

## **Antiviral Chemotherapy – A Frontier for Health and Learning**

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Antiviral chemotherapy has been too long perceived as being relatively impossible. Such notions adversely affect the acquisition of important specific clinical information, whereas much new knowledge is available about viral replication and cell biology which enhances the prospects for effective chemotherapy. Some immediate goals can be recognized that will further determine the ability to influence viral infections and properly interpret the drug effects. In recent controlled observations there is reason for expectant optimism, but the demonstration of antiviral chemotherapy is both disease- and host-dependent, with important nonpharmacologic aspects. Rapid specific and sensitive diagnostic tests are of paramount importance; that they can be devised is a generally accepted conclusion among virologists. Problems in the scientific evaluation of antiviral chemotherapy in man have led to the recommendations of compounds that have no proved effect; amantadine, Ara A, and interferon, however, have been shown to be efficacious. Acyclovir and bromvinyldeoxyuridine have demonstrated virus-directed chemotherapy with impressive specificity. The frontier of antiviral chemotherapy holds great promise for additional learning and improved health through the implementation of developing knowledge.

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### A PERSPECTIVE

Within broad segments of the medical profession and lay persons, there are some engrained perceptions and preconceptions about viral diseases and antiviral chemotherapy. Often the notions tend to be negative, uncritical, inaccurate, or at best pragmatic. They exert a stultifying influence on the challenge of understanding viral infections and their control, on the desire for the specific diagnosis of viral diseases to define their clinical spectrum and epidemiology, and on developing more complete knowledge about the vital biology of the interactions among viruses, cells, the immunologic system, and the regulatory mechanisms of each of them. In other respects, the common views are realistic or at least defensible in the context of the relatively benign nature of most viral infections and the historical successes (or more often lack of success) from the clinical application of antiviral chemotherapy. But the belief that successful drug treatment of viral infections is impossible is wrong. It ignores important needs and the availability of knowledge about basic cellular biology (and even engineering) that could be applied to viral infections and the effects of drugs in altering them. Thus antiviral chemotherapy is an exciting frontier with opportunities for making major contributions to improved health from the control of acute, persistent, and latent viral infections that are highly prevalent

among people in both the developed and underdeveloped countries of the world. Like other frontiers it has a relative poverty of funds, some deficiencies in skills, has suffered setbacks from failures, but has promise for the future through developing the biologic research and clinical experience that is required. The axiom, "It is not so important where we are, but the direction we are going," aptly applies to the field of antiviral chemotherapy, and the direction is impressively forward.

### SOME IMMEDIATE GOALS

Among the things that are necessary in order to further the progress in antiviral chemotherapy, we must:

1. disavow the engrained belief that antiviral chemotherapy is unlikely because of the intracellular location of viral infections and the similarity of virus replication to cellular metabolism;
2. determine the amount of disease that is reversible by antiviral containment of viral replication and establish the limits of the incisive period during which antiviral chemotherapy can be useful;
3. develop and apply easy methods for rapid, specific diagnosis of viral infection;
4. improve general awareness of knowledge about specific drugs with demonstrable antiviral activity in man, extend the understanding of the basis (mechanisms) of their action, and devise new modes to solve the problems of how to make them rapidly available and deliver them safely and effectively;
5. establish practical goals for the clinical application of antiviral drugs to achieve effective prophylaxis against infection and illness (as an adjunct to vaccines) and for therapy that will be understandable and useful to physicians and acceptable to consumers;
6. research additional needs for antiviral chemotherapy, especially a means for control of *in vivo* reservoirs of latent viruses, quenching virus (and incomplete virus) production in chronic, persistent infections, and preventing viral transformation of cells, tumor formation, or cancer;
7. learn the optimum collaboration between drugs and the host defense systems to remedy specific host deficiencies and to augment the beneficial and depress the pathologic host immunologic responses initiated by viral infections.

### A BASIS FOR EXPECTANT OPTIMISM AND NEED

In recent years controlled trials have provided measurable clinical benefit from antiviral chemotherapy [1,2,3,4,5,6]. Already chemoprophylaxis or treatment is definitively established for ulcerative herpetic keratitis, herpes simplex encephalitis (when biopsy-proven of recent onset), varicella zoster (among patients with leukemia and/or those who are immunosuppressed), and influenza A. Investigational studies are in progress with promise in the treatment of herpes labialis, genital herpes, varicella zoster in the nonimmunocompromised person, chronic active hepatitis B virus infection, influenza B, and other viral pneumonias. Also there is perhaps a broader opportunity for effective application of antiviral chemotherapy owing to the emergence of certain viral infections because of an aging population, iatrogenic immunosuppression, more intensive care of patients with cancer, increased sexual activity at an earlier age with a more permissive social fabric at all

ages, intrauterine and postnatal diagnosis of vertical and neonatal transmission of viral infections, recognition of the high prevalence of some chronic, persistent, and slow virus infections, and the continuing frequent affliction of the general population with acute viral infections of the respiratory, enteric, and central nervous systems. Varicella zoster is among the most rapidly increasing diseases of the elderly; genital herpes is estimated to occur in 20 percent of young, sexually active persons, and HSV-2 with its greater propensity for latent infection of sacral ganglia and recurrences now accounts for more than 90 percent of these infections [7,8]. Active infection with hepatitis B virus can be found in as many as 2 percent of certain hospital populations in developed countries and 10 percent of the population of some other countries [9]. Cytomegalovirus affects about 0.5 percent of live births and is considered to be among the leading causes of deafness; rubella persists as a cause of infant abnormalities. Vaccines are available or being developed to prevent some of these diseases and, when effective, should be advocated for broad use. However, many biologic and social conditions demand chemotherapy as an adjunctive or necessary measure. While research is increasing the number of known specific kinds of viral infections, established and new technology is improving the accuracy of diagnosis of their occurrence. Together these efforts are reducing the unknown segment of viral diseases and providing the knowledge required for effective antiviral chemotherapy. Concomitantly, antiviral drugs with potent antiviral activity, a high degree of virus host selectivity, and improved pharmacologic properties are being developed. In these several diverse but related areas, the frontier for health improvement through antiviral chemotherapy is being mapped and readied for settlement.

#### DISEASE-DEPENDENT DEMONSTRATION OF ANTIVIRAL CHEMOTHERAPY

The evaluation of antiviral drugs has required the reemphasis of several disease-related events that confound and/or limit the demonstration of benefit from antiviral chemotherapy. These include the presence of an early signal of infection, objective signs that can be quantitatively measured, and a general predictability of the clinical course that permits differentiation of untreated persons with the disease. These are not unique to antiviral chemotherapy, but the nature of viral infections exaggerates them because of the often silent nature of the infection well in advance of the clinical syndrome. In antiviral chemotherapy this disease dependence may be a problem with greater need for attention than the discovery of new antiviral drugs.

Considerable improvement in astute clinical observations and confirmatory tests must be realized to counter the dependence on the insidious production of symptoms in order to permit the initiation of antiviral chemotherapy at a time when there is still gain to be realized from the inhibition of virus replication. Such an opportunity always exists, but the time-critical period for the effective and beneficial application of antiviral chemotherapy in acute viral infections may be, relatively, exceedingly brief. Thus the earliest successes and best demonstration of antiviral chemotherapy have come in those diseases where the features noted above can be met. If the disease is severe, as with herpes encephalitis or lassa fever (in primates) with death or disability as an end point that has not been predetermined by the stage of disease, a therapeutic effect of antiviral chemotherapy can be demonstrated [1]. Some other objective sign that can be observed and measured, such as a dendritic ulcer, serves the same purpose. But if the disease is mild and brief, such as herpes labialis, genital

herpes in antibody-positive persons, herpes zoster in a nonimmunocompromised host, or Influenza A (H<sub>1</sub>N<sub>1</sub>) in healthy young students, the race to hasten the cure by antiviral treatment before it is accomplished by natural host defenses requires more subtle measures such as the duration of fever, time to healing, altered function tests, or the persistence of infectious virus [10,11]. If the therapeutic effect is subliminal, its presence or absence may be clinically moot, but nevertheless defensible to affect and prevent the most severe variants of the disease. Improvement of host responses increases the scope for a demonstrable drug effect. Thus the predictability of the course as affected by the host is a part of the disease-dependent demonstration of effective antiviral chemotherapy [12].

Because timing is critical for effective antiviral treatment, prophylactic use of an antiviral drug offers the greatest, and sometimes, depending on the action of the drug, the only easily demonstrable effect. Prophylactic chemotherapy requires that the drug be readily available, and because protection lasts only as long as the drug is taken, it needs to be safe for long periods of administration; also, the likelihood of a significant exposure to infection must be great enough to produce a clinical difference among drug-treated and untreated persons, and in practice be cost-effective.

These disease-dependent features that impinge on effective antiviral chemotherapy pose major nonpharmacologic sociomedical challenges. Effective antiviral chemotherapy most likely will require a willingness to modify standard post-illness therapeutic prescription practices, broader use of epidemiologic clues to identify the earliest signs of infection, new uses of modern communication media for lay instruction, and, in some cases, the establishment of new therapeutic goals such as decreased transmission of virus and prophylactic treatment of contacts.

#### SPECIFICITY AND SENSITIVITY IN THE RAPID DIAGNOSIS OF VIRAL INFECTIONS

The cliché, "It's a virus," is stone-age medicine in the context of modern virology. Uncritical satisfaction with that level of clinical diagnosis has lasted so long for several reasons, partly because the technology for rapid, sensitive, and specific diagnosis of viral diseases is just beginning to be mobilized for clinical applicability. The intimate nature of the virus-host cell relation increases the likelihood of need for biochemical and biologic specificity in the antiviral effects of drugs. The need for such specificity in conjunction with the time-critical nature of antiviral chemotherapy makes it apparent that rapid specific diagnosis is of paramount importance in the future development and success of antiviral chemotherapy and that the diagnostic tests must be sensitive enough for the identification of a small amount of virus or viral product at an early stage of infection. That the needed diagnostic tests for rapid and specific identification of viral diseases at a high level of sensitivity could be developed is now a recognized conclusion of most virologists. The impetus to do so is intertwined with the improved outlook for antiviral chemotherapy. Although virus isolation and identification offer the standard proof of a cause-and-effect relation with the disease, the time required makes the outcome of only confirmatory help in most applications of antiviral chemotherapy. Morphologic recognition of the virus by immunoelectronmicroscopy can be faster than virus recovery and applicable to some viruses for which recovery systems are difficult. Other tests for the physicochemical, immunologic, or radiologic detection of viral antigens, a viral gene, or gene product by counter immunoelectrophoresis, immunofluorescence, enzyme-linked immunospecific assay, radiolabeled reagents, and fluorescein labeled substrates can reduce the time required for the availability of

results to a few hours and increase the sensitivity of detection to as high as one part in a  $10^{-12}$  dilution in body fluids or secretions while retaining exquisite specificity [13]. The further development and application of these tests to identify and differentiate specific viral diseases rapidly at an early stage of infection, when therapeutic and control measures will be most beneficial, is another frontier which is already well defined, and its fulfillment is but a matter of education, interest, and time with the development of antiviral drugs having promise in the clinical improvement of specific viral infections.

#### WELL-TESTED ANTIVIRAL AGENTS OF IMPORTANCE AND NO IMPORTANCE IN HUMAN DISEASE—PRESENT AND FUTURE

Owing to the foregoing difficulties, the differentiation between testimonial and scientific evidence in determining the efficacy of antiviral chemotherapy for systemic viral diseases has sometimes posed a problem. Vitamin C, levamisole, 2-deoxy D glucose, cytosine arabinoside, topical ether, aspirin, and lysine are among recently recommended remedies that have been quite well tested in humans but for which little or no scientific data support the claim of efficacy. Other modalities of treatment such as photosynthetic inactivation of viruses mediated by aromatic dyes, if effective in decreasing infectious virus, leave functional expression of viral genes that is undesirable. Several compounds that are effective have been too toxic or have pharmacologic properties that are unmanageable for clinical use.

On the other hand, well-controlled investigations and confirmatory experience have established that a significant prophylactic or therapeutic benefit can be derived from amantadine, ara A, and interferon under specific conditions of application [3,4,5,6,14]. Consensus about the recommendations for their use is beginning to evolve [15]. Each probes different mechanisms of selective chemotherapeutic antiviral actions, and thus provides encouragement for exploring the multiplicity of potential opportunities of developing antiviral drugs [16]. Added to the modest successes that have been obtained is the promise of acyclovir, bromvinyldeoxyuridine, and other substituted nucleosides with a selectivity that is activated and directed by viral products and amplified in the specificity of inhibitory action against viral as compared to mammalian polymerases, and that have the potential for oral use [17,18,19,20]. Other compounds with other mechanisms ensure that additional investigational new drugs will appear. With them, antiviral chemotherapy should progressively move into the realm of clinical practice with abandonment of the confining views that have been so prevalent. If this is so, a rewarding development of this frontier can be anticipated, with improved health and further learning through the implementation of our improving knowledge of viruses, viral infections, cellular regulation, rapid specific diagnosis, and the ability to evaluate selectively tailored antiviral drugs.

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