June 29, 1984

John Simoons, PhD
5140 Revere Road
Parkwood, Durham, NC 27713

Dear John:

Here are my comments on Turner's proposal:

1. Most importantly, we will not be able to satisfy his financial conditions so rapidly. I assume that we will not begin payment for several months, pending FDA approval. By then we will surely have $25,000 to pay him, but we cannot continue paying at the rate specified. After all, they will be getting a large chunk of money from us in advance, the test lasts for a year, and they want to play with our money during the interim. Swain specified that we could support the project provided we could pay in monthly increments. We've budgeted $10,000 per month for the job. Considering a $25,000 down payment, we should not be paying but $10,000 per month thereafter.

Can you negotiate with Turner prior to our meeting in Atlanta July 14?

2. I am also quite concerned that we are suddenly stopped from announcing our funding of Bowman Gray School of Medicine. Our major funding campaign hinged on making the announcement at end of June in our membership newsletter. I get a lot of flack from folks who want to know why we don't deliver, or why we don't deliver our promises in a reasonable time. We asked for and got permission to use their names. We printed thousands of newsletters containing the good news. Now we are asked not to use the Bowman Gray name until approval is received from the higher ups, and that approval seems to be contingent on negotiating over this Turner proposal. On the one hand he asks that we deliver thousands of dollars, and on the other hand our very means of making the delivery is halted. Can you do something to explain to Turner and Bowman Gray School of Medicine that we need the approval early in order to collect funds?

3. Page 2 of Turner's proposal is inaccurate, where he states "Another imidazole, metronidazole has been tried in rheumatoid arthritis without significant side effects but with doubtful efficacy."

He should see the following published materials:

Pybus, Paul K. "Metronidazole in Rheumatoid Arthritis." *SA Med. J.*, Vol. 65, 454, Mar. 24, 1984.

_____"Metronidazole in Rheumatoid Arthritis." *SA Mediese Tydskrif.* 261-262, Feb. 20, 1982.

Ursing, B., C. Kamme. "Metronidazole for Crohn's Disease." *The Lancet*. 775-776, Apr. 5, 1975.

Wyburn-Mason, Roger. *The Causation of Rheumatoid Disease and Many Human Cancers*, IJI Pub. Co. Ltd., Tokyo, Japan, 1978.

In addition to the above published materials, there is also an abundance of evidence available through the Physicians list attached, each of them having had experience in using metronidazole with RD.

It is simply false to state that metronidazole has had "doubtfrul efficacy."

Page 3: Selection of subjects: isn't 70 years of age a little old? The immunological system is usually unpaired by this time -- the thymus turns off at about 30 — and according to our theory

of infectious protozoa, the weaker the immunological system, the more recurrance of reinfection. Wonder if ages 18 through 50 wouldn't be a better selection?

Page 4: Number of patients: Forty patients have been selected, and this seems to check out well from a purely statistical point of view, regarding Type I and Type II errors. However, I expect the control groups to improve at as high as a 30% rate based on immediate attention being given them. This is called the Hawthorne effect, named after the Hawthorne Plant of Western Electric Co. who first reported the effect. For that reason I believe the number of patients should be as high as 64 in number. I think the increased number is especially important in view of Turner's classical measures of "improvement," and lack of understanding of the Herxheimer.

Page 9: if group I and II subjects are to receive three choices: drug, placibo, or neither, the number of patients increases accordingly, and should be structured well above the 40, in my opinion. One starts with anticipated change rates, say, 70% in clotrimazole group, and after selecting Type I and Type II confidence levels, determines the N required. With three choices, the N must increase accordingly.

Page 8: Adverse Experiences: Without sufficient and thorough knowledge of the Herxheimer, further evaluations are bound to be misconstrued. The PDR and other published literature contains sufficiently documented cases to see that many researchers and physicians, not understanding the Herxheimer, immediately terminate the trials, or label the medicine as dangerous. By not understanding the Herxheimer, Turner and his people will be classifying symptoms as being an intensification of RD. This is their very least action.

The symptoms of the Herxheimer should be carefully spelled out in advance, as should the symptoms of clotrimazole toxicity. Incidentally, I don't believe that the effects listed on page 21 are evidence of toxicity, but rather evidence of the Herxheimer. That listing is a very good example of what I am talking about. The very real danger, that researchers will see something that ain't so.

When I say the symptoms of the Herxheimer should be spelled out in advance, I am saying that we should list in our protocol agreement the following: intensification of symptoms, naseau, lethargy increased swelling, and so on.

At the same time there should be made a listing of clotrimazole toxicity symptoms, possibly more oriented toward chemical checks than outward symptoms, but in any case, not to include those symptoms that we know fall in the Herxheimer.

Adverse patient experience in other words, must be properly classified and identified.

Finally, a strategy of Patient advice and/or patient continuance must be agreed upon in advance, or we'll be in the position of paying for our own downfall, to detriment of everyone.

Again, see page 21 for what we can expect if they are not handled beforehand.

Cordially,

Perry A. Chapdelaine,

Oh yes! I puzzled over the dosage of 20mg/kg for over an hour and couldn't come to any conclusion, but after talking with Jack Blount I find my intuition was better than my knowledge of dosages. 20mg/kg is too small. We are giving 2 grams per day for the average person. 20mg/kg, according to Jack, amounts to about 1.4 grams. How do we get into these problems?