

5th September, 1951.

Dear Dr. Discombe,

I have, I am afraid, only just seen your letter of July 26th, but I hope that what little I have to say may still be in plenty of time.

As I understand it, your experiment is concerned only with the relief of pain as reported by the patient. I infer that you do not aim at so long a series as would be needed to pick up cases of agranulocytosis if this condition were to occur as a result of treatment. Perhaps, however, I have misunderstood you on this point and it may be that the condition is only found to set in after repeated or prolonged treatment with amidopyrin.

As regards the numbers of patients which would be required before satisfactorily clear results are obtained, I think it will be essential to ^{guided} be, as we say, sequentially, by the results as they come out. For example, if the cells were filled with equal numbers, the first hundred cases would give about 18 or 19 comparisons between the placebo and one of the analgesic drugs. It might well be at this stage, that the placebo would have fulfilled its purpose and that you would still desire more data in which two different drugs could be compared.

On the question of "synergistic action", the essential comparison among your four would seem to be that between

C and D, and it might be, though it cannot be confidently foreseen, that as the data accrue you would find yourself inclined to run nearly all patients to the two cells C_C and C_D .

It is one advantage of a truly random assignment of patients to treatment, that one can legitimately, according to the weight of evidence already accrued, modify the form of experiment in this way.

Yours sincerely,