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

We gave 5 g of cholestyramine or methylcelluose 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.

R VAN LEUSEN
J C KUTSCH LOJENGA
A TH RUBEN

Municipal Hospital,
Arnhem, Netherlands

[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.

T J BASSLER

Inglewood, California

[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.

DAVID SCHWARTZMAN

Department of Economics,
Graduate Faculty of Political
and Social Science
New School for Social Research
New York

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-

haemolytic streptococci ($2{\cdot}9 \times 10^5$ organisms/ml) which were serologically group B (the organisms were, unfortunately, not typed). Pasteurisation at 62°C for 30 min in a purpose-built Holder pasteuriser (Oxford[1]) eliminated the organisms, as predicted from their known heat sensitivity.

The early-onset, septicaemic form of group B streptococcal infection is thought to originate from colonisation in passage through the birth canal; there is little information, however, on the pathogenesis of the less common, late-onset, meningitic form of the disease. Kenny and Zedd[2] and Schreiner and Coates[3] have suggested that in the latter disease form breast milk may be a source of infection; these authors have reported three cases of infection in neonates whose mothers' milk has grown group B streptococci. In our own studies it is not certain that the organism originated from the milk itself, but, whatever the source, the profuse growth of group B streptococci in a human milk pool again raises the important and unresolved question as to the bacteriological safety of using untreated pooled breast milk for feeding premature infants.

The advantages of untreated milk, with its live cells and intact protective properties, may be outweighed by its bacteriological disadvantages when using pooled milk from a milk bank, where cross-contamination and pathogenic bacterial overgrowth are inevitable problems. Optimal procedures in milk banking have yet to be defined, but at present pasteurisation would seem a satisfactory method of processing human milk. There is evidence for considerable preservation of the protective properties in milk with this form of heat treatment[1 4] and our own preliminary data suggest that pasteurisation satisfactorily destroys most common pathogenic bacterial.

A LUCAS
C D ROBERTS

Department of Paediatrics,
John Radcliffe Hospital,
Oxford

[1] Gibbs, J H, *et al*, *Early Human Development*, 1977, **1**, 227.
[2] Kenny, J F, and Zedd, A J, *Journal of Pediatrics*, 1977, **91**, 158.
[3] Schreiner, R L, and Coates, T, *Journal of Pediatrics*, 1977, **91**, 159.
[4] Ford, J E, *et al*, *Journal of Pediatrics*, 1977, **90**, 29.

Changing mortality from ischaemic heart disease

SIR,—Dr C du V Florey and his colleagues (11 March, p 635) point to the associations between the recent slight decrease in mortality due to coronary disease in men and a number of concurrent changes in diet and in cigarette smoking. They draw only tentative conclusions from these associations, and this is particularly understandable in relation to a condition that has many causes.

In regard to diet the hesitation of the authors is even better founded than they themselves realise. The figures they use for food intake are those of the National Food Survey,[1] which measures only that which is consumed in the home and also omits entirely a range of items that include confectionery, ice cream, soft drinks, and alcoholic drinks. As a result the intake of some dietary constituents is considerably underestimated. For example, the survey assesses current average sugar intake at about 12 ounces (340 g) a week, but the real total is more than twice as much as this, at around 30 ounces (850 g) a week. More importantly, the survey records a continuing smooth fall in sugar intake of some 30% between 1970 and 1976 (apart from the exceptional fall due to the world shortage of 1975), whereas total intake has changed very little over that period: less than 6% between the extremes if we again omit the figure for 1975.

To accept figures from the National Food Survey as accurately representing the amounts of food that people eat is as logical as to accept attendances at cinemas as accurately representing the number of films that people watch while ignoring those that are seen on television.

JOHN YUDKIN

London NW3

[1] Ministry of Agriculture, Fisheries and Food, National Food Survey Committee, *Household Food Consumption and Expenditure for the Years 1968-76*. London, HMSO, 1970-7.

SI, moles, and drugs

SIR,—I read with interest your leading article on this subject (18 March, p 668). My experience is that most doctors are intelligent people who, on the whole, have made it. SI units may be "trying" initially, but "exhausting" seems an overstatement for all but the most tired.

Symbols such as kg^{-1}, meaning "per kilogram," appear straightforward. To suggest that they are ugly or even worse that they are "difficult to comprehend" could give rise to misinterpretation of the calibre of the profession by an outside observer.

The new units certainly require some work by the clinician. The difficulties outlined in the leading article are probably not insurmountable, and with a more positive attitude the new units will, like any other hurdle, be jumped successfully by the vast majority.

G V RIGBY

Uxbridge, Middx

SIR,—Your leading article (18 March, p 668) will restimulate interest in SI unit practice, which is good. However, I am now convinced you are wrong in opposing the recommended change in the method of indicating concentration per litre, from "/l" to "l^{-1}." "/l" is perfectly safe when typed or in print, but about one in five of our young staff find it almost impossible to make the solidus (/) diagonal and they write it vertical, which is very dangerous next to a figure 1. It is not difficult to manipulate a typewriter in full flood to introduce the symbol for the inverse power of a litre, that is, l^{-1}. A slight turn of the left wrist and simultaneous tapping upon the - followed by the 1 (not, of course, by the l) makes a quick neat job of this symbol. If necessary a key can be made to do it in one jab. All the youngsters from school and university nowadays are trained in the use of this symbol. Where safety and speed matter we older ones must try to catch on.

Another point. We in this laboratory have used grams per litre for haemoglobin concentrations for several years now and are delighted that it is to be recognised as more desirable than grams per decilitre with its decimal point and general ability to confuse among the indices. We recognise that millimoles may come when a way round the monomer/tetramer controversy is thought out. A tip when changing over the grams per litre from grams per decilitre: always state the unit in full every time a haemoglobin concentration is mentioned, never just the figure. It's dangerous to answer, "What's the haemoglobin?" with "a hundred"; but perfectly safe if you say the unit out in full, "grams per litre."

G A C SUMMERS

York

SIR,—I would like to correct an unfortunate error which crept into my letter (1 April, p 853), in which I stated that 513·5 mg of chlormethiazole edisylate and 161·65 mg of chlormethiazole base both provide 10 mmol of chlormethiazole (as edisylate or base). This should, of course, be 1·0 mmol. As I stated, care is needed in conversion!

GRAHAM BALL

Department of Chemical Pathology,
Whittington Hospital,
London N19

Serum IgE in mycosis fungoides

SIR,—After reading the paper by Dr P L Amlot and Mr L A Green on IgE in Hodgkin's disease and other lymphomas we considered it of relevance to collect the knowledge available of the relation between IgE and mycosis fungoides. Mycosis fungoides is a T-cell lymphoma originating in the skin, sometimes disseminating to lymph nodes and viscera. In three reports an elevation of serum IgE concentration (>1000 U/ml) has been found in mycosis fungoides, occurring in about 20% of cases.[1-3] However, the numbers of patients reported on were rather small—14, 22, and 23 respectively.

In the Scandinavian Mycosis Fungoides Study Group we have collected data on serum IgE levels in cases of mycosis fungoides since July 1974. Our findings are presented in the accompanying table. Among 75 patients the serum IgE level exceeded 1000 U/ml in only eight cases, and four of these had levels above 4000 U/ml. Neither a family or personal history nor clinical evidence of atopy (eczema, hay fever, or asthma) was recorded in these cases. In this series no relation could be found between the clinical type, stage, or response to treatment and the occurrence of elevated serum IgE concentration. In one of the cases the IgE level increased during treatment (from 1200 to 5200 U/ml) and in another case the level decreased (from 4000 to 300 U/ml); both patients were treated with psoralen and long-wave ultraviolet light (PUVA) to complete remission. No correlation was found in the series between IgE and the other immunoglobulins (IgA, IgG, IgM). At present we are not able to draw any conclusions from these

Serum IgE concentrations in mycosis fungoides

Stage of MF	Serum IgE concentrations (U/ml)			Total
	<500	500-1000	>1000	
Plaque stage ..	42	10	7	59
Tumour stage ..	8	2	1	11
Tumour stage with extracutaneous involvement ..	5	—	—	5
Total ..	55	12	8	75