All isolates resistant to trimethoprim before 1980 were also resistant to sulphonamide. Since then we have isolated an increasing number of strains resistant to trimethoprim and sensitive to sulphonamide; six during 1980, 11 during 1981, and 30 during 1982. Most (27) were isolated from general practice.

Comment

It is essential, when considering the prevalence of resistance, to compare like with like; only normally susceptible Gram negative urinary pathogens were included in this survey, the laboratory techniques were unchanged, the same period was studied each year, and there were no outbreaks of hospital cross infection during the study periods. Inevitably such figures, especially those for hospital patients, must include more than one isolation from some patients, but this factor is not likely to vary from year to year.

Percentage of normally susceptible Gram negative urinary pathogens resistant to trimethoprim. Figures in parentheses are numbers of isolates tested

	1978	1979	1980	1981	1982
Hospital (inpatient and outpatient)	NA	NA	NA	19 (326)	24 (381)
General practice	NA	NA	NA	7 (521)	15 (507)
Total	9 (709)	12 (821)	13 (794)	12 (847)	19 (888)

NA = Figure not available: hospital and general practice records analysed separately only in 1981 and 1982.

It appears that a plateau of resistance had been reached by 1979 (before trimethoprim was available alone). Our figure of 12% is in broad agreement with those from other centres in Great Britain at that time,^{2,3} and suggests that the routine laboratory method used provides reasonably accurate results. In any case the method has not changed, and therefore the change in the findings is likely to be a true one.

One must wonder whether this sharp rise in resistance is related to the increasing use of trimethoprim alone. As a result of our experience with the emergence of *Staphylococcus epidermidis* infection in patients with catheters who were treated with trimethoprim⁴ we have encouraged the use of co-trimoxazole in hospital. (Figures from this hospital pharmacy show that the ratio of the use of co-trimoxazole to trimethoprim is 16:1.) Trimethoprim has been widely promoted in general practice, however, where the level of resistance has more than doubled during the past year. Clearly in those hospitals which serve a local population there must be some overlap between hospital and general practice patients, and the rise in hospital resistance, after a plateau for three years, may be related to the use of trimethoprim in general practice. Furthermore, most of the increasing number of isolates resistant to trimethoprim but sensitive to sulphonamide came from general practice.

Lacey has recently reported no change in the level of resistance of *E coli* to trimethoprim in the hospitals of the King's Lynn Health District, where co-trimoxazole was completely replaced by trimethoprim in 1980.⁵ His study concluded in January 1982 and did not include Gram negative pathogens other than *E coli*. His figures are therefore not comparable with the figures reported here.

Co-trimoxazole has been a highly effective agent for treatment of urinary infection for the past 14 years; if the use of trimethoprim alone is now resulting in increased resistance it is important that this should be recognised.

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Hypothermia during chemotherapy for Hodgkin's disease

Fever is common in advanced Hodgkin's disease. We describe three patients with advanced Hodgkin's disease and fever who developed hypothermia during chemotherapy.

Case reports

Case 1—A 75 year old woman presented with stage IVB mixed cellularity Hodgkin's disease affecting the liver and a fever of 38°C. Bacteriological investigations gave negative results and chemotherapy was started with 10 mg vinblastine intravenously on day 1 followed by 14 days of chlorambucil 10 mg daily, prednisolone 40 mg daily, and procarbazine 50 mg thrice daily. On day 2 her temperature fell from 38°C to 35°C and on day 3 her rectal temperature was 34°C and remained low for 10 days (figure). Further chemotherapy with vinblastine and prednisolone was not associated with hypothermia.

Case 2—A 36 year old man presented with stage IVB mixed cellularity Hodgkin's disease in relapse. He had received outpatient chemotherapy with the same regimen as case 1, but relapsed one month after completing treatment, with sustained fever, lymphadenopathy, and liver enlargement. Chemotherapy was restarted with intravenous infusion of 30 mg doxorubicin, 10 mg bleomycin, 8 mg vinblastine, and methotrexate 250 mg/m² on day 1, with prednisolone 50 mg daily. His temperature, 38.5°C on admission, fell to 34°C and remained low for four days (figure). Unfortunately, six weeks after chemotherapy, he developed chickenpox and died with disseminated varicella infection. Necropsy showed hepatic Hodgkin's disease.

Case 3—A 34 year old woman presented with nodular sclerosing Hodgkin's disease in relapse. She had first been seen 15 months previously with clinical stage IA disease and had received mantle radiotherapy. Eight months later she relapsed with para-aortic node enlargement, which was treated with radiotherapy. At second relapse she had widespread disease affecting bone marrow, liver, and spleen. Chemotherapy was started using the regimen described for case 1. Within 24 hours her temperature fell from 38°C to 35°C and remained low for a week (figure). One week later she developed a right

Effect of chemotherapy on sublingual temperature of three patients with Hodgkin's disease.

hemiplegia and became drowsy. Computed tomography showed a contrast-enhancing lesion deep in the left hemisphere suggestive of intracerebral Hodgkin's disease. Radiotherapy produced no improvement and she died one month later.

Comment

Spontaneous hypothermia in Hodgkin's disease is rare.¹ Some patients with Hodgkin's disease develop hypothermia after administration of salicylates,² but none of our patients received these. There is one report of hypothermia in Hodgkin's disease after chemotherapy with mustine and vinblastine,³ but the cytotoxics used here differed slightly and only vinblastine and prednisolone were common to all patients: hypothermia is not a recognised side effect of any of these drugs. Case 3 was later found to have intracerebral Hodgkin's disease, which could have affected hypothalamic function, but she was otherwise similar to the other patients.

The cause of fever in Hodgkin's disease in the absence of infection is unknown. Experiments have shown that a substance, "endogenous pyrogen," is produced by Kupffer's cells in rabbits in response to endotoxin. This is also produced in vitro by lymphoid tissue from

patients with Hodgkin's disease.⁴ Kupffer's cells may be one source of endogenous pyrogen in man and it is interesting that sustained fever is more common in patients with hepatic Hodgkin's disease. All our patients had hepatic Hodgkin's disease and fever of several days' duration. Human leucocytes produce endogenous pyrogen *in vitro* when exposed to endotoxin: this response is blocked by the cytotoxic agent actinomycin C.⁵ Production of endogenous pyrogen in our patients may have been inhibited by the cytotoxics, the homeostatic mechanisms controlling temperature causing prolonged rebound hypothermia.

Though we have no certain explanation for the abrupt onset of hypothermia, these observations raise several points. How often does hypothermia complicate cytotoxic treatment? Hypothermia often escapes diagnosis because low reading thermometers are not used. As it may be a serious complication in the old and weak, patients with sustained fever during cytotoxic treatment should be carefully observed.

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Cycling in patients with chronic airflow limitation

Patients with chronic airflow limitation have reduced exercise tolerance when walking due to breathlessness.¹ Conventional treatment—for example, with β_2 agonists or portable oxygen—leads to only modest improvement in exercise tolerance (roughly 10%).^{2,3} While walking is a relatively efficient means of propulsion, cycling is considerably better.⁴ We have investigated cycling in patients with severe chronic airflow limitation.

Present study

We studied seven patients (five men; mean age $61.6 \pm \text{SD } 11.0$ years) with severe chronic airflow limitation (forced expiratory volume in one second 0.80 ± 0.24 l; forced vital capacity 2.21 ± 0.82 l). All were non-smokers and were being maintained with inhaled bronchodilators, which were withdrawn on study days. Variables studied were breathlessness and exercise tolerance, and ventilation and oxygen consumption.

Patients cycled around a rectangular tarmac track (100 × 80 m; Wapping Sports Centre) using three cycles—a bicycle (Dawes Ladybird: five gears, 15 kg), an NHS tricycle (Pashley Ltd: three gears, 25 kg), and a lightweight tricycle (K Rogers Ltd: 10 gears, 15 kg). Walking tests were performed across the width of the track. Patients were instructed to go as far as they could in six minutes on each of the three cycles and during a six minute walk. The distance travelled and breathlessness induced (10 cm visual analogue scale; range not breathless to extremely breathless) were noted. Tests were performed in random order, with an hour's rest between tests.

In a separate study we compared ventilation, oxygen consumption, and distance travelled in the seven patients when (a) walking for six minutes at their own reduced pace and (b) tricycling for six minutes at the normal walking pace of AAW. Patients wore a close fitting facemask, and total ventilation and oxygen consumption were measured for each six minute period (Oxylog; P K Morgan Ltd).

RESULTS

Patients adapted quickly to the cycles, though several (especially those with bicycle experience) had initial difficulty cornering on the tricycle.

Exercise tolerance and breathlessness—Patients cycled between three and four times further than they walked in six minutes (289 ± 75 m). Of the three cycles, the greatest distances were achieved with the lightweight tricycle (1147 ± 197 m) and the bicycle (1055 ± 278 m): distances covered with these machines were significantly greater than with the NHS tricycle (833 ± 192 m) ($p < 0.05$). Patients were significantly less breathless after the lightweight tricycle (visual analogue scale 6.8 ± 2.2) than after the NHS tricycle (8.1 ± 0.8), the bicycle (7.6 ± 2.8), and walking (7.9 ± 2.7), despite having travelled the greatest distance ($p < 0.05$).

Ventilation and oxygen consumption—When patients tricycled at the walking pace of AAW they travelled at twice their own walking speed (4.47 ± 0.79 km/h v 2.26 ± 0.73 km/h; $p < 0.001$). This was achieved at lower ventilation (20.5 ± 5.2 l/min v 22.3 ± 6.5 l/min) and with a lower oxygen consumption (577 ± 183 ml/min v 662 ± 182 ml/min); hence the efficiency of tricycling was more than twice that of walking.

Comment

We tested three readily available cycles. The bicycle was chosen for lightness and ease of mounting. The NHS tricycle is designed for use by mentally and physically disabled adults. It is heavy and not ideal for use with breathless patients but was tested because it is prescribable. The lightweight tricycle was modified from a tricycle designed for racing by fitting standard handlebars. It is light, stable, and has a low rolling resistance.

Patients with severe airflow limitation increased the distance travelled in six minutes up to fourfold by cycling. Patients travelled furthest and were least breathless on the lightweight tricycle. Tricycling was more than twice as efficient as walking in terms of oxygen consumption, and also patients could adopt a good breathing posture on the tricycle by fixing the upper thorax and may be able to sustain a greater ventilation with less discomfort. The tricycle is stable at slow speeds and if a patient became breathless he can stop without dismounting, being in an ideal posture to recover. Shopping and supplemental oxygen can be carried with minimal disadvantage.

We believe that lightweight tricycles might be useful in rehabilitating patients with chronic airflow limitation. They are relatively cheap to buy (£250) and maintain and are a good form of exercise. All of the patients were severely disabled by breathlessness when walking and were amazed to have covered between half a mile and one mile (0.8 and 1.6 km) in six minutes when cycling. The improvement in distance travelled on the tricycle compared with walking (297%) was almost 30 times greater than achieved with conventional medical treatment^{2,3} (table).

Mean percentage improvements in distances travelled in six minutes' walking and using the three cycles. (Seven patients with severe chronic airflow limitation)

	Salbutamol	Portable oxygen	Tricycle
Improvement in 6 minute distance (%)	10	12	297

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