enough to have adequate statistical power: more than 1200 patients had to be identified over three years to obtain 620 who were able and willing to participate. The infusion protocol may also have helped to control plasma glucose more rapidly than protocols used in previous studies.^{14 15}

What relevance might the findings have to people without a history of diabetes who present with myocardial infarction and a plasma glucose concentration at admission of 8–11 mmol/l? There is evidence that mortality in hospital is increased in this group even when patients with a previous diagnosis of diabetes are excluded.^{4 17} During the 1960s and 1970s, combined infusions of glucose, insulin, and potassium were widely used in the acute management of myocardial infarction even in non-diabetic patients, especially in Italy. In a small randomised study, this seemed to increase ejection fraction and to reduce pulmonary artery end diastolic pressure.¹⁸

Despite the wide confidence intervals for the size of effect, the Swedish trial is impressive evidence that rigorous control of plasma glucose by insulin infusion improves the long term outcome of myocardial infarction for patients with established diabetes or plasma glucose concentration greater than 11 mmol/l on admission. The possibility that glucose and insulin infusions could benefit patients with lesser degrees of hyperglycaemia is one worth investigating in future trials.

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Thrombolysis in acute stroke

Defining the risk to benefit ratio for individual patients remains impossible

Treating acute stroke is one of medicine's most difficult challenges as this millennium ends. It remains handicapped by deep rooted ignorance, fatalism, nihilism, and scepticism. This contrasts with the well accepted management of acute myocardial infarction, although the treatment of "heart attacks," as for "brain attacks," relies more on general and intensive care, including thrombolysis, than on drugs that specifically protect myocardial cells.

The most encouraging prospects for treating acute stroke include protecting ischaemic brain tissue (neuroprotection) and recanalising the occluded artery (thrombolysis).² Interest in thrombolysis in acute stroke has been emphasised recently by several randomised trials.³ Nearly 3000 patients with acute stroke were studied in more than 10 trials. Meta-analysis of these data shows that intravenous thrombolysis was associated with a 20% reduction in the odds ratio for poor outcome (death or severe disability) but also with a 44% increase in the odds ratio of death—mainly due to a more than threefold increase in brain haemorrhage.⁴

The only positive trial of thrombolysis is that organised by the National Institute of Neurological Disorders and Stroke,⁵ which included 624 patients randomised to receive either intravenous placebo or alteplase (0.9 mg/kg to a maximum of 90 mg) given as a 10% bolus followed by an infusion lasting 60 minutes within three hours of onset of ischaemic stroke. There was no significant difference in neurological recovery at 24 hours, but at three months the patients given alteplase were about a third more likely to have no or minimal disability than the control patients. This corresponded to odds for "favourable outcome" of 1.7 (95% confidence interval 1.2 to 2.6). Mortality was not significantly

different. The European cooperative acute stroke study (ECASS) of 620 patients was similar in design, except that treatment could be initiated within six hours of the start of stroke and the dose of alteplase was higher (1.1 mg/kg to a maximum of 100 mg).⁶ The general results were not encouraging—the mortality at three months was higher in the treated group than in the controls (22.4% v 15.8%, $P < 0.04$), with no compensating improvement in functional state. However, after excluding over 100 protocol violators (mainly with early ischaemic signs on computed tomography, which is a marker for severe haemorrhagic transformation), analysis of the "target population" showed a better functional outcome in the patients given alteplase than in those given placebo (median shift in disability from moderate to slight on the scale used). In contrast, the three recent large trials of streptokinase used within four to six hours of the start of stroke showed clearly negative results—all three were stopped because of an increase in mortality and brain haemorrhage.^{7–9}

There is therefore an important disparity between the negative or neutral findings of the European and Australian trials of streptokinase and the European trial of alteplase on the one hand,^{6–9} and the positive findings of the American trial of alteplase on the other.⁵ This disparity may explain the difference between an American committee's clear recommendation to treat selected patients with alteplase (within the inclusion criteria of the National Institute of Neurological Disorder and Stroke trial)¹⁰ and the more cautious statement by a European committee that this treatment may be indicated for selected patients in units specialising in intensive care of stroke.¹

Making generalisations about a potentially dangerous treatment on the basis of a single trial is controversial. Moreover, although the National Institute of Neurological Disorder and Stroke trial was well designed and conducted, it has several problems. Firstly, the risk to benefit ratio is narrow—the 12% absolute increase in the favourable outcome was associated with a 6% absolute increased risk of symptomatic brain haemorrhages, almost half of which were fatal. In fact, the risk of haemorrhagic transformation was particularly high in this trial—it was increased by a factor of 10 in the group treated with alteplase, compared with the threefold to fourfold increase found in the other trials. Another problem relates to the excessive number of patients with presumed lacunar stroke who were allocated to receive alteplase (16% *v* 10% of controls, $P < 0.03$). Patients with lacunar stroke represent a subgroup in which the potential benefit of thrombolysis is suspect, and those who were given placebo had a much worse evolution than expected from the literature on the natural course of this condition.¹¹ In contrast, alteplase was less effective in the patients with large artery disease or thromboembolism than in those with lacunar stroke. This is puzzling since stroke due to arterial or cardiac embolism is the primary target of thrombolytic treatments.

Given these uncertainties, together with the clear dangers associated with thrombolysis, there seems to be a more cautious attitude among many European experts, in clear contrast to the more enthusiastic approach of many American experts at the recent international conference on thrombolysis in stroke (Copenhagen, May 1996). However, an important consensus was achieved on the need to consider acute stroke as an emergency (needing medical attention within six hours, preferably in less than three) and the need to ensure specialist management of patients with stroke, especially if thrombolysis is considered.

Many problems remain unsolved. Intra-arterial thrombolysis is attractive because it allows direct evaluation of occlusion and recanalisation. However, its availability is, and will remain, limited, and it has not so far been submitted to an appropriate randomised trial. With both intravenous and intra-arterial thrombolysis, there may be substantially different responses to treatment in relation to the site of occlusion, nature of embolic material, availability of collateral circulation, and subtype of stroke. Indeed, stroke is not a single disease, although early differentiation of subtypes remains difficult. In this setting

there may be a room for new imaging techniques to show what proportion of ischaemic tissue may still be saved, such as diffusion and perfusion magnetic resonance imaging.² The idea would be to select within the first few hours of the start of stroke the patients with potential for recovery or improvement. Time is probably the most important factor for defining the therapeutic window in acute stroke, but it is modulated by individual factors that may be critical. It may be that we must improve our skills in selecting the right patients for the right treatments.

Putting all the available data in perspective, it is difficult or impossible to define clearly a specific risk to benefit ratio in individual patients with acute stroke. Even for patients who fall within the inclusion criteria of the National Institute of Neurological Disorder and Stroke trial, many are probably not suitable for thrombolysis. Further trials of thrombolysis are needed, but the aim of this research should be to define better which patients should be randomised rather than to generalise treatment prematurely to all patients admitted within three hours of the start of stroke.

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Deprivation payments revisited (again)

Equity remains a problem with current method of allocation

With the rising workload in general practice and an emerging manpower crisis, destabilising influences such as unpredictable shifts in income are to be avoided. Unfortunately, continuing to allocate deprivation payments to practices on the basis of geographical wards has resulted in large shifts in resources. This is because data from the 1991 census have now replaced the 1981 data, which had been used to calculate deprivation payments since the introduction of the new general practitioner contract in 1990.¹ The short report in this week's *BMJ* by Majeed *et al* (p 669) models the effects of applying census data to the existing rigid formula for allocating deprivation awards. Small shifts in the Jarman deprivation score around the payment bands can translate to practices gaining or losing tens of thousands of pounds, with no discernible change in their clinical workloads: one practice reported a 15% shift in income after a change in a ward boundary.² Such a lottery of winners and losers has been predicted since the introduction of deprivation payments,^{3,4,5} and

it is depressing that nothing has been done to try to limit the deficiencies in the current system.

The most obvious change would be to base deprivation payments on the Jarman score at the level of enumeration district (about 500 people) rather than ward (about 25 000 people). Now that all patients' addresses are computerised and postcoded at local authority level, it is difficult to see why this change has not been implemented. It would considerably improve the sensitivity of Jarman scores based on census data (and was advocated by Jarman from the start⁶). Allocation by enumeration district would also reduce the risk of wide swings in payments to individual practices at the time of changing censuses.

A second fundamental change would be to alter the current banding system for paying general practitioners.⁴ At present there are only three payment bands, which come into force at Jarman scores of 30, 40, and 50. Additional payment bands, starting at lower scores, have been advocated,⁶ but a continuous payment schedule could be even better.

See p 669