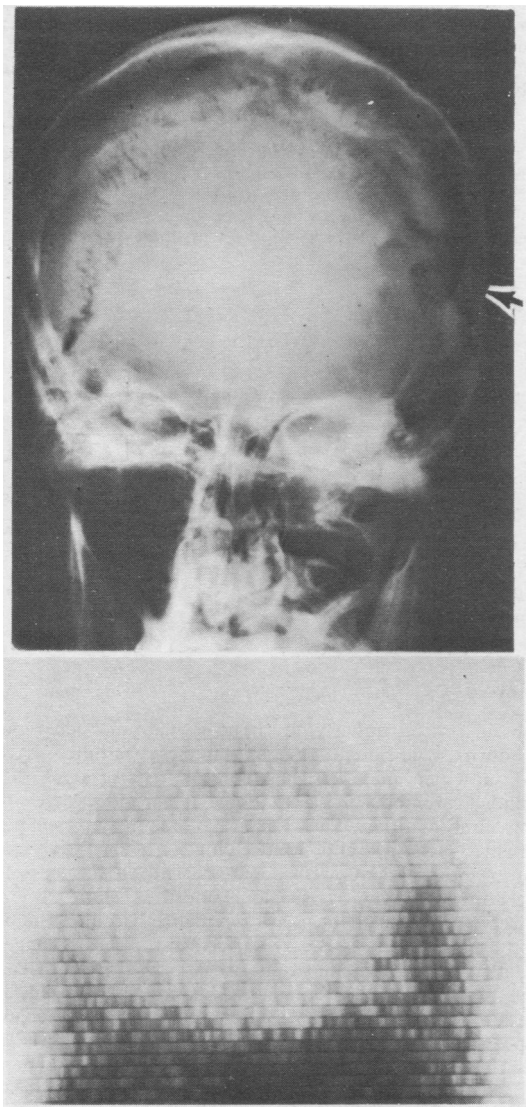

Above: Skull radiograph showing localised area of osteoporesis in left frontotemporal region (arrowed). Below: Technecium brain scan showing increased uptake in left frontotemporal region at site of bone erosion.

waves in the left temporal region; technecium brain scan, increased uptake in the left frontotemporal region at the site of the bone erosion (see figure); and left carotid arteriogram normal. Skull biopsy (Professor Sissons, Institute of Orthopaedics): bony trabeculae showed intense focal osteoclastic resorption together with an irregular pattern of cement lines; the spaces between the trabeculae were occupied by vascular fibrous tissue. The appearances suggested Paget's disease. The patient was treated with phenobarbitone, 60 mg daily, and has had no further attacks.

Case 2—A West Indian of 38 was admitted to hospital in October 1976 having developed generalised involuntary convulsive movements with frothing at the mouth while sitting at home. He was confused and complained of headache on regaining consciousness five minutes later. A similar attack had occurred three years before, but there was no family history of epilepsy. Results of examination and investigations were as follows: no abnormal neurological signs; skull radiography, thickening of both vault tables with some invagination of the skull base at the foramen magnum; electroencephalography, a mild diffuse abnormality with left-sided emphasis but without paroxysmal changes; technecium brain scan, a large head with a broad band of activity around the periphery in all three views; cerebrospinal fluid normal; serum alkaline phosphatase 105 U/l (normal <90 U/l); urine hydroxyproline 0·72 mmol/24 h (94·6 mg/24 h) (normal 0·076-0·38 (10-50)); and serum calcium and phosphorus concentrations normal. The patient has had no further attacks since taking phenobarbitone 60 mg daily.

Comment

These cases illustrate the association of grand mal epilepsy with two types of Paget's disease of the skull—osteoporosis circumscripta and generalised thickening of the bone. It might be argued that the association is coincidental, as both are common diseases. In case 1, however, the focal features of the attack, together with focal abnormalities on the EEG at the site of the bony defect and the increased uptake on the gamma scan there, suggest the association is more than fortuitous. In case 2 the bony abnormality was generalised, but the relatively young age of the patient and late onset of the epilepsy suggest that the conditions are related.

In case 1 there was doubt about the diagnosis until confirmed by bone biopsy but case 2 showed typical *x*-ray appearances together with increased hydroproline excretion and serum alkaline phosphatase.

The explanation for the association can only be speculative, but the increased vascularity of the bone overlying the brain may have triggered the attacks. The finding of an abnormal isotope scan in epilepsy could be misleading if Paget's disease is not considered in the differential diagnosis. In case 1 a meningioma with bone erosion was suggested, but bone biopsy gave the diagnosis. In case 2 the scan appearance was similar to chronic subdural haematoma.[3]

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(*Accepted 6 October 1977*)

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Deaths associated with gold treatment: a reassessment

Gold is said[1] to be the most toxic drug in the *Pharmacopoeia*; none the less the use of gold treatment in progressive rheumatoid arthritis is steadily increasing. In a survey[2] of deaths of patients taking medicaments, Girdwood found that gold was associated with the highest mortality rate of all drugs when the annual numbers of deaths reported to the Committee on Safety of Medicines (CSM) were related to the number of EC10 prescriptions for those drugs in England and Wales. Despite Girdwood's warnings that his data lacked scientific accuracy, his findings are often quoted without this warning.

Two possible sources of error may have combined to put gold at the top of the list. Firstly, the three drugs with the highest ratio of deaths to EC10 prescriptions were all hospital-based drugs—gold, phenindione, and warfarin—and therefore poorly represented by EC10 prescribing. Secondly, patients with rheumatoid arthritis receive many different drugs, all with different side effects, in varying amounts over the years. To test the hypothesis that Girdwood's figures were an overestimate, I obtained details of the CSM's reports of deaths from 1964 to 1976 in which the use of gold was mentioned, and the likely contribution of gold to the causation of each death was independently assessed. Finally, the amount of gold supplied in the UK in those years was ascertained.

Findings

From 1964 to 1976, reports of 46 deaths to the CSM listed gold treatment. Blood dyscrasia caused death in 39 cases (aplastic anaemia 30, agranulocytosis 5, thrombocytopenia 3, myeloproliferative disorder 1); gold was thought to be the probable cause in 16 cases, a possible cause in 17, and an unlikely cause in six. Some of these 39 patients had been taking other antirheumatic drugs known to cause blood dyscrasia: phenylbutazone 20, oxyphenbutazone 3, penicillamine 3, chlorambucil 2, and indomethacin 13. In the seven other cases the contribution of gold to the cause of death was even more unlikely; in six the gold had been discontinued years before death, and often other medications were more likely causes. The immediate causes of death were: renal disease attributed to indomethacin; gastric ulceration during prednisone and azathioprine treatment; hepatic necrosis and renal failure; Goodpasture-like syndrome with coagulation disorder

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.

We thank the Committee on Safety of Medicines and May and Baker Ltd for ready access to information; Dr W H Inman for his considerable help and for his independent assessment of the implication of gold; and Professor W Watson Buchanan for constant stimulation.

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(*Accepted 10 October 1977*)

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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.

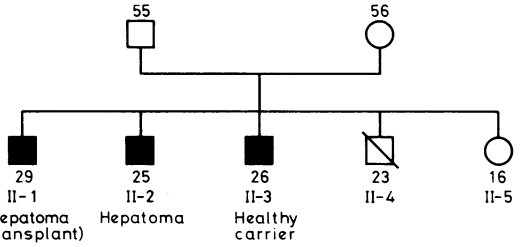
Case history

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.

We are indebted to the many colleagues who helped in the care of this patient, and to Linda Rimmer for editorial work.

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(*Accepted 10 October 1977*)

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