which when occupied by an agonist molecule augments the effect of GABA on the post-synaptic membrane. Unfortunately, benzodiazepine therapy in epilepsy is limited by the development of tolerance during the first few months of treatment. Barbiturates bind to the picrotoxin receptor and in the presence of GABA increase the opening time of the chloride channels. This effect may be important in their anticonvulsant action.[29] Other compounds that bind to this site on the receptor complex may be developed as anticonvulsants.

An alternative approach to antiepileptic drug development is the design of chemicals to suppress excitatory activity, since the release of excitatory transmitters is thought to be responsible for onset of seizure activity. Although research in this sphere is less well advanced, agents such as 2-amino-7-phosphonoheptanoic acid, an antagonist of the excitatory neurotransmitters glutamate and aspartate, have shown promising antiepileptic activity in animal seizure models.[30]

These advances in the understanding of neurotransmitters and epilepsy have provided a rational basis for the development of new antiepileptic agents and we may now look forward to a time when abnormal mechanisms in epilepsy can be specifically modified to prevent seizures.

INOSINE PRANOBEX AND MUCOCUTANEOUS HERPES

WE are told that when the children of Israel first saw the miraculous food in the wilderness they exclaimed "What is it?" and so it got its name Manna. Whether or not that is good history or etymology, it reminds one of the perplexity of an individual trying to comment on the drug 'Imunovir'. The naming of drugs is supposed to help us appreciate what we are talking about, but this substance has been called among other things, isoprinosine, inosiplex, inosine pranobex (British approved name), and methisoprinol, and has been described both as an antiviral and as an immunopotentiating agent.

The drug inosine pranobex is formed from the *p*-acetamidobenzoate salt of N,N-diethylamino-2-propanol and inosine in a 3:1 molar ratio. Because it is absorbed but rapidly metabolised and excreted,[1] it is prescribed in repeated oral doses. It seems to be non-toxic by a range of tests in several species and is also well tolerated by man, although there is a risk that uric acid will accumulate if large amounts are given (uric acid being the main excretion product of the inosine component). The agent was originally promoted as an antiviral and, in tissue culture, concentrations of drug ranging from 0·005 to 150 μmol/ml have reduced the growth of a laboratory strain of an influenza A virus by up to 75%. However, unlike all known effective antivirals, even at high concentrations it does not inhibit virus replication completely. In laboratory animals there is some evidence of antiviral activity but effects on immunity are also reported; for instance, the drug seems to prevent the immunosuppression that accompanies experimental influenza infections in mice and enhances the lymphocyte transformation induced by phytohaemagglutinin.[2] Therefore the antiviral effects in animals may result partly from immunostimulation. In the laboratory, the immunostimulant properties of inosine pranobex seem to be different from those of levamisole or muramyl dipeptide.[3] In the early 1970s inosine pranobex was used against a variety of virus infections in several countries, but none of the reports describes a good clinical trial. It was tested against experimental common colds and influenza in volunteers: some careful studies showed no effect at all, others some benefit. Nevertheless the drug is now licensed for sale in sixty countries, for indications ranging from infectious hepatitis, via influenza, to subacute sclerosing panencephalitis (SSPE).

When in 1982 we surveyed the evidence for the drug's efficacy in SSPE we were unconvinced, even though large numbers of patients had received the drug.[4] Review of the published evidence on other reported benefits again leaves many questions unanswered. What about the management of mucocutaneous infections due to herpes simplex virus (type I and/or type II), for which the drug is licensed in the UK? Double-blind placebo-controlled trials are reported from several centres in which 1 g was given four times daily to patients, most of them otherwise healthy, who had recurrences of genital herpes or cold sores. There was early relief of pain, soreness, and swelling and more rapid crusting and healing in the treated group.[5-8] The reports are somewhat lacking in detail, for instance on the comparability of the groups, but the effects look clinically useful. Patients treated this way do show enhanced cellular immune responses.[6] Galli et al[9] claim that the frequency of recurrences can be roughly halved by giving the drug at about the same dose for one week in every month.[9] There are, however, alternative ways of treating this group of conditions—for instance, with a potent mucocutaneous antiviral drug such as acyclovir.[10-14] Acyclovir is certainly beneficial in severe herpes in immunosuppressed subjects and in primary or recurrent

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labial or genital herpes in normal subjects. The ointment is ineffective and intravenous infusion is seldom justified but oral preparations or a cream apparently work, though they reduce the duration by only a couple of days or so. Recurrent infections respond less well and the drug must be started early, ideally when premonitory symptoms arise. Although prophylaxis with acyclovir is possible there are worries about whether it is safe or justifiable.[15,16] The whole matter is unresolved;[16] furthermore, there are other promising drugs such as phosphonoacetic acid, which seems to be effective when used locally in recurrent genital herpes. Because of the many different ways in which drugs are used, the published work allows no conclusions about which is the best agent for "mucocutaneous herpes". Inosine pranobex and other therapies need to be compared for both therapeutic and prophylactic efficacy. Until such evaluations are complete, inosine pranobex should be reserved for conditions in which there is good evidence of benefit: it should certainly not be used for virus infections in general.

MORE ON MELANOMA

THE incidence of cutaneous malignant melanoma is said to be increasing in all parts of the world where records are kept, and the incidence of publications is more than keeping pace. What has this information explosion yielded in clinically relevant advances? What gaps in our knowledge have been clearly established, and how much of the paperwork must be designated to the category of "yet another series of 50–100 patients" with emphasis on the author's particular views? The range of writing is well illustrated in an issue of the *American Journal of Dermatopathology*[1] devoted to malignant melanoma. The pathological features most useful in prognosis remain the Breslow[2,3] thickness and Clark level of invasion,[4] and no-one who offers a new prognostic feature should fail to adjust the data statistically for tumour thickness by the log-rank test or multiple sequential logistic regression. Using these methods appropriately, North American groups have suggested that microscopic ulceration,[5] pathological evidence of partial tumour regression,[6] and body site[7] of the lesion are additional prognostic features. All, however, are lightweight by comparison with tumour thickness, and in some cases other groups have not been able to confirm[8,9] their validity. Since there is still disagreement among investigators about the relevance of such observations in groups of patients, the dermatologist or surgeon in the clinic cannot hope for much guidance in the context of the individual patient.

A worrying item is the report by Schmoeckel[10] of differences of opinion among 15 world experts in melanoma pathology concerning the malignancy or benignity of nine "borderline" lesions. This is certainly a difficult area of dermatopathology, but if those who make the rules and write the major papers disagree, the general pathologist in a busy district general hospital who sees only 6–12 new cases of malignant melanoma a year will be hard placed to obtain expert advice. This matter also has implications for epidemiologists; could it be that, in those parts of the world where the incidence of malanoma seems to be rising most sharply, more of the pathologists are including these "borderline" lesions in the malignant melanoma group?

Ten pages of the journal are devoted to resection margins around cutaneous malignant melanomas. Until the mid-1970s the dogma in surgical units was that 5 cm of clinically normal skin in all directions around a primary melanoma was a "normal" or "adequate" excision margin. This was based on a 1907 report by Sampson Handley[11] concerning one patient with cutaneous metastases (not a primary malignant melanoma). After the clear observations by Breslow[12] and by Clark[13] that melanomas could be divided into good, intermediate, and poor prognostic lesions according to tumour thickness or depth of invasion into the dermis, this teaching began to be questioned. Cosimi et al[14] have lately described local excision in 49 cases with a 1 cm margin of clinically normal skin and direct closure[14] of lesions measuring 1·2 mm or less in tumour thickness; and their judgment is that this smaller, cosmetically more acceptable margin of normal skin does not reduce five-year survival, and that neither local recurrence nor distant metastases are commoner in the group having the narrower margin of excision. A controlled trial to answer this question (WHO Melanoma Group Trial 10) is now in progress: patients with tumours 1·5 mm or thinner are randomised into two groups, one to undergo narrow excision with a margin of 1 cm of clinically normal skin, the other to have wider excision with a margin of 3 cm of clinically normal skin. Since the bulk of the observed or apparent increase in the incidence of malignant melanoma seems to be in patients with these thinner tumours, this information is much needed.

A corollary to the policy of tailoring excision margins to measured tumour thickness is the fact that an excision biopsy of the tumour must be done to enable this measurement to be obtained, so that further surgical policy can be rationally planned. For accuracy, this thickness measurement should ideally be performed on paraffin-processed rather than snap-frozen tissue, and a two-stage surgical procedure may therefore be needed in those patients who are found to have thicker tumours possibly requiring wider excision. This could create organisational difficulties in a busy surgical unit and in many centres will require the patient to be informed

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