of the pancreas. He had previously suffered from depression, and this recurred, culminating in his taking an overdose of aspirin and chlorpromazine four weeks before his admission to hospital. He had not taken other drugs at this time or for some months previously. His alcohol intake was negligible and had not changed for some years.

On admission he was icteric, and the liver was palpable 5 cm below the costal margin. Investigations, which suggested an obstructive jaundice, were: Hb 15.0 g/100 ml; E.S.R. 29 mm in the first hour; bilirubin 9.0 mg/100 ml; SGOT 31 units/l., SGPT 30 units/l.; alkaline phosphatase 164 K.A. units. The serum albumin was 4.6 g/100 ml and globulin 2.7 g/100 ml. Protein electrophoresis and immunoglobulins were normal. Bile but no urobilinogen was present in the urine. Alkaline phosphatase isoenzyme studies suggested an increase in both liver and bone constituents. Skeletal survey showed changes consistent with Paget's disease. The hepatitis-associated antigen test was negative, as also was the smooth muscle and antimitochondrial antibody tests. Lupus erythematosus cell test and antinuclear factor were not performed at this time.

The liver biopsy showed evidence of cholestatic jaundice, the centrilobular bile canaliculi being distended with bile plugs (fig. 1). There was some infiltration with inflammatory cells including eosinophils in the portal areas. There was no evidence of hepatocyte necrosis and no fibrosis. The interlobular bile ducts appeared to be normal, although extrahepatic obstruction could not be fully excluded. An exploratory laparotomy was undertaken and no appreciable abnormality was found. A wedge biopsy of liver was taken at operation, and showed only the features which had been noted in the original small needle biopsy (fig. 2). Accordingly, it was thought that the cholestasis and mild portal hepatitis were consistent with the diagnosis of chlorpromazine poisoning.

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FIG. 1—First liver biopsy (percutaneous). (Neutral red. $\times 133$.) Cholestasis is severe on centrilobular zone on left; portal tract on right shows a mild infiltrate of chronic inflammatory cells.

FIG. 2—Second liver biopsy (wedge). (Haematoxylin and eosin. $\times 60$.) Cholestasis involving bile canaliculi and centrilobular zone is the only notable abnormality.

FIG. 3—Third liver biopsy (percutaneous). (Haematoxylin and eosin. $\times 153$.) Chronic inflammatory reaction is seen with cholangiolar and fibroblastic proliferation. Destruction of adjacent periportal hepatic parenchyma is also noted.

The patient made a satisfactory recovery from surgery but continued to complain of anorexia and lethargy over many months. Liver function tests over this period showed a continuing high alkaline phosphatase with levels ranging from 100-150 K.A. units. The serum bilirubin level fluctuated, was normal for a time, but after eight months rose to levels varying from 2.5-4.5 mg/100 ml. The serum transaminase and

serum albumin levels remained normal, but the total globulin rose to 5.2 g/100 ml with a rise of gammaglobulin shown on electrophoresis. Immunoelectrophoresis at this time showed raised levels of immunoglobulin G. The E.S.R. rose steadily to 80-100 mm in the first hour. The hepatitis-associated antigen, smooth muscle, and antimitochondrial antibody tests remained negative. Tests for antinuclear factor remained negative, but one positive test for lupus erythematosus cells was obtained at this time. A repeat percutaneous liver biopsy was performed eight months after the initial presentation and showed striking changes in liver structure compared with the previous specimens. Bile stasis was no longer present but the chronic inflammatory reaction in the portal tracts was now much more intense with destruction of adjacent liver parenchyma, this being characteristic of fairly aggressive chronic active hepatitis (fig. 3). Connective tissue stains showed a striking degree of portal fibrosis but no established cirrhosis. Eosinophils were prominent in some portal areas where the inflammatory infiltrate was otherwise typical of chronic active hepatitis.

Comment

Chlorpromazine and other drugs of the phenothiazine group cause jaundice (characteristically cholestatic) in 1% of cases. The reaction is not related to dose, and may occur up to three weeks after ingestion of the drug (Hollister, 1957). Although jaundice after chlorpromazine ingestion has been known to last for some years (Read *et al.*, 1961), the continuing lethargy, weight loss, mild jaundice, and the rise of E.S.R., gammaglobulin, and immunoglobulin G raised the possibility of some additional hepatic pathology. A further hepatic biopsy was thus performed and the diagnosis of active chronic hepatitis confirmed. This patient showed initially the histological changes characteristic of jaundice after chlorpromazine ingestion and subsequently, eight months later, progressed to the typical histological changes of active chronic hepatitis. It was also noted that the eosinophilic infiltrations thought to be a feature of drug-induced hepatic injury had persisted. This suggests that there was continuation of the consequences of the initial effect of the drug on the liver.

Chlorpromazine is thought to act as a haptene and the antibodies become attached to the liver cells. Ingestion of the drug may precipitate an antigen-antibody reaction on the surface of the antibody-attached cell, and thus cause damage in the liver. In the susceptible patient, as in the present case, this damage may further precipitate an autoimmune process, leading to the development of active chronic hepatitis.

There was nothing to suggest a preceding viral hepatitis in this patient; the onset was not suggestive of this, there was no history of contact, and the repeatedly negative hepatitis-associated antigen test suggested that long-incubation (or serum) hepatitis was unlikely. There seems little relation between the presence of hepatitis-associated antigen and the occurrence of active chronic hepatitis (Kaplan and Grady, 1971). Alcohol is also unlikely to be aetiological in this patient. There was no history of notable alcohol intake, and none of the hepatic biopsies showed changes suggestive of alcoholic damage.

It is thus probable that in this patient chlorpromazine damage to the liver may have initiated the autoimmune processes leading to the development of active chronic hepatitis.

References

- Hollister, L. E. (1957). *American Journal of Medicine*, 23, 870.
- Johnson, G. D., Holborow, E. J., and Glynn, L. E. (1965). *Lancet*, 2, 878.
- Kaplan, M. M., and Grady, G. (1971). *Lancet*, 1, 159.
- Mackay, I. R., Taft, L. I., and Cowling, D. C. (1956). *Lancet*, 2, 1323.
- Morin, Y., Turmel, L., and Fortier, L. (1964). *American Journal of Medical Science*, 248, 633.
- Read, A. E., Harrison, C. V., and Sherlock, S. (1961). *American Journal of Medicine*, 31, 249.
- Reynolds, T. B., Peters, R. L., and Yamada, S. (1971). *New England Journal of Medicine*, 285, 813.
- Sherlock, S. (1968). *Diseases of Liver and Biliary System*, 4th edn., p. 425. Oxford, Blackwell Scientific.
- Waldenström, J. (1950). *Leber, Blutproteine und Nahrungseisens*, p. 8, Stoffwechsels Khrh, Sanderbund: XV Tagung, Bad Kissingen.
- Whittingham, S., Mackay, I. R., and Irvine, J. (1966). *Lancet*, 1, 1333.
- Williams, E. R., and Khan, M. A. (1967). *Journal of Therapeutic and Clinical Research*, 1, No. 6, p. 5.