Duration of diabetes at entry (years)	Excretion rate at entry (mg/24 h)	Estimated annual rate of increase (%)	Estimated excretion rate at follow up (mg/24 h)	Estimated time from entry to overt nephropathy (years)
16	75	12.6	246	12
26	75	7.8	158	20
37	75	5.5	128	26

Forsblom and colleagues found that only five of 26 microalbuminuric patients developed overt nephropathy, suggesting that microalbuminuria has a low predictive value.¹

It has been suggested that the rate of progression of urinary albumin excretion (percentage increase per year) is constant over time in individual patients, but varies considerably between patients.^{2,3} Observational studies indicate that the median rate of increase is 20% a year (range 10–58%) in patients progressing to overt nephropathy.^{2,4} If a constant rate of increase is assumed the predicted urinary albumin excretion rate can be estimated as:

$$UAER(t) = UAER(0) \times (1 + s/100)^t$$

where UAER(t)=urinary albumin excretion rate at time t, UAER(0)=urinary albumin excretion rate at onset of diabetes, t=time (years), and s=annual rate of increase (%).

In Forsblom and colleagues' study the mean duration of diabetes at entry of the microalbuminuric patients was 26 years (range 16 to 37 years) and the urinary albumin excretion 92 mg/24 h (range 30 to 265, estimated median 75 mg/24 h). The table shows the estimated annual rate of increase in urinary albumin excretion, the urinary albumin excretion rate at follow up, and the time from entry to the development of overt nephropathy obtained with the formula above for three patients with urinary albumin excretion rates of 10 mg/24 h at the onset of diabetes and 75 mg/24 h at entry to the study (corresponding to the range in the study). Despite a significant increase in the albumin excretion rate in all three patients, none of them would develop clinical nephropathy during a 10 year follow up. This could explain the observed low predictive value of microalbuminuria.

Normally patients are classified as normoalbuminuric, microalbuminuric, or macroalbuminuric. Thereby the quantitative information given by the actual excretion rate is reduced to semiquantitative information. A patient may, however, experience considerable deterioration but remain in the same group. Identifying patients with fast progression, slow progression, and non-progression by calculating the rate of increase for each patient on the basis of repeated measurements may thus be more relevant. When progression of microalbuminuria is being studied the rate of increase may prove to be a more sensitive outcome variable than the conventional semiquantitative classification as it can even be used as a continuous outcome variable in the analysis.

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AUTHORS' REPLY.—In reply to Philippe Fressinaud and Michel Marre, a calendar effect is unlikely to explain our results. The table shows that progression to manifest albuminuria in the microalbuminuric patients was associated with higher diastolic blood pressures (95 v 80 mm Hg; $p < 0.01$). Two of the five microalbuminuric patients who developed macroalbuminuria were subsequently treated with angiotensin converting enzyme inhibitors. Of the 13 originally microalbuminuric patients who did not progress to overt nephropathy, only four had hypertension at the initial screening. During follow up an additional patient developed hypertension. These patients received combination treatment with β blockers or calcium channel blockers and diuretics. None of them received treatment with an angiotensin converting enzyme inhibitor. The table shows that treatment did not reduce blood pressure enough in these patients.

Of the three initially macroalbuminuric patients who regressed to microalbuminuria, one had hypertension at the initial screening and another developed hypertension during follow up. In accordance with treatment policy at that time, both these patients were treated with angiotensin converting enzyme inhibitors.

Thus the data do not support the view that the lower rate of progression in our patients was due to more efficient antihypertensive treatment. In contrast, they indicate that progression to macroalbuminuria in these patients was associated with failure to normalise the blood pressure.

In reply to Gian Carlo Viberti and Rogerio Friedman, our paper dealt with microalbuminuria as a risk factor for progression to overt nephropathy in patients with longstanding insulin dependent diabetes mellitus compared with patients with disease of shorter duration. Unfortunately, we had to extract the latter data from published reports.^{1,2} The difference between our and the quoted studies was, however, obvious—28% v 88% or 86%—suggesting that the patients with longstanding disease are less susceptible to progression to overt nephropathy. We did not particularly address the issue of whether microalbuminuria in general is a risk factor for both diabetic nephropathy and cardio-

vascular disease, although the data could be retrieved from the paper. It is clear that microalbuminuria in patients with longstanding insulin dependent diabetes mellitus confers an increased risk of nephropathy. The risk is, however, only one third of the risk reported in patients with a shorter duration of disease.^{1,2}

As outlined above, arterial hypertension was associated with the progression from microalbuminuria to macroalbuminuria. The blood pressures in our study, however, did not differ significantly from those reported in the two previous studies.^{1,2} Although high blood pressure seems crucial for the progression to overt nephropathy in patients with insulin dependent diabetes mellitus, it is unlikely to explain the difference between the current and previous studies.

We agree with Viberti and Friedman that if patients with longstanding insulin dependent diabetes mellitus are to be excluded from trials aiming at preventing the progression from microalbuminuria to macroalbuminuria it may be most rewarding to exclude patients with disease of more than 20 years' duration. Finally, given the paucity of data, these guidelines should be regarded as tentative until confirmed by a larger independent study.

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Managing depression in general practice

EDITOR.—As a former general practitioner I enjoyed E S Paykel and R G Priest's comprehensive report on the recognition and management of depression in general practice.¹ But to describe the traditional tricyclic antidepressants as cheap on the basis of drug costs is inappropriate as it disregards expensive problems associated with their use.

Johnson found that 68% of patients in general

Mean blood pressure (95% confidence interval) and prevalence of antihypertensive treatment at initial screening and at follow up in insulin dependent diabetic patients with normoalbuminuria, microalbuminuria, and macroalbuminuria

	Initial screening			At follow up		
	Systolic blood pressure (mm Hg)	Diastolic blood pressure (mm Hg)	No receiving antihypertensive treatment	Systolic blood pressure (mm Hg)	Diastolic blood pressure (mm Hg)	No receiving antihypertensive treatment
Albuminuria at follow up						
Normoalbuminuria (n=20)	128 (120 to 136)	78 (74 to 82)	0	132 (126 to 138)	81 (76 to 86)	2
Microalbuminuria (n=4)	126 (104 to 148)	79 (70 to 89)	0	127 (95 to 159)	82 (70 to 94)	1
Macroalbuminuria (n=2)	120 (47 to 119)	83 (47 to 119)	0	135 (63 to 207)	84	1
Microalbuminuria initially (n=18)	135 (120 to 150)	80 (75 to 85)	3	137 (125 to 149)	79 (70 to 88)	4
Macroalbuminuria initially (n=5)	150 (116 to 184)	95 (88 to 102)	3	162 (137 to 187)	90 (78 to 102)	5
Microalbuminuria initially (n=22)	146 (109 to 183)	94 (62 to 126)	1	135 (78 to 192)	81 (59 to 103)	2
Macroalbuminuria initially (n=12)	147 (135 to 159)	93 (85 to 101)	9	136 (118 to 154)	83 (79 to 87)	12
End stage renal failure (n=7)	147 (127 to 167)	87 (82 to 93)	6	145 (133 to 157)	81 (61 to 101)	7

ACE=Angiotensin converting enzyme.

practice who were treated with tricyclic antidepressants were non-compliant after four weeks.² In another study psychiatric outpatients taking traditional tricyclic antidepressants showed compliance of only 46%, compared with 71% for patients given newer antidepressants.³ Even when compliance is adequate, concern over side effects (for example, sedation, orthostatic hypotension, anticholinergic effects, long term weight gain) means that patients receive inadequate doses⁴ and are treated for an insufficient time.

The cardiovascular toxicity of tricyclic antidepressants results in some 300 deaths from overdose every year.⁵ This must be a primary consideration—not just in economic terms. Impairment of psychomotor function by tricyclic antidepressants may increase liability to accidents. In a review of motorway accidents drowsiness was the direct cause of 27% of accidents and 83% of the deaths.⁶ The relation between falls in elderly people, involving femoral fractures, and sedative drugs is well established.⁷

The newer antidepressants, such as the specific serotonin reuptake inhibitors, cost more but increase the likelihood of compliance at an adequate dose for a sufficient time and without serious toxicity. They appreciably improve the risk:benefit ratio for antidepressant treatment with drugs. Specific serotonin reuptake inhibitors have been shown to be as effective as tricyclic antidepressants in treating depression. They can be started at an effective dosage (in a single tablet daily), unlike tricyclic antidepressants, which must be titrated from an initial low dose to an effective dose. They are unlikely to sedate.⁸ They do not exhibit the typical side effects of tricyclic antidepressants, and they have a greatly reduced toxicity in overdose.⁹ Side effects are usually predictable and dose related, principally in the gastrointestinal and central nervous systems, and are generally acute and mild and ameliorate with continued treatment.⁹

The main component of the cost of treatment is the cost of failure of the treatment. The largest contributor to the direct costs of depression is not the cost of drugs but the cost of inpatient and outpatient care.¹⁰ When viewed in the wider context of cost-benefit the traditional tricyclic antidepressants may deserve the label of an expensive therapeutic option and the newer drugs may be more cost effective.

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despite the authors' admission that neither the dosage nor the duration of such treatment has been established. Indeed, no antidepressant apart from sertraline is licensed in the United Kingdom for the prevention of recurrence in depression, which means that practitioners are expected to take upon themselves the liability for these drugs' unlicensed use.¹ Lithium, mentioned only as being effective in prophylaxis against bipolar affective disorder, is effective in augmentation treatment for the one third of patients who do not respond to the first drug used¹ and is also licensed for long term treatment of unipolar depression.¹ Further, there is evidence that overall mortality and suicide rates are decreased in patients with recurrent mood disorders who are treated with lithium compared with untreated patients.⁵

General practitioners (who see and treat 95% of depressed patients) should be encouraged to consider a wider range of drugs than the older tricyclic agents for managing their depressed patients.

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Informing patients about clinical trials

EDITOR,—The public has many misconceptions about the nature and conduct of clinical trials, and this may contribute to the overall low level of participation in trials. Even after giving conventional informed consent patients often forget or misunderstand the basic elements of a particular study.¹ Explaining such difficult concepts as clinical uncertainty or randomisation to patients, some of whom may still be in a state of emotional shock after learning their diagnosis, remains a major communication challenge for health professionals. Kim A Priestley and colleagues highlight the poor readability of many consent forms for specific research protocols and the need for a simpler writing style.²

Attention is now focused on improving the methods used to educate patients about clinical trials. We have recently developed a patient information booklet on clinical trials entitled *Understanding Clinical Trials: Questions and Answers*.³ This is available as an information resource for patients interested in taking part in a clinical trial and supplements the detailed information usually provided on a particular study. It describes the nature and purpose of clinical trials, their potential benefits and risks to patients, the main features of a properly designed trial, and suggested questions for the patient to ask the doctor about a particular trial.

The importance of piloting such a handout for patients among both colleagues and a sample of the target consumers was reinforced by Tony Smith.⁴ Pretesting of educational materials helps reduce the uncertainty of producing material that may be misunderstood. For our booklet we assessed

factual accuracy, comprehension, and various attitudes towards its contents by testing its use on about 100 health professionals and patients before distribution.⁵ From the information gleaned substantial improvements have been made: the language has been simplified, the section on benefits and risks expanded, and illustrations and a page for patients' notes added.

We believe that such a booklet is a helpful adjuvant to individual discussion and for enlisting the cooperation of patients and their families in clinical trials. Exactly what information patients consider to be pertinent to their decision to accept or refuse entry to a trial remains unclear: different educational strategies will probably work for different groups of patients. A clinical trial is planned to evaluate this booklet's contribution to patients' comprehension, recruitment, and compliance in a national trial in cancer and AIDS.

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The health divide

EDITOR,—Richard G Wilkinson's editorial reminds us that the widening of health inequalities in the United Kingdom is responsible for our declining position in the international health league.¹ The author emphasises that countries with smaller differences in health between socio-economic groups also have lower overall mortality and that this is linked to narrower differences in income. While other governments, in line with the World Health Organisation's "health for all" strategy,² are tackling socioeconomic disadvantage in health practically, this seems to be neglected in the white paper *The Health of the Nation*.³

Shewry *et al* showed clearly that the more socially disadvantaged had more risk factors for coronary heart disease and suggested that health education and management resources should be targeted according to the socioeconomic profile of an area.⁴ It seems that the revised strategy for health promotion and management of chronic disease in general practice will ignore this and instead be based on capitation and list size. Thus many deprived populations will once again lose out and be marginalised.

Baker observed that patients in underprivileged areas were served by less developed practices⁵ and suggested that family health services authorities and medical audit advisory groups should target their efforts towards supporting the development of these practices. The Association of Community Health Councils for England and Wales says that the move towards population based funding for health districts will see some inner city areas losing up to 24% of their budgets; it has called for regional health authorities to add a deprivation weighting when allocating money to districts.⁶

The message is clear: that accurate targeting of resources to deprived areas is essential to improve the health of the nation.⁷ The Jarman underprivileged area score is a move in the right direction,

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EDITOR,—The consensus statement on the recognition and management of depression in general practice provides useful guidelines,¹ but one of the recommendations gives cause for concern.

Antidepressants are recommended for long term prophylaxis against unipolar affective disorder