

## Discussion

The clinical findings of reversible central nervous system toxicity with high dose interferon are of considerable interest. In our study they were the major cause of dose limiting toxicity. The preparation used was highly purified, and therefore contaminating molecules were unlikely to be the cause. Previous studies have shown that interferon does not cross the blood-brain barrier and cannot be identified in cerebrospinal fluid, even in the presence of high circulating blood concentrations.<sup>2</sup> The mechanism for these effects cannot be explained, and a study is in progress to determine if any subgroups of patients who are at particular risk of developing this distressing syndrome can be identified. It is as yet too early to assess the effectiveness of this interferon in the management of breast cancer.

We thank Drs S De Garis, S Fein, and I Lenox-Smith of Hoffmann-La Roche for their helpful advice; Hoffmann-La Roche for providing the interferon; Miss P Hall for electroencephalographic studies; and our colleagues for referring patients for this study.

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# Quinine-induced granulomatous hepatitis

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## Abstract

Many adverse reactions to quinine have been reported. A 65 year old woman taking quinine sulphate for nocturnal leg cramps presented for investigation of episodes of malaise, fever, nausea, vomiting, and polyarthralgia. Granulomatous hepatitis was diagnosed, for which no common cause was found. She was challenged with quinine sulphate; within hours her temperature had risen and her symptoms returned; transaminase activities rose within 48 hours, as did erythrocyte sedimentation rate. After withdrawal of the drug symptoms abated and transaminase activities returned to normal.

The biochemical response to challenge with quinine implicates the drug as the cause of the liver disturbances. Quinine should be added to the list of drugs known to cause granulomatous hepatitis and should be considered in cases where symptoms are episodic or where no other cause is apparent.

## Introduction

Quinine and quinidine are optical isomers, and many adverse reactions, including cinchonism and gastrointestinal and haematological disturbances, are common to both. Quinidine has been reported to induce granulomatous hepatitis.<sup>1</sup> We present the first case report of quinine-induced granulomatous hepatitis.

## Case report

A 65 year old woman was referred for assessment of four episodes of malaise, fever, nausea, vomiting, and polyarthralgia over the preceding five months. The episodes were of varying severity and duration, spontaneously subsiding after three to 28 days. There was no known

contact with infectious disease and no weight loss. She had been taking pindolol and methylothiazide daily for two years for hypertension, and quinine sulphate, initially prescribed five months before referral, for nocturnal leg cramps. Apart from a period in hospital 25 years earlier after a severe reaction to penicillin, she had no medical history of note. She rarely consumed alcohol.

On examination she was obese with a blood pressure of 155/65 mm Hg. She had widespread psoriasis, but no other physical abnormality. Full blood tests showed no abnormality; erythrocyte sedimentation rate was 58 mm in the first hour. Liver function tests showed a bilirubin concentration of 9  $\mu$ mol/l (0.52 mg/100 ml) (normal 0-29  $\mu$ mol/l (0-1.7 mg/100 ml)), alkaline phosphatase activity of 306 IU/l (normal 21-266), aspartate transaminase 129 IU/l (normal 10-30), alanine transaminase 298 IU/l (normal 6-36), and  $\gamma$ -glutamyltranspeptidase 238 IU/l (normal 8-63). Serological tests detected no hepatitis B. Other investigations also gave negative results, apart from a positive Mantoux reaction. There was no evidence of active tuberculosis. During the period of investigation the patient felt well, and a spontaneous improvement in the results of liver function tests was noted (fig 1). Percutaneous needle biopsy of the liver showed normal

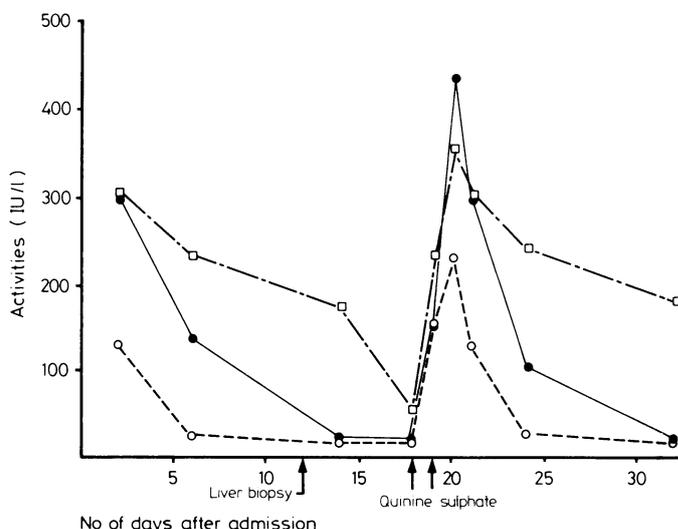


FIG 1—Results of liver function tests showing a transient rise after challenge with quinine sulphate. Normal values: aspartate transaminase (○—○) 10-30 IU/l, alanine transaminase (●—●) 6-36 IU/l, alkaline phosphatase (□—□) 21-266 IU/l.

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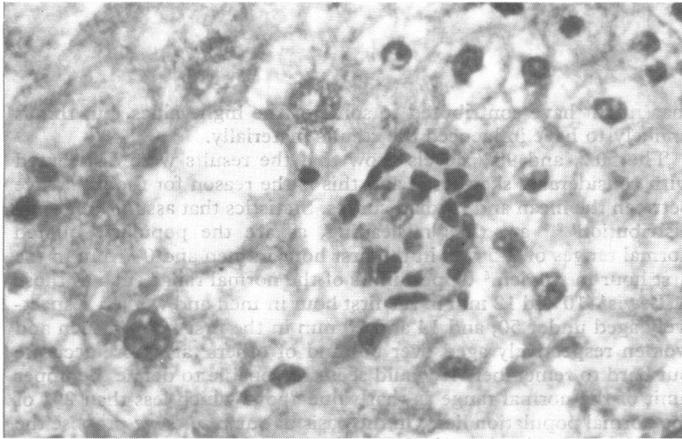


FIG 2—Intralobular microgranuloma found in liver biopsy specimen. Haematoxylin and eosin  $\times 400$  (original magnification).

architecture, diffuse fatty changes, and scattered intralobular microgranulomas. The granulomas consisted mainly of histiocytes with occasional eosinophils, while others, mostly around the central veins, were microlipogranulomas. There were no giant cells or caseation, and stainable iron was not seen (fig 2).

After the more common causes of granulomatous hepatitis had been excluded, the possibility of a drug-induced disorder was considered. The episodic nature of her illness drew attention to the patient's intermittent use of quinine sulphate. After the patient had given fully informed consent, 300 mg of quinine sulphate was administered orally on two successive days. Within hours of the first dose her temperature rose to 37.6°C, associated with a mild recurrence of her symptoms. There was a concomitant rise in the hepatic transaminase activities, which had returned to normal before the challenge. Over 48 hours the aspartate transaminase activity rose to 264 IU/l, and the alanine transaminase to 437 IU/l. There was a modest rise in the alkaline phosphatase activity, the bilirubin remained in the normal range. The erythrocyte sedimentation rate rose from 33 mm in the first hour to 61 mm. There was no prolongation of the prothrombin time, eosinophilia, or thrombocytopenia. The symptoms of anorexia, nausea, and arthralgia abated by the fifth day, and the aspartate transaminase activity had returned to normal by one week, the alanine transaminase by two. The liver biopsy was not repeated.

## Discussion

The dramatic biochemical response after challenge with quinine sulphate implicates quinine as the causative agent of the liver disturbance. The liver biopsy showed granulomas, and the

presence of eosinophils supports the hypothesis that the disease was induced by a drug aetiology. The clinical and histological findings resemble those in the case reports of quinidine-induced granulomatous hepatitis.<sup>1-3</sup> Chajek *et al*<sup>1</sup> first reported quinidine-induced granulomatous hepatitis, showing resolution with drug withdrawal and recurrence with rechallenge. As quinine is the optical isomer of quinidine it is not unexpected that quinine should also be found to induce granulomatous hepatitis. Hepatic granulomas are found in 2-7% of all liver biopsy specimens, sarcoidosis and tuberculosis accounting for up to 60% of these.<sup>4</sup> Granulomatous hepatitis related to the use of drugs accounted for about 2% of 1500 consecutive liver biopsy findings reported by McMaster and Hennigar.<sup>5</sup> In up to one quarter of cases no cause is found. Quinine sulphate should now be added to the list of drugs known to cause granulomatous hepatitis, which now includes<sup>5</sup> sulphonamides, penicillin, allopurinol, phenylbutazone, methyldopa, hydralazine, carbamazepine,<sup>6</sup> isoniazid, nitrofurantoin,<sup>7</sup> diazepam, and quinidine.

The mechanism of hepatotoxicity with quinidine and quinine has not been established, but as quinidine-induced thrombocytopenia has been reported on only one occasion in association with granulomatous hepatitis it is reasonable to suggest that a different pathological mechanism probably exists.<sup>3</sup>

As a patient may be exposed to quinine only intermittently, either because of occasional use of quinine sulphate for nocturnal cramps, or in soft drinks containing quinine, specific inquiry about its use should be made in all patients with granulomatous hepatitis where the symptoms are episodic or where no other cause is apparent.

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GARDEN PURSLAIN (being used as a salad herb) is so well known that it needs no description; I shall therefore only speak of its virtues as follows.

'Tis an herb of the Moon. It is good to cool any heat in the liver, blood, reins, and stomach, and in hot agues nothing better: It stays hot and choleric fluxes of the belly, women's courses, the whites, and gonorrhoea, or running of the reins, the distillation from the head, and pains therein proceeding from heat, want of sleep, or the frenzy. The seed is more effectual than the herb, and is of singular good use to cool the heat and sharpness of urine, venereous dreams, and the like; insomuch that the over frequent use hereof extinguishes the heat and virtue of natural procreation. The seed bruised and boiled in wine, and given to children, expels the worms. The juice of the herb is held as effectual to all the purposes aforesaid; as also to stay vomitings, and taken with some sugar or honey, helps an old and dry cough, shortness of breath, and the phthisick, and stays immoderate thirst. The distilled water of the herb is used by many (as the more pleasing) with a little sugar to work the same effects. The juice also is singularly good in the inflammations and ulcers in the secret parts of man or woman, as also the bowels and haemorrhoids, when they are ulcerous,

or excoriations in them. The herb bruised and applied to the forehead and temples, allays excessive heat therein, that hinders rest and sleep; and applied to the eyes, takes away the redness and inflammation in them, and those other parts where pushes, wheals, pimples, St Anthony's fire and the like, break forth; if a little vinegar be put to it, and laid to the neck, with as much of galls and linseed together, it takes away the pains therein, and the crick in the neck. The juice is used with oil of roses for the same causes, or for blasting by lightening, and burnings by gunpowder, or for women's sore breasts, and to allay the heat in all other sores or hurts; applied also to the navels of children that stick forth, it helps them; it is also good for sore mouths and gums that are swollen, and to fasten loose teeth. Camerarius saith, the distilled water used by some, took away the pain of their teeth, when all other remedies failed, and the thickened juice made into pills with the powder of gum Tragacanth and Arabic, being taken, prevails much to help those that make bloody water. Applied to the gout it eases pains thereof, and helps the hardness of the sinews, if it come not of the cramp, or a cold cause. (Nicholas Culpeper (1616-54) *The Complete Herbal*, 1850.)