HALOTHANE JAUNDICE

(REPORT OF A CASE)

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Since March 1963 13 fatal cases of halothane hepatitis and many non-fatal cases have been the subject of much discussion, but the precise type of liver injury which halothane produces will only be established by many more reports of this relatively rare injury sometimes following an otherwise useful anaesthetic. Barton[1] was among the first to report on jaundice associated with halothane anaesthesia, but he did not provide useful details which might have clarified the site and mode of action of halothane on the liver; critics also pointed out that these Pietermaritzburg patients had blood transfusions in addition to other known hepatotoxic drugs and disease states. It is certainly no easy task to rule out factors other than halothane, such as pre-operative malnutrition, hypoxia, hypercarbia, alcoholism, hypotension, hypovolaemia, and recent drug therapy with chlorpromazine and related compounds, methyl-testosterone, all of which may cause jaundice in the surgical patient. However, after many unsuccessful attempts to find a patient in the Johannesburg Hospital who became jaundiced after halothane anaesthesia in the absence of other hepatotoxic factors, we finally encountered a case of pure halothane hepatitis.

CASE REPORT

A previously healthy man, aged 63, developed pyloric stenosis following ingestion of hydrochloric acid 3 months previously. Although he had lost 30 lb. weight during the latter period, he looked healthy and still weighed 150 lb. He gave no history of jaundice, alcoholism or any other significant disease. His haemoglobin was 14 mg./100 ml., prothrombin index 73%, and clinical examinations were entirely negative.

A gastro-enterostomy was performed under halothane anaesthesia which lasted 1¼ hours. Anaesthesia was induced with 300 mg. of thiopentone, and nitrous oxide was used in addition. Although the anaesthetist did not take the blood-pressure frequently, and kept no record, he stated after completion of the operation that there had been no episodes of anoxia, hypercarbia or hypotension. 'Flaxedil' (gallamine) was also used and the respirations assisted and controlled only during the action of the muscle relaxant. A small dose of suxamethonium was used for laryngeal intubation and atropine and a small dose of neostigmine were also employed.

Jaundice became apparent 3 days after the operation. At this time his liver function was as follows: thymol turbidity 3·5 units, thymol flocculation test ++, colloidal red test +, cephalin cholesterol flocculation test ++++, Takata Ara reaction (Ucko's modification) −ve, zinc sulphate turbidity 12·8, total lipid 42·1 (normal 500 to 700 mg./100 ml.), alkaline phosphatase (King Armstrong) 9·2 units, Van den Bergh reaction weakly prompt direct, bilirubin direct 1·8 and total 4·0 mg./100 ml., total protein 8·2 G/100 ml., albumin 3·1 G/100 ml., globulin 5·1 G/100 ml., gamma globulin 1·8 G/100 ml., cholinesterase 38% of average normal activity, serum glutamic oxalacetic transaminase (SGOT) 33 units, serum glutamic pyruvic transaminase (SGPT) 36 units and lactic dehydrogenase 200 units.

After 3 days the jaundice was still apparent clinically, but all the above tests yielded much more normal results except the SGPT which *rose* to 72 units. Six days later, 12 days after the operation, the jaundice had disappeared; direct bilirubin being 0·4 mg./100 ml. and total bilirubin 0·8 mg./100 ml. The albumin was still only 2·6 G/100 ml., the globulin 4·2 G/100 ml. and the SGPT 54 units. The convalescence was otherwise unremarkable.

Needle biopsy of the liver performed 10 days postoperatively, during the period of jaundice, showed fatty change and patchy

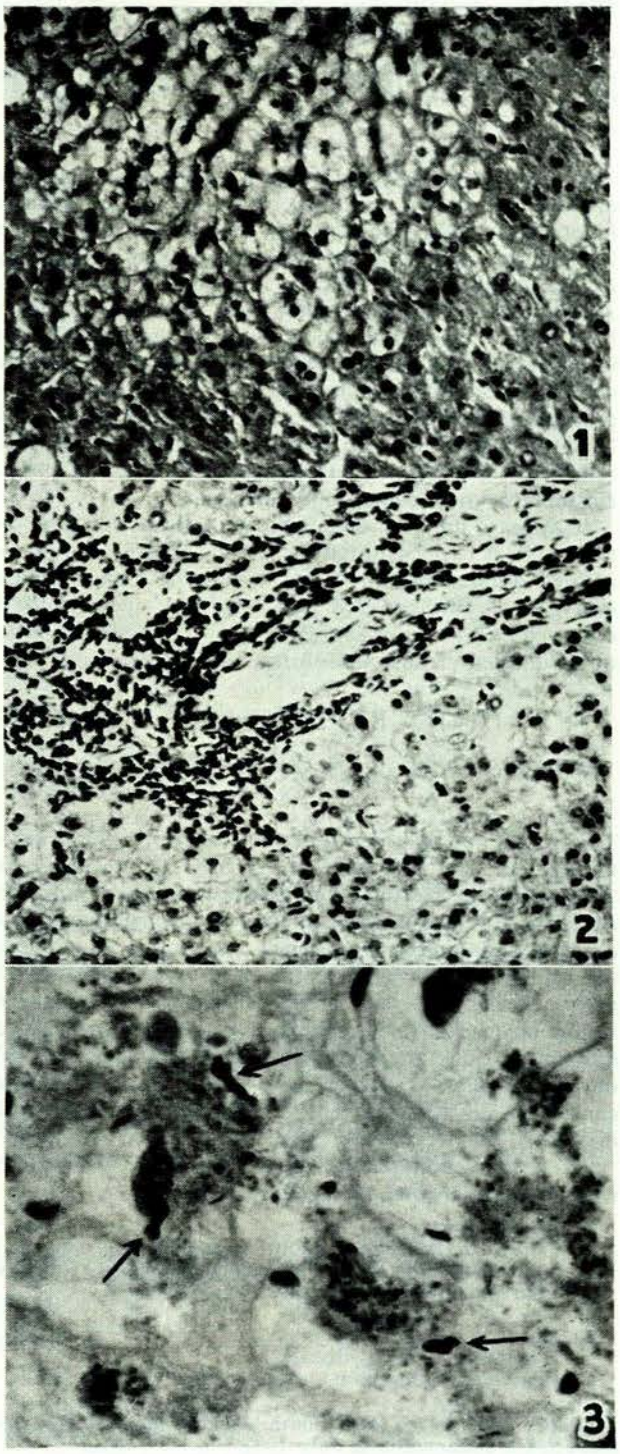

Fig. 1. Fatty change and patchy necrosis of the parenchymal cells (H. & E. x 200).
Fig. 2. Moderate round cell infiltrate around the portal tracts (H. & E. x 200).
Fig. 3. Bile thrombi in some of the biliary canaliculi (H. & E. x 750).

necrosis of the parenchymal cells (Fig. 1). The necrotic foci showed no particular zonal distribution, but were to be found throughout the lobules. Slight evidence of regeneration of liver tissue was noted adjacent to the necrotic areas. The lobular architecture was well preserved. There was a moderate round-cell infiltrate in the portal tracts (Fig. 2) but no evidence of proliferation or obstruction of the bile ducts was present. The biliary canaliculi showed numerous bile thrombi (Fig. 3).

The histopathological findings were those of a toxic hepatitis and were similar to the features described by Heidenberg *et al.*[8] except for the presence of bile retention which was not observed in Heidenberg's case.

DISCUSSION

Although this patient had only one, fairly brief halothane anaesthetic, all the evidence is in favour of resultant halothane hepatitis. The painless icterus, high transaminase level, the ++++ cephalin flocculations and the histological examination all indicate a hepatocellular type of jaundice. However, the pathological changes seen in the liver biopsy from this patient are indistinguishable from those that follow therapy with chlorpromazine and related compounds,[2] and methyltestosterone[3] in which the most prominent change is marked intracanalicular bile stasis. It has very little in common, on the other hand, with those of viral hepatitis, patients with hepatic necrosis after iproniazid therapy,[4] or metahexamide jaundice.[5]

It appears unlikely that these pathological changes are the result of hypersensitivity to halothane since it followed a single administration of halothane, after a short incubation period, without any accompanying fever, and no eosinophilia was noted in the liver. At the same time it was quite different from chloroform hepatitis which shows a conspicuous fatty change and an absence of inflammatory cellular reaction in the portal zones.[6] The most likely mode of action of halothane in producing liver damage appears to be the hepatotoxic potentiality inherent in halogenated hydrocarbon compounds, which is potentiated by concomitant hypoxia and particularly hypercarbia;[7] the former by the almost invariable early hypotension during halothane anaesthesia, and the latter, hypercarbia, by the failure of most anaesthetists to provide artificial ventilation in the face of the pronounced respiratory depression during all degrees of halothane anaesthesia.

SUMMARY

A case is reported of halothane jaundice in which the case history and manifestations do not favour hypersensitivity to the drug. Although not of the same type as chloroform damage to the liver, halothane hepatitis is likely to be caused by the same modes of action as in the other halogenated hydrocarbons; that is by hypoxia resulting from hypotension and particularly by hypercarbia.

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REFERENCES

1. Barton, J. D. M. (1959): Lancet, **1**, 1097.
2. Stein, A. A. and Wright, A. W. (1956): J. Amer. Med. Assoc., **161**, 508.
3. Brick, I. B. and Kyle, L. H. (1952): New Engl. J. Med., **246**, 176.
4. Kahn, M. and Perez, V. (1958): Amer. J. Med., **25**, 898.
5. Mach, B., Field, R. A. and Taft, E. B. (1959): New Engl. J. Med., **261**, 438.
6. Sherlock, S. (1963): *Disease of the Liver and Biliary system*, 3rd ed. Oxford: Blackwells.
7. Morris, L. E. and Feldman, S. A. (1963): Anaesthesia, **18**, 32.
8. Heidenberg, W. J., Torio, I. and Cebula, J. (1963): Lancet, **1**, 1185.