LATE PROGNOSIS OF CHLORPROMAZINE JAUNDICE

BY

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Jaundice, the best known of the complications of chlorpromazine therapy, has an incidence of about 1%. The prevalence in a general hospital population has been investigated by Graham (1957), who noted that, of 55 patients admitted in one year suffering from jaundice, chlorpromazine was the cause in five cases. The clinical, pathological, and biochemical features have been extensively investigated—for example, by Werther and Korelitz (1957)—and are now well recognized. It is believed that jaundice is caused by hypersensitivity to the drug within the liver, which may result in an increased permeability of the cholangioles (*British Medical Journal*, 1957). The characteristic histological picture is one of biliary stasis, with infiltration of the portal tracts by polymorphs, among which eosinophils are frequent; portal-zone fibrosis and hepatic cellular damage are either slight or absent.

In most patients the period of jaundice is brief, lasting a few weeks only; but in 10% of a group of cases collected by Brick and Buckley (1957) jaundice persisted for three months or longer. Unless there is serious coexisting disease, clinical recovery is eventually complete. Little is known, however, of the ultimate effect, if any, of chlorpromazine jaundice on liver structure and function. The aim of the present investigation has been to ascertain whether disappearance of the jaundice is followed by complete histological and functional restoration.

Two patients were studied after clinical recovery from chlorpromazine jaundice. Neither had suffered previously from liver disorder, and no clinical stigmata of chronic liver disease were noted while they were under observation. The purpose of the investigation was explained to the first patient and her consent was obtained. In the case of the second subject, who was a certified patient, permission to investigate was obtained from his nearest relative and from his regular medical

attendant. The results of tests which showed no abnormality have been omitted.

Case 1

A woman aged 52 was admitted to hospital on January 30, 1957, for treatment of a depressive illness with agitation. Chlorpromazine in dosage of 200 mg. daily was given from February 5 to March 5. Clinical jaundice, with typical changes in liver-function tests, was first noted on February 28 and had disappeared by April 8. She was discharged on May 14. Thereafter she was observed as an out-patient, apart from two subsequent occasions when for brief periods she was admitted to hospital for the purpose of liver biopsy. The relevant biochemical data are recorded in the Table.

Result of Liver-function Tests in Case 1

Date	Serum Bilirubin (mg./100 ml.)	Alkaline Phosphatase (K.A. Units)	Bromsulphthalein Retention (%)
6/2/57	0.2	4.9	
19/2/57	0.3	7.6	
5/3/57	6.0	53.8	
9/3/57	8.0	43.8	
11/3/57	4.0	46.4	
19/3/57	1.0	38.8	
26/3/57	0.5	38.7	
2/4/57	0.6	30.3	
5/4/57	0.6	—	26.3
9/4/57	0.2	31.9	
19/9/57	0.2	13.3	4.8
24/3/58	0.2	10.3	3.0

Needle biopsy of the liver on March 13, while jaundice was present, showed cellular infiltration of the portal tracts with a moderate fibrous-tissue reaction; the liver cells were normal (Fig. 1). The examination was repeated on September 21, and revealed little change (Fig. 2). A third liver biopsy on March 25, 1958, showed considerable fibrosis in the portal zones with slight cellular infiltration. No bile-duct proliferation was observed and the liver cells remained normal in appearance (Fig. 3).

Case 2

A man aged 48 had been a certified patient in a mental hospital for 14 years. At first his illness had been characterized by depression, with delusions, outbursts of temper, and ideas of influence and of reference. Suicide had been attempted. More recently he had been morose, suspicious, and hallucinated. Electric convulsion therapy had conferred little benefit. Treatment with chlorpromazine in dosage of 225 mg. daily was begun on October 11, 1956. Jaundice appeared on October 30 and persisted until February 1, 1957. A second course of chlorpromazine, 300 mg. daily, was followed by recurrence of jaundice on

FIG. 1.

FIG. 2.

FIG. 3.

FIG. 4.

FIG. 1.—Case 1. Cellular infiltration in portal zone with moderate fibrous-tissue reaction. Normal bile duct and parenchymal cells. (H. and E. $\times 240$.) FIG. 2.—Case 1. Some persistent fibrosis in portal tract. (H. and E. $\times 294$.) FIG. 3.—Case 1. Portal zone shows considerable fibrosis with slight cellular infiltration. Liver cells normal. No bile-duct proliferation. (H. and E. $\times 240$.) FIG. 4.—Case 2. Considerable amount of newly formed fibrous tissue around portal tracts. Minimal cellular infiltration. Liver cells normal. No dilatation of bile ducts or canaliculi. (van Gieson $\times 240$.)

September 27, 1957. The jaundice had cleared by October 29, and since that date no physical illness has been reported.

The patient was investigated in May, 1958, when the following tests of liver function were recorded: serum bilirubin, 0.4 mg. per 100 ml; serum alkaline phosphatase, 46.7 K.A. units; bromsulphthalein retention, 13.8%. Needle biopsy of the liver on March 9, 1958, showed a considerable increase in fibrous tissue in the portal tracts, with slight cellular infiltration. Bile-duct proliferation and abnormality of parenchymal cells were not observed (Fig. 4).

Discussion

Chlorpromazine is of such recent introduction that enough time has not yet elapsed for the ultimate prognosis in all patients who develop jaundice to become clear. The present investigation indicates that restoration of normal liver histology or function, or both, may be long delayed. If permanent changes were to ensue, the original, cholangiolytic, type of lesion is of a nature that could lead to biliary cirrhosis. Myres *et al.* (1957) have observed such a case; one year after the onset of chlorpromazine jaundice, biliary cirrhosis, confirmed by liver biopsy, was present and portal hypertension was also noted. Twenty patients who had apparently recovered from chlorpromazine jaundice were studied by Kelsey *et al.* (1955), and early cirrhotic changes were reported in two cases. Eleven of the 20 cases, however, had previously suffered from diseases which could have involved the liver, and, as other drugs had been used in the two cases mentioned, the authors could not be certain that chlorpromazine was solely responsible.

Sensitization reactions to chlorpromazine within the liver are believed by Shay and Siplet (1957) to occur in 25% of patients who receive the drug, and are ascribed by them (Shay and Siplet, 1958) to the presence of the chlorine atom at the carbon-2 position in the promazine molecule. Such reactions are characterized by a cellular reaction within the portal tracts.

Needle biopsy of the liver was carried out by Sims *et al.* (1955) in 18 patients prior to chlorpromazine treatment and again at its conclusion. No patient became jaundiced, and biochemical tests of liver function remained normal. Four patients developed the characteristic hepatic lesions. A similar investigation was performed by Bartholomew *et al.* (1958) on 25 patients, two of whom became jaundiced. Of 16 patients in whom the pre-treatment liver biopsies had been normal, five developed the typical histological changes. The incidence of liver reactions to the drug is therefore much higher than the frequency of clinical jaundice would indicate.

When a history of previous chlorpromazine administration is not obtained from the jaundiced patient, extrahepatic biliary obstruction may be thought responsible and laparotomy performed. Surgical intervention for diagnostic purposes constitutes an additional hazard to the patient, and had been found necessary in 17.5% of a series of cases collected by Brick and Buckley (1957). Chlorpromazine jaundice is of intrahepatic cholestatic type, and in this variety Popper and Schaffner (1957) think that surgical procedures are apt to result in parenchymatous liver injury.

Chlorpromazine is a drug which is potentially toxic to the liver, as well as to leucopoietic and other tissues. When it occurs jaundice can be prolonged, and histological changes take place in the liver in a proportion of patients who do not develop jaundice. Sensitive tests of liver function may remain abnormal for long

periods after jaundice. Restoration of normal liver architecture may be long delayed, and permanent liver damage, though probably rare, has been reported. Despite its excellent general utility, these considerations suggest that chlorpromazine should be given to patients only when absolutely essential and if a less toxic drug of similar pharmacological action is not available.

Summary

Two patients who had chlorpromazine jaundice six months and one year previously have been studied by means of liver-function tests and needle biopsy. In both cases there were persistent histological changes, but biliary cirrhosis was not observed; in one case liver-function tests remained abnormal. The ultimate prognosis of chlorpromazine jaundice is discussed, and it is suggested that, since the drug is potentially toxic, it should not be used without careful consideration.

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ECTOPIC GESTATION

A STUDY OF A DECADE OF ABERDEEN CASES

BY

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Ectopic gestation remains a condition which exercises the diagnostic ability of the surgeon to the full, and occasional deaths still occur.

The object of this study has been to investigate the symptomatology, aetiological or predisposing factors, and prognosis of the condition. It is based on an analysis of the case records of all patients admitted within the decade 1946 to 1955 to the surgical and gynaecological wards of all the hospitals in the city of Aberdeen, and in whom the diagnosis of ectopic gestation was confirmed. (All the extrauterine pregnancies were situated in the tube, with one exception where it occurred in the ovary.)

The Investigation

There were 224 ectopic pregnancies in 215 patients, since the condition recurred in nine. Fifty-two cases were treated in the surgical wards and the remaining 172 in the gynaecological wards. Of the 215 patients, 127 resided within the city boundary, and they have been used to study the epidemiology of the condition.