thyroxine as in patients with newly diagnosed thyroid diseases, to suggest that they are no longer measured would be retrograde.

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1 Gow SM, Caldwell G, Toft AD, *et al.* Relationship between pituitary and other target organ responsiveness in hypothyroid patients receiving thyroxine replacement. *J Clin Endocrinol Metab* (in press).

SIR,—My doubts about the value of biochemical tests in monitoring patients receiving thyroxine replacement have been laid to rest after meditating on the article by Dr W D Fraser and his colleagues.

They make the unjustified assumption that their clinical assessment of patients receiving thyroxine is correct. Gross biochemical evidence of hypothyroidism can be found in patients with neither signs nor symptoms, and a claim could be made that every woman is hypothyroid until proved otherwise. Time teaches the sad but salutary lesson that hypothyroidism cannot be consistently diagnosed clinically. Thyroid function tests confirm compliance, which has been shown in numerous studies to be surprisingly low, often less than 50%.[1] A normal or high serum thyroxine concentration confirms recent compliance. A raised serum thyroid stimulating hormone concentration shows that replacement is inadequate. These tests can often indicate whether patients have recently run out of thyroxine tablets or whether they have taken them for a few days before attending the clinic to mollify the doctor.[2] This unusual opportunity to give details of their non-compliance has a salutary effect on the patient.

Inadequate replacement can be associated with hypercholesterolaemia. In the same issue Drs Madeleine Bell and J I Mann (p 769) write: "The risk of coronary artery disease is directly related to the amount of cholesterol circulating in low density lipoproteins." This is the reason for adequately ensuring treatment of hypothyroid patients. Cardiologists and thyroidologists should meet some time.

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1 Sackett DL, Haynes RB, Tugwell P. *Compliance in clinical epidemiology*. Boston: Little, Brown, 1985:199-222.
2 Keynes WM, Fowler PBS. *Hypometabolic states in clinical endocrinology*. London: Heinemann, 1984:239-42.

When things go wrong

SIR,—We read the leading article by Dr Richard Smith (23 August, p 461) with interest. With every year that passes, as defence insurance premiums mount inexorably, we may complain but are required by contract to pay our subscriptions anyway. Presumably, the single level of premium, regardless of specialty, reflects an underlying concept of the unity of medical practice. This year, however, the 70% increase in annual subscriptions imposes a severe strain on any feelings of unity we might have. We, the undersigned, cannot see how defence societies can continue to justify the same premium for all medical practitioners regardless of risk or salary.

Firstly, let us take the aspect of risk. Virtually all insurance policies rise with risk. In medicine the major risks are borne by surgeons, gynaecologists, and general practitioners. Pathology, for example, is a low risk specialty (as recognised by considerably lower premiums in the United States, for example) and rarely figures in medical litigation cases. Therefore it is clear that the risk borne by surgeons, etc, is being subsidised by low risk specialties such as pathology. We would probably tolerate this if there was an equitable distribution of financial reward between the specialties. The low risk specialties such as pathology, however, have a considerably lower reward than high risk specialties such as surgery and general practice.

The survey quoted in the recent Medical Defence Union report on the rise in subscriptions (about which no one in this department was asked for an opinion) is hardly likely to be representative or equitable. Low risk specialties such as pathology are relatively small and are always likely to be outvoted by the high risk, highly rewarded specialties. The cost of medical defence, however, is beginning to represent a sufficiently large proportion of a junior pathologist's salary that he must protest against this unfairness. Indeed, we would hope that our representatives in the Royal College of Pathologists will take steps to find alternative insurance if the traditional defence unions continue to exploit us.

Finally, the comparisons with other professions are grossly misleading. We know that the insurance premiums of colleagues in law, accountancy, and architecture are paid by their institutions and that they bear no relation to their personal salary. On top of this, compare the salary of solicitors, accountants, and architects with that of pathologists, particularly those in training grades. We note that the question of differential subscriptions has been left open, and we hope that the defence organisations will therefore respond to the needs of the low risk minorities in medicine.

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Haem arginate in acute hepatic porphyrias

SIR,—Like Dr Pertti Mustajoki and others (30 August, p 538) we have used haem arginate to treat acute hepatic porphyrias.

We gave the drug to four patients with an acute porphyric attack in which abdominal symptoms predominated (three patients with acute intermittent porphyria, one with variegate porphyria). Haem arginate was given as 3 mg/kg once a day for four successive days in two patients, for three days in one patient, and for two days in one. A single dose of 3 mg/kg was also given to seven women in the subacute phase of acute hepatic porphyria (three with acute intermittent porphyria, one with variegate porphyria, three with hereditary coproporphyria), all of whom had abdominal symptoms.

The table shows mean urinary values before and after treatment in six of the subacute cases and three of the acute cases. Two patients in the subacute phase also had faecal values measured before and after treatment: in one, with hereditary coproporphyria, coproporphyrin values fell from 673 to 203 μg/g wet stool and protoporphyrin values from 131 to 43 μg/g; in the other patient, with variegate porphyria, respective values were 363 to 133 μg/g and 841 to 261 μg/g. In patients with acute abdominal symptoms the pain completely regressed during treatment. One patient showed considerable improvement of intestinal peristalsis after the first infusion.

Coagulation tests were performed in six patients, two of whom were given haem arginate repeatedly. Tests carried out before treatment and 2, 24, and 48 hours afterwards included thrombocyte counts, Quick test, thrombin time, activated partial thromboplastin time, euglobulin fibrinolysis test, fibrin/fibrinogen degradation products, fibrinogen and ethanol gelisation test. The results obtained showed only light activation of the haemocoagulation system with only mild deviations in values and a rapid return to normal; no clinical correlations were found in any of the cases studied. Thrombophlebitis was not observed, even after repeated application to the same vein. Electromyography in five patients showed no remarkable changes after infusion; in one patient with an acute attack a tendency to normalisation, suggesting regeneration of neurones, was observed after treatment.

Changes in the concentration of serum haemopexin (haem-haemopexin complex degradation is much faster than that of haemopexin itself) observed after haem arginate treatment were only transient and did not correlate with clinical effects. No appreciable changes were found in liver and kidney function, haemoglobin concentration, and leucocyte count.

Our findings showed a favourable clinical effect of haem arginate in acute attacks of porphyria as well as regression of abdominal complaints in the subacute phase; these effects were confirmed by a reduction in excreted porphyrins and their precursors.

Early treatment in the initial phase of clinical symptoms is essential, as haem arginate seems to have little effect when severe conditions have already developed. In these conditions haemoperfusion followed by haem arginate might be clinically beneficial.[1]

We thank Dr Josef Stibor for performing the coagulation studies, Dr Jiří Vacek for performing electromyographic examinations, and Dr Zbyněk Hrkal for determining serum haemopexin concentrations. These findings were presented in part at the Gordon Research Conference, Wolfeboro, NH, USA, 28 July-1 August 1986.

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1 Kordač V, Martásek P, Horák J, Jirsa M. Hemoperfusion in acute intermittent porphyria. *Br Med J* 1984;288:1458.

Urinary porphyrin and precursor values in patients with porphyria. (Values are means (ranges))

	Patients with subacute attacks (n=6)		Patients with acute attacks (n=3)	
	Before	After	Before	After
δ-Aminolevulinic acid (μmol/24 h)	154 (41-263)	8·35 (21-91)	1365 (374-1952)	58 (36-96)
Porphobilinogen (μmol/24 h)	69 (7-208)	17 (0·44-24·3)	461 (57-850)	15 (10-19)
Total porphyrins (nmol/24 h)	1035 (765-1477)	513 (116-849)	7136 (1427-10 210)	866 (670-1129)

Clearance of psoriasis with low dose cyclosporin

SIR,—I write to confirm the recent report by Dr C E M Griffiths and colleagues (20 September, p 731) regarding the treatment of psoriasis with the immunosuppressant cyclosporin A and to mention two possible drawbacks of this treatment. I have now completed a preliminary trial of cyclosporin A in seven elderly patients with intractable psoriasis who had received all the standard treatments, including antimitotic treatment with methotrexate or hydroxyurea. An approved trial was set up to

find the lowest effective dose of this compound in psoriasis. All seven patients were 60 or older and had classic plaque type psoriasis. Only one of the patients found the cyclosporin mixture unacceptable and had to be withdrawn from the trial. Others showed a rapid response to the treatment, requiring 1 mg cyclosporin A/kg body weight for the first month to control the rash, although later the dose had to be raised in some cases to 3 mg/kg body weight. The patchy psoriasis cleared rapidly in all cases and then relapsed equally rapidly when treatment was stopped. Careful records of the main haematological variables and the biological profile were kept. As expected, no effect was observed on the blood picture, but a rise in blood urea and serum creatinine concentrations occurred in all cases. I believe it is important to note the rapid relapse after treatment is stopped, in contrast to the sometimes long remissions achieved with traditional local tars and dithranol.

If cyclosporin becomes an accepted long term treatment for psoriasis the effect on renal function should be carefully monitored and the drawback of the rapid relapse on withdrawal of the drug should be appreciated.

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Low dose maintenance medication for schizophrenia

SIR,—The conclusion by Professors Rahul Manchanda and Steven R Hirsch (30 August, p 515) that the results of low dose maintenance medication research are encouraging and that this approach should now be tried in the outpatient management of patients with chronic schizophrenia is both premature and incautious.

It is correct that Marder *et al* reported an equal effect of 5 mg and 25 mg for fluphenazine decanoate at 12 months,[1] but during the second year the low dose group become significantly disadvantaged with a wide separation of the survival curves after 15 months (Marder JR, American Psychiatric Association meeting, 1985). The apparently equal outcome at 12 months may have been an artefact of the entry procedure into the trial since most relapses in the standard group occurred within the first three months and stabilisation on the trial dose schedules may not have been achieved at that time.

I have personal knowledge of two further low dose trials in the process of publication and neither supports the adoption of the low dose prescription. Our own study confirms the significantly increased risk of relapse shown in the trials of Kane *et al*[2] and Marder *et al* but, more importantly, suggests that a minimum follow up of two to three years is required for any valid conclusion. Even the apparent short term gain of reduced total medication may be false and over a longer period these patients may be prescribed a higher total dose. This was shown to be the case with patients who discontinued medication altogether.[3]

The correct treatment of schizophrenia is an important issue and the relative benefits and risks of long term maintenance therapy continue to be researched and debated. As yet there are no clear indications that the standard practices of the last few years can be abandoned.

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1 Marder SR, Van Putten T, Mintz J, *et al*. Costs and benefits of two doses of fluphenazine. *Arch Gen Psychiatry* 1984;**41**: 1025-9.
2 Kane JM, Rifkin A, Woerner M, *et al*. Low dose neuroleptic treatment of out-patient schizophrenics. *Arch Gen Psychiatry* 1983;**40**:893-6.
3 Johnson DAW, Pasterski G, Ludlow JM, Street K, Taylor RDW. The discontinuation of maintenance neuropleptic therapy in chronic schizophrenic patients: drug and social consequences. *Acta Psychiatr Scand* 1983;**67**:339-52.

AUTHORS' REPLY—If Dr Johnson feels that our conclusion is incautious I hope he will agree that our article is less so. We emphasised the evidence of high relapse rates when neuroleptics are omitted or doses are reduced in the maintenance phase but pointed out the potential compensating factor of lower side effects and fewer signs of tardive dyskinesia and parkinsonism. Moreover, evidence to date suggests that relapse is less severe and responds readily to an increase in dose. We accept the potential criticism of Marder's work, but it was quoted only as an example of more radical findings. We also have personal knowledge of unpublished studies, including our own, which suggest fewer side effects and no increase in hospital admissions as a benefit of a specialised medication regimen. As Dr Johnson would suggest, the cost to the patient is an increase in the number of clinical episodes of neurotic and psychotic symptoms, but these respond quickly to intermittent medication.

There are two factors that need greater emphasis. Firstly, patients need to be well selected; they should be well stabilised, have few or no active signs of psychosis, and be willing to risk relapse in the hope of feeling better on lower dosage. The second key issue is whether a return of psychotic symptoms is regarded as the be all and end all of successful treatment. We would argue that a wider view of the patient, taking into account his subjective feelings while on medication, his experience of side effects, and the particular risks that he would engender if symptoms return would lead some patients and their doctors to try a lower dose medication and see if the benefits outweigh the hazards in their own case.

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Informed consent

SIR,—The correspondence following Jonathan Glover's leading article (19 July, p 157) makes several references to my writings and to the Institute of Medical Ethics; I should like to comment on a few points.

Messrs R R Hall and P H Smith (9 August, p 389) are correct to say that informed consent was my main concern in the articles.[1,2] I wrote about the Medical Research Council's trial of immediate and deferred orchidectomy in carcinoma of the prostate. Some of their other comments are less accurate.

The correct version, for instance, of what is said about informed consent in the protocol of the MRC trial, for which they are responsible, is: "It is the MRC's view that there is no ethical requirement for informed consent when the consultant in charge of the case is satisfied that each option used in the trial may reasonably be believed to be in the individual patient's best interests." In other words, informed consent need only be obtained when the consultant thinks that participation in the trial would not be in the patient's best interests. (It would then, of course, be a moot point whether the consultant was behaving unethically in recommending a course of action not in the patient's best interests.)

It seemed likely that surgeons concerned in the trial would follow this advice from the MRC: on inquiry this proved to be so. Surgeons told me that in some cases they had not told patients that they were in the trial and in other cases had not told them of alternative possible treatments. It was presumably my reporting of this information that led Messrs Hall and Smith to make their unfounded suggestion that I believe that British urologists do not talk to their patients.

Since Messrs Hall and Smith "accept that every patient has an absolute right to be informed," it is a pity that their letter does not indicate how in practice they recognise those patients who "do not wish to exercise this right." If a patient has not been told that he is a candidate for a trial, it is a little difficult to see how he could tell the surgeon that he does not want to know about it.

Dr J King (30 August, p 562) discusses the need to consider the empirical evidence showing what patients really want to know and what effects the informed consent procedure may have on them. Her thorough review of this subject will be published soon in *IME Bulletin*, because, contrary to Dr D Burley's opinion (6 September, p 627), the purpose of the *Bulletin* is to provide information relevant to medical ethics, rather than to provide another forum for debate. Indeed, his complaint that the debate on informed consent would have been better conducted in the pages of *IME Bulletin* is belied by the fact that he chose to write to you about it and not to me as editor of the *Bulletin*. The decision not to have a correspondence column in *IME Bulletin* was approved by the governing body of the Institute of Medical Ethics. Dr C W Burke, who made critical comments (9 August, p 389) about the lack of "constructive medical input" into institutes such as this one, might care to note that more than half the members of the governing body are medically qualified and that half the senior staff are also medically qualified.

One final comment is needed on Dr W Tarnow-Mordi's letter (30 August, p 562). He wishes there to be debate about exceptions to the requirements for informed consent. He also acknowledges that it is sometimes impossible to obtain consent from parents of neonates before starting research on the latter. He then says, "Those who fuel headlines accusing paediatricians of 'experimenting on babies without their parents' permission' could very well polarise [the debate] beyond recall." As one of those who has, as editor of a book on the subject,[3] fuelled such headlines, I find this statement extraordinary. The information in that headline is such as would surprise and shock many members of the general public: it is inevitable therefore that newspapers should carry such headlines. Since Dr Tarnow-Mordi acknowledges that the information is accurate, one can only assume that he does not wish it to become public. Is the sensitive debate that he wants to be conducted only among doctors?

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1 Anonymous. Research ethics. *IME Bulletin* 1986;March:1-7.
2 Anonymous. News and notes. *IME Bulletin* 1986;April:10-11.
3 Nicholson RH, ed. *Medical research with children: ethics, law and practice*. Oxford: Oxford University Press, 1986.

Change from porcine to human insulin

SIR,—Earlier this year one of your leading articles stated that there is currently no good general reason for transferring established diabetics from porcine to human insulin.[1] Therefore the recent announcement by Novo Laboratories Ltd of the withdrawal of their porcine insulins (Actrapid MC