CONCEPTS IN QUESTION REGARDING HIV INFECTION

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The development of therapeutics for human immunodeficiency virus (HIV) infection requires judgments concerning the target patient population under study and the outcome measures which are to be employed. In dealing with these considerations, we have had occasion to note that the collective thinking on such matters contains certain assumptions that may not be fully justified.

In staging patients with HIV infection, clinicians have come to rely increasingly on the number of $CD4^+$ cells as an index of patient status. It is certainly clear that—following initial HIV infection—there is a progressive reduction in numbers of $CD4^+$ cells over time, and that the rate of decline varies from patient to patient. Various studies have shown that the risk of acquired immunodeficiency syndrome (AIDS)-defining sequelae such as opportunistic infections, and correspondingly the risk of mortality, increases as $CD4^+$ numbers decline. While it appears that these facts are established, it is interesting to us that certain $CD4^+$ levels have now assumed the character of prognostic milestones, which they may not perhaps deserve. For example, levels of less than 400 $CD4^+$ cells/mm^3 and 200 $CD4^+$ cells/mm^3 have been taken as important diagnostic landmarks. But these numbers cannot be viewed in a vacuum and they are but one indicator, albeit an important one, of patients' status. Since HIV infection results in a progressive loss of immune function, it may be more pertinent to focus on the *residual level of immune function* rather than $CD4^+$ cell number at a given time. Clearly, if there are no $CD4^+$ cells there is no immune function, and there is a progressive loss of immune function over time as $CD4^+$ cells fall, but it certainly does not follow that a given level of $CD4^+$ cells is necessarily equated with a specific residual level of immune capability in a given patient. As an example, let us consider two patients with $CD4^+$ levels of 420/mm^3, one of whom is anergic (cannot respond to challenge with recall antigens) and the other of whom responds normally to antigenic challenge: it would seem obvious that the anergic patient is at greater risk because his immune system has manifestly failed. We submit, therefore, that one should not give undue credence to a particular $CD4^+$ number *in the absence of information concerning the immune functional status of that patient*. This is of particular importance in selecting patients for clinical trials of experimental drugs. Patients with given levels of $CD4^+$ are not necessarily immunologically equal.

Testing of experimental drugs also requires that measures of treatment outcomes be specified and determined. In assessing the impact of experimental drugs on progression of HIV disease, several considerations arise. It is clear that the total scope of the natural history of HIV disease is not known and continues to emerge. Initially, a patient was diagnosed as having AIDS if he had an opportunistic infection, most commonly *Pneumocystis carinii* pneumonia (PCP) and/or Kaposi's sarcoma. In August 1987, based on data gathered since the disease's initial description in 1982, the Centers for Disease Control (CDC, Atlanta, GA) broadened the definition of AIDS for surveillance purposes. Thus, clinical indicia such as "wasting syndrome," tracheobronchial candidiasis, and encephalopathy are now considered to be AIDS-defining. In assessing efficacy of investigational drugs in HIV infection, there is, in our view, a tendency to place undue emphasis on these CDC-defined prognostic outcome measures, rather than to assess the value of a particular outcome measure as an index of disease progression.

As a result, the CDC criteria appear to have been canonized as the definitive criteria for the definition of AIDS. Apart from the fact that these criteria were not intended to serve this role, such an approach may well obscure the true progression of HIV disease in a given patient. For example, if an HIV-positive patient clearly develops peripheral neuropathy can this truly be said not to be an indication of disease progression? In this regard, CDC has recently stated (Morbidity & Mortality Reports, August 18, 1989, p. 562) that as a result of *underdiagnosis* and underreporting of AIDS cases, and severe manifestations of HIV infection that do not meet the CDC AIDS surveillance case definition, the reported AIDS cases underestimate the number of persons severely affected by HIV since 1981. These questions are of considerable import in designing clinical trials to test experimental drugs for efficacy in this disease. Rather than impose arbitrary criteria as indicia of progression, it would be more logical to look at what we learn by testing a new drug against a placebo in a randomized double blind trial. In such an instance, clinical judgments are made by blinded clinicians, and the behavior of the placebo group defines the standard against which the drug is to be judged. Thus, one has a real-life standard for assessing disease progression, rather than having to arbitrarily determine whether an outcome measure or endpoint is a true indicator. Put in other terms, one cannot ignore the behavior of patients in the placebo group of a randomized clinical trial. A necessary corollary is that it is the totality of the cases in the placebo group that is relevant; one must be wary of attempts, usually initiated post-hoc (after the code is broken) to reduce a clear clinical effect to nonsignificance by discarding individual cases from the placebo group. Such an approach is fundamentally wrong by the standards of good clinical trial practice.

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