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Commentary

Opportunities in Drug Discovery for Treatment of AIDS

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The AIDS pandemic seems to be easing a bit in the U.S., at least in terms of annual deaths. Worldwide, however, the disease is still spreading with appalling rapidity. The World Health Organization estimates that 40 to 50 million individuals will be HIV (human immunodeficiency virus) positive by the turn of the century (1). Even in the United States, there is a resurgence of disease in some population groups, especially women, children and intravenous drug users. It has recently been anecdotally reported that young gay men are again frequenting bathhouses and engaging in high-risk sexual behavior.

To what may the apparent decline in AIDS deaths in the United States be attributed? Almost certainly, this is due entirely to the use of "drug cocktails" involving treatment of patients with (usually) three drugs simultaneously. Such therapy has reduced viral load (detectable proliferating virus) to undetectable levels in a majority of patients who follow the demanding regimen to the letter. Compliance failure, however, often leads to rapid reemergence of virus, sometimes in a mutated form resistant to one or more of the drugs used in the combination. Furthermore, the requirement that 15 to 20 pills be taken daily, on a precise schedule, and the fact that these drugs cost $10,000 to $12,000 per year, make these exciting therapeutic approaches totally unattainable in the less developed countries in which AIDS is rampant.

Eleven drugs are currently approved in the U.S. for treatment of AIDS. These fall into three classes; five are nucleoside reverse transcriptase inhibitors, two are non-nucleoside reverse transcriptase (NNTR) inhibitors, and four are inhibitors of viral protease. Despite the recent success with therapies using a drug from each of these classes, the demanding nature and high cost of the therapy, the potential for development of resistance and the lack of firm evidence that even complete compliance will lead to permanent cures mandates that continued research into new classes of drugs with reduced (or complementary) toxicity, novel mechanisms of action and lower cost should remain a high priority.

Promising gene therapy approaches, in which a gene encoding for a protein which protects cells from viral replication is introduced into pluripotent hematopoietic stem cells, are in Phase I/II clinical trial. At least one inhibitor of HIV integrase, a stable oligonucleotide, is also in Phase I/II clinical trials (2).

Other targets of opportunity for anti-retroviral drug discovery include virus attachment and cell entry, integrase (the enzyme which incorporates the viral genetic information permanently into the genomic DNA of the host cell), interference with viral protein processing at loci other than protease, virion assembly, and budding and cell lysis. Many research groups in both industry and academia are vigorously pursuing these various targets, and it is likely that in the next several years drugs interfering with virus attachment/penetration, integrase inhibitors and inhibitors of transactivation (stimulation of viral protein synthesis by the protein *tat*) or *rev*, a protein which facilitates the transport of viral mRNAs into the cytoplasm, will be approved (3). A corollary task is to achieve positive therapeutic outcomes in a way that is both affordable and deliverable to less developed countries, since it is clear that allowing AIDS to expand unchecked outside the borders of Western countries will surely give rise to mutant strains which will move back into Western populations; in other words, the United States has a substantial national interest in accomplishing these goals.

Unfortunately, influential political voices are being raised suggesting that the amount of federal money being spent on AIDS basic and applied science is inappropriately large in comparison with other diseases such as cancer, heart disease and stroke. Representative Ernest Istook, Jr. recently wrote "...[NIH] priorities fall short when compared to which diseases cause the most death or the most suffering, or when compared to which generate the most expense to the largest number of Americans (or the most expense to taxpayers, via government health programs)" (4). Two points should be made in response. First, as the case with the space program and military research spending, knowledge gained in one field of biomedical endeavor frequently finds application in another. For example, the first anti-HIV drug approved for use by the FDA, zidovudine (AZT), was initially synthesized as a potential anti-cancer agent. In my own laboratory antitemplate oligo- and polynucleotides showing potent anti-HIV and CMV (cytomegalovirus) activity were initially prepared as part of an NCI-funded project seeking improved therapeutics for leukemia (5). Exciting new approaches to therapy such as antisense and ribozyme technology, and development of delivery systems to enhance the activity of these polar and relatively unstable oligonucleotides, frequently funded under the auspices of AIDS programs, are equally applicable to cancer, inflammatory disorders, restenosis

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following coronary bypass surgery, management of other viral diseases, and many other disease states. Secondly, cancer, heart disease and stroke are most commonly diseases of aging, whereas AIDS most frequently occurs in young, sexually active individuals. The consequences of the latter are increasing numbers of women and children infected with the virus and proportionately greater economic loss associated with early death.

In the absence of adequate funding for high-priority projects, opportunities for drug discovery will surely be lost. Political bickering and "body-count" approaches to allocation of funding fail to recognize the wide applicability of biomedical advances to many disease states, and risk placement of our hard-earned dollars in areas which may offer a lesser degree of scientific opportunity. The resources devoted to AIDS research have been, and will continue to be, a wise investment in the future of our country and our planet.

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