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The evaluation of placebos in clinical trials

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Synopsis—A model is proposed for the response of living organisms to the action of drugs when placebo reaction is likely to occur. The estimation of the parameters in the model is discussed together with tests of hypotheses about the parameter values.

Introduction

The clinical evaluation of drugs and medicaments is as old as medicine itself but it is comparatively recently in the history of the subject that the actions of various drugs have been recorded and compared in a quantitative and scientific fashion.

The value of a treatment can only be expressed in meaningful terms by reference to the state of affairs when the treatment is not used, either because of an alternative treatment or because of the absence of any treatment.

If a disease is severe so that the mortality rate for sufferers from the disease is high and if no treatment is currently known it is clear that any substantial reduction in the mortality rate is a sufficient indication of the value of a new treatment. A more common state of affairs is the case of a well established treatment for a disease where two questions may arise:

i. Is the customary treatment more effective than no treatment?

ii. Is the customary treatment less effective than one or more new possible treatments?

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The second question may usually be answered by comparison in a clinical trial but ethical considerations require that new treatments are admitted to a trial only if there are good grounds for expecting them to be as least as effective as the old treatment. The first question is more subject to ethical difficulties in the answering, since only in the mildest diseases may treatment be stopped in order to study the effect of no treatment.

The ethical considerations referred to above are not unequivocably interpreted, as has been pointed out by Hill (1), since the only well established treatment may actually be inferior to the absence of treatment, as in the use of anti-coagulant in cerebrovascular disturbances.

No scientist is completely free from the ethical implications of his work and this applies to the statistician as much as to any other scientist. We may, however, consider the scientific aspects of a problem without reference to its ethical context.

When attempting to answer the first of the two questions above, a placebo is frequently administered instead of merely neglecting those patients who are to receive no treatment. One of the original meanings of *placebo* is derived from the same root as *placate*, that is the placebo is given in order to please the patient or to keep him from the knowledge that he is being neglected. Lasagna (2) has given several meanings for *placebo*; we are at present concerned with the administration of a dummy treatment (3), which may also and incidentally please the patient either consciously or in more subtle ways. There is little to be gained by distinguishing formally between placebos and dummies (4).

Quantitative responses to drugs

When a drug or medicament is administered to a patient the response is likely to be quantitative if the treatment has pharmacological properties but it may be quantitative or qualitative if the effect of the treatment is psychological or psychosomatic. The effect of a pharmacological preparation on a living organism must depend on the potency of the preparation and on the dose used but the mode of observation of the effect may either be quantitative as well or it may only be possible to observe success and failure of the treatment. The psychological results of the administration are likely to be qualitative; the treatment either pleases or it does not, although degrees of pleasure may sometimes occur.

Both pharmacological and psychological effects are probably present in most clinical trials, each to a greater or lesser extent. If the observed

response is quantitative we may suppose that pharmacological factors predominate although this is not always the case since, for example, Wolf *et al* (5) found it possible to affect the eosinophile count by placebo action.

Such quantitative observations would occur, for example, in a trial to test the effects of treatments by various fruit preparations on the vitamin C content of the blood. These effects can only be measured against a standard which in this case consists of the absence of treatment. However those persons receiving the fruit preparations are thereby also receiving extra water, sugar and other components besides vitamin C so that the absence of treatment should be interpreted as receiving equivalent amounts of water, sugar, etc., and perhaps even sulphur dioxide, rather than as complete neglect. At the same time any psychological factors will be equalized between the active treatments and the blank treatment or placebo. The function of the placebo experiment, in such a trial is to avoid bias in the results just as in, say, the direct determination of oxygen in rubber by the Unterzaucher method (6) it is necessary to do a blank determination, or as in absorption spectrometry the intensities must be corrected for the background absorption. An important additional characteristic of the clinical trial is the pronounced variability between individuals receiving the treatments. It is therefore particularly important to design the trial so as to control and reduce sampling error especially by the random allocation of treatments and by ensuring that the individuals studied form a random and representative sample of the population for which the treatments are intended. A comprehensive account of the application of statistics to the design and analysis of clinical trials has been given by Hill (7) and the general principles of experimental design have been discussed nonmathematically by Cox (8).

Quantal responses to drugs

If the observed response of an individual to drugs or other medicaments is *success* or *failure* of the treatment the response is termed quantal. The object of the treatment of serious diseases is normally the survival of the patient, and chronic conditions usually require the alleviation of pain or other symptoms. In the first case *success* denotes survival, and in the second improvement, versus death and no improvement respectively.

The reaction of a patient to the administration of pharmacologically inert substances is usually referred to as placebo reaction. This reaction is normally quantal so that in clinical trials where there is a possibility of

placebo reaction as well as of pharmacological action the observed response is likely to be quantal.

The distinction between graded and quantal responses to the action of drugs is not absolute since any quantitative response may be made quantal. Conversely, quantal data may be made numerical by the use of scores, particularly if there are more than two possible outcomes. Hewlett and Plackett (9) have studied the relation between the quantal and graded responses to a drug in terms of a bivariate Normal distribution of graded response and critical graded response.

Since the placebo reaction is usually observed quantally it is appropriate that the corresponding drug action is also discussed in the same terms, although it might be possible in a further investigation to consider a trivariate distribution of graded response and critical graded response to drug action jointly with quantal response to placebo action.

The effect of placebo reaction on drug action

In clinical trials as reported in the literature, where placebo reaction is considered, the usual design is equivalent, in the simplest case of one treatment, to allocating individuals to a group of placebo reactors or to a group of nonreactors according to the results of tests with placebos. Each of the groups is then separately tested for responses to a given dose of a drug.

In a suitably designed trial the observed proportion of placebo reactors is an unbiased estimate of the proportion in the population. However placebo reactors are not always consistent, for example Lasagna (10) found that 55 per cent of patients receiving the placebo were inconsistent, that is 79 per cent of reactors to the placebo did not react on every occasion they received the placebo. Similarly the response to drug action is not consistent in given individuals; Berkson (11) has compared this variability with the variation in the weights of human beings from time to time and Hewlett and Plackett (9) have stated that this variation does not invalidate the interpretation of drug action on a particular occasion. It follows that if the groups are allocated by means of single observations on the placebo then each group may be contaminated by the other and so the difference in drug action on the two groups is liable to be underestimated.

Moreover even if individuals in a trial are correctly allocated as reactors or not, the difference in response to an active drug will depend on the dose given in general. This is illustrated in *Fig. I* for a high dose A with a small difference between the groups and for a low dose B with a large difference between them.

It is clear that in order to evaluate drug action in the presence of placebo action it is necessary to study a range of doses, preferably spanning from zero level to a dose corresponding to about 95 per cent response. In view of the difficulty in separating the placebo reactors from the non-reactors it is proposed to analyse data from mixed groups.

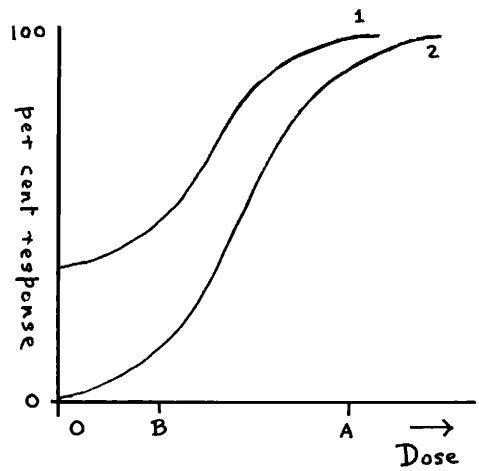

Figure 1 Comparison between placebo reactors (2) and non reactors (2)

A MODEL OF PLACEBO REACTION

The population of persons to be treated by drugs for a particular disease or condition may be regarded as composed of a proportion Π_1 of placebo reactors, I, and a proportion $\Pi_2 = 1 - \Pi_1$ of nonreactors to placebo, II.

A common model for the quantal response of living organisms to given doses, χ, of a drug is the probit or normit transformation (12) defined by

$$\theta = \Phi\left(\frac{\chi - \mu}{\sigma}\right) = \Phi(\alpha + \beta\chi) \qquad \text{I}$$

$$\alpha + \beta\chi = \Phi^{-1}(\theta) = y_p - 5 = y \qquad \text{II}$$

where θ is the probability of a response to a dose χ, Φ denotes the standard normal probability integral and μ, σ are two parameters which are often transformed to α, β. The empirical probit of an observed proportion p of successes is given by y_p and the normit by y when θ is replaced by p. The parameters μ and σ are sometimes interpreted as the mean and standard deviation, respectively, of an underlying normal distribution of tolerances to the drug in the population but this interpretation is not essential to the use of the probit method.

The normit model may be extended to the two classes I and II separately so that in the mixed population

$$\theta = \Pi_1 \theta_1 + \Pi_2 \theta_2 \qquad \text{III}$$

$$= \Pi_1 \Phi(\alpha_1 + \beta_1 \chi) + \Pi_2 \Phi(\alpha_2 + \beta_2 \chi) \qquad \text{IV}$$

where $\Phi(\alpha_1) > \Phi(\alpha_2)$.

The quantities of especial interest to be determined by a clinical trial are

i. the proportion Π_1, of placebo reactors in the population,

ii. the dose, χ_0, such that, say, 99.9 per cent of nonreactors to the placebo will be successfully treated by the drug,

where $\chi_0 = (3{\cdot}09 - \alpha_2)/\beta_2$. V

If these quantities can be estimated satisfactorily then the potency of a drug may be assessed without the complications that a drug may be rejected if the proportion Π_1, of placebo reactors is high and that the effective dose of an accepted drug may be underestimated for the same reason. Lasagna *et al* (10) have stressed the importance of these complications and have also suggested that the presence of placebo reactors may alter the dose response relationship and so alter the sensitivity of the clinical trial.

If β_1 is non zero then the placebo reactors are also subject to the pharmacological action of the drug whereas if $\beta_1 = 0$ then the placebo reaction is independent of the dose and there is no advantage in administering the drug to this group.

Modifications to the model

If the population contains any placebo reactors then $\Pi_1 \Phi(\alpha_1)$ will not be zero and therefore $\Pi_1 \Phi(\alpha_1 + \beta_1 \chi)$ is not negligibly small for all negative values of χ. Although the model may fit the data from a clinical trial satisfactorily it is difficult to interpret the model when χ is negative. This objection may be overcome by putting

$$\Phi = \Pi_1 \left\{ \tfrac{1}{2} + \int_0^{\alpha_1 + \beta_1 \chi} (2\Pi)^{-\frac{1}{2}} \exp(-t^2/2)\, dt \right\} + \Pi_2 \Phi(\alpha_2 + \beta_2 \chi), \qquad \chi \geqslant 0. \qquad \text{VI}$$

The dose response relationship for many drugs is given by the probit transformation in terms of the logarithm of the dose as metameter (12, p 23). If this is the case then either χ may be replaced by $\log(\lambda + \chi)$ for some $\lambda > 0$ or β_1 may be deleted from the model.

The two classes of patient taken separately may not have a linear relationship between the probit and the dose and it may be necessary to consider polynomial forms. In this case it is preferable to use the logit transformation.

$$y = \log p - \log (1 - p) \qquad \text{VII}$$

where p is the observed proportion of successes and then to put

$$y = \alpha + \beta \chi + \gamma \chi^2 \qquad \text{VIII}$$

for example.

The logit transform is equivalent to taking

$$\theta = e^y/(1 + e^y) \qquad \text{IX}$$

where y may be given any one of a number of functional forms, possibly different in the two classes.

The estimation of the parameters in the model

If the population contains only one homogeneous class the parameters for the probit or normit and the logit models may be estimated by the method of maximum likelihood, by the method of minimum chi-square (13), and by weighted least squares (14).

In the case of a population consisting of two classes the maximum likelihood method is the most appropriate since the other methods lose any computational advantage they may have in the generalization to two groups.

The method of maximum likelihood will be applied to the model given in equation (IV); the various modifications may be treated similarly.

Let the observed frequencies of successes be r_i when n_i individuals are treated and the dose is χ_i, for i=1,2, . . . , k. The likelihood is the joint probability of the observed results taken as a function of the unknown parameters.

The maximum likelihood is found by solving the following equations for the estimates $\hat{\alpha}_1$, $\hat{\beta}_1$, $\hat{\alpha}_2$, $\hat{\beta}_2$, $\hat{\Pi}_1$:

$$0 = \frac{\partial L}{\partial \alpha_1} = \Pi_1 \sum_{i=1}^{k} \frac{r_i - n_i \theta_i}{\theta_i (1 - \theta_i)} Z_{1i} \qquad \text{X}$$

$$0 = \frac{\partial L}{\partial \alpha_2} = \Pi_2 \sum_{i=1}^{k} \frac{r_i - n_i \theta_i}{\theta_i (1 - \theta_i)} Z_{2i} \qquad \text{XI}$$

$$0 = \frac{\partial L}{\partial \beta_1} = \Pi_1 \sum_{i=1}^{k} \frac{r_i - n_i \theta_i}{\theta_i (1 - \theta_i)} Z_{1i} \chi_i \qquad \text{XII}$$

$$0 = \frac{\partial L}{\partial \beta_2} = \Pi_2 \sum_{i=1}^{k} \frac{r_i - n_i \theta_i}{\theta_i (1 - \theta_i)} Z_{2i} \chi_i \qquad \text{XIII}$$

$$0 = \frac{\partial L}{\partial \Pi_1} = \sum_{i=1}^{k} \frac{r_i - n_i \theta_i}{\theta_i (1 - \theta_i)} (\theta_{1i} - \theta_{2i}) \qquad \text{XIV}$$

where θ_i, θ_{1i}, θ_{2i} are the values of θ, θ_1, θ_2 when $\chi = \chi_i$, respectively, and $Z_{1i} = (2\Pi)^{-\frac{1}{2}} \exp(-(\alpha_1 + \beta_1 \chi_i)^2/2)$ XV

$$Z_{2i} = (2\Pi)^{-\frac{1}{2}} \exp(-(\alpha_2 + \beta_2 \chi_i)^2/2) \qquad \text{XVI}$$

for L = log likelihood =

$$\text{constant} + \sum_{i=1}^{k} r_i \log \theta_i + \sum_{i=1}^{k} (n_i - r_i) \log (1 - \theta_i) \qquad \text{XVII}$$

There are no explicit solutions for equations X through XIV and it is necessary to use a method of successive approximations.

The following equations have been obtained by a generalization of the Bliss and Fisher solution of the probit equations (12). If $\hat{\alpha}_1, \hat{\beta}_1, \hat{\alpha}_2, \hat{\beta}_2, \hat{\Pi}_1$ are approximate solutions then better solutions are obtained by taking

$$\hat{\alpha} + \Delta\alpha_1, \hat{\beta}_1 + \Delta\beta_1, \hat{\alpha}_2 + \Delta\alpha_2, \hat{\beta}_2 + \Delta\beta_2, \hat{\Pi}_1 + \Delta\Pi_1,$$

where $\Delta\alpha_1, \Delta\alpha_2, \Delta\beta_1, \Delta\beta_2, \Delta\Pi_1$ are obtained as the solutions of the equations:

$$\sum \frac{r_i - n_i \hat{\theta}_i}{\hat{\theta}_i (1 - \hat{\theta}_i)} \hat{Z}_{1i} = \Delta\alpha_1 \hat{\Pi}_1 \Sigma \hat{\omega}_i \hat{Z}_{1i}^2 + \Delta\alpha_2 \hat{\Pi}_2 \Sigma \hat{\omega}_i \hat{Z}_{1i} \hat{Z}_{2i} + \Delta\beta_1 \hat{\Pi}_1 \Sigma \hat{\omega}_i \hat{Z}_{1i}^2 \chi_i + \Delta\beta_2 \hat{\Pi}_2 \Sigma \hat{\omega}_i \hat{Z}_{1i} \hat{Z}_{2i} \chi_i + \Delta\Pi_1 \Sigma \hat{\omega}_i \hat{Z}_{1i} (\hat{\theta}_{1i} - \hat{\theta}_{2i}) \qquad \text{XVIII}$$

$$\sum \frac{r_i - n_i \hat{\theta}_i}{\hat{\theta}_i (1 - \hat{\theta}_i)} \hat{Z}_{2i} = \Delta \alpha_1 \hat{\Pi}_1 \Sigma \hat{\omega}_i \hat{Z}_{ii} \hat{Z}_{2i} + \Delta \alpha_2 \Pi_2 \Sigma \hat{\omega}_i \hat{Z}_{2i}^2 + \Delta \beta_1 \hat{\Pi}_1 \Sigma \hat{\omega}_i \hat{Z}_{1i} \hat{Z}_{2i} \chi_i + \Delta \beta_2 \hat{\Pi}_2 \Sigma \hat{\omega}_i \hat{Z}_{2i}^2 \chi_i + \Delta \Pi_1 \Sigma \hat{\omega}_i \hat{Z}_{2i} (\hat{\theta}_{1i} - \hat{\theta}_{2i}) \qquad \text{XIX}$$

$$\sum \frac{r_i - n_i \hat{\theta}_i}{\hat{\theta}_i (1 - \hat{\theta}_i)} \hat{Z}_{1i} \chi_i = \Delta \alpha_1 \hat{\Pi}_1 \Sigma \hat{\omega}_i \hat{Z}_{1i}^2 \chi_i + \Delta \alpha_2 \hat{\Pi}_2 \Sigma \hat{\omega}_i \hat{Z}_{1i} \hat{Z}_{2i} \chi_i + \Delta \beta_1 \hat{\Pi}_1 \Sigma \hat{\omega}_i \hat{Z}_{1i}^2 \chi_i + \Delta \beta_2 \hat{\Pi}_2 \Sigma \hat{\omega}_i \hat{Z}_{1i} \hat{Z}_{2i} \chi_i + \Delta \Pi_1 \Sigma \hat{\omega}_i \hat{Z}_{1i} \chi_i (\hat{\theta}_{1i} - \hat{\theta}_{2i}) \qquad \text{XX}$$

$$\sum \frac{r_i - n_i \hat{\theta}_i}{\hat{\theta}_i (1 - \hat{\theta}_i)} \hat{Z}_{2i} \chi_i = \Delta \alpha_1 \hat{\Pi}_1 \Sigma \hat{\omega}_i \hat{Z}_{1i} \hat{Z}_{2i} \chi_i + \Delta \alpha_2 \hat{\Pi}_2 \Sigma \hat{\omega}_i \hat{Z}_{2i}^2 \chi_i + \Delta \beta_1 \hat{\Pi}_1 \Sigma \hat{\omega}_i \hat{Z}_{1i} \hat{Z}_{2i} \chi_i^2 + \Delta \beta_2 \hat{\Pi}_2 \Sigma \hat{\omega}_i \hat{Z}_{2i}^2 \chi_i^2 + \Delta \Pi_1 \Sigma \hat{\omega}_i \hat{Z}_{2i} \chi_i (\hat{\theta}_{1i} - \hat{\theta}_{2i}) \qquad \text{XXI}$$

$$\sum \frac{r_i - n_i \hat{\theta}_i}{\hat{\theta}_i (1 - \hat{\theta}_i)} (\hat{\theta}_{1i} - \hat{\theta}_{2i}) = \Delta \alpha_1 \hat{\Pi}_1 \Sigma \hat{\omega}_i (\hat{\theta}_{1i} - \hat{\theta}_{2i}) \hat{Z}_{1i} + \Delta \alpha_2 \hat{\Pi}_2 \Sigma \hat{\omega}_i (\hat{\theta}_{1i} - \hat{\theta}_{2i}) \hat{Z}_{2i} + \Delta \beta_1 \hat{\Pi}_1 \Sigma \hat{\omega}_i (\hat{\theta}_{1i} - \hat{\theta}_{2i}) \hat{Z}_{1i} \chi_i + \Delta \beta_2 \hat{\Pi}_2 \Sigma \hat{\omega}_i (\hat{\theta}_{1i} - \hat{\theta}_{2i}) \hat{Z}_{2i} \chi_i + \Delta \Pi_1 \Sigma \hat{\omega}_i (\hat{\theta}_{1i} - \hat{\theta}_{2i})^2 \qquad \text{XXII}$$

where $\hat{\omega}_i = \dfrac{n_i}{\hat{\theta}_i (1 - \hat{\theta}_i)}$

The calculations are iterated until the estimates do not change and a goodness of fit test may be used as a criterion of convergence as in probit analysis (12). The complexity of the calculations makes it necessary to use a digital computer when solving these equations.

Initial approximations for the solutions

In order to apply the method of successive approximations given above it is necessary to choose suitable starting values. These may be

obtained graphically from an arithmetic probability plot of the observed responses. The case of fifty per cent reactors with the two groups differing only in the value of α which is sufficient to clearly separate the groups is given in *Fig. 2*. It can be seen that the curve for the mixed groups tends to the first line for low dosage and to the second for high dosage. *Fig. 3* illustrates the behaviour when the two groups are not so clearly separated

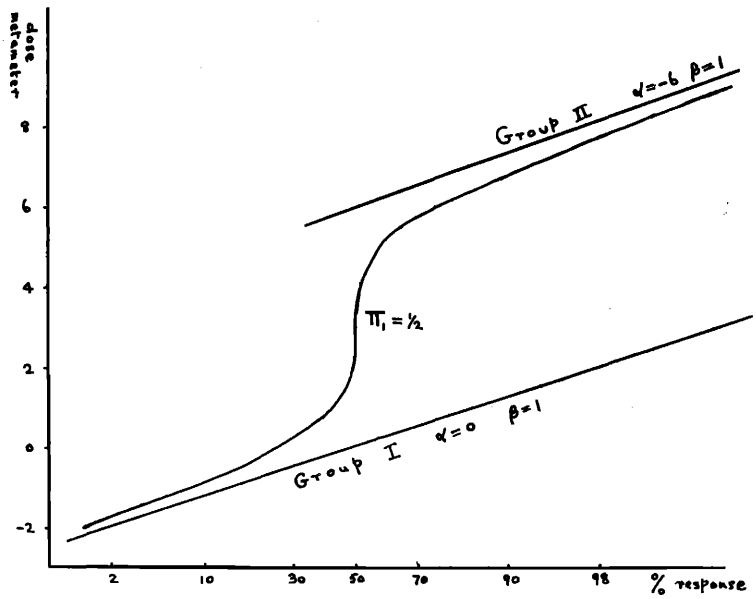

Figure 2 50% placebo reactors.

and where the values of β are different. In this case also the mixture curve tends to the separate groups at the extreme values of the dosage.

The initial values for α_1, α_2, β_1, β_2 may be obtained by drawing lines through the points on the A.P. plot at the ends of the range of dosage and these values used with an intermediate point to estimate Π_1. It is advisable to take $\alpha_1 \neq \alpha_2$ and $\beta_1 \neq \beta_2$ since otherwise equations XVIII through XXII become identical with the equations for fitting a single straight line to the A.P. plot and the above method is liable to converge to the wrong solutions.

When the observed responses are plotted the points will be scattered about the population curve and straight lines should be drawn so that the points lie close and slightly below line II and above line I.

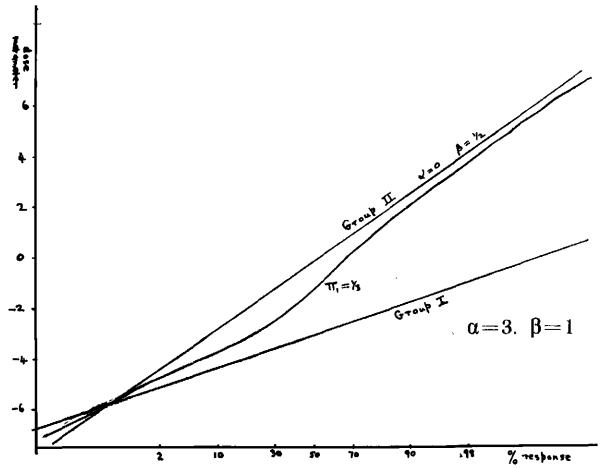

Figure 3 33% placebo reactors.

TESTS OF HYPOTHESES ABOUT THE PARAMETERS

If it is desired to compare two models for their applicability to a given set of data, for example, to test whether $\beta_1=0$ in the model of equation IV the likelihood ratio test (15) should be used. In this test the maximum likelihood estimates of α_1, α_2, β_1, β_2, Π_1 are used to calculate the likelihood and then the whole procedure is repeated after deleting β_1 from equations XVIII through XXII. The ratio of the second likelihood to the first may be entered in a chisquare test by taking –2 log (ratio of likelihoods), with one degree of freedom in this case.

SUMMARY

Since placebo reactions are usually quantal and drug responses may be observed quantally if desired, a suitable model for the action of drugs in a mixed population of placebo reactors and nonreactors is given by a linear combination of normal probability integrals with different parameters or by the corresponding logit model. This model allows for the possible inconsistency in placebo and drug response.

The maximum likelihood method is applied to obtain estimates of the parameters in the model but it is expected that the calculation of the estimates will require the use of a computer.

In order to test whether or not the model gives satisfactory evaluations of placebo effects it will be necessary to carry out clinical trials in which

several dose levels of each drug are administered in place of the customary trials in which each drug is used at only one or two levels.

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Introduction by the lecturer

If the two populations are not sufficiently separated it may be difficult to distinguish between the curve for the mixed population and the corresponding straight line approximation in view of the random fluctuations which will occur. However, there is less practical importance in the separation into two groups for this case since a straight line approximation will give results which are very similar to the hypothetical curve. For example, if $\alpha_1 = 0$, $\alpha_2 = -2$, $\beta_1 = \beta_2 = 1$, and $\pi_1 = \frac{1}{2}$, then the following results are obtained by means of a straight line approximation drawn by eye.

x		–1	0	1	2
percent	exact	8.0	26.1	50.0	73.9
response	approx.	9.0	24.8	50.0	75.0

The conclusion is that, for a mixture of two distinct groups of reactors and non-reactors with only a small difference in their reaction to drugs, it is still possible to fit the data and obtain satisfactory results.

One characteristic of most clinical trials on placebo reaction in the past is the use of only two, or at most three, dose levels including zero. Inherent in the proposed method is the use of sufficient points in the effective dose range to determine the shape of the curve. The increase in the amount of information from a clinical trial is dependent on a considerable increase in expenditure.

At the moment, a student at Brunel University is writing a programme for this method and also to simulate some data, because one of the things when you introduce a new model is to find out whether it works reasonably in terms of the assumptions. Then you can apply it to real data to determine whether the assumptions hold in practice.

DISCUSSION

MR. N. J. VAN ABBÉ: Since a range of dose levels, as such, is not normally applicable to cosmetics and toiletries, would it be correct to interpret your model in terms of either (a) a range of concentrations of active constituent in the base, or (b) a range of increasing time intervals for observation?

THE LECTURER: Although I have spoken primarily in terms of drug action, I am really concerned with medicaments and X does not have to be interpreted as the dose; the normal procedure is to use a so-called dose metameter which is often the logarithm of a dose because it so happens that in the majority of situations one gets closer to a straight line on A.P. paper if the log of the dose rather than the dose itself is plotted. X only denotes some characteristic which, when it varies, will produce a variation in the probability of response and it can be the duration of treatment, or the concentration in some base, or both. I suspect that the random fluctuations would be much too large to make much use of a model with several such variables but there is no objection in principle. Instead of X we could use concentration and time of treatment as two variables, providing, of course, that we have a consistent way of determining successes. If we have prolonged treatment then we have to look at its success or failure at the end rather than at stages. Otherwise it is necessary to use sequential analysis and I believe that this was discussed at a previous meeting. There is no attempt in my model to introduce sequential ideas.

DR. K. H. R. WRIGHT: Why is there a difference between β_1 and β_2?

THE LECTURER: I based this more or less on a desire to be as general as possible and the most general case would be that the two betas are different. In one paper in the literature it was pointed out that it appeared that placebo reactors did respond differently with respect to the level of dose, but there is nothing to say that one can not restrict the model to equal betas, Another way in which one can restrict the model is to assume that the placebo reactors do not react to the drug at all, in which case we will put B_1 equal to zero. All these things are possible and the equations can be modified accordingly. I have suggested that one can formally make this a matter of statistical test as to whether $\beta_1=\beta_2$ or whether one of them is zero. I think that we want some experience with the method before we get too sophisticated. It might be a good idea to start off with $\beta_1=\beta_2$. We are just trying to carry out some clinical trials, observe the proportion of responses and match it by means of a model so that for different values of dose we can predict the response in the general population. Any model which fits our data well can be used for this, irrespective of whether it reflects some underlying physiological or pharmacological action. You can certainly make $\beta_1=\beta_2$, particularly if there is some justification for doing so.