positive findings in the average investigation is about right, but an economist might well suggest an improvement on this.

If the profession has some guidance on cost-effectiveness targets as a whole it has a basis for the assessment of the significance of the 2% figures that you quote. I propose that the BMA should set up an economic research department to quantify the economics of medical care and the benefits thereof. I feel sure that the results of such study would benefit our position in future pay negotiations.

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Toxicity of interferon

SIR,—Our data do not support the suggestion by Dr D Fumarola (18 July, p 235) that the pyrexia seen after interferon administration is due to endotoxin contamination.

Using Wellcome lymphoblastoid interferon (a highly purified preparation containing a mixture of α-interferons) we observed pyrexia in all patients during the course of an initial dose-toxicity evaluation.[1] Material from the batches used in this study we tested for endotoxin contamination by the limulus amoebocyte lysate assay and the rabbit pyrogenicity test. The limulus assay revealed endotoxin levels of 0·15-0·45 ng/ml (it is generally considered that levels below 10 ng/ml are insignificant and substantially higher concentrations would be necessary before clinical effects would be seen).

In the rabbit pyrogenicity test six rabbits received 1 μg in 1 ml endotoxin per kg body weight, and six more rabbits were given 6·44 megaunits of interferon in 1 ml per kg body weight. Both preparations were administered intravenously. The salient features of the temperature curves for the two groups of animals are their shape and kinetics rather than the actual degree of temperature elevation, the latter being essentially a dose-dependent phenomenon.

It has been suggested that the temperature curves of rabbits given bacterial pyrogen intravenously provide the most characteristic evidence of a response to endotoxin, with a typical biphasic curve with peaks at 1 and 3 hours.[2,3] Our rabbits given bacterial pyrogen showed this typical picture with the additional characteristic feature of the second temperature peak being higher than the first. By contrast, the response to interferon was monophasic with a delayed onset, and was similar to that reported following the injection of other agents, such as *Corynebacterium parvum*[4] and other Gram-positive organisms, which are thought to provoke fever by the release of endogenous pyrogen. This supports the results of the limulus test discussed above, indicating that pyrexia was not due to endotoxin contamination.

This view is reinforced by our clinical observations. Firstly, while the pyrexia seen following endotoxin administration is usually biphasic,[2,3] in our patients all fevers were monophasic. Secondly, endotoxin administration provokes a leucocytosis in man[5,6]; but in our study there was no evidence of leucocytosis, and both polymorph and lymphocyte populations were uniformly depressed following interferon administration. Thirdly, all the interferon in the present series was given by intramuscular injection, and it has been reported that the pyrogenic effects of endotoxin are best seen after intravenous administration and seldom occur when the material is given by the intramuscular route.[7] Finally, with four batches of Wellcome interferon with endotoxin contents (measured by the limulus test) differing by as much as a factor of 33 there was the same pyrogenic response in man when $2·5\text{-}3 \times 10^6$ international units of each were injected intramuscularly.

In summary, our data suggest that the interferon molecules are themselves responsible for the production of fever in man and the rabbit. Obviously contamination with bacterial endotoxin during manufacture must be excluded, and for this purpose the limulus test can be used as a monitor.

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Red cell indices and iron stores in patients undergoing haemodialysis

SIR,—Dr K L Lynn and colleagues (27 June, p 2096) have demonstrated that in a group of patients undergoing haemodialysis in the London area there was a positive correlation between both mean cell volume (MCV) and mean cell haemoglobin (MCH) and iron stores assessed by serum ferritin. They therefore suggest that a low MCV or MCH may be used to confirm iron deficiency in haemodialysis patients.

We have recently reported that a severe microcytic anaemia is one of the early manifestations of aluminium intoxication in haemodialysis patients.[1] The anaemia was characterised by being resistant to iron therapy and associated both with high plasma aluminium and high serum ferritin, suggesting that aluminium may interfere with iron utilisation. Thus, while red cell indices may be used as a guide to iron deficiency in London, where the water aluminium is very low, this cannot apply to other areas. In general, one would advise great caution in using MCH or MCV in isolation as evidence of iron deficiency in haemodialysis patients unless one can be confident that the patient has not been exposed to aluminium.

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Endocrine function and immunity

SIR,—Your leading article "Endocrine function and immunity" (11 July, p 88) correctly draws attention to the fact that while the effect of hormones on lymphatic tissue is relatively well documented little information is available on the relationship to peripheral activity.

In the course of a study of cytotoxicity in early breast cancer we have observed that natural killer activity varies during the menstrual cycle. Natural killer activity measures the ability of unimmunised lymphocytes to recognise and kill cells of neoplastic phenotype. There is significant reduction of natural killer activity in the first half of the menstrual cycle compared with that in the luteal phase, as shown in the accompanying table.

Variation in natural killer activity of unimmunised lymphocytes during the menstrual cycle

Time of cycle	No of subjects	Mean % specific cytotoxicity	p*
First half	15	14·7 : 8·25	< 0·001
Second half	10	41·5 : 13·4	

*Significance of difference from control calculated by two-sample *t* test.

These results confirm and extend the data derived from experimental work using high-dose oestrogen administration in the mouse suggesting that natural killer activity may be modulated by hormones.[1] All these results provide a link between endocrine function and a cytotoxic mechanism which has been implicated in surveillance against spontaneously arising tumours.[2] This would be of particular importance in the development of cancer of the breast, in which, as your article points out, many of the associated risk factors are related to endocrine function.

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Calcium homoeostasis during pregnancy

SIR,—Mr Malcolm Whitehead and his colleagues (4 July, p 10) put forward an interesting hypothesis concerning the roles of calcitonin and the vitamin D metabolite 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) during pregnancy. They found raised levels of both hormones *throughout* pregnancy and suggest that $1,25(OH)_2D_3$ augments maternal calcium absorption whereas calcitonin opposes the bone-resorbing activity of $1,25(OH)_2D_3$. Thus dietary calcium is available for fetal mineralisation and the maternal skeleton is protected. The hypothesis that these hormonal changes arise, or are required, because of the major demands of the fetus for calcium appears to be an oversimplification.

The total calcium content of a full-term infant is approximately 32 g and represents a significant maternal "calcium stress." However the stress occurs almost exclusively during late pregnancy, whereas the hormone changes described were present by the 10-12th week of pregnancy. At 12 weeks' gestation the fetus weighs approximately 100 g and has a calcium content of 200 mg.[1] This represents an average calcium challenge during the first trimester of only 2-3 mg daily. The demand for calcium rises progressively during pregnancy and exceeds 250 mg/day between 36 and 40 weeks' gestation. This represents a significant proportion of the recommended dietary intake of calcium at this time (1200 mg daily[2]).

Thus plasma levels of calcitonin appear to rise early in pregnancy whereas calcium demands do not. Plasma levels of $1,25(OH)_2D_3$ also rise in early pregnancy, but this could be due to increased protein binding rather than to an increase in free $1,25(OH)_2D_3$.[3] The further rise in $1,25(OH)_2D_3$ shown in late pregnancy might, however, match the increased calcium demands. $1,25(OH)_2D_3$ is a potent bone resorbing agent in vitro, but there is surprisingly

little evidence that physiological quantities of $1,25(OH)_2D_3$ in vivo increase bone resorption in mammals,[1] although this may occur in egg-laying birds.[5] This suggests that a hormone protecting the maternal skeleton need not be a significant biological requirement in pregnancy, and that calcitonin remains a hormone seeking a function in man.

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Rheumatoid arthritis and food: a case study

SIR,—The paper by Drs A L Parke and G R V Hughes (20 June, p 2027) entitled "Rheumatoid arthritis and food: a case study," printed under the general heading "For Debate," seems to have produced no correspondence at all, which I find surprising. I suspect that the doctors who work in the field of food allergies are more anxious at present to get on with their work and establish their ground scientifically than to stir up a hornets' nest of correspondence, and I for one do not blame them. But many GPs already know of equally dramatic cases, in both rheumatoid arthritis and osteoarthritis.

The most impressive patient in my own experience had had active rheumatoid arthritis for 25 years, was taking azathioprine and soluble aspirins (Disprin), had already had a plasma exchange and was slowly but steadily going downhill. She also had proved pulmonary involvement, which meant an increased anaesthetic risk from the splenectomy which had been contemplated. Her most important food allergen proved to be corn, which, of course, as maize starch, was the packing in her azathioprine and Disprin tablets. There was no question of stopping her azathioprine or Disprin at that stage and it was therefore necessary to counter any possible allergic effect of the corn in her tablets by a simple method which there is not space to go into here. Her improvement after one week on an exclusion diet was so dramatic that the experiment seemed worth pursuing, but after six weeks her arthritis flared badly and it seemed that, sadly, the placebo effect of a new approach had worn off. It transpired, however, that during that week cornflour thickening had been added to her gravy against instructions and without her knowledge and as soon as this was stopped her joints resumed their improvement. Her erythrocyte sedimentation rate fell steadily from 75 to 31 in one hour and she began to put on weight. She is now off all tablets and feeling and looking better than she has done for over 20 years. I saw her five weeks ago and can confirm this. She attends hospital at three-month intervals instead of weekly and, as the staff freely admit, she goes there in their interest, not hers. Her chest *x*-ray appearances have become clear and her lung function has returned, she believes, to normal.

Of course this case is anecdotal, like that reported by Drs Parke and Hughes, in which the food allergen proved to be dairy produce. But both happened. The investigation required is simple, safe, and non-invasive, and it costs virtually nothing. All that is required is a co-operative patient with the will to persevere, careful instruction sheets, which already exist, and a doctor to monitor the experiment. One knows within a week, or at the most 10 days, whether the thing is worth pursuing. It will not be clear at that stage what the food allergen is, but there will be strong indications whether one does or does not exist and the patient will be in no doubt at all.

No one would be foolish enough to claim that every case of rheumatoid arthritis is associated with a food allergy, but if only one in 20 is—and I suspect that it is considerably more—I question whether we have the right to withhold such a simple, safe, brief, and non-invasive investigation in a disease of such appalling chronicity.

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Pharmacists as doctors

SIR,—Your interesting leading article (25 July, p 264) should convey the message to the administrative authorities, pharmacists, clinicians, and the public in general that we should evaluate critically the rationale—and impact—of the global practice of over-the-counter prescribing by pharmacists and counter assistants. Solution of this problem depends on understanding—and rectification—of the essential factors that facilitate the operation of this practice, including in the developing countries.

There are enough reasons to drive the patients to pharmacists for treatment. Firstly, the service is readily available, convenient, and also quicker than in a hospital. Secondly, the patient feels spared many investigations as the pharmacist does not demand any. Thirdly, the patient feels the remedy "magical" as he becomes well, even though apparently, in a short while. This is largely attributable to prescription of drugs that give quick symptomatic relief without affecting the undiagnosed underlying disease process. This is especially true of antibiotic and corticosteroid abuse. Fourthly, the consultation fee is either small or not charged at all.

A major proportion of the patients who seek medical advice from pharmacists, are not educated—or not well educated—and belong to medically and socially underprivileged rural communities. They consider a pharmacist practically as good as a clinician. Patients who experience some fresh or recurrent vague symptom, and those who suffer from some apparently minor illness are the ones who swell the clientele of the pharmacists. Provision of quick symptomatic relief for such patients makes this wrong practice more popular among them.

Patients are the sole victims of this practice. They welcome quick and comfortable service, but neither the patients nor the pharmacists realise that the presenting sign or symptom may be indicative of the prodromal phase of an illness or a manifestation of some systemic illness, especially some syndrome complex. Thus the disease process may remain masked and undiagnosed for a long time. Moreover, inadequate and ineffective treatment may generate problems like drug resistance and drug dependence.

It is mandatory to take immediate steps to counter this practice. No single-stranded measure will prove adequate, and rapid results should not be expected. The measures adopted should be three pronged: educational, medical, and legal. Educational measures should be aimed at making the people understand the rationale of early and proper diagnosis and treatment of the disease by qualified clinicians. Pharmacists should be made to realise their limitations as prescribers. A healthy co-operation of pharmaceutical colleagues is very essential in this regard. It does not seem appropriate to delegate prescribing to them, even if some knowledge of clinical medicine is incorporated in their course in future. Medical measures should include provision of readily accessible and promptly available comprehensive health care to the people, especially in the rural areas. Legal measures should be directed to limit the prescribing of drugs to qualified clinicians only.

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Care in the community

SIR,—In his Letter from Westminster Mr William Russell (1 August, p 391) states that the Green Paper *Care in the Community*[1] seems to have had a fairly favourable reception. The paper is financially ignorant and unsound and the proposed transfer of resources from an underfunded hospital service to community care is likely to be to the detriment of those patients who remain in the hospital service. The "shift in the balance of resources" which is advocated should be obtained by a total increase in resources, with most of the increase going to the community.

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Trial marriage between primary and secondary health care

SIR,—It is inevitable that even a scheme so eminently sensible and reasonable as that for a trial integration of primary and secondary care will provoke protest. Potential critics should ponder carefully the many advantages. Apart from those mentioned by Professor C J Dickinson (8 August, p 417), integration and involvement by general practitioners in health districts seem an important bonus. During the recent BMA conference season, general practitioners were strongly recommended to seek greater involvement in district management structures, and so they should. Naturally the reverse should also follow.

Perhaps the single most disappointing aspect of the present arrangements is that new developments in community care, such as screening clinics and other preventive services, including family planning, are increasingly being developed outside family practice; and yet their natural locus is within that service.

There should be strong encouragement for a pilot study such as Professor Dickinson envisages.

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