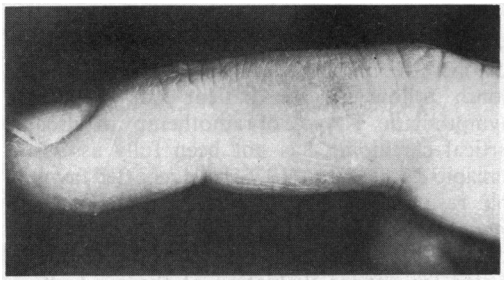

Figure 1. Eczema on radial aspect of middle finger

Patch tests with his own Virginia cigarette tobacco leaf, and with four other tobaccos from Virginia and Europe, were all positive. Leaves of *Nicotiana tabacum* (the wild plant from which tobacco cultivars are derived) were dried and extracted with ether for 24 hours. A patch test to the ether-extracted material was strongly positive in the patient and negative in 20 control subjects. Further attempts to identify the precise allergen by thin-layer chromatography have so far proved unsuccessful.

Since the patient has stopped smoking, his hand eczema has resolved although it recurred slightly at the original sites during patch testing. He has also noted facial burning and nasal pruritus, which are maximal six hours after exposure to a smoke-filled atmosphere and are again associated with a flare of his hand dermatitis.

Discussion

Irritant reactions from tobacco are not uncommon in factory workers and may present as erythema, urticaria or irritant contact dermatitis. Causes include mechanical trauma from tobacco leaf and irritant reactions from pastes used on cigars and boxes, processing and flavouring agents, and the primary irritancy of tobacco itself, due to alkaloids such as nicotine (Schwartz *et al.* 1957, Rycroft 1980). There are few well-documented cases of allergic contact dermatitis from tobacco in factory workers. Karrenberg (1928) and Stauffer (1929) described individual patients with case histories strongly suggestive of allergic contact dermatitis. Vero & Genovese (1941) described 3 cases of allergic contact dermatitis amongst cigar makers in one factory. Out of over a thousand cases of hand eczema seen in a large cigar factory, only three had proven allergic contact dermatitis to tobacco leaf (Samitz *et al.* 1949). Since the manufacture of cigarettes is more highly automated than that of cigars, skin reactions in cigarette factory employees are less common (Rycroft *et al.* 1981).

Allergic contact dermatitis to tobacco smoke residues in a smoker has been described on two previous occasions (Weary & Wood 1969, Neild 1981). Positive patch tests were obtained in both patients using the smoked cigarette filter. It is probable that our patient was sensitized by direct contact with tobacco leaf in his cigarette rather than to a volatile component of tobacco or to a product of combustion. We have so far been unable to determine the precise allergen, although previous studies suggest that it is unlikely to be nicotine itself (Silvette *et al.* 1957).

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Juvenile rheumatoid arthritis and milk allergy[1]

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Rheumatoid arthritis in association with food allergy has been reported in adults (Parke & Hughes 1981, Williams 1981, Little *et al.* 1983), but juvenile rheumatoid arthritis (JRA) associated with milk allergy has not been noted. The 14-year-old patient reported here had a 6-year history compatible with a diagnosis of JRA and recovered after the elimination of all cow's milk protein from her diet. Dietary provocation on 4 occasions (2 inadvertent and 2 planned) reproduced the signs and symptoms of her illness. She was lactase-deficient and there was a family history of milk allergy. An association between lactase

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deficiency and milk allergy has been noted in children (Matsumara *et al.* 1971), as well as among adults with asthma or migraine (Ratner *et al.* 1983). Enzyme-linked immunosorbent assay (ELISA) demonstrated specific milk antibodies in both the IgG and IgM fractions of the patient's serum.

Case report

A Jewish girl of European ancestry, born in Israel, was first admitted to hospital at the age of 8 years because of unexplained fever of 2 weeks' duration with evening spikes to 39°C, a maculopapular, symmetrical erythematous rash on the face and trunk, and pain and swelling of the wrist with limitation of motion. The patient's parents were healthy; her birth followed a normal full-term pregnancy and normal delivery, and an only sister was healthy. No family history of atopy was given. Her general condition was good, and no hepatosplenomegaly was noted. WBC was 18 400, Hb 11.0 g, ESR 60 mm in the first hour, and urinalysis normal. Serum electrolytes, lipids and bilirubin, uric acid, creatinine and fibrinogen were all normal. Tests for rheumatoid factor, lupus erythematous cells and antinuclear antibody were all negative. ECG, chest X-ray and an ophthalmic examination were all normal. Serum electrophoresis showed an elevation of alpha-2-globulin. The IgM was 204 mg/dl.

With continued high fever, rash and pain in the neck, wrist and elbow, amidopyrine (0.3 g × 4) was started with good results. The patient was discharged 7 days later in good general condition, with minimal joint pains, afebrile, and with a diagnosis of seronegative JRA.

During the following 6 years she was admitted 9 times to hospital with a diagnosis of 'exacerbation of JRA' (Table 1). Each admission was for joint pains and swelling, fever and rash, with the exception of one admission for severe anaemia (7.5 g Hb). She was always seronegative and the joint involvement varied, including the small joints of the hands and feet, wrists, hips and knees. She was treated with amidopyrine, aspirin, indomethacin, dexamethasone, penicillamine and ACTH injections. In addition to treatment at a community hospital, she had been seen in consultation at two university hospitals and a diagnosis of JRA had been made each time. Three years prior to her present illness she had one asymptomatic period of 3 months, which coincided with a trial of a vegetarian diet; this was discontinued by her physician because of anaemia. During her fourth admission, 5 years ago, an elevated IgM (410 mg/dl) was noted, which remained elevated.

The patient's intellectual development was normal, although she had a high absentee rate (30%) from school because of illness, and was frequently taken to school by automobile because of joint pains and fatigue. Menarche had occurred 2 years prior to the present illness, at age 12.

At the age of 14 the patient presented at the emergency room with fever (39°C), pallor, swollen

Table 1. Summary of main clinical events

Age	Days of fever over 38°C	Manifestations	Days in hospital	Treatment
8 yr 6 mo	19	Rash, arthritis, leukocytosis	8	Amidopyrine
8 yr 7 mo	14	Rash, arthritis	9	Aspirin, penicillin
8 yr 8 mo	8	Rash, joint pains	13	Aspirin
10 yr	9	Arthritis	2	Aspirin
10 yr 5 mo	10	Rash, arthritis, limping	6	Aspirin
10 yr 8 mo	17	Rash, arthritis	22	Aspirin discontinued
	4	Anaemia		Indomethacin (unsuccessful), dexamethasone
10 yr 9 mo	None	Urinary tract infection	7	Nitrofurantoin (Furadantin)
		Arthralgia		Aspirin
11 yr		Symptom-free	None	Vegetarian diet
12 yr	10	Arthritis, arthralgia	2	Aspirin, ACTH
13 yr	2½ months intermittent fever	Rash, arthralgia, weight loss, arthritis	6	Aspirin, indomethacin, penicillamine
14 yr	5	Arthralgia, arthritis fatigue, pallor		Cow's milk protein-free diet and remission
14 yr 6 mo	Asymptomatic	Challenge with dairy foods caused fever, arthralgia, arthritis		
15 yr	Asymptomatic	Challenge with dairy foods caused arthralgia and fatigue and the patient refused to continue		

wrist, and swelling and tenderness of the proximal interphalangeal joints of both hands. She complained of fatigue and pain in the knees. The chest X-ray and ECG were normal; WBC was 12 000, Hb 11.0 g. The patient had been taking aspirin and penicillamine for the past $1\frac{1}{2}$ years. On several recent occasions she had received injections of ACTH because of fever. The patient's diet was based primarily on dairy foods since she had an aversion to meat.

The past history of JRA was noted, and a family history revealed that a baby brother, age 9 months, had been given a soya formula instead of milk because of milk intolerance, expressed as intractable diarrhoea.

The patient was started on a cow's milk protein-free diet and no change was made in her medications. The serum was negative for rheumatoid factor and the IgM was 400 mg/dl. A lactose tolerance test showed a flat absorption curve and the patient had marked diarrhoea and cramps during and after the test.

Three days after starting the diet the fever disappeared and after one week the joint swelling subsided. The joint pains disappeared completely after 3 weeks and the patient gradually discontinued the penicillamine and aspirin. After 2 months Hb was 13.0 g and the patient was asymptomatic.

The patient went on vacation and returned home after 2 weeks with fever (38°C), joint pains and a swollen wrist. During her vacation she had eaten 2 English candy bars containing milk chocolate (Kit-Kat) daily. With the reinstitution of a strictly milk-free diet she became asymptomatic. After another 2 asymptomatic months the patient was left with her grandmother for 2 weeks and returned home with fever and joint pains. She had eaten cereal and milk every morning. Following this second, unplanned provocation she was asymptomatic for 6 months with a milk-free diet, and took no medication. Then, at our initiative, she returned to her former diet which contained dairy products at least twice a day. Twenty-three days after the dietary change she had fever, joint pains and a swollen wrist. The dairy food was stopped and the patient became asymptomatic after 10 days. Thirteen months after this dietary provocation she remained in good health and participated in sports and aerobic dancing. The change in her general health was dramatic and the IgM was 326 mg/dl.

Eighteen months after the start of the diet free of dairy products the IgM was 240 mg/dl and it was decided to repeat the dietary challenge by returning to dairy foods at least twice a day. Ten days following the change in diet the patient complained of arthralgias and fatigue and refused to continue eating dairy food. Serum was tested for antibodies using the ELISA technique (Voller *et al.* 1980) and antibodies to milk were found in the IgG and IgM fractions.

Discussion

For 6 years the patient suffered intermittent high fever, rash, anaemia, leukocytosis, arthritis and arthralgia. The diagnosis was polyarticular, seronegative JRA with a systemic onset (Schaller & Wedgwood 1983). The prognosis is variable and some patients have a spontaneous remission. The 4 positive provocation tests indicate a connection between the milk-free diet and the clinical remissions in our patient. Except for provocative trials, there is no specific test for milk allergy at present.

The patient's persistent anaemia is consistent with JRA, although the one admission complicated with severe anaemia may have been secondary to medication, particularly aspirin which can cause gastrointestinal bleeding. Milk allergy is also known to result in gastrointestinal bleeding. Although the patient was lactase-deficient, she had no prominent gastrointestinal complaints except irregular bowel habits, which became regular with the milk-free diet. We have used lactase deficiency as a useful marker for milk allergy in adults (Ratner *et al.* 1983).

Cow's milk allergy is known to cause multiple system involvement (Bahna & Heiner 1980) and joint swelling in food allergy has been described previously (Crook 1975). In our case, the possibility of milk allergy was reinforced by the family history of milk intolerance in a baby brother. This history of course did not exist at the time of the original admission and during most of the course of the patient's illness. It has been estimated that if one child is allergic to milk, a sibling has a 1 in 3 chance of also being allergic (Gerrard 1974).

The case of rheumatoid arthritis reported by Parke & Hughes (1981) was seronegative and allergic to milk. It took their patient 3 weeks to respond to an elimination diet, a similar reaction time to that observed in our patient. This slow response to dietary elimination is not typical of IgE-mediated food allergies (Goldman & Heiner 1977). None of the 7 cases of food sensitivity and arthritis reported by Little *et al.* (1983) was sensitive to milk, and 6 were seropositive; furthermore, their reaction time following challenge was measured in hours, indicating that both our case and that of Parke & Hughes (1981) belong in a different category. The 2 planned dietary challenges were not blind since the amount of milk protein that can be given in a concealed form for any length of time is limited. However, the 2 unplanned, inadvertent dietary challenges would be additional evidence of milk allergy.

Any of the immunoglobulins can be elevated in JRA, and our patient had a persistently elevated IgM during most of her illness. Our data show an elevated IgM in many patients allergic to milk (Ratner *et al.* 1984). We have demonstrated specific antibodies to beta-lactoglobulin. In many patients allergic to milk, 2 or more of the proteins (i.e. casein, alpha-lactoalbumin, beta-lactoglobulin and bovine serum albumin, among others) are allergenic (Goldman & Heiner 1977). Since milk is polyantigenic, we use diluted skimmed milk as the screening 'antigen' in the ELISA technique. The demonstration of milk antibodies in both IgG and IgM fractions in our patient would reinforce the diagnosis of milk allergy. Of course, the ultimate test of milk allergy – as with any food allergy – lies in the clinical response to an elimination diet and a subsequent positive challenge.

Milk allergy has many clinical presentations, and in older children and adults is probably not IgE mediated (Deamer *et al.* 1979, Lessof *et al.* 1980). In our experience RAST, which is based on IgE reactions, has been unreliable in diagnosing milk allergy. IgM antibodies have been shown in infants allergic to milk (Bahna & Heiner 1980), and although no data are available for adults, the elevated IgM in our patient may be significant with respect to milk allergy. After a prolonged asymptomatic period (18 months) the IgM declined from 400 to 325 and the last determination was 240 mg/dl (within normal limits). The patient did not suffer from any disease, such as liver dysfunction or parasitosis, which would elevate the IgM. High IgM levels have been reported among children suffering from the nephrotic syndrome, another disease of unknown aetiology with associated atopic manifestations (Meadow *et al.* 1981, Giangiancomo *et al.* 1975). The work done by Peskett *et al.* (1981), showing no difference in IgE levels among patients with JRA as compared to normals, suggests that JRA associated with milk allergy may be mediated by heavier immunoglobulins (IgM, IgG) such as in our case.

In view of the excellent clinical result in this case, we suggest that other cases of JRA which are seronegative, lactase-deficient and have a family history of milk allergy, be given a 3-week trial of a diet completely free of cow's milk protein.

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Amenorrhoea, low body weight and Turner's syndrome[1]

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A case is reported with the unusual association of concurrent anorexia nervosa and primary amenorrhoea in association with Turner's syndrome mosaic. The patient possessed no abnormal somatic features despite a relatively high percentage of XO cells.

Case report

SC presented with primary amenorrhoea at the age of 19. Turner's syndrome mosaic was diagnosed from a chromatin-positive buccal smear and lymphocyte karyotype analysis showed 40% of the cells to be XO with 60% XX.

Laparoscopy showed a small uterus, small ovaries two-thirds normal size, but with follicles

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