the first period alone. If the response for the second period was taken to be the difference between the response at the end of the second period and the initial value then no evidence for a treatment period interaction was found, but there is no reason to prefer this approach to the one used here. In the absence of a "washout" period between the first and second treatment periods, the best method of analysis is bound to be uncertain but that used here is at least as plausible as any other.[2]

This re-analysis shows that the trial of Fisher et al provides no firm evidence for the efficacy of homoeopathic treatment of fibrositis.

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Blackfoot disease

SIR,—Blackfoot disease is a unique peripheral artery disease in an endemic area of chronic arsenicism on the south-west coast of Taiwan. The aetiology seems to be multifactorial, involving a familial tendency, undernourishment, and drinking artesian well water, besides arsenic.[1] Dr Lu (July 14, p 115) implicated humic acid in well water as the main cause of the disease.

Blackfoot disease was first observed in 1954 after residents in the endemic area had been using high-arsenic artesian well water for more than 35 years. The induction period of the disease has been estimated as 20–30 years.[2] The disease is basically chronic and progressive, though clinical progression from erythematous swelling to ulceration to gangrene may be acute.[2]

Pathologically, blackfoot disease is compatible with arteriosclerosis obliterans and thromboangiitis obliterans, but the fundamental vascular change is a severe arteriosclerosis, leading to pure arteriosclerotic gangrene of the extremities in 69% of cases; the thromboangiitis obliterans is superimposed upon this arteriosclerosis.[3]

There have been two animal experiments with high-arsenic artesian well water from the endemic area. Intramuscular injection of 60-fold concentrated artesian well water induced gangrenous changes in rats.[4] In the same study, injection of pure sodium hydroxide (pH 12·0) solution had the same effect. In Lu's experiment, similar symptoms resulted from an intraperitoneal injection of dissolved crystallised fluorescent compounds in mice. However, neither study reported changes compatible with what is found in blackfoot disease—including significant arteriosclerotic changes with severe atheroma, calcification, bone formation, hyalinisation, and increased elastic fibres in the intimal coat.[3] Since occlusion of peripheral arteries, by acute thrombosis or by chronic ateriosclerosis, may result in similar symptoms, any animal study of the cause of blackfoot disease should be based on pathological changes instead of symptomatic similarities alone. Sporadic instances of symptoms similar to those of blackfoot disease in non-endemic areas are therefore unsurprising, especially since such symptoms are frequent in patients with prevalent disorders such as diabetes and atherosclerosis.

Humic acid seems to induce acute thrombosis via an action on blood coagulation. Whether it causes arteriosclerotic change remains to be seen. The intake (after ingestion or injection), gastrointestinal or peritoneal absorption, tissue distribution, metabolism, and excretion of fluorescent compounds deserve further examination.

Arsenic was associated with blackfoot disease in a dose-response epidemiological study on over 40 000 people;[5] and mortality from cardiovascular disease was significantly associated with ingested arsenic levels in the endemic area[6] (as it was with inhaled arsenic in Swedish copper smelter workers). There has been no epidemiological study of the humic acid hypothesis, however.

LIFETIME RISK OF CORONARY HEART DISEASE AND INTERNAL ORGAN CANCERS DUE TO ARSENIC INTAKE 10 µg/kg DAILY

Disease	Male	Female
Coronary heart disease	0·012	0·016
Lung cancer	0·020	0·030
Liver cancer	0·013	0·009
Bladder cancer	0·022	0·035
Kidney cancer	0·008	0·015

Arsenic has been accepted as a human carcinogen without substantial evidence from animal experiments. This discrepancy may be due to a difference in absorption, methylation, and/or excretion of arsenic. Arsenic seems to have a role in the late stage of carcinogenesis,[7-9] and it has been suggested that long-term animal studies may not detect some environmental agents that act late in the carcinogenic process.[9] Arsenic could cause vascular disorders via smooth-muscle-cell proliferation.[10] In an attempt to apply the Armitage-Doll multistage model to mortality from coronary heart disease induced by arsenic, my colleagues and I observed a life-time risk of the disease comparable with that of internal organ cancers (table). Blackfoot disease seems to be a multistage, multifactorial disease resulting from chronic progressive arteriosclerosis: it is too early to conclude whether arsenic or humic acid is the main cause.

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Zinc supplementation during diarrhoea: a fortification against malnutrition?

SIR,—Dr Briend and colleagues (May 12, p 1157) raise important questions about the relation between diarrhoea and malnutrition. We accept that their data from Bangladesh[1] show no impact of diarrhoea on weight gain, but would caution too rapid a dismissal of the possibility of impact on linear growth. Their data show that when children with diarrhoea were measured at the end of 3-month observation periods there was no difference in height gain. Significant differences, however, were noted when the diarrhoea occurred at the beginning of the observation period, and even when a 6-month interval was used 30% of children remained stunted. This may reflect the lag in linear growth following an episode of diarrhoea such that impaired linear growth can only be accurately estimated some time after the acute attack. Briend et al raise the question of micronutrient deficiency as a possible factor increasing diarrhoeal prevalence.

We have examined the effect of zinc supplementation on linear growth of children in urban Dhaka presenting with acute diarrhoea (under 3 days) and followed them at home over eight weeks during

their catch-up growth phase. A double-blind, randomised controlled trial with a zinc acetate supplement of 15 mg/kg daily was undertaken in 64 children aged between 3 and 24 months (mean 11·1) at the ICDDR B. At entrance the groups did not differ with respect to history of diarrhoea, socioeconomic and environmental factors, and nutritional status:

Measurements at entry	*Zinc supplemented*	*Placebo*
Weight (kg) (mean, SD)	6·2 (1·1)	6·4 (1·1)
Height (cm) (mean, SD)	67·6 (5)	68·6 (5·9)
Weight/age*	67·1%	67·3%
Height/age*	91·8%	91·9%

*National Centre for Health Statistics (NCHS) standards.

The children received a 14-day course of a multivitamin syrup as placebo or the same syrup containing zinc supplement. They were followed every week after the two-week supplementation period and weight and length were measured. The unsupplemented group at follow-up (n = 32) had gained a mean of 8·40 mm (SD 4·7) in height whereas the zinc supplemented group (n = 32) attained 11·8 mm (5·5) (t-test, $p < 0.05$) over the first four weeks of monitoring. From week 3 to week 9 the difference between the groups was maintained (9·7 mm and 12·8 mm, respectively; $p < 0.05$). The linear growth in the unsupplemented group was similar to that reported by Briend et al[1] (7·8 mm per month). The addition of zinc enabled a 25% increase in linear growth predominantly over the fourth to ninth week after presentation with acute diarrhoea.

Diarrhoea may determine zinc status by reduction of dietary intake, impaired intestinal absorption, or increased intestinal loss of endogenous stores.[2] Zinc requirements are increased during catch-up growth and are essential for lean-tissue deposition and bone growth.[3] These data suggest that diarrhoeal episodes have an important effect on a child's zinc status and that recurrent illness leads to depletion of zinc stores. In Bangladesh, widespread zinc deficiency may be an important factor in suboptimum linear growth. If zinc status were to be improved as part of a diarrhoeal control programme, the mean attained height of children at risk might be raised. Zinc deficiency may well be a major contributor to stunting of many children in Bangladesh. We therefore propose that there is a "zinc deprivation cycle" in which restricted dietary zinc intake produces suboptimum linear growth, which when compounded by diarrhoea results in a deterioration of zinc status, thus leading to further stunting and increased diarrhoeal risk.

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How much of which antipsychotic?

SIR,—Information on the relative potencies of neuroleptic drugs in terms of their antipsychotic effect is not widely available. Compendia such as the *British National Formulary* offer little guidance on this matter. This can cause problems in prescribing if patients are changed from one neuroleptic drug to another. In particular, inappropriate substitution by too high a dose of a high potency neuroleptic can cause severe extrapyramidal side-effects.

A 54-year-old woman had suffered intermittently from isolated auditory hallucinosis in her left ear. She had no other features of schizophrenia, depression, or organic mental illness and she denied alcohol abuse. She was treated with trifluoperazine (10 mg per day) for several years without hallucinations or extrapyramidal side-effects. On discontinuation of trifluoperazine because of symptoms of dizziness, her hallucinations recurred and chlorpromazine (300 mg per day) was prescribed by her general practitioner. At this dose she had severe symptoms of postural hypotension, so chlorpromazine was replaced with pimozide (20 mg per day). Subsequently, severe akathisia developed, with resting tremor and cogwheel rigidity which persisted even on reducing the pimozide dose to 10 mg per day and prescribing maximum doses of anticholinergic agents. Further reductions in the pimozide dose to 6 mg per day led to less akathisia but she still had some tremor and cogwheel rigidity. Further gradual reduction of the pimozide was planned.

The relative ability of neuroleptics to block in vitro dopamine systems correlates well with their antipsychotic efficacy and with the power to generate extrapyramidal side-effects,[1,2] and this has been confirmed by in vivo positron emission tomography studies.[3] Information on equivalent doses can aid prescribing:[4]

*Oral medication**		*Depot medication*	
Chlorpromazine	100 mg	Clopenthixol	20 mg 2 × weekly
Thioridazine	100 mg	Flupenthixol	40 mg 2 × weekly
Trifluoperazine	5 mg	Fluphenazine	25 mg 2 × weekly
Haloperidol	2 mg	Haloperidol	100 mg 4 × weekly
Pimozide	2 mg		
Sulpiride	200 mg		

*Daily doses.

Individual pharmacokinetic variation and the variation between drugs with respect to other receptor affinities mean that dopamine-receptor-binding potency can only be used as a rough guide to the necessary dose of an antipsychotic. We suggest, however, that informed prescribing is more likely to be good prescribing, and that information about relative dopamine-receptor-blocking potencies would reduce significant overdosing with high potency neuroleptics thus reducing the risk of severe acute extrapyramidal side-effects.

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Parvovirus B19 infection in the fetus

SIR,—Dr Soothill (July 14, p 121) is wrong to say "Parvovirus B19 is thought to affect only the blood precursor cells in utero". Parvovirus B19 infection of fetal cardiac myocytes has been documented by in-situ hybridisation[1] and electronmicroscopy;[2] in the latter instance, cardiac dysfunction consistent with myocarditis was present. Hepatocyte necrosis,[3] rises in concentrations of hepatocellular enzyme activities,[4] and periportal fibrosis with bileduct proliferation,[5] suggesting direct or indirect hepatocyte injury, have also been associated with fetal parvovirus B19 infection. Although transfusional support in antenatal parvovirus B19 infection may be worthwhile, the prognosis for infected fetuses should still be assessed with caution.

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