Cyclosporin and the clinical investigator

To the Editor — The February issue Commentary by Drs. Flowers and Melmon on the role of clinical investigators in pharmaceutical innovation[1] included some discussion of cyclosponin A and adds a new item to the long list of false statements on the discovery and development of this drug. Some of the untrue and misleading previous accounts on the history of cyclosporin have already been examined[2].

Work of Calne's group with cyclosporin certainly was very important for the development of this immunosuppressant. However, Flowers' and Melmon's conclusion "that Calne and White originated the idea ... for the development of cyclosporin for prevention of allograft rejection" and the conjecture "probably ... they [researchers of Sandoz] did not conceive of the indication [graft rejection] themselves ..." are clearly incorrect. To realize that, it will suffice to consult the Discussion in our first full paper on the immunosuppressive effects of cyclosporin[3]. There, among the possible indications, organ transplantation is listed in the first place. This publication also reports the results of our transplantation experiments (skin and bone marrow) with cyclosporin in animals. The manuscript of this paper was submitted in January 1976, several months before cyclosporin became known to Calne and White. In addition, there are documents which prove that my then coworker S. Lazary and I had organ transplantation already in mind when, in June 1967, we proposed further development of the (preclinical) predecessor of cyclosporin (ovalicin, another immunosuppressive fungus product without bone marrow toxicity[4]). Organ transplantation, particularly that of bone marrow, had caught our attention as well because we had been working since the 1950's in cancer chemotherapy, incidentally with compounds which also showed immunosuppressive activity[5].

Cyclosporin differs from the compounds which emerged from the brilliant work of Hitchings and Elion at Burroughs Wellcome in so far as it was not the result of systematic biochemical research, but was picked up in a screening which was designed to detect, among others, immunosuppressive effects[2]. Another difference between the group at Burroughs Wellcome and ours at Sandoz may have contributed to an earlier realization of possible clinical indications of our compounds: many researchers in the (preclinical) Pharmacology Department of Sandoz, including myself and my superiors, were MDs. Therefore, we were perhaps more inclined to constantly keep in mind possible clinical applications of our research than the people in the Biochemistry Department at Burroughs Wellcome who apparently had a more basic research-oriented approach.

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Flowers and Melmon reply — We appreciate Dr. Stähelin's letter and recognize that his review[2] and comments reflect a detailed, first-person account of the discovery and development of cyclosporin as it appeared within Sandoz. We did not study this complex setting but our data do not conflict with his recounting of Calne's role in the development of cyclosporin.

Our intention was to demonstrate that Calne and White's becoming clinical champions was integral to the transfer of the drug to a human application. Rather than focusing on who did the first transplantation experiment using cyclosporin in animals, we hoped to draw attention to the fact that Calne and White recognized the value of using cyclosporin as an immunosuppressant in the context of transplantation and initiated collaboration with Sandoz. One might have thought that Sandoz would have recognized the benefit of collaborating with an outside researcher because of Calne's proven track record for promoting the successful development of an immunosuppressant (azathioprine) in dog renal transplantations experiments and later in man, and his continued research in this area. However Stähelin's comments suggest that not only did Sandoz fail to recognize the value of external clinicians for promoting drug development, but the company also underestimated the contributions of its own clinical and fundamental researchers.

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Importance of anti-HIV-1 antibodies

To the editor — We were surprised to read the recent letter by Parren, Burton and Sattenau concerning the importance or otherwise of anti-HIV-1 antibodies[1]. In it they suggest that "the antibody response to HIV-1 is not directed to the virus, but instead is directed to viral debris", based upon what is presented as a well known fact — that anti-HIV-1 antibody is unable to clear or control HIV-1 infection in any but the most rare and exceptional examples. Some twelve years ago we showed that while indeed both healthy HIV-1-infected and AIDS patients had anti-viral antibodies, healthy individuals, and only they, had high levels of antibodies tha readily neutralized high levels of HIV-1, *in vitro*[2], correlating with well-being, high levels of CD4 T-cells and failure to detec infectious HIV-1 in the plasma[3]. More to the point, when plasma from healthy in fected individuals was administered to AIDS patients in trials of passive imunotherapy, the viremia of the AIDS recipients — that is, what would be primary isolates of HIV — was no longer detectable, even by PCR[4].

As far as control of infection is concerned, we and subsequently various others have carried out trials of passive