July 16,1997

Comments of J.A.Sonnabend, M.B., F.R.C.P.Ed. regarding the Guidelines for the use of Antiretroviral Agents in HIV-infected adults and adolescents.

The panel convened by the Department of Health and Human Services to develop guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents has performed a valuable service. Their recommendations will undoubtedly be greatly relied on by the many physicians without extensive experience in the management of HIV-infected patients.

The recommendations regarding treatment in more advanced disease (where evidence derived from controlled clinical trials is available), will be of great benefit to patients in this category. However it is far from clear that this will be the case for asymptomatic patients, even some of those with fewer than 500 CD4 lymphocytes / mm3 . The potential risks detailed in Table III are far from trivial. For an individual facing more than 5, or even possibly 3 years free of disease, instigation of combination antiretroviral therapy with agents whose long term toxicity is unknown, may in fact have the net effect of shortening that individuals life. The issue of quality of life is also of concern, as is the likelihood of a failure in compliance over a long period, with the attendant risk of the development of resistance, with the possible consequence that effective therapies may be unavailable at later stages of the disease.

For asymptomatic individuals it is quite possible that the risks of early intervention outlined in Table III will outweigh the benefits. The potential benefits listed in the table are conjectural; the potentially serious risks cannot even be approximately quantified with the little experience accumulated thus far. Faced with such difficulty in recommending when to initiate therapy in asymptomatic individuals, I believe that the panel might have devoted more consideration to the rate of disease progression in individual patients as a factor that should influence the decision as to whether or not to start antiretroviral therapy. Rates of disease progression vary widely, and it might require a 6 to 12 month period of observation to assess this rate in an individual patient.

Given the availability of potent antiretroviral agents and the potential benefit that may be associated with their use, the uncertainty as to when to start therapy with these agents in asymptomatic patients is perhaps the most important issue that needs to be addressed at this time. It was therefore most surprising that the panel did not call for controlled clinical trials to resolve this important question. There is the unfortunate implication that in the area of AIDS medicine, convening a panel to make recommendations on such areas of clinical uncertainty has now replaced clinical studies as a means of guiding treatment decisions.

The recommendations regarding treatment of patients with advanced disease are sound as they are supported by evidence derived from clinical studies. I would suggest that the recommendations regarding treatment of asymptomatic individuals, and treatment of acute HIV infection rather be called interim suggestions pending the results of controlled studies. I hope the department of Health and Human Services will acknowledge the pressing need to obtain a clear answer to the question of whether early intervention is of benefit, is harmful or is without effect, and encourage the development of appropriate studies. Admittedly enrollment in such trials would be difficult at this time - in part because of the availability of recommendations regarding treatment , with the implication that the questions have been answered. It is therefore also to be hoped that the Department of Health and Human Services will help to prepare the ground for such trials by educating patients and providers that there is indeed considerable uncertainty regarding when treatment should begin in asymptomatic individuals, and that the clearest answer to this question can only be obtained through appropriate clinical studies.