MEDICAL RESEARCH COUNCIL.

Telegrams: "MEDRESCO HAVER, LONDON." ~~[illegible]~~

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PRIVY COUNCIL.

NATIONAL INSTITUTE
FOR MEDICAL RESEARCH,
HAMPSTEAD,
LONDON, N.W. 3.

4·11·31

Dear Doctor Fisher

Thank you very much for taking so much trouble with my paper. I hope you will forgive me for writing a rather long reply. It is mainly because I was to get the matter clear in my own head and you mustn't feel obliged to reply in detail.

Tests of the kind which I am considering are becoming more & more important not only scientifically but also commercially & legally. The new edition of the Pharmacopoeia, which will be published next year lays down that insulin & digitalis shall be tested in this way so that the ~~standard dose~~ number of animals used shall be such that the standard error of the result shall not be more than ± 10 per cent I think it is. No one with formal scientific training has taken any active interest in the subject & we have had to do the best we could for ourselves. It is therefore important that the mathematics should be correct.

The paper by Godfrey Thomson is clearly relevant & I am very grateful to you for telling me about it.

I am very ~~surp~~ surprised to hear that you condemn inverse probability arguments so whole heartedly. I know that they have led to serious errors in the past but I didn't know that one could do without them altogether. For example, if one knows that positive errors of measurement are more frequent than negative errors it seems to me ~~rational~~ to ~~assume~~ conclude that it is more probable that the true ~~value~~ lies below ~~the~~ any given observed value than above, unless one has other reasons for believing that small ~~readings will~~ values will be less frequent than large ones. Is this conclusion irrational? An argument based on inverse probability gives an exact measure of ~~the~~ its probability.

In the case of the binomial distribution I ~~hopp~~ happened to discover that the ~~par~~ particular ~~co~~ convention I adopted compensated almost exactly for the asymmetry, so that of the distribution is normal for small samples. I differed from previous writers on this topic not only in change of convention, but in suggesting that some convention was necessary & was, in fact, tacitly assumed.

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A change of convention cannot, as you say, make the solution exact for small samples but it can & does practically abolish the error introduced by subsequently assuming that an asymmetrical curve is normal. Thomson, ~~made this assumption that the~~ in applying weights, made this assumption that the distribution was normal & therefore seems to me to have made tacitly an assumption practically identical with that which I made explicitly. The application of a weight to a reading implies some form of rational belief about the probability of different possible populations & I ~~cannot~~ do not know of any justification for applying a weight $\frac{1}{\sigma^2}$ except some form of inverse probability argument. Can you tell me of any paper I can read which will help me on this point? I should like to know more about the calculation of likelihood & the solution of the central problem of inductive logic.

I did not make the mistake you suggest about the number of degrees of freedom with which the χ^2 table should be entered in dealing with a fourfold table. I had discovered that your book differed from Pearson's & looked up papers by you & Yule & Greenwood on the subject. I think the fact that the χ^2 method gives a different result from mine depends on the fact that mine is based on an inverse probability argument. Surely you would not expect me to get the same result.

The reason for my assertion that the χ^2 ~~method~~ argument involves the assumption that the curve giving the sampling errors of the binomial is normal in shape was that I thought that the whole reasoning of the χ^2 method depended on the variables with which it dealt being normally distributed. Is this not so? I realize that I was wrong to suggest that the sampling error of the marginal frequencies was not taken into account.

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My real object is not to make new discoveries in statistics, but to get a method of calculation ~~for~~ for practical use.

The kind of problem which arises is

① Is a given series of observations compatible with the assumption that the distribution of individual lethal doses is normal.

② What is the variance of an estimate of toxicity based on such a test

③ Does a given series of experiments, each composed of a set of observations, prove that the variance varies? or in particular does the variance of the curve fitted to one set of observations differ significantly from that fitted to another.

The kind of method proposed by G Thomson can be used to solve the problems when the number of animals used is very large & p does not approach 0 or 1.

I thought that I had found justification for applying similar methods when the number of animals was small or approached 0 or 1. I thought I could solve the problem.

(4) If it has been observed that one animal died out of 10 what is the probability that the true probability of death is less than 0·01 (or 0·0001). ~~It~~ The probability (or likelihood) clearly diminishes as p approaches 0. How does one calculate it?. The method adopted by Thomson ~~[illegible]~~ + Trevan seems to be to calculate the probability of a true probability of death of 0·1 producing a mortality of less than ~~of~~ 0·01 (or 0·0001) in 10 animals. This is clearly unsound because there is quite a high probability that ~~that~~ none of the ten animals will die. I cannot see that the problem is solved by calculating the probability that a true probability of death of 0·01 (or 0·0001) will produce one or more deaths out of 10 animals since it is known for certain that only one death actually occurred. Is this problem soluble? How can one weight such an observation?

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The application of weight seems to be to imply some knowledge of the distribution of likelihood.

Forgive me for writing at such length. I think I shall probably have to accept Thomson's results ~~as the~~ (which were identical with mine) as the best it is possible to do at the moment. Thomson's method of calculating χ^2-Pearson is rather different from mine. Is Thomson right?.

Yours sincerely

John Gaddum.

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4.11.31

Dear Dr. Fisher

I sent off rather a long letter to you this afternoon, but I think I omitted to discuss one point. The fact that G. Thomson & I got the same answer is not so satisfactory as it appears at first sight. As far as I can make out Thomson compensated for a mistake by introducing a gratuitous & unnecessary complication

In his paper the probability integral Y is weighted with a weight

$$\frac{1}{4pq} \quad \text{(Urban's weight)}$$

I should have thought that the expression

$$\frac{1}{pq} \cdot \left(\frac{dp}{dY}\right)^2$$

would have been more suitable.

However the $\left(\frac{dp}{dY}\right)^2$ comes into the equation earlier in the paper under the name of Müller's weight in order that $\Sigma (v_i)^2$ (the residuals of p) shall be minimal rather than $\Sigma (v_i^*)^2$ (the residuals of y). I can't see why this is desirable. ~~If any~~ why should he prefer one lot of residuals to ~~the other~~? If my inverse probability argument were sound it would be, I think, best to make the second expression $\Sigma(\nu_2)^2$ minimal. Otherwise I can see no reason for preferring one lot of residuals to another. ~~In neither case~~.

I expect this all seems terribly naif to you – but it is only by making a fool of myself – so to speak – that I

can explain my difficulties
Yours apologetically
John Goddum