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LONDON, N.W.10

28th July 1951.

Dear Professor Fisher,

May I ask your advice on a problem of design of experiment?

I have been concerned by the occurrence of fatal agranulocytosis in patients who have received a mixture of a barbiturate with amidopyrin to relieve their pain. My estimate of the incidence of agranulocytosis is about 1.1%, based on four separate series of 200-500 patients at risk, observed in Denmark, Switzerland and California, U.S.A..

The pharmaceutical houses question this estimate, because very few cases of agranulocytosis have been reported from Belgium, France and Switzerland, where amidopyrin is used as freely as is aspirin in this country. They also claim almost miraculous "synergistic action" between amidopyrin and barbiturates, which form a molecular compound.

I think it necessary to carry out a comparison

of the effect of no treatment; the effect of a commonly used analgesic - aspirin, phenacetin, codeine, similar to Vegamin; the effect of amidopyrin barbiturate mixture; and the effect of an aspirin barbiturate mixture which has been suggested as a substitute.

The only criterion of efficiency is the sensation of the patient - i.e. is the pain partly or completely relieved. The matter is complicated ~~less~~ by the fact that pain sometimes results spontaneously.

I have therefore suggested that an experiment on factorial lines be carried out. If A, B, C, D are the treatments, patients could be assigned at random to one of the boxes of the experiment drawn below

	A	B	C	D
A	A <sub>A</sub>	A <sub>B</sub>	A <sub>C</sub>	A <sub>D</sub>
B	B <sub>A</sub>	B <sub>B</sub>	B <sub>C</sub>	B <sub>D</sub>
C	C <sub>A</sub>	C <sub>B</sub>	C <sub>C</sub>	C <sub>D</sub>
D	D <sub>A</sub>	D <sub>B</sub>	D <sub>C</sub>	D <sub>D</sub>

If we define a "trial" as "a report on the relief of pain afforded by ingestion of a 'tablet'", it is suggested that two trials should be undertaken by ~~the~~ each subject on successive days, forming one "experiment". In this way each subject would



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provide at least one experiment, and perhaps more than one.

The diagonal ~~column~~  $A_A, B_B, C_C, D_D$  would give a measure of the variability of the patient's response, while the other squares would give comparisons between the effect of the different tablets, A with B, A with C, A with D, B with C and so on, — a total of six comparisons, each made in two ways, tablet A, for example being taken either before or after tablet B.

Were it possible to express the pain relief quantitatively, the experiment would be simple: but the only criteria will be "no relief", "some relief", "complete relief" and "sleep".

Can I use this design by giving arbitrary numerical scores to the results reported by the patients? or is there some other way in which I can score their reports? I am quite ready to regard "complete relief" and "sleep" as equivalent, but I should like to be able to obtain a separate estimate of the relative ~~sleep~~ hypnotic activities of the four substances

under trial.

I should be most grateful for your advice. As ~~now~~ I am going on leave shortly, there need be no sense of urgency - I cannot start the experiment before October at the earliest, & probably not until later, because I shall have to obtain the co-operation of a pharmaceutical manufacturing house, and have envelopes and report-cards printed, & so on.

I expect the dummy to produce between 10 and 30% relief, Veganin 30-60%, and the others 50-100%. Can you give me any idea how many experiments in each box would be needed?

Thank you very much

Yours sincerely

Ernest S. Combe.  
DISCOMBE.

10.8.57.

P.C. send in acknowledgment.