Medical College of Virginia
Virginia Commonwealth University

12/29/86

Dr. Paul K. Pybus
Chief Medical Advisor
The Rheumatoid Disease Foundation
404 United Building
181 Church Street
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Dear Dr. Pybus,

Thank you for your recent letters following receipt of my November progress report. I am gratified that you found my synopsis of current ideas on the immuno-pathogenesis of rheumatoid arthritis informative.

We have extended our *in vitro* studies on the immuno-modulatory properties of clotrimazole. The substance of recent findings is that the drug inhibits a variety of T helper cell functions, most notably the production of the lymphokines interleukin 2, interleukin 3, and interferon. Previously we found that clotrimazole does not inhibit the response of activated lymphocytes to prefabricated sources of IL-2 and IL-3. Therefore, while the drug suppresses the production of lymphokines, it does not appear to inhibit activities of the lymphokines.

It has been suggested that the anti-inflammatory effects of clotrimazole might derive from adrenal gland stimulation (I. Otterness and J. Biblack, Lancet 1:148, 1976). Corticosteroids suppress many of the same T helper cell functions as we have observed with clotrimazole. Since our studies have been conducted *in vitro*, however, the activities observed do not depend on adrenal function. Furthermore, clotrimazole exhibited activities in certain assays that were unaffected by hydrocortisone. Therefore the basis for the anti-inflammatory effects of clotrimazole *in vivo* apparently is not (entirely) corticosteroid mediated.

How clotrimazole influences T helper cell functions is being probed further. Current concepts of rheumatoid pathogenesis and your observations on patient specimens lead me to believe that we should also focus attention on effects of clotrimazole on macrophages. Clotrimazole may have specific effects on macrophages that, interpreted in light of the data we have gathered so far, would point to a presumptive therapeutic mechanism. My conjecture at this point is that clotrimazole is not simply cytotoxic for macrophages, just as it is not simply cytotoxic for T helper cells. On the whole, macrophages are more robust cells. Moreover, a

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generalized toxic effect on macrophages would have deleterious systemic consequences. Rather, I interpret your observation that fewer macrophages are found in the joint effusions of patients after drug treatment as a result of effects of clotrimazole on the inflammatory process within the synovial tissue, with the consequence that there is a reducted discharged of macrophages from that tissue into the synovial fluid. I will keep you posted of our progress in this area.

Best wishes for a happy and healthy New Year.

Sincerely yours,

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cc: Mr. Perry Chapdelaine, Sr.