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Acyclovir

How soon will antiviral drugs be found that will match the impact of antibiotics over the past 40 years? Herpes virus infections may not be the most clinically important virus diseases, but they look likely to be the first for which effective treatment is available. Herpesviruses contain DNA as their genome, and the earliest antiherpes drugs—idoxuridine, cytarabine, and vidarabine—are all DNA nucleoside analogues. They inhibit herpes by blocking DNA replication, but unfortunately they also affect the DNA metabolism of the host cell, so that side effects, sometimes severe, can be a problem when they are given systemically. They are not toxic when given topically, however, and local idoxuridine has proved a successful treatment for herpetic ulceration of the cornea and zoster lesions of the skin.

Earlier this year a new antiherpes drug, acyclovir,[1] was marketed which has considerable advantages over its predecessors.[2–4] Also a nucleoside which inhibits virus DNA synthesis, acyclovir has ingenious properties which give it selective toxicity—that is, the inhibition of virus replication without damage to the host cell. Firstly, in order to become active acyclovir must be phosphorylated—a process carried out by virus thymidine kinase but virtually not at all by host cell enzymes.[1 3] Acyclovir does not, therefore, act in uninfected cells. In addition, it inhibits virus DNA polymerase (the main enzyme responsible for virus DNA replication) more than cellular counterparts.[1] This mode of action implies that only viruses which code for an appropriate thymidine kinase should be sensitive to acyclovir; these include the human herpesviruses herpes simplex and varicella zoster.[1 5] Cytomegalovirus is less susceptible,[6 7]—perhaps because it does not appear to code for a thymidine kinase.[5 7]

Clinical trials of acyclovir are now being reported and broadly confirm the early promise of the laboratory studies. Given topically, acyclovir both accelerates healing and prevents early recrudescences of infection in herpetic corneal ulcers[8]—though reports differ as to whether it is better than other antiviral drugs such as idoxuridine, now widely and successfully used in ophthalmic herpes.[9–11] Acyclovir applied locally has, however, proved disappointing in treating herpes of the skin. There was no response in cold sores,[12] and, though in primary genital herpes it lessened symptoms and shortened the duration of virus shedding, the appearance of new lesions was not prevented and there was little effect on recurrent disease.[13–15]

Given intravenously, on the other hand, acyclovir produces a significant benefit in both herpes simplex and zoster. Controlled trials have shown that symptoms and lesions lasted a shorter time and the formation of new vesicles was prevented in both genital herpes[16] and zoster.[17 18] The time of virus shedding was also reduced[16 18]—an important point in genital herpes, since this should lessen the chance of the patient infecting sexual partners. Unfortunately residual neuralgia after zoster was not prevented, though there was less pain in the acute phase in treated patients.[17 18] Herpes simplex is a particular problem in immunocompromised patients and acyclovir has proved effective both for the treatment of established disease[19 20] and for prophylaxis.[21] The prophylactic trial is of interest. Carried out in recipients of bone marrow transplants, treatment with intravenous acyclovir for 18 days starting from three days before transplantation prevented the appearance of herpes in 10 patients. In contrast, seven of the 10 control patients with transplants developed mucocutaneous herpes.[21]

Toxicity was not a problem in the trials of intravenous acyclovir, though a few patients have developed transient rises in serum creatinine[16 18 20 22] or blood urea concentrations.[23] Acyclovir is excreted by the kidneys, and the dosage must be reduced in patients with impaired renal function.[24 25]

Intravenous treatment is practicable only in hospitals, so that acyclovir in this form would be restricted for use in severe cases of infection. Fortunately, however, the drug can also be given orally,[26] and Nilsen and his colleagues in Scandinavia have recently reported that genital herpes can be treated successfully by a five-day course of oral acyclovir.[27] This encouraging result, however, raises some questions. If acyclovir were to be prescribed widely and for mild forms of infection—for example, cold sores—drug-resistant mutants might emerge. Indeed, acyclovir-resistant herpes simplex has already been isolated from treated patients.[28 29] Perhaps more ominously acyclovir-resistant mutants have also been found in clinical isolates of herpes simplex virus which were not exposed to the drug.[30] Though in animals some acyclovir-resistant mutants were less virulent there is no evidence that this would also be the case in man.[31]

Could acyclovir be used to prevent herpes simplex—and possibly varicella zoster too—from becoming latent in nerve ganglia? In mice the drug had no effect on latent virus once latency was established, but treatment starting before experimental inoculation of herpes simplex had some effect in pre-

venting latency.[32] Whether the prevention of latency would be either practicable or desirable in human populations is another matter. It may be that latent virus helps to maintain the levels of virus-neutralising antibody—possibly as a result of reactivation of virus both with and without symptoms.

An interesting era in antiviral treatment is developing. Acyclovir seems set to become one of the first effective antiviral agents that can be given systemically in safety. It is almost certainly the forerunner of more.

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Peer review weighed in the balance

> "I know that the paper I have just sent in [to the Royal Society] is very original and of some importance, and I am equally sure that if it is referred to the judgment of my 'particular friend' X that it will not be published. He won't be able to say a word against it, but he will pooh-pooh it to a dead certainty.
>
> "You will ask with some wonderment, Why? Because for the last 20 years X has been regarded as the great authority on these matters, and has had no one to tread on his heels, until at last, I think, he has come to look upon the Natural World as his special preserve, and 'no poachers allowed.' So I must manoeuvre a little to get my poor memoir kept out of his hands."[1]

Is peer review, or refereeing,[2] the "lynch pin of science,"[3] or do its shortcomings and potential for abuse outweigh any merits? Certainly the practice has a long tradition, dating back to the early years of both the *Transactions of the Royal Society* and the *Journal des Sçavans*,[4] and yet, for a system which is widely used throughout the scientific community—whether for assessing articles for publication or applications for research grants—little research has been done into either the process or the outcome. Important questions have now been raised by an article published in the June issue of *Behavioural and Brain Sciences*.[5] Its methods and results should provoke wider discussion; already, the journal has printed no fewer than 59 invited commentaries on the article, together with a final riposte from the authors.

Early, brief accounts of the study appeared some time ago,[6] but the full details have only just been published,[5] because the authors' own article was rejected by the first two journals to which it was submitted (*Science* and *American Psychologist*). From a sample of broadly based, highly cited psychological journals D P Peters and S J Ceci randomly selected 12 articles by respected authors at prestigious institutions and changed a number of minor details. In particular, they gave new, false names to the authors and their institutions (such as the Tri-Valley Center for Human Potential) and altered the titles of the articles, the text of the abstracts, and the opening paragraph of the introductions. They then resubmitted these slightly altered articles to the same 12 journals that had published them some 18-32 months previously. The editors