

From Dr. Pybus

12 January 1987

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Dear Dr Susskind,

Thank you very much for your letter of the 29th December. I see that you are going along very well in your researches.

You will note that clotrimazole takes the production of interleukin 2 and 3 and interferon, but not interleukin 1 which is made by macrophages. Clotrimazole does not affect macrophages and therefore interleukin 1 is still produced.

You say in paragraph 4 of your letter that "fewer macrophages are found in the joint effusions of patients after drug treatment as the result of the effects of clotrimazole on the inflammatory process within the synovial tissue with the consequence that there is a reduced discharge of macrophages from the tissues into the synovial fluid". You must remember that clotrimazole is unavailable in South Africa, so I do not think this observation of yours is quite relevant and in addition, I would like to say that all the cases on whom we observed this phenomenon - none had ever received metronidazole before we did the test.

We can definitely say we have seen that with metronidazole the macrophages in the joint fluid are destroyed. Furthermore, the herxheimer reaction is considerably greater than that which has been reported from Bowman Grey using clotrimazole. Is it that the two drugs act in different places - namely metronidazole on macrophages and clotrimazole on the T lymphocyte? I think this is a distinct possibility as it would explain the difference in the herxheimer reaction.

Where does the phospholipase A<sub>2</sub> come into the picture? What is the structure of interleukin 1 and PLA<sub>2</sub> and are there any similarities. We know that a concentration of PLA<sub>2</sub> increases in active Rheumatoid Arthritis and I suspect is increased even further during the herxheimer reaction and I have attempted to get specimens sent to Dr Franson for just this investigation. I do not know the chemical structure of either PLA<sub>2</sub> or interleukin 1. From the evidence you have both given me, it would appear that they should be closely similar, or even identical as they are both produced by macrophages and both could be increased by the action of both drugs even if both drugs should act at different places.

Professor Brian M Susskind, Ph.D  
VIRGINIA, USA

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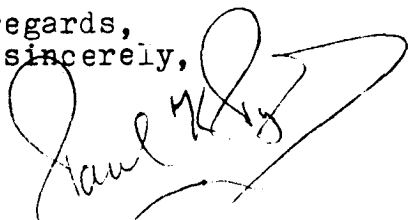
Both Dr Davis and myself have observed macrophages dissolved by metronidazole and you have seen that the concentrations of interleukin 2 and 3 and interferon are suppressed by clotrimazole. In both cases the level of interleukin 1 would be increased, possibly more so in the metronidazole cases than in the clotrimazole ones.

Thus, if we could show that either or both PLA<sub>2</sub> or interleukin 1 were responsible for the herxheimer response and temporary exacerbation of symptoms that is observed temporarily, then the whole theory would fit the facts like a glove. I do feel that this bit of investigation should be done and I am sending a copy of this letter to Mr Chapdelaine to see if he can stir his doctors into producing some specimens for you.

Please let me know what you think of this idea and if my reasoning is sensible. I feel that we are not far away in finding out why these drugs work in the case of rheumatoid arthritis and probably in other forms of auto immune disease. It does however, still rest to find a suitable antigen to determine the cause of the condition.

Thank you very much for your good wishes. I am pleased to say that I am now very much better and walking almost as well as when I saw you. I do hope truly that one day we shall have another chance to talk all these ideas over.

Kind regards,  
Yours sincerely,



Paul K Pybus

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