and invited confirmation, though the mechanism of action was unknown.

We gave 5 g of cholestyramine or methylcellulose twice daily in a double-blind crossover trial to five patients receiving chronic haemodialysis, using the same grading of pruritus. The daily pruritus score was calculated and the mean scores before, during four weeks of cholestyramine, and during four weeks of placebo treatment were compared. The results are shown in the accompanying table.

Mean pruritus scores before and during treatment with placebo and cholestyramine

Patient No	Before	Placebo	Cholestyramine
1	2.7	2.7	2.5
2	1.2	0.5	0
3	2.0	1.0*	1.6
4	1.7	0	1.3
5	2.7	2.5	2.5

*Placebo intake irregular because of nausea and vomiting.

Pruritus is a very difficult complaint to evaluate and we believe that only a double-blind crossover trial in a large series of patients can provide definite proof of the effectiveness of cholestyramine. We could not find any influence on pruritus at all in our five patients. A higher dose might be more effective but would often be accompanied by gastric complaints so that we are not optimistic about long-term "patient compliance."

Relief of pruritus in cholestatic jaundice by cholestyramine may be explained by binding of bile acids in the gastrointestinal tract, but in such cases cholic acid levels in serum are raised. We have estimated the plasma bile acid levels in chronic haemodialysis patients and found them to be similar to those in normal controls.¹ Mostly the plasma levels are too low for any effect of cholestyramine to be detected.

Of course cholestyramine may bind other, unknown, molecules which may play a part in the pathogenesis of pruritus in uraemia. It seems quite unlikely to us that removal of bile acids has any role in this respect.

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¹ van Berge Henegouwen, G P, Ruben, A Th, and Brandt, K-H, *Clinica Chimica Acta*, 1974, **54**, 249.

Hard water, food fibre, and silicon

SIR,—Your leading article "Progress in the water story" (4 February, p 264) calls attention to the studies which show an association between water hardness and a lower mortality from cardiovascular and other diseases. You note the "lack of any cogent theoretical explanation" for this protection.

Schwarz *et al*¹ have reported higher levels of silicon in the hard water of west Finland. They studied private wells in areas of high and low incidence of heart disease. Hard water had twice the silicon content of soft water. They suggested that "the silicon in drinking water may have a determining effect on atherosclerosis." This would support the "Schwarz hypothesis."² He cited human necropsy studies which showed an inverse relation between tissue levels of silicon and the

degree of atherosclerosis and arthritis. Silicon plays a role in connective-tissue aging by forming -O-Si-O- bridges and adding to the stability of collagen. Dietary sources of silicon, as reported by Schwarz, include hard water and fibre (cereal bran, alfalfa, and pectins).

Our interest in the "Schwarz hypothesis" was stimulated by his analysis of hair samples from cardiac patients (unpublished observations). We submitted samples from cardiac patients, marathon runners, and patients who were in exercise rehabilitation programmes. Some cardiac patients who were disabled by musculoskeletal injuries during training had "very low" levels of hair silicon (under 4 ppm). Normal levels were found in champion marathon runners (over 20 ppm). Patients who were supplementing their diets with bran and alfalfa had elevated levels (up to 100 ppm).

These results suggest that silicon is the "hard water factor" and the "food fibre factor." We now advise cardiac patients to increase their fibre intake until their stools float. To date 102 cardiac patients have "graduated" from rehabilitation programmes by running 42 km. If Schwarz is correct, the high intake of silicon will "protect" against both arthritis and atherosclerosis.

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¹ Schwarz, K, *et al*, *Lancet*, 1977, **1**, 538.
² Schwarz, S, *Lancet*, 1977, **1**, 454.

"Innovation in the Pharmaceutical Industry"

SIR,—In his review (22 October, 1977, p 1076) of my *Innovation in the Pharmaceutical Industry* Professor M D Rawlins doubts my conclusion that the return from investment in pharmaceutical research has been low for two reasons: (1) he has discovered an error in my computations; (2) continued investment in pharmaceutical research. Dr Rawlins is right to examine this estimate, for it is central to the conclusion that the regulation of drug marketing has made research unprofitable.

Concerning the alleged error, Dr Rawlins accepts my statement that a US-based company can earn over 10% after taxes on its investment in research and development for a new drug only if the world sales of the drug exceed \$23.5m annually. Since 68% of their total sales are in the United States, the required US sales are \$16m. Dr Rawlins refuses to accept this estimate because US drug companies are subsidiaries of multinationals and the US market represents only 18% of the world market. Accordingly, he estimates that US sales need to be only 18% of \$23.5m, or \$4.2m, in order to yield an acceptable rate of return. The fact that the US market is only 18% of the world is irrelevant to my estimate. US companies cannot expect to capture a much larger part of the world market than they already have. There is no need to change my estimate of the expected rate of return of 3.3% from investment in pharmaceutical research by US companies.

Companies based in other countries cannot expect to do much better. Though they may face a less arduous process of winning the approval of regulators before marketing in other countries, the demands of these regulators have been increasing. What is more, companies which depend on the European market also have to put up with the regulation of prices, and drug price regulators have not been known for generosity.

On the second point concerning the continued investment by drug companies I do not fundamentally disagree with Dr Rawlins. He argues

that if I am right, then the drug companies would have stopped investing in this research. I am saying that if the expected rate of return continues at a low level the drug companies eventually will stop investing in research. It takes time for companies to adjust to changes in economic prospects, particularly when fundamental views about the nature of the industry must be altered.

Dr Rawlins considers my argument that the industry's promotional expenditure has been inadequate rather than excessive to be absurd. I do not claim that drug companies' representatives give unbiased assessments of drugs. But I do say that when experts disagree, as is often the case, then doctors must use their own judgment and they must rely on different sources of information, including the rival claims of different companies.

A major objection to promotional expenditure has been that it is excessive. Usually, however, the critics fail to consider the consequences of doctors not being informed about the availability of drugs and particularly of new ones. Nor do they realise that total expenditure is high because there are large numbers of companies, drugs, and doctors. Many companies send information about many drugs to many individual doctors. The usual emphasis on total industry expenditure per doctor is misleading. When we hear that the US industry spends an average of \$3600 per doctor promoting drugs we are likely to take this to mean that individual large companies' representatives call frequently on each doctor and each company inundates him with mail. But each of the eight leading companies sends representatives to each doctor only 3.2 times per year on the average. Each company sends only 1.1 pieces of mail weekly to each doctor. Yet Dr Rawlins and others have successfully urged governments to put pressure on pharmaceutical manufacturers to reduce their total promotional expenditure. The companies may be able to find better and cheaper ways of informing doctors about the many dimensions of their numerous products, but it is naive simply to condemn promotional expenditure as excessive. To force them to reduce their promotional activities may result in a loss of information by doctors.

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Group B streptococci in pooled human milk

SIR,—In view of the recent emergence of group B streptococcal infection as an important neonatal disease we wish to report on the presence of group B streptococci in a pool of untreated human milk and its eradication by pasteurisation.

As part of a larger survey on human milk bacteriology we have so far studied six pools of milk donated to the Oxford bank. The donors in this study contributed the milk, which in some lactating mothers drips from the opposite breast during breast-feeding.¹ All the milk samples were collected in the mothers' homes into sterile shells and containers. The milk was then stored in the donor's refrigerator for up to four days before being collected and brought to the neonatal unit to be pooled. Each milk pool consisted of 75-100 24-h samples from 25 donors collected over a 3- or 4-day period. In one of the six pools studied there was a heavy growth of β-