to be implicated in excitotoxic brain damage, epilepsy, learning and memory, and possibly psychosis (Barnes, 1988).

The neurotransmitter at NMDA receptors is probably L-glutamate, an excitatory amino acid which may kill the neuron if present in excess ('excitotoxicity'). Blockade of the receptor by ketamine can prevent this damage, which occurs in ischaemia, epilepsy, and other conditions (Barnes, 1988). Thus an endogenous blocking agent would have neuroprotective properties. An endogenous agent, which has been labelled 'alpha endopsychosin' (Quirion *et al*, 1984), has in fact been discovered for the PCP site. It is thus possible that a flood release of alpha endopsychosin could serve the function of reducing excitotoxic damage in the ischaemic brain, for example in the situation of a cardiac arrest. A by-product may be a temporary, dissociative hallucinogenic effect on consciousness. This is a more specific version of Carr's (1981) theory concerning the secretion of psychoactive peptides in stressful situations. However, while the endorphins, as suggested by Carr, may play a role in the NDE, they are not usually regarded as potent hallucinogens, unlike many of the substances active at the PCP binding site.

A further matter to consider is the possible role of this site in the formation and retrieval of memory. In his discussion of the psychological bases of the NDE, Siegel (1980) suggested that memories may normally be suppressed by a mechanism which acts as a gate to data from the outside. If this external input is decreased (as occurs in the patient who has had ketamine) while awareness remains, stored perceptions are released and may be dynamically organised. Blockade of NMDA receptors, by ketamine or perhaps alpha endopsychosin, suggests a neural substrate for the 'gate' of the sensory deprivation theory – i.e. it closes the 'gate' to external input so that old memories come to the fore instead, a feature of some NDEs.

In conclusion, the NDE is an entity of considerable interest and it may be of some value to apply the recent explosion of knowledge in neuroscience to our attempts to understand the phenomenon. Elucidating the properties of the endopsychosins, and the development of substances which are more specific for the PCP site (ketamine also binds to several other sites), may be of some value in this attempt.

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Affective 'switch mechanisms'

SIR: The notion of "switch mechanism" in affective disorders (Carney *et al*, *Journal*, January 1989, **154**, 48–51) is a challenging one, with both theoretical and clinical applications. I am sceptical about the conclusion that because "S-adenosyl methionine enters the CSF, is linked with CSF 5HIAA and folate metabolism, and influences prolactin" these "suggest an effect on dopamine metabolism" and the "dopamine system should be further explored".

I do agree that the dopamine system is an important neurotransmitter in the study of affective disorders, but I do not see the results of these open trials as being sufficient to highlight solely the role of dopamine and not serotonin if we have to concentrate on either.

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What's so special about two years anyway?

SIR: One of the most important criteria to be taken into account when assessing a patient for psychosurgery is that all reasonable treatments should have been tried and failed. In other words, the patient needs to have a treatment-resistant illness, usually depression, and some describe this as chronic depression. I was therefore interested in Dr Scott's review article with the title 'Chronic depression' (*Journal*, September 1988, **153**, 287–297).

Dr Scott accepts the definition of chronicity, previously suggested by others, as "symptomatic non-recovery for a period of two or more years". She goes on to consider the factors that may relate to chronicity, which include – among others – the illness (length of episode, course, symptom profile, etc), treatment, family and personal history, and personality.

The treatment aspects, which include inadequate and inappropriate treatment, do not appear to be given any weighting over and above the other factors. Yet treatment is the only aspect that can be decisively influenced by the clinician. He cannot alter the symptom profile, the past history nor the pre-morbid personality. But he certainly can treat adequately or inadequately and Dr Scott herself gives many references reporting examples of substandard treatment, subtherapeutic doses of antidepressants and even no treatment at all. Her observation that, "it is noteworthy that the introduction of a wide variety of new treatments has not significantly altered the prevalence of the disorder" may be true, but introducing new treatments does not ensure that they are used effectively.

Therefore, a span of two years before depression can be considered as chronic seems entirely arbitrary and without clinical meaning unless it is linked to the use of some defined and potent forms of therapy. The opinion that, "with regard to depression being treatment-resistant, the definition of the term is problematical as there is little agreement on the ... treatments that should be used" simply evades a fundamentally important issue. For example, we now regard it as essential for a combination of tryptophan, clomipramine, and lithium (Hale *et al*, 1987) to be tried unsuccessfully before a patient with an affective disorder is considered for psychosurgery.

A textbook of psychiatry (Gelder *et al*, 1983) observes of psychosurgery that "the operation should never be carried out until the effects of at least a year of vigorous in-patient treatment has been observed". I would agree if this meant that one year of intractable illness is usually the minimum in practice before psychosurgery should be seriously considered. But it could mean that, regardless of the clinical circumstances, the patient must wait for at least a year. Similarly, another textbook (Kendell & Zeally, 1988) takes this unit to task for stating that we would, if it were clinically indicated, assess a patient for psychosurgery less than one year after the onset of the illness and this, the authors observe, seems unjustified. Treatment-resistant depressions of that duration are not uncommon and spontaneous remission does occur". This has the rigidity that I am concerned about. The authors are likely to find it more comfortable to wait a full year than some severely depressed patients would. Surely the patient can be allowed to decide when distressing symptoms are quite intolerable, especially when the doctor has been unable to prove relief. Linking treatments to arbitrary periods of time is an autocratic and not particularly logical way of managing psychiatric illnesses.

For psychosurgery to be appropriate, the essential needs are for an appropriate and truly intractable illness (intractability will take time to be sure of, it is true) and a really desperate and incapacitated patient. But the time factor alone is not at all the issue. I believe that the shortest illness from onset to surgery that we have treated was about 10 months. During this period, earlier responses to antidepressant medication and ECT were soon lost. Suicidal drive and weight loss due to depressive anorexia became major and increasing problems. Why should we have waited a further therapeutically sterile two months, even although remission *might* have occurred?

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CPK levels and neuroleptic malignant syndrome

SIR: I read with great interest the two cases presented by Goldwasser *et al* (*Journal*, January 1989, **154**, 102–104). Their correlation of creatinine phosphokinase (CPK) profiles with clinical state and drug treatment is convincing – perhaps too convincing. Their findings certainly support the idea that elevated CPK values are a major sign of NMS and should be considered as 'classic'. However, moderate increase of MM isoenzyme fractions of this enzyme is also found in muscle injury, physical exertion, muscle cramping, intramuscular injections, and acute psychotic episodes (Zilva & Pannall, 1981).

The cases presented by the authors are young black males with features of rigidity, acute psychosis, and severe aggression, requiring forceful restraint and intramuscular injections. In spite of their impressive demonstration of "CPK steadily falling toward normal – even with the use of intramuscular medications and restraints" (case 1), is it not necessary to correct for these and other factors that contribute to rising CPK levels? Or are they not significant here? What are the levels and mode of degradation of CPK in black, aggressive psychotic patients needing restraint, but without NMS?

It seems difficult to accept the elevation of CPK as a 'classic sign' of NMS when so many other variables