

*Jack  
Blount*

CONSULTING HOURS:  
MON. TUES. THURS. FRI.  
8.00 A.M. - 5.00 P.M.  
WED. 8 - 12 NOON

OBSERVATIONS ON PROPOSED DOUBLE BLIND TRIAL OF  
CLOTRIMAZOLE

1. The most glaring deficiency in this is the complete disregard of the Herxheimer reaction. These Herxheimer reactions are very intense and if somebody who did not know what this was, the Herxheimer reaction would be labelled as a prohibitive side effect.
2. The obvious toxic effect of the drug. There are far better drugs available.
3. The dose proposed will probably be inadequate.
4. In previous trials they seem to have had 10% of patients developing severe neutropaenia.
5. The duration of trial seems to be one year. I see that during this period all would have had more or less identical treatments.
6. I see that you are going to have haemocult cards given to the patients to test occult blood. This of course could also probably be due to the concomittent NSAID.
7. Drop out patients. These are usually 20%, so this should probably include 8, but with the Herxheimer reaction this will probably be very much greater.
8. Visul analog scales on Appendix f should have a vertical line at the beginning and end of the line as patients tend to point either one way or the other beyond it. It is specified in the book you sent me.
9. Page 28 says the adrenal glands show cellular enlargement.

This has already previously been done, and will put any beneficial result down to the effect of cortisone. I do, however, note that no patients in the trial shall have had previous cortisone.

10. I agree with Perry Chapdeliane when he says, that the statement that metronidazole has been tried in Rheumatoid arthritis with significant side effects but with doubtful efficacy, is absolute rubbish. What they are missing, of course is the Herxheimer reaction which give you these side effects.
11. Clinics in North America suggest a pre-test of about 10 patients. The observation that the older patients are more likely to re-infection may be a quite significant observation due to the decreased immunological response.
12. Burnt out cases should be excluded. These will not respond.
13. X-ray changes require years to assess. They should not be used as a monitoring of improvement.
14. On page 503 of Clinics in Rheumatic Disease, December, 1983 it is said "Some medications will have effects that unmask the Physician. Such drugs may need to be evaluated in a single blind trial". Perhaps this would be a better proposition, or preferably a double blind trial on the Herxheimer reaction alone.
15. I see also that joint tenderress is going to be monitored. Joint tenderness does not in itself exist. Tenderness is felt always in the same place over the nerve and is really nerve tenderness. Investigators would have to be made aware of this fact. This is most important.

#### CONCLUSION

I feel that this test as it stands at present is a good way of crucifying ourselves at great expense. I would rather suggest a single blind trial with Flagyl, or alternatively a double blind trial with the Herxheimer reaction closely monitored.

3.

If done in its present state, if successful, only a few will accept the results, unless these are overwhelmingly convincing. If marginal, all will be forgotten and if unsuccessful, the result could be the destruction of our Foundation.