Strategies of drug resistance in herpes simplex

from H. J. Field and G. K. Darby

ALTHOUGH effective anti-viral drugs are only just being developed it already seems likely that viruses have diverse strategies of drug resistance. Foremost among the anti-viral drugs is acyclovir (ACV)*, a nucleoside analogue which has shown great promise particularly against herpes simplex virus (HSV) infection. A wealth of encouraging results already exist for animal model systems [1-8], and clinical trials in man are now underway in Britain and the US.

Workers at Burroughs Wellcome first showed that two virus specified enzymes are involved in the mechanism of action of this compound[9-11]. Firstly ACV is 'activated' in infected cells by conversion to its triphosphate, the initial step in this process being carried out by the virus-coded enzyme, thymidine kinase (TK). For the drug to block the multiplication of the virus, the ACV-triphosphate must then interact with a second virus-coded enzyme, DNA polymerase[9,12].

Elion and her colleagues[9] showed that a virus unable to induce thymidine kinase was resistant to the drug. It also seemed that a second class of resistant virus — one with an altered DNA polymerase function — was theoretically possible. Investigations of resistant viruses generated by passage of HSV in the presence of the drug[13] suggested that resistance could indeed arise in this way, although initially it was only observed in TK^- viruses. Evidence that mutations in the DNA polymerase gene of HSV could confer resistance to ACV was provided independently by Coen and Schaffer [14] and Schnipper and Crumpacker[15]. In both cases viruses were investigated in which exposure to phosphonoacetic acid (PAA) — a compound acting predominantly at the level of DNA polymerase[16] — had produced PAA resistance. The TK^+ viruses selected for resistance to PAA had also frequently acquired resistance to ACV, and it was concluded that the most likely location for this second ACV-resistance locus was the polymerase gene. Both groups also observed that selection of resistant strains in the presence of ACV generally yielded TK-deficient viruses although Coen and Schaffer[14] described one strain which appeared in addition, to have acquired resistance at the polymerase locus.

Is ACV resistance likely to become a clinical problem in man? To answer this we must look at the biological properties of resistant viruses. TK^- viruses arise readily in tissue culture in actively dividing cells where TK is a non-essential virus function. Evidence is accumulating, however, that such viruses are attenuated in animal model systems, particularly in their interactions with the nervous systems[13, 17,-21]. This may make their establishment *in vivo* unlikely and may also explain the lack of reports of such isolates from animals undergoing treatment with ACV.

In contrast with the frequent isolation of TK-deficient viruses, the change to resistance at the DNA polymerase locus occurs much less readily[13-15]. Since in this case the enzyme function is essential for virus replication, there must be considerable constraints on structural alterations. Nevertheless, studies on PAA-resistant viruses[22] and a TK^+, ACV-resistant virus[13] suggest that these viruses may not be attenuated as much as TK-deficient strains and may therefore be more of a problem. It is interesting in this context that a study by Hirano *et al.* last year[23] revealed that resistant strains of HSV isolated from patients treated with Idoxuridine were TK^+, leading the authors to speculate that these were DNA polymerase mutants. This contrasts with the TK^- phenotype commonly associated with Idoxuridine resistance generated *in vitro*.

In the next few months information should become available on isolates obtained from humans treated with ACV. The *in vitro* work to date suggests that the analysis of such isolates will be complex and may well reveal unexpected strategies employed by HSV to outwit the nucleoside chemist. □

**9-(2-Hydroxyethoxymethyl) guanine, also known as acycloguanosine.*

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Primeval galaxies and the X-ray background

from Beatrice M. Tinsley

YOUNG galaxies must have been spectacular objects, with very high rates of star formation and associated bright stars, supernovae, optical nebulosities and X-ray sources. Some years ago, Partridge and Peebles noted that primeval galaxies might be detectable not only as individual objects (*Astrophys. J.* **147**, 868; 1967) but also as a source of diffuse background radiation at wavelengths from ultraviolet to infrared. (*Astrophys. J.* **148**; 1968). The search for primeval galaxies began with those papers and continuing into the present has branched into X-ray astronomy.

Most of the effort has focussed on individual primeval galaxies, with optical searches for them and theoretical models for their properties in all parts of the electromagnetic spectrum, (for a review see Sunyaev *et al. Comments Astrophys.* **7**, 183; 1978; Meier & Sunyaev *Scientific American* Nov. 1979 and Tinsley *Phil. Trans. R. Soc.* **296**, 303; 1980). Galaxies have been found in deep counts that have much bluer colors and probably higher rates of star formation than their nearby descendents (Bruzual & Kron *Astrophys. J.* in the press), but it is not know whether these are young or luminous enough to quality as *bona fide* primeval galaxies.

Searching for the integrated background light of young galaxies has proved to be an extremely difficult task at optical wavelengths because the diffuse extragalactic

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