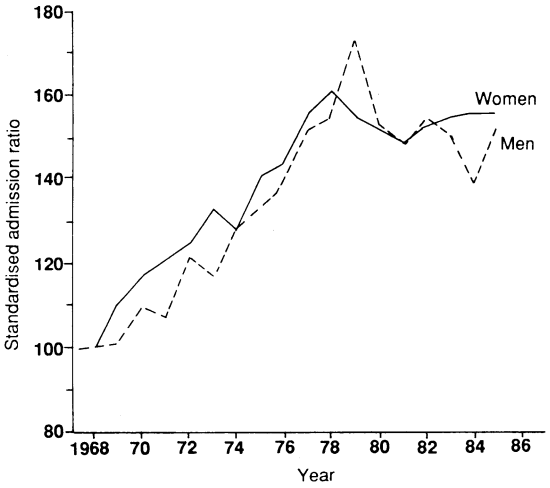
been proposed, including changes in diet, sunlight, reproductive and gynaecological factors, use of oestrogens and sedatives, and increased life expectancy.



Ratio of observed to expected numbers of patients aged over 45 admitted to hospital with hip fracture in England and Wales, 1968-85. (Data obtained from Hospital In-Patient Enquiry and standardised for age on basis of age specific rates in 1968)

All these, however, need to account for the parallel changes in men and women and the worldwide increase in incidence. Although several factors may have operated the most likely single factor is change in activity. Physical activity is related to both bone density and the risk of the elderly falling. Disuse is strongly related to rapid bone loss in most age groups. Moreover, musculoskeletal strength related to activity is probably the most important factor influencing hip fractures in the over 75s, among whom most such fractures occur.[4]

The only major study showing a levelling off of the incidence of hip fracture showed a fall in the rate of increase in women in Rochester, Minnesota, in the mid-1950s.[5] Rates in men continued to rise, and the authors were unable to explain these findings on the basis of environmental factors. Possible reasons for the changes in the United Kingdom remain speculative. In most developed countries since the second world war work has become less physically arduous and people walk less. Increases in social services, transport, and retirement homes may have reduced physical activity in the elderly. The age at which activity has a maximal beneficial effect is uncertain. Our data might be explained by activity having fallen dramatically from the 1950s to the 1970s and then stabilised either in middle life or in old age; alternatively, there may be a threshold beyond which a further reduction in activity has no added effect on skeletal state. Further work is needed to confirm these findings and to understand the mechanisms entailed.

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Reversible cardiomyopathy induced by interferon

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Clinical trials with interferon have been carried out principally with patients with advanced non-treatable cancer. The best results have been achieved in patients with hairy cell leukaemia.[1] Side effects are generally mild, are usually dose dependent, and disappear after treatment is stopped.

A case of cardiomyopathy due to interferon and confirmed at necropsy was reported recently.[2] We report a case of severe cardiomyopathy induced by interferon in a patient who had a complete clinical recovery after interferon treatment was withdrawn.

Case report

A 74 year old man with no history of heart disease was admitted to hospital with congestive heart failure. Eight months earlier hairy cell leukaemia had been diagnosed. Splenectomy was recommended, but the patient preferred conservative treatment and was given daily injections of 3×10^6 units of recombinant interferon alfa 2.

After seven months of treatment he was readmitted with severe congestive heart failure. Electrocardiography showed T wave flattening in leads V4-V6. Radiography showed cardiomegaly with pulmonary congestion and large pleural effusions shown to be transudate. Echocardiography showed severe global hypokinesia with mild aortic stenosis, and radionuclide imaging showed a left ventricular ejection fraction of 18% with severe diffuse hypokinesis. The patient received frusemide with spironolactone and gradually improved. Treatment with diuretics and interferon was continued. Three months later he was readmitted with progressive dyspnoea and radiological signs of pulmonary congestion. Electrocardiography showed T wave changes in V4-V6, and radionuclide angiography showed severe diffuse hypokinesia with an ejection fraction in the left ventricle of 13% and 18% in the right ventricle. He was given digoxin, frusemide, and spironolactone and gradually improved, but repeated radionuclide angiography and echocardiography showed no changes in cardiac function. Because we found no other obvious causes of myocardial failure we thought that interferon might be playing a part, and treatment was stopped. Six weeks later the patient's condition noticeably improved. A further radionuclide angiogram showed an ejection fraction of 42% in the left ventricle and 50% in the right ventricle. Diuretic treatment was tapered off. Three months later he had no symptoms and was taking frusemide 40 mg every second day. Radionuclide angiography showed normal wall motion with an ejection fraction of 50% on the left and 62% on the right. Echocardiography showed nearly normal wall motion.

Comment

It was first suggested that interferon might be cardiotoxic in humans after four deaths from myocardial infarction in patients treated with interferon.[3] In 11 reports on 35 patients the effect of interferon consisted primarily of arrhythmias, though atrioventricular block and sudden death were also reported. In 1988 Cohen *et al* reported on a patient with interferon related cardiomyopathy who developed cardiac symptoms after one week of treatment with interferon.[2] Heart failure in our patient occurred after six months of treatment and was clearly unrelated to coronary artery disease. Myocarditis was excluded clinically and by negative viral titres. His heart failure resolved completely with left ventricular ejection fraction improving to over 50% two months after interferon treatment was stopped.

The mechanism of injury in patients with interferon induced cardiotoxicity is not known. Together, interferon and cardiac tissue may stimulate an autoimmune or inflammatory reaction, or the increased demand for oxygen caused by fever, chills, and tachycardia may precipitate infarction in a compromised myocardium, or interferon may induce coronary spasm. Since the effect of interferon was reversible in our patient we suggest that cardiomyopathy was induced through impaired myocyte metabolism rather than through histological damage.

Our patient's dramatic improvement could not have been due to drug treatment alone because diuretics do not greatly improve ventricular function, and most of his drugs had been stopped. It seems, therefore, that in the absence of pre-existing heart disease withdrawing interferon leads to cardiac function returning to normal.

A report has now appeared on reversible cardiac dysfunction associated with interferon treatment in a patient with AIDS.[4] The potential cardiotoxicity of interferon was attributed to a synergistic interaction with HIV infection. Our case suggests that other mechanisms are responsible for the cardiotoxic effect of interferon.

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Falciparum malaria resistant to quinine and pyrimethamine-sulfadoxine successfully treated with mefloquine

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Falciparum malaria has become increasingly resistant to chloroquine. It must be treated with quinine (when this is available), which can be followed by a single dose of pyrimethamine-sulfadoxine (Fansidar). This three drug regimen is usually curative,[1] but we have recently observed an increasing number of recrudescences of disease.

Case reports

During the 12 months September 1988 to August 1989, 229 patients with falciparum malaria were seen at this hospital. Five were not cured by treatment with quinine followed by one dose of pyrimethamine-sulfadoxine (table). Four of these patients received treatment in hospital; one (case 4) took her last few days' treatment with quinine and the pyrimethamine-sulfadoxine at home. Blood films obtained at the end of the regimen were negative for parasites in cases 1, 2, 4, and 5; in case 3 the film showed scanty trophozoites on the day of discharge. The patients stayed in the United Kingdom throughout the study, and none had any medical condition that might impair the response to treatment.

Recrudescences occurred 17-77 days after the regimen was started; each blood film was examined by several experienced observers to confirm the finding of parasites. All patients subsequently responded to mefloquine or quinine followed by mefloquine. One (case 2) developed a self limiting anxiety state 48 hours after taking mefloquine.

Details of five patients who developed recrudescence of falciparum malaria after treatment with quinine and pyrimethamine-sulfadoxine (Fansidar)

Case No	Ethnic origin	Sex	Age (years)	Country visited	Quinine-Fansidar regimen*			
					Dose of quinine (mg)	Duration of quinine (days)	Time to diagnosis of recrudescence (days)	Final treatment†
1	African	F	32	Ghana	600 Thrice daily	7	17	Quinine, mefloquine
2	White	M	24	Zimbabwe	600 Twice daily	5	46	Mefloquine
3	White	M	24	Ghana	600 Thrice daily	4	34	Quinine, mefloquine
4	African	F	3	Nigeria	125 Twice daily	7	19	
					125 Twice daily	7	77	Mefloquine
5	Burmese	M	50	Burma	600 Thrice daily	10	22	Mefloquine

*A course of quinine was given orally (except in cases 2 and 4, in which the first two and first four doses, respectively, were given intravenously) and was followed by three tablets (total 75 mg pyrimethamine, 1·5 g sulfadoxine) of Fansidar (except in case 4, in which only one tablet was given).
†Mefloquine 750 mg was given on two occasions 12 hours apart (except in case 4, in which 250 mg was given twice).

Comment

The development of resistance to a regimen comprising quinine and pyrimethamine-sulfadoxine is worrying. So far this resistance has presented as an initial clearance of the parasitaemia and clinical resolution followed by relapse and has been described in Thailand and east Africa.[1,2] Three of the five patients reported on here contracted their disease in west Africa. We believe that these are the first cases of malaria resistant to quinine and pyrimethamine-sulfadoxine from that region to be described.

In cases of malaria resistant to quinine alternative regimens include either quinine in combination with tetracycline or one of several new drugs such as halofantrine or mefloquine; mefloquine is soon to be marketed in the United Kingdom. These new drugs may be used alone or after a course of quinine. Mefloquine alone cures about 98% of patients with falciparum malaria,[3] but in our experience patients with severe infection should receive quinine before mefloquine. Quinine lowers the parasitaemia and leads to improved tolerance of mefloquine. To reduce toxicity at least 12 hours must elapse between the last dose of quinine and the first dose of mefloquine.[4] Mefloquine may cause nausea and malaise, and some reports suggest that neuropsychiatric complications occur in 1-2% of patients treated.[3,5] Thus patients should be kept in hospital during treatment.

Physicians should be aware that falciparum malaria is sometimes resistant to a regimen comprising quinine and pyrimethamine-sulfadoxine. As this is, however, rare we recommend that the regimen is used as first line treatment.

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