A Strategy for the Chemotherapy of Infectious Disease

Biochemical science and technology permit the discovery of specific inhibitors for all parasitic disease.

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Until the present we have lacked a rational strategy applicable to overcoming infectious disease. In 1907, Paul Ehrlich pointed to the future development of a specific chemotherapy which killed the parasite without harming the host; the selectivity and efficacy of the sulfanilamides and various antibiotics in treating bacterial disease were only discovered in the late 1930's and subsequent decades. These initially empirical findings served to indicate the fundamental biological and biochemical differences between prokaryotic and eukaryotic cells (*1*). Differences among eukaryotic cells also underlie many discoveries in the chemotherapy of other parasitic disease (*2*). Despite these advances in comparative biochemistry, present approaches to chemotherapy still involve mainly the empirical search for toxic agents whose ability to leave the host unscathed is almost the terminal step in a long series of investigations. The earlier steps involve discovery, publication, random subsequent appreciation, and advances by separate groups of workers; this process is repeated (and often duplicated wastefully) at ever more complex levels of investigation. The process slows enormously, and in areas of pharmacology, human toxicology, and clinical trial is frequently not begun or properly completed. Occasionally, a pharmaceutical house does contribute significant therapeutic discovery and carries the result through to successful clinical trial expeditiously (within 5 years). Such limited successes, however, have been achieved generally without theoretical and practical attention to the development of specificity against infectious agent or infected cell, have involved expensive and wasteful screening operations, and in the areas of virus disease have been essentially unsuccessful.

In the period 1952–1957, my collaborators and I discovered a unique viral constituent and the virus-induced enzyme which made this nucleic acid constituent (*3*). That almost all viruses carry genes for the synthesis of new metabolic machinery was demonstrated in the next two decades. Because virus-infected cells contain unique enzymes and proteins essential for virus reproduction, it should be possible to inhibit virus disease specifically.

After 1960, the relationships between sequences of nucleotides in genetically important nucleic acids and sequences of amino acids in genetically determined polypeptides were also established. It was shown that these sequences in the genes of viruses and prokaryotic cells are so different from those of eukaryotic cells that almost no sequence homologies in nucleic acids or proteins among these groups can be established. Furthermore, the evolutionary divergencies among fungi, protozoa, lower animals, and mammalian cells were developed so early and are now so extensive that sequence homology among these groups may be practically negligible. These facts demonstrating that the infecting organisms determine proteins very different from those of their hosts provide the biological and chemical bases for our therapeutic strategy.

In the 1970's, the technology of protein and enzyme isolation and characterization has been enormously improved and simplified. It is now feasible to isolate a particular protein quickly from relatively small amounts of material, as well as to define amino acid sequences and intimate structure in the region of the catalytically active and other essential sites. For the first time organic chemists charged to develop inhibitors of a particular enzyme can be provided with detailed data on the structure they must complement, modify, block, and inhibit reversibly or irreversibly. Such substances can be tested for their effectiveness and specificity in inhibiting the multiplication of parasites in various model systems. Thus, not only has the potential basis for specific inhibition been demonstrated to exist but also, within the past decade, the necessary technological capabilities in biochemistry, synthetic chemistry, and the biology of model systems have been developed.

It is proposed, therefore, that a multidisciplinary project be established to devise specific enzyme inhibitors. An enzyme crucial to the multiplication and development of the parasite should be selected as a subject of study, isolated in a pure state, sequenced, and characterized with respect to its active site. Such structural information would then be applied to the synthesis of a specific inhibitor that would be modified to enhance penetrability and effectiveness. The inhibitor would then be studied in appropriate model systems, such as tissue cultures and organ cultures. When such effectiveness and specificity are demonstrated, the studies can be carried to animal systems, and eventually to man. The development of this complex enterprise will require a marked improvement in our skills in mounting multidisciplinary problem-oriented projects (*4*).

Initial areas of study might be:

1) Infection produced by herpesvirus. Two substances, developed empirically in recent years, are now known for the relatively specific inhibition of herpesvirus-induced enzymes. These are 5′-amino,5-iododeoxyuridine, which is activated only by the virus-induced thymidine kinase (*5*), and phosphonoacetate, which inhibits only the virus-induced DNA polymerase (*6*). It may be asked whether we can do a better job with our "rational" efforts on these enzymes than that effected by the extensive empirical studies that eventually revealed these active compounds. Much is known about these enzymes that can be thought of as providing controls for the test of the strategy. Herpes infections can also be obtained in several types of pharmacological model systems, as well as in significant clinical situations. Potentially, studies of herpes systems could provide much information on nuclear sites of multiplication, as well as on phenomena

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of virus penetration, packaging, and exit, areas that are quite relevant to those of cancer.

2) Study of infection by influenza A virus, which highlights RNA replication, as well as budding processes. A considerable knowledge of this disease, including that of some virus-induced proteins, should facilitate this work.

3) Study of a protozoan infection such as trypanosomiasis or malaria which demands new and modern approaches. Infectious disease is responsible for 44 and 11 percent of the mortality rate in developing and developed countries, respectively (*7*). Although many of the parasitic diseases common in the developing countries are essentially confined to those countries, the effects of those diseases in causing world poverty, and ultimately in provoking world tensions, cannot be overestimated.

The theses presented in this proposal are a challenge to almost every biomedical discipline. The routes to the stepwise solution of the various scientific problems cannot be expected to involve mere repetitions of earlier successful investigations. Each biological system, etiological agent, enzyme, synthesis, and so forth, will provide its own new and special problems and difficulties; nevertheless, the existing and rapidly evolving capabilities of modern science and technology are clearly up to the tasks outlined above. The development of pharmacological science and skills is greatly needed in the development of therapy. There should be a positive gain to science in this area during the evolution of the project. Integrated efforts within the project should be most helpful in this aspect of the work, as well as in strengthening the chemical efforts. The studies should also contribute to cancer-related problems, and indeed such work will prepare for the possibility that many cancers may arise following the vertical transmission of certain viral genomes (*8*).

It has been suggested that the worldwide cure of infectious disease would exacerbate the problem of growing world population. However, as stated recently by McNamara for the World Bank (*9*), a decrease of infant mortality has been and will be a condition for a decrease in population growth rate in all developing countries.

References and Notes

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Prices of Physics and Chemistry Journals

New survey reports high prices that reduce access to needed publications for academic scientists.

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Scientific journals can be quite expensive. The 1976 subscription price for the *Journal of Organometallic Chemistry*, for example, was $961.50 and for *Nuclear Physics, A and B* was $1540. While these prices are extreme cases, the average subscription cost of journals for some scientific subjects is $100 or more (*1*), excluding abstracting and indexing journals (which are omitted here).

The high cost of journals has forced some scientific libraries to reduce drastically or eliminate entirely the purchase of books in order to maintain journal and other serial subscriptions (*2*). The scientific community is not unaware of the high cost of scientific journals or of the difficulties that this entails for libraries, as is clear from comments by Walsh and others (*3*). The scientific community in the United States, however, does not have satisfactory information on this subject because the two major American periodical price surveys have significant limitations insofar as scientific journals are concerned (*4*).

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A New Survey

The annual American Library Association (ALA) survey (*5*) covers only U.S. periodicals and uses some price categories, such as chemistry and physics, which cover more than one subject. Clasquin's survey (*1*) shows prices for journals on lists selected from indexing or abstracting services such as *Physics Abstracts*, which are called authority groups. Since some authority groups include journals on more than one subject, the Clasquin survey does not necessarily provide price data by subject (*6*). Our new survey reported here is based on these earlier American surveys, but avoids their limitations in regard to scientific journals. Our survey uses specific—but separate—subject categories, and price averages and indexes, as in the ALA survey. It is also international in scope, is based on an authority group, and makes use of weighted averages, as in the Clasquin survey. The weighted average is a popularity factor; this factor gives the average cost of all subscriptions to each title on a given list which are sold through the F. W. Faxon Company periodical subscription agency to any of approximately 18,000 libraries. The weighted average may thus give a more accurate idea of average prices paid by libraries for titles on a given list than does the unweighted average. Since this weighted average is obtained from the sales records of one agency, it is not