comparable to the inpatients. This point is clearly made in the article. Secondly, we were *unable* to find subjects over the age of 40 whom we could call "normal."A large proportion of the middle-aged population have extensive but occult vascular disease. It could be argued that the changes claimed by Dr Meade to be related to age are just as likely to be caused by occult atherosclerosis, especially as they are not seen in the women, who are known to be much less afflicted by atheroma. The fact that the fibrinolytic activity falls and then rises may also indicate the prevalence of occult disease in the population being surveyed, particularly as the fibrinogen does not fluctuate but shows a steady rise in both sexes.

The above comments are presented to show how difficult it is to study a disease which is common in what we thought to be normal subjects as well as those with clinical manifestations. Large numbers are unlikely to solve this problem. Exact quantification of the disease, occult and overt, will but is not yet possible.

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Effects of adrenaline during treatment with propranolol and metoprolol

SIR,—Adrenaline causes vasodilatation in muscle by activation of $beta_2$-adrenergic receptors. After a single intravenous dose of the non-selective beta-blocking agent propranolol this vasodilating action is lost: adrenaline induces a vasoconstriction with a resulting increase of the peripheral vascular resistance and a rise in blood pressure, presumably by stimulation of α-receptors. After a single intravenous dose of the selective $beta_1$-blocking agent metoprolol, however, the vasodilating action of adrenaline is largely preserved.[1]

These observations could be of interest in the choice of a beta-blocking drug in the treatment of hypertension if the difference between the effects of the two drugs were still present after a longer therapeutic use in hypertensive patients. Therefore, we compared the effects of propranolol (80 mg thrice daily) and metoprolol (100 mg thrice daily) in eight patients with essential hypertension (diastolic blood pressure between 100 and 120 mm Hg) in a double-blind crossover trial. There were four periods of four weeks' duration each: placebo—drug—placebo—drug. The active drugs were given in randomised order. At the end of each period we studied the effects of an infusion of adrenaline (8 μg/min for 6 min) on the blood pressure and the blood flow in the forearm by means of mercury strain-guage plethysmography.

The results, as changes arising during adrenaline infusion, are shown in the accompanying table. Apparently the vasodilating action of adrenaline is still present after treatment with the $beta_1$-selective blocker for four weeks. It should be noted that on metoprolol this effect is not entirely normal: the decrease in vascular resistance is smaller than during placebo treatment. There is, however, no significant rise in mean arterial pressure. During propranolol treatment on the other hand the rise in blood pressure induced by adrenaline is considerable and significant. At the same time there is an important decrease in the blood flow in the forearm and a clear increase in the vascular resistance.

These results may be of clinical significance. During emotional stress endogenous adrenaline release increases,[2] while the blood flow through muscle rises.[3] It is conceivable that adrenaline release caused by such stresses as emotion, anginal attacks, or hypoglycaemia is comparable with these adrenaline infusions. Then, during treatment with propranolol, considerable rises in blood pressure would result. This would not be the case during metoprolol treatment. Our results therefore seem to favour a selective $beta_1$-blocker over a non-selective one in the treatment of hypertension.

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[1] Johnsson, G, *Acta Pharmacologica et Toxicologica*, 1975, **36**, suppl 5, p 59.
[2] Levi, L, *Stress and Distress in Response to Psychosocial Stimuli*. Oxford, Pergamon Press, 1972.
[3] Brod, J, *et al*, *Australian and New Zealand Journal of Medicine*, 1976, **6**, suppl 2, p 19.

Effects of adrenaline on mean arterial pressure (MAP), blood flow, and vascular resistance (MAP/flow) in forearm in eight hypertensive patients (mean ± SEM) and results of Student's t test for paired observations

	MAP		Blood flow		Vascular resistance	
	mm Hg	P	ml/100 ml tissue/min	P	MAP/flow	P
Placebo	0 ± 2		+ 2·6 ± 0·5	<0·001	− 22 ± 4	<0·01
Propranolol	+ 21 ± 3	<0·01	− 0·7 ± 0·4	>0·10	+ 21 ± 7	<0·01
Metoprolol	+ 5 ± 3	>0·10	+ 0·7 ± 0·3	<0·05	− 5 ± 2	<0·05
Placebo *v* propranolol	P<0·001		P<0·01		P<0·01	
Placebo *v* metoprolol	P>0·10		0·05<P0·10		P<0·05	
Propranolol *v* metoprolol	P<0·01		P<0·05		P<0·01	

Dangers of dextropropoxyphene

SIR,—I read with interest your leading article on the "Dangers of dextropropoxyphene" (12 March, p 668) and would like to make the following observations.

(1) I think it is true to say that any pharmaceutical preparation of any clinical use is bound to have one side effect or another, and if side effects are not present it is highly likely that the preparation does not have any great effect.

(2) You discuss the problem of drug dependency and addiction but quote only one case where any possibility of addiction is present, and this due to evidence of the drug being found in the cord blood of a baby shortly after birth; this surely is not statistically significant. I also note with interest that there are no English references on the problem of drug dependency.

(3) The problem most interesting to me is that of self-poisoning. The accident and emergency department of the Hull Royal Infirmary uses dextropropoxyphene-containing compounds in considerable quantity, and there is evidence (you quote 2·5 million NHS prescriptions in England in 1970) to suggest that such compounds are perhaps the most commonly prescribed analgesic in the North Humberside area. I cannot, however, recollect having seen in the last year one overdose except in those cases where the overdose consisted of polypharmacy.

You conclude by asking the question, "How good is the case for using the drug at all?" The major problem stressed in your article is that of self-poisoning, and I think it would be fair to say that paracetamol, the preparation which causes us most concern, can be bought without restriction from any chemist in the country, and that any drug if taken in sufficient quantity will have overdosage side effects. I think we must also keep the problem of overdosage in perspective and note that, despite the massive usage of dextropropoxyphene over the past 12 years, it in no way compares with other preparations as far as the problem of overdose is concerned.

I suppose we must now look forward to a period where the drug firms will go into competition over the usage or non-usage of dextropropoxyphene, and will receive daily circulars extolling the virtues of their simpler, "less dangerous," but also less effective, products.

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Vitamin C and drug metabolism

SIR,—Your leading article (19 March, p 735) on vitamin C deficiency in liver disease rightly points out the lack of information in man on the effect of such deficiency on drug metabolism by the liver. In guinea-pigs vitamin C deficiency results in decreased antipyrine metabolism[1] and reduced liver cytochrome P-450 levels.[2] Both these abnormalities are reversed by correcting the deficiency; indeed, there is some evidence that vitamin C supplementation in non-deficient animals might stimulate metabolism.[3]

However, in man administration of vitamin C to non-deficient volunteers does not appear to enhance the metabolism of antipyrine.[4] In liver disease low concentrations of leucocyte ascorbic acid do seem to be associated with impaired antipyrine metabolism,[5] although it is possible that both are reflecting the severity of the disease.

We have studied the effect of vitamin C deficiency on antipyrine metabolism in old age. The metabolic clearance rate (MCR) in 10 deficient people was 25·3 ± 8·8 ml/h/kg, compared with 33·5 ± 11·5 in 27 non-deficient old people. This difference is significant ($P < 0·05$). When eight of the deficient group were given vitamin C for two weeks the MCR improved from 26·1 ± 9·6 ml/h/kg to 36·5 ± 12·9 ml/h/kg. The difference was again significant ($P < 0·025$). No such improvement could be demonstrated in the non-deficient group.

It seems clear that vitamin C deficiency in man causes a small but demonstrable impairment in drug metabolism that can be reversed by correction of the deficiency. As vitamin C deficiency is known to occur in about half of the old people admitted to geriatric wards[6] it could account for at least part of the reduction in drug metabolising ability found in the elderly.[7]

As vitamin supplementation in people with no demonstrable deficiencies does not alter drug metabolism, it can be concluded that no