

factor was reduced from 2+ to 1+. At the same time the platelet count rose from $147 \times 10^9/L$ to $260 \times 10^9/L$. At weekly intervals, PAA was assayed on freshly drawn peripheral blood.^{2,3} A day or two later the PANSS psychiatric rating⁴ was carried out by a different group uninformed about the PAA value.

The results of the PAA profile and the psychiatric ratings are shown in the figure. Within the first trial period the PAA value was reduced and in the midst of the second period it reached normal values (top figure). 4 weeks after terminating azathioprine, PAA was again raised and approached the initial level. The PANSS ratings indicated psychiatric improvement that followed the decrease in PAA but remained unchanged when the latter relapsed. The patient is now in a state of remission (symptoms below the twenty-fifth percentile in the PANSS scale) and her appearance and social performance are close to normal.

A spectrum of examinations (data not shown) have indicated that the observed effects could not be attributed to an anti-lupus action of azathioprine, or to a non-specific steroid effect. It seems plausible, therefore, that in our case immunosuppression induced by azathioprine acted on a putative autoimmune arm of schizophrenia, which was associated with PAA.

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Ultrasonography surveillance of endometrium in breast cancer patients on adjuvant tamoxifen

SIR—Kedar and colleagues (May 28, p 1318) confirm that tamoxifen can cause potentially malignant changes of the endometrium, and that transvaginal ultrasonography could be used to select subjects who should have endometrial sampling.

Surveillance of postmenopausal breast cancer patients receiving adjuvant tamoxifen (20 mg daily) has been done at our centre since 1993. Symptom-free women are examined yearly by pelvic sonography, and routine endometrial biopsy is done if endometrial thickness is abnormal (>4 mm). Abdominal sonography is simpler, faster, and more acceptable to postmenopausal women than the endovaginal technique and is as reliable in measuring endometrial thickness.

So far we have examined 275 patients aged 50 years or more with symptoms, who have received tamoxifen for 1–7 years. Abnormal endometrial thickness was recorded in 171 (62%), which is much higher than the 99 of 1767 (5.6%) healthy postmenopausal women undergoing pelvic sonography in the course of a pilot study for endometrial cancer screening. The unusual “cystic” appearance of the endometrium, described by Goldstein,¹ was commonly seen in patients treated with tamoxifen. Endometrial biopsy in subjects with abnormal endometrium identified 1 case of endometrial cancer (overall prevalence 0.36%), 2 of typical

hyperplasia, and 3 of polyp among patients on tamoxifen, whereas 2 endometrial cancers (overall prevalence 0.11%) and 1 typical hyperplasia were detected among the healthy women.

These data provide additional evidence that tamoxifen can cause proliferative endometrial changes and warn of possible adverse effects of chemoprevention studies of tamoxifen to reduce breast cancer incidence in healthy women.

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Campari-Orange anaphylaxis due to carmine allergy

SIR—Life-threatening or lethal anaphylactic reactions to food containing potent allergens (eg, nuts) are well known. In addition, food additives, including dyes, can induce a wide range of adverse reactions in sensitive individuals. A prevalence of 0.03–0.2% is estimated for these reactions in western countries. However, only a few are caused by IgE-mediated mechanisms. We describe a severe anaphylactic reaction to carmine (E120), a red dye that gives Campari its characteristic colour. 5 cases of occupational asthma due to inhaled carmine,¹ 1 case of extrinsic allergic alveolitis secondary to inhaled carmine,² and 3 cases of allergic cheilitis due to lip salve containing carmine³ have been described. To our knowledge, this is the first documented case of an immediate-type reaction to carmine in which specific IgE antibodies to carmine could be shown.

At a garden party, a 34-year-old atopic woman had a severe anaphylactic reaction 15 minutes after drinking a Campari-Orange. After initial sneezing, rhinitis, and conjunctivitis, she developed generalised pruritus, followed by widespread urticaria, Quincke's oedema, dyspnoea, bronchospasm, chills, nausea, vomiting, and diarrhoea. She required emergency treatment (intravenous corticosteroids, inhaled β_2 -mimetics, and antihistamines) in the casualty department and was discharged home after several hours' observation. She had a history of allergic rhinoconjunctivitis and mild allergic bronchial asthma with positive skin-prick tests to seasonal and perennial inhalation allergens and animal dander. Skin-prick and intracutaneous tests as well as specific IgE antibodies were negative to common food allergens and to the food allergens ingested at the garden party (orange juice, pistachio nuts, salted pretzels). A skin-prick test done with a drop of Campari was strongly positive, suggesting that an ingredient of Campari was the cause of the reaction. By contrast, 10 healthy atopic controls were negative to Campari with the skin-prick test. So that we could characterise further the component to which the patient was reacting, the manufacturer (Campari SA, Milano, Italy) provided us with the red dye added in the manufacture of Campari and correctly declared on the bottle as E120. The patient displayed a strong positive skin-prick test (0.1% in water) to the dye, whereas 10 healthy atopic controls remained negative. A subsequent skin-prick test in the patient with commercially available carmine 0.5% (Brial Allergen GmbH, Greven, Germany) gave a similar, strongly positive result. We learned that sensitisation was probably due to the use of cosmetic products containing carmine (lipstick, mascara, eye shadow) and other makeup, since every time the patient had used these products before the initial severe anaphylactic reaction itching in the eyes and burning skin developed. Skin-prick and scratch tests with

these cosmetic products were also positive. A disk was prepared with carmine to detect serum IgE antibodies to carmine by radioallergosorbent test (RAST).⁴ Serological analysis initially was negative but revealed specific IgE to carmine (class 2 positive, 0.8 Pharmacia RAST unit) after a year during which the patient repeatedly suffered from minor allergic episodes due to undeclared red-dyed food, such as ice cream.

It is well known that after a generalised anaphylactic reaction, such as after hymenoptera stings, the RAST test, which measures circulating specific IgE antibodies, can temporarily be negative. Carmine (E120) is a naturally derived red pigment or dye that is extracted from cochineal. Cochineal is the dried, pulverised bodies of a female mealybug *Dactylopius coccus* (or *coccus cactus*) that lives on the prickly pear *Opuntia coccinellifera*. The brilliant red colour of carmine is due to carminic acid secreted into intracellular vesicles of the insects. Carmine is preferentially used for colouring beverages, food, medicines, and cosmetics. The cochineal mealybug is still cultivated in the Canary Islands, Algeria, Spain, Honduras, Peru, and Mexico. It requires about 70 000 insects to make 500 g of cochineal, which contains about 10% pure carminic acid.⁵

Our case highlights the importance of a detailed allergological assessment especially by means of skin-prick tests with the natural allergen or fresh food in cases of sudden anaphylactic reactions, because the causative agent can be diagnosed and fatal anaphylaxis can be avoided. Knowing the relevant allergen, patients can eliminate it from their diets. In addition, they can be provided with an emergency kit (adrenaline metered aerosol, 100 mg prednisolone, and 20 mg cetirizine) for use in case of dietary indiscretion.

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Evaluation of new treatment for primary biliary cirrhosis

SIR—In their May 28 commentary Goddard and Warnes discuss the difficulty in assessing hard endpoints such as survival in a chronic, slowly progressive disease such as primary biliary cirrhosis. In place of these endpoints, they suggest that surrogate markers, such as serum markers of fibrosis and dynamic liver function tests may be helpful. They go on to suggest that combination therapy of ursodeoxycholic acid (UDCA) with colchicine or methotrexate may be more efficacious. I disagree.

The effect of UDCA treatment in primary biliary cirrhosis on these surrogate markers has already been examined by several groups. Floreani and colleagues' study of 54 patients treated with UDCA for 2 years showed no improvement in serum hyaluronate and type III procollagen aminopropeptide, both serum markers of fibrosis.¹ This finding is in line with histological studies that failed to show any improvement in hepatic fibrosis. Primary biliary

cirrhosis patients on UDCA do not show substantial improvements in their dynamic liver function tests, such as aminopyrine breath test and galactose elimination capacity.^{2,3} However, such tests are poor markers of disease severity in cholestasis. In UDCA treatment in primary biliary cirrhosis, the greatest benefits are likely to be improvement in hepatic excretion and reduction in the retention of toxic bile acids. Jazrawi and colleagues⁴ examined the kinetics of hepatic bile acid handling in primary biliary cirrhosis before and after UDCA treatment and showed that UDCA improved hepatic bile acid excretion and reduced bile acid transit time through the liver. Their results suggest reduction in cholestasis.

Is the use of an agent such as colchicine or methotrexate in combination with UDCA likely to be useful? Preliminary reports from a large double-blind trial of UDCA used in conjunction with colchicine do not suggest any greatly increased benefit compared with UDCA alone.⁵ The toxic effects of methotrexate make it unattractive as a long-term agent for primary biliary cirrhosis.

UDCA is a safe well-tolerated drug that improves liver function tests and reduces the cholestasis in primary biliary cirrhosis. Whether this translates into long-term clinical benefit has not been adequately examined. Existing trials are not designed to assess survival. Although not a proven cure for primary biliary cirrhosis, it is at present the best treatment we have, short of liver transplantation.

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SIR—Goddard and Warnes correctly say that placebo-controlled trials of UDCA have not shown survival benefit in the first 2 years of treatment. However, there does seem to be some slowing of progression of disease, and the French-Canadian study showed a clear reduction in the development of liver failure and the requirement for transplantation between 2 and 4 years.

A local 7-year follow-up study of UDCA treatment has shown a small survival benefit compared with historical controls, but this is only apparent after the first 2 years. Overall survival of patients with primary biliary cirrhosis remains much worse than that in the general population; but there have been no deaths, liver failure, or transplantations in 13 patients with stage I disease for up to 7 years, with a median treatment period of 2 years. There is rather better evidence to justify the use of UDCA in primary biliary cirrhosis than any other drug, and this drug is certainly less toxic than most of the proposed alternatives.

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