during penicillamine treatment; fibrosing alveolitis during gold treatment; analgesic nephropathy in a patient who had taken chloroquine, cyclophosphamide, gold, indomethacin, naproxen, penicillamine, and phenylbutazone; and perforated duodenal ulcer with over 24 different drugs listed.

Reported deaths listing gold increased gradually to a peak of eight in 1970; 18, including five of the seven "remote" ones, occurred in 1972-6 compared with 23 in the previous five years. The use of gold (ampoules a year) has steadily increased, nearly two-and-a-half times as much being issued in 1976 as in 1964.

The magnitude of error caused by using EC10 prescriptions for gold (1968-70)[2] as a guide to the amount of gold used was considerable. On this basis each EC10 prescription would have been for 15 ampoules or 15 weeks' treatment at the usual rate of one ampoule a week. As in 1969 many patients were receiving maintenance treatment, then usually one ampoule a month, the underestimate would be even greater.

Comment

The number of reported deaths in which gold is mentioned as a possible factor has decreased while the use of gold has increased, suggesting that the toxicity of gold is not a simple factor relating only to use. Major changes in our use of the drug have occurred; in particular, flexible dosage regimens tailored to the individual patients' needs[3 4] reduce the likelihood of toxic reactions, while maintenance treatment has increased the long-term beneficial effect.[5] More careful monitoring of patients receiving gold treatment and the use of flow sheets to chart blood count results, gold dose, and possible side effects[3] alert the doctor to possible toxicity.

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[1] Buchanan, W Watson, *et al*, in *Rheumatoid Arthritis*, ed J L Gordon and B L Hazleman, p 70. Amsterdam, North Holland Publishing Co, 1977.
[2] Girdwood, R H, *British Medical Journal*, 1974, **1**, 501.
[3] Kay, A G L, *British Medical Journal*, 1976, **1**, 1266.
[4] Gumpel, J M, *Rheumatology and Rehabilitation*, 1976, **15**, 217.
[5] *Lancet*, 1974, **1**, 789.

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Rheumatic Diseases Study Group, Northwick Park Hospital, Harrow, Middlesex
J M GUMPEL, BM, MRCP, consultant physician

Familial HBsAg-positive hepatoma: treatment with orthotopic liver transplantation and specific immunoglobulin

Reports of familial hepatoma, particularly those associated with HBsAg, are rare.[1-3] In the present family two of three brothers, both positive for HBsAg, have so far developed a hepatoma. One treated by liver transplantation received large doses of specific immunoglobulin to prevent reinfection of the donor liver by HB virus.

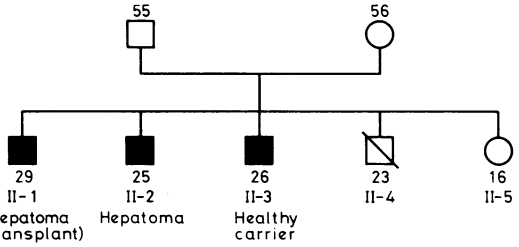
Case history

A 29-year-old garage mechanic was found to have a hepatoma in June 1975, HBsAg also being detected in the serum at that time. At laparotomy a few months later (Mr J L Dawson) the main tumour mass in the left lobe was shown to extend posteriorly into the right lobe, thus precluding resection. Two hepatic arteries supplying the left lobe were ligated and on 30 December 1975 liver transplantation was carried out. Immediately the diseased liver had been removed the patient was given an infusion of 500 ml of human anti-HBs immunoglobulin (10 g protein per 100 ml solution with an antibody titre of 1/16 by immunodiffusion and 1/8000 by haemagglutination) diluted in 500 ml normal saline over 20 minutes. Serum HBsAg titre fell over four hours from 1/4096 to 1/32. It remained at this concentration for the next six days, when a further 600 ml was given. Two hours later HBsAg was no longer detectable in the serum by radioimmunoassay.

The surface of the removed liver appeared coarsely nodular as a result of subcapsular scarring, but the parenchyma was otherwise devoid of fibrous tissue. Microscopical examination showed a well-differentiated hepatocellular carcinoma with HBsAg in many of the normal hepatocytes, but not within the tumour tissue.

The patient is currently well and at full-time work. Serum α-fetoprotein (previously positive, 5000 μg/l) is normal (<20 μg/l).

Other family members—One of the patient's brothers had died in 1973 at the age of 25 years. Both HBsAg and α-fetoprotein were detected in the serum, the histological appearances at necropsy being those of a moderately well-differentiated hepatocellular carcinoma with some minor underlying portal tract fibrosis. The third brother with HBsAg in the serum has normal liver histological appearances on a biopsy specimen, apart from ground glass transformation of the cytoplasm consistent with the carrier state (figure).



Family members. HBsAg-positive ●; HBsAg-negative Ø; not tested for HBsAg ○.

Discussion

The absence of an underlying cirrhosis has not been reported in English journals, although several Japanese families have been described in which members positive for HBsAg have developed hepatocellular carcinoma in association with a wide range of underlying liver abnormalities. The exact relationship between hepatoma development, HBsAg, and underlying cirrhosis is uncertain. Significantly more patients with hepatoma and cirrhosis are HBsAg-positive than those with cirrhosis alone, and the hepatitis B virus may have a direct oncogenic effect. Recent evidence based on the presence of antibody to the hepatitis B core antigen in the serum suggests that virtually all patients with hepatoma in Africa and South-east Asia, where the incidence of hepatoma is high, are, or have been, infected with the virus. Nevertheless, in temperate climates hepatoma in HBsAg-positive individuals without underlying cirrhosis is rare. The fact that the patient's brother had developed a hepatoma in association with HBsAg infection suggests a common genetic susceptibility.

Transplantation in the presence of HBsAg infection is a serious risk.[4 5] Although specific immunoglobulin will give protection from hepatitis, as shown in several trials after inoculation accidents, clinical infection may be delayed beyond the normal incubation period and become apparent up to nine months later. Our patient is now well past this time.

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[1] Denison, E K, Peters, R L, and Reynolds, T B, *Annals of Internal Medicine*, 1971, **74**, 391.
[2] Kaplan, L, and Cole, S L, *American Journal of Medicine*, 1965, **39**, 305.
[3] Hagstrom, R M, and Baker, T D, *Cancer*, 1968, **22**, 142.
[4] Starzl, T E, *et al*, *Transplantation Proceedings*, 1972, **4**, 759.
[5] Calne, R Y, and Williams, R, *British Medical Journal*, 1977, **1**, 471.

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Liver Unit, King's College Hospital and Medical School, London SE5
P J JOHNSON, MB, MRCP, research fellow
M H WANSBROUGH-JONES, MB, MRCP, lecturer and hon senior registrar
B PORTMANN, MD, MRCPATH, consultant histopathologist
A L W F EDDLESTON, DM, MRCP, senior lecturer and hon consultant physician
ROGER WILLIAMS, MD, FRCP, director and consultant physician

Lister Institute of Preventive Medicine, Elstree, Herts WD6 3AX
W D'A MAYCOCK, FRCP, FRCPATH, director, Blood Products Laboratory

Department of Surgery, Addenbrooke's Hospital, Cambridge CB2 2QQ
R Y CALNE, MS, FRCS, FRS, professor of surgery