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Factors Predisposing to a Placebo Response in New Out-patients with Anxiety States*

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Introduction

Whenever one person seeks to influence the behaviour of another, the outcome may be affected by a multiplicity of factors. When the deliberate manipulation of one of these is followed by a given response, we regard the manœuvre as specific and causal for that event. While this conclusion is acceptable logically, in practice it frequently proves to be misleading because certain implicit assumptions are overlooked.

Validity of interpretation depends on accurate definition of experimental variables. In assessment of medical treatment, this implies homogeneity of the patient population, operational specification of treatment and target disorder, and a sensitive and reliable measure of response. It is especially difficult to define these factors in psychiatric practice, since we can seldom be sure which aspects are relevant. Adoption of the controlled clinical trial has led to a clearer appreciation of these problems and has enabled the specific effects of treatment to be ascertained more precisely.

Paradoxically, this very approach to evaluation has highlighted the influence of non-treatment or non-specific factors in response to therapy. Mainly of a psycho-social nature, non-specific influences can be regarded as functions of the three components of the treatment situation: the patient, the therapist and the setting in which treatment is carried out. The experimental use of a placebo as a treatment vehicle offers a situation in which the relation of such non-specific factors to response can be examined.

The literature on the placebo response and the placebo responder has been amply reviewed (Shapiro, 1960; Liberman, 1962; Honigfeld, 1964) and no further survey will be attempted here. However, it is worth while commenting on one difficulty in interpreting some of these studies. The problem is exemplified by Trouton (1957) who, discussing the observations made by Lasagna *et al.* (1954) on the personality of placebo responders, concluded: "The specificity or generality of the placebo reaction might well be determined before attempting to correlate the supposed trait with types of personality." Since the specificity or generality of the placebo response has not been determined, one cannot assume that a class of placebo responders exists; and because the placebo response is a dependent variable, it is impossible to infer antecedent causes that have general validity. Therefore, in order to examine the relationship between personality factors and placebo response it is not sufficient to describe the characteristics of placebo responders. What is necessary is to define certain characteristics independently of the response and then to test the hypothesis that people in that class are (or are not) predisposed to respond to a placebo.

The present investigation was conceived with two questions in mind. (1) When patients suffering from a particular disorder are given placebos therapeutically, can one independently classify them in a way which will also differentiate their response to placebo? (2) When patients with the same disorder receive active medication, does the same classification predict which of these will improve the most?

Method

The study was carried out over a period of 15 months at five London hospitals. The Bethlem Royal and Maudsley Hospitals (a post-graduate psychiatric teaching hospital) and St. Charles' Hospital provided the majority of patients; the remainder were seen at Padding-

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ton General Hospital, New End Hospital, and the North Middlesex Hospital. The last four are general hospitals and all predominantly serve patients in the local neighbourhood.

The design of the study incorporated the following requirements: (1) patients should have had no previous direct contact with the hospital; (2) those selected should form a homogenous diagnostic group as agreed by two psychiatrists; (3) the condition should carry diagnostic implications for medication, yet be susceptible to treatment by placebos as an ethical alternative; (4) the same doctor should see, treat and assess all patients; (5) the setting of treatment should approximate to usual out-patient conditions; (6) duration of treatment should be sufficient to allow any consistent response to become evident.

Selection of Patients

New psychiatric out-patients were seen in the customary way by a senior psychiatrist. If he concluded that the patient was suffering from an anxiety state and was willing for him to be treated with either a placebo or sodium amylobarbitone, that patient was referred to me at the same session with the introduction, "I would like you to see a doctor who is especially interested in people with troubles like yours."

The diagnosis of anxiety state was defined and agreed with the participating psychiatrists to be a condition of predominant apprehension and tension, experienced mentally or physically, persisting independently of external factors and not considered secondary to other disorders.

Final selection was based on the following criteria: new out-patients, aged 18–60 years, with adequate understanding and usage of the English language and a Western cultural background; agreement on diagnosis of an anxiety state whose duration was not less than three weeks; and no relevant medication within the preceding week.

Representativeness of the Sample

Examination of a random sample of new out-patients attending the Maudsley Hospital during the first three months of the study showed that 16 (9·4 per cent.) were diagnosed as anxiety states out of a total of 171. Of these 16 potential patients for the investigation, 7 were actually referred. Seven others were not considered suitable: one was considered to need psychotherapy, 3 were already improving and in 3 there were obvious precipitating or exacerbating factors; in only 2 cases was there no acceptable reason for non-referral. Thus, nearly 80 per cent. of eligible patients were referred during the first three-month period; this proportion was confirmed by another check over the following four months. On these grounds there is no reason to suppose that patients referred to the study were other than typical of patients with anxiety states who attend a psychiatrist for the first time. It will also be shown that these patients have virtually the same extraversion and neuroticism scores on the Maudsley Personality Inventory as an independent series of neurotic out-patients.

Procedure

Patients were seen in the usual out-patient consulting rooms. At my first interview, after ascertaining that the patient knew why he had been referred (over 90 per cent. had been given the above introduction), I asked him to describe his present troubles as fully as possible before enquiring about other symptoms. Selected patients were told that I was going to start them on tablets which had proved helpful to many people with troubles like theirs; they were given an euphonious coded hospital prescription for either placebo, one three times daily, or sodium amylobarbitone gr. 1 three times daily, which was repeated on subsequent visits. Patients were seen weekly for three weeks; interviews lasted 15–20 minutes and were devoted to assessment and to enquiry about taking medication and any change of circumstance. I attempted to maintain a cautiously optimistic attitude throughout the experimental period, showing mild pleasure when improvement was evident and offering encouragement when it was not.

Measures

1. *Independent variables*

The *Out-patient Attitude Scale* (OAS) was constructed for the present investigation as

a measure of patients' attitudes to psychiatry, to psychiatric treatment and to hospital (Black, 1965). Favourable and unfavourable attitudes are reflected by high and low scores respectively. The scale is part of the Out-patient Inventory, and each item alternates with another from the

Confidence in Doctors Scale (CD). Constructed for an earlier study (Black, 1959), it was designed to assess whether a patient's attitude to doctors before attending hospital was favourable (low score) or unfavourable (high score).

Concern with Health (CH). This measure consists of 27 items from the Cornell Medical Index chosen for their close content similarity to those having a loading of 0·3 or more on Health Concern, the first factor obtained by Comrey (1957) on factor analysis of the MMPI Hypochondriasis Scale. The number of questions answered "Yes" constitutes the score.

During the entire period of study the Cornell Medical Index and the Out-Patient Inventory (OAS and CD) were completed by all new out-patients after registration and before they saw a hospital psychiatrist.

The *Maudsley Personality Inventory* (MPI) (Eysenck, 1959) provided measures of neuroticism (N) and introversion-extraversion (E). Some of the filler items were replaced by ones from the

Reactor-Non-reactor (RN) *Scale*. This comprises 10 items from the Bernreuter Personality Inventory, mainly related to self-confidence, which were found by Joyce (1959) to differentiate and to predict medical student placebo reactors.

The MPI and RN scale were completed by all anxiety state patients after their first interview with me. The remaining independent variables were age, sex and duration of illness. No patient's questionnaire measurements were scored until after he had completed the study period.

2. *Dependent Variables*

Hamilton's (1959) *Anxiety State Rating Scale* was completed at the end of each interview and without reference to the previous week's entry.

Self-rating forms were returned by post twice weekly by all patients receiving placebos. They indicated how much the tablets had helped in the last two days by marking a 12-cm. line labelled from left to right, Very poor effect, No effect, Very good effect; a patient's score is the distance in centimetres from the centre of the line (No effect) to his mark, being positive on the right and negative on the left. Patient's weekly ratings were not examined until after I had completed my own assessment.

Hypotheses

Based on the results of previous studies, the following predictions were made:

1. Among patients receiving a placebo: (*a*) age, (*b*) sex, and (*c*) duration of illness will be unrelated to outcome; those who express (*d*) high confidence in doctors, (*e*) favourable attitudes to hospital, psychiatry and psychiatric treatment, (*f*) more complaints about their physical health, and who are (*g*) more sociable and extraverted individuals, will show a better response than patients with the opposite attributes.

2. The same predictions were made for patients on sodium amylobarbitone, since there was no reason to expect them to differ from those made for the placebo patients.

Results

Population

Of 49 patients selected for the investigation, 44 completed the three-week period of study. The 5 who dropped out after the first interview did not differ significantly on the measures employed from the remainder.

There are no significant test differences between the 11 women and the 33 men, irrespective of treatment, and their scores are treated together. Mean age was 34·6 years, S.D. 8·9 years; median 32·5 years; range 19–52 years. Mean duration of illness ascertained for 40 patients, was 15·6 months; median 9 months; range 0·75–96 months.

Placebo Sample

1. *Dependent measures*. The first 29 patients received placebo. Weekly ASRS scores differ significantly ($F = 3{\cdot}41$, $p < 0{\cdot}025$), initial and final scores being positively correlated: $r = +0{\cdot}51$ ($p < 0{\cdot}01$). Differences between mean initial score (13·9) and subsequent scores indicated a significant week-by-week improvement; mean final score is 9·6 ($t = 4{\cdot}87$, $p < 0{\cdot}001$). Inspection of the scatter plot of individual values (Fig. 1) suggests a curvilinear relationship between initial and final scores,

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but this is not supported on formal testing. The equation for the regression line of final (Y) on initial (X) scores is: $Y = 0 \cdot 79X - 1 \cdot 5$.

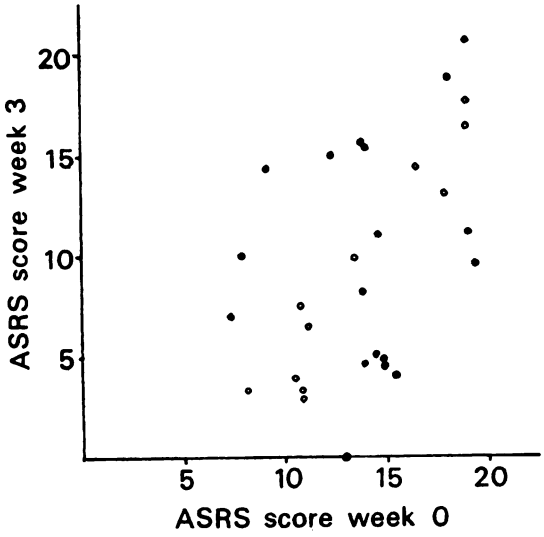

FIG. 1.—Scatter plot of initial (week 0) and final (week 3) ASRS scores of patients in placebo sample (n = 29).

The existence of linearly correlated scores raises the question of how best to compare individuals' responses to treatment when their initial levels differ. Solutions yielding various adjusted final scores have been proposed, first by Lacey (1956) and more recently by Benjamin (1963). Since, in the present study, interest centres on differences between groups composed of different individuals, each patient's final score was corrected for regression on his initial score. Following this adjustment the correlation of final and initial scores falls to $r = +0 \cdot 05$. Unless otherwise stated, all further reference will be to these or to similarly adjusted final third week scores, ASRS 3. The fact that this measure is significantly related to patients' self-ratings at the third week supports its use as a meaningful index of residual illness. The size of the correlation, $r = -0 \cdot 58$ ($p < 0 \cdot 01$), is acceptable considering the crudity of the self-rating measure and the fact that the two variables deal with different aspects of the patient's response.

2. *Relations between independent and dependent variables.* For each of the independent variables except duration, patients were first grouped into high and low scorers about the mean; for duration, the high group included patients ill for one year or more, and the low group, those ill for less than one year.

Analysis of variance shows that two variables are associated with significantly different mean ASRS 3 scores—duration and OAS. Patients who have been ill for under one year, and those who are more favourably disposed to the hospital, treatment and psychiatry, are less severely ill after three weeks' treatment with placebo than the others ($F = 4 \cdot 56$, $p < 0 \cdot 05$, and $F = 4 \cdot 76$, $p < 0 \cdot 05$, respectively).

Inspection of the remaining results prompted further analyses of ASRS 3 scores to be made for trichotomized groups of patients. The overall differences between ASRS 3 means of these duration and OAS groups just exceed the 5 per cent. probability level. Extraversion now appears as a significant discriminator ($F = 6 \cdot 06$, $p < 0 \cdot 01$), the high E group being least ill with a mean ASRS 3 of 6·2, middle E 9·4, and low E 12·8 (high E *vs.* low E: $t = 3 \cdot 47$, $p < 0 \cdot 002$; other comparisons, not significant). However, it is known that E scores decline with age (Eysenck, 1959; Coppen and Kessel, 1963), and the present data confirm this. The mean E score of the high (41–52 years) age group, 17·3, is significantly lower than that of the middle (30–38 years), 25·4, and the low (19–29 years), 22·5, age groups combined ($F = 5 \cdot 32$, $p < 0 \cdot 05$). Some bias is evidently introduced by age even though age is not itself a significant discriminator of response. New analyses were therefore carried out on reconstructed E groups, omitting patients over 38 years: the significance of the relation between E and ASRS 3 persists, but at a reduced level.

To what extent do these results agree with the predictions? Age, sex and duration were not expected to differentiate response to placebo. This is seen to hold for age and sex; however, duration is significantly related, suggesting that the null hypothesis for this variable should be rejected.

Patients with high confidence in doctors (CD), favourable attitudes (OAS), high extraversion (E), and concern with health (CH) were predicted to show better responses to placebo than patients rated low on these variables.

There is no evidence to support the prediction about CD or CH. Results for OAS do agree with expectation significantly for dichotomized, and non-significantly for trichotomized final scores. The relationship between E and final scores is also supported, significantly for trichotomized, and non-significantly for dichotomized groups.

Sodium Amylobarbitone Sample

1. *Dependent measures.* Fifteen patients received sodium amylobarbitone. Their mean initial score was 14·1 and the raw final score 9·5, a difference which is highly significant ($t = 4 \cdot 09$, $p < 0 \cdot 002$). The correlation between these scores, $r = 0 \cdot 57$ ($p < 0 \cdot 01$), is similar to that for the placebo sample; so also is the equation for the regression line of final (Y) on initial (X) ASRS scores: $Y = 0 \cdot 82X - 1 \cdot 8$. Again, there is a graphical hint of curvilinearity in the relationship (Fig. 2) which is not confirmed statistically.

Individuals' final scores were therefore adjusted for regression on their initial scores; the resulting correlation, r = +0·045.

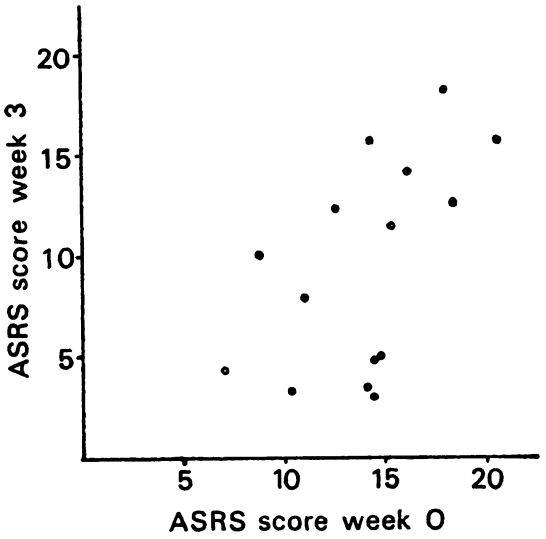

FIG. 2.—Scatter plot of initial (week 0) and final (week 3) ASRS scores of patients in sodium amylobarbitone sample (n = 15).

2. *Relations between independent and dependent variables.* When mean ASRS 3 scores for dichotomized independent variable groups are compared, only Extraversion appears as a significant discriminant: the high E group is less ill with a mean of 6·9 compared with the low E group mean of 11·8 (F = 6·86, p <0·025). There is a tendency for patients with greater confidence in doctors and those with more favourable attitudes also to show the better responses.

Extraversion remains the only significant variable (F = 3·90, p <0·05) on analysis of trichotomized group ASRS 3 means: high E 6·3; middle E 11·5; low E 11·8 (high E *vs.* middle E: t = 2·36, p <0·05; middle E *vs.* low E: t = 0·14, N.S.; high E *vs.* low E: t = 2·35, p <0·05).

The distribution of mean E scores by age—high 17·0, middle 21·4, low 21·4—is similar to that of the placebo sample. However, the group differences are not significant and re-analysis of ASRS 3 scores omitting the oldest patients scarcely alters the results.

The predictions made for the sodium amylobarbitone sample were the same as for patients receiving placebo. Those relating to age, sex and duration are confirmed. Of the personality and attitudinal variables, E group responses support the hypothesis to a significant extent and results for dichotomized CD and OAS groups are in the expected direction; CH is the only variable to fail completely as a predictor.

Comparison of Placebo and Sodium Amylobarbitone Samples

In both samples, patients who are extraverted and who express favourable attitudes improve most with treatment. Although length of illness does not significantly differentiate response to sodium amylobarbitone (in accordance with the hypothesis), the associated pattern of response is very similar to that in the larger placebo sample for whom duration is a significant factor. The differential effects of neuroticism and the RN variable, while not significant, are also similar in the two sets of patients.

Since the responsivity profiles of the two samples are so much alike, one wonders if the samples are alike in other relevant ways; if so, it would be justifiable to pool the data and to analyse the combined results.

Comparison of sample means and variances (Table I(a)) shows that there are no significant differences with respect to any of the independent and dependent variables. For duration, the proportion of each sample who had been ill for under 1 year and under 2 years is also similar (exact p > 0·16 and > 0·20 respectively). It would therefore seem legitimate to combine the data from the two samples. (Since the regression coefficients and equations are almost identical, no further adjustment of ASRS 3 scores has been made.)

Combined Sample

Combined Sample. Table I(b) gives means and standard deviations for the total of 44 patients. Extraversion and neuroticism (N) values show that on these parameters at least, the sample is representative of neurotic outpatients. The mean E score of 21·1, SD 7·7 and mean N score of 32·8, SD 8·8, may be compared with those reported by Sainsbury (1960) for 116 such patients: mean E score 21·4, SD 10·1 and mean N score 31·95, SD 9·2.

Relations between independent and dependent variables. The pooled data have been grouped and analysed (Tables II and III) as previously; however, the increase in sample size, with smoothing of distributions, has improved the basis for trichotomization, the range for each middle group now being defined as 0·5 SD above and below the mean. For duration only, because it has a very skewed distribution, the group boundaries were fixed arbitrarily, as before: low, 0·75–5 months (n = 15); middle, 6–18 months (n = 12); and high, 24–96 months (n = 13).

TABLE I

(a) *Comparison of Variances and Means of Independent and Dependent Variable Scores for Placebo Sample (P) and Sodium Amylobarbitone Sample (S);* (b) *Means and Standard Deviations for Total Sample*

		(a)							(b)	
Variable	Sample	Mean	SV	F	p	SE	t	p	Grand Mean	SD
Age ..	P	35·8	101·31	1·95	NS	3·04	0·95	NS	34·6	8·9
	S	32·9	51·93							
OAS ..	P	5·1	11·19	2·26	NS	0·94	0·44	NS	5·0	2·9
	S	4·7	4·96							
CD ..	P	3·7	1·13	1·19	NS	0·34	0·95	NS	3·8	1·0
	S	4·0	0·98							
E ..	P	21·2	71·36	1·45	NS	2·52	0·13	NS	21·1	7·7
	S	20·8	49·32							
N ..	P	33·0	99·25	2·16	NS	2·87	0·24	NS	32·8	8·8
	S	32·3	45·96							
CH ..	P	6·2	16·18	1·46	NS	1·23	0·62	NS	6·5	3·8
	S	7·0	10·80							
RN ..	P	6·8	17·10	1·46	NS	1·41	0·21	NS	6·9	4·3
	S	7·1	24·92							
ASRS 0	P	13·9	13·28	1·03	NS	1·15	0·16	NS	13·9	3·5
	S	14·1	12·03							
ASRS 3	P	9·6	22·90	1·22	NS	1·47	0·01	NS	9·5	4·5
	S	9·5	18·63							

Abbreviations: SV = best estimate of sample variance.
SE = standard error of difference between sample means.

The results are little different from those obtained for the separate samples. Duration, OAS and E significantly discriminate high and low ASRS 3 scores; E achieves this for trichotomized groups as well, while the F-ratio for trichotomized duration groups (3·20) only just fails to reach significance (with 2/37 df, the 5 per cent. level of F = 3·25).

One new variable emerges—RN: patients who have extreme scores on this factor show significantly higher ASRS 3 scores than the middle group. The same pattern is also seen for the placebo and sodium amylobarbitone samples separately, though not to a statistically significant extent. As no predictions were made about the influence of RN, exploration and discussion of this result will be dealt with elsewhere. (It is perhaps worth noting that finding such a U-shaped relationship depends on the use of trichotomized data; it cannot be revealed by analysis of dichotomized groups nor would it be, unless previously expected, by a correlational analysis.)

DISCUSSION

Within the limits of the diagnostic criteria, there is little to suggest that the selection of patients referred to the study was unduly biased. Patients were seen in the setting of an ordinary out-patient clinic and their management was made as unexceptional as possible. By using the same doctor and by trying to keep his attitude and the setting relatively constant, it was hoped that response to treatment would mainly reflect the differential influence of patient variables.

Despite the advantages of a single doctor seeing patients, one drawback is the difficulty in estimating directly the reliability of his ratings. However, the Anxiety State Rating Scale has been found to have a high inter-rater reliability in other studies (Roberts and Hamilton, 1958; Robinson *et al.*, 1965). The significant correlation between the placebo patients' self-ratings and my independent ASRS ratings suggests that it is a reasonably valid measure of response in the present study. One further scoring error that may arise in an extended study—although not peculiar to single

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TABLE II
Comparison of ASRS 3 Means of High and Low Independent Variable Groups for the Combined Sample
(n = 40 to 44)

Independent Variable	Mean ASRS 3 Score		F	p
	High Group	Low Group		
Age	9·7	9·4	<1	—
Duration	11·6	7·8	7·63	<0·01
OAS	8·0	11·1	5·43	<0·025
CD	10·2	8·9	<1	—
E	7·7	11·5	9·25	<0·01
N	10·1	8·8	<1	—
CH	9·3	9·6	<1	—
RN	9·7	9·4	<1	—

observers—is a gradual drift of the baseline. That this is unlikely to have happened is shown by the temporal stability of pre-treatment scores: mean ASRS 0 of the first 15 patients is 14·3, of the second 14 patients, 13·4, and of the last 15 patients, 14·1 ($F < 1$).

At the start of the investigation, two broad questions were posed. To what extent do the results enable these to be answered?

Among patients who received placebo, three variables discriminate their degree of response: duration, extraversion and attitudes. Patients who had been ill for under a year before referral, who are relatively extraverted and who express favourable attitudes to hospital, psychiatry and psychiatric treatment when they first attend an out-patient clinic, are significantly less ill after three weeks' treatment with placebo than the remainder. For this sample, therefore, the answer to the first question is "yes": patients can be independently classified in ways which also differentiate their response to placebo.

For patients who were treated with sodium amylobarbitone the same variables differentiate their response but, perhaps because of smaller numbers, only extraversion achieves this at a statistically significant level. However, in view of the close similarity between this sample and the placebo sample on the independent variables, the fact that their mean final scores at three weeks are also nearly the same—9·5 and 6·6—suggests that the sodium amylobarbitone was no more effective than the placebo. It may be concluded either that under the conditions of the present study the placebo response was

TABLE III
Comparison of ASRS 3 Means of High (H), Middle (M) and Low (L) Independent Variable Groups for Combined Sample
(n = 40 to 44)

Independent Variable	Mean ASRS 3 Score			F	p
	H	M	L		
Age	11·9	8·9	8·4	1·62	—
Duration	10·9	9·4	7·5	3·20	—
OAS	8·9	8·5	11·2	1·55	—
CD	9·8	9·6	9·3	<1	—
E	6·2	10·6	12·0	8·39	<0·001
N	10·2	10·4	8·2	1·02	—
CH	8·9	10·8	8·9	<1	—
RN	11·9	7·5	11·3	5·28	<0·01

E groups: H *vs* M: t = 3·00; p>0·01. M *vs* L: t = 0·95; NS. H *vs* L: t = 3·89; p>0·001.
RN groups: H *vs* M: t = 2·74; p>0·01. M *vs* L: t = 2·57; p>0·02. H *vs* L: t = 0·29; NS.

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larger than that found in many clinical trials; or that the dosage of sodium amylobarbitone was inadequate to exercise a specific effect; or, as is likely, both these considerations apply. If the drug sample cannot therefore be regarded as having received specific medication, the conditions relating to the second question are not fulfilled and the question itself must remain unanswered.

Fortunately, some advantage can be recouped from this situation. Since the sodium amylobarbitone sample is in all relevant ways similar to the placebo sample, it can be regarded as a placebo replication group; as such, the results confirm and so strengthen the original ones.

Turning now to the individual hypotheses, it was predicted that age, sex and duration of illness would bear no relation to response. The results for age agree with prediction and are in keeping with the inconsistency of previous reports (Gliedman *et al.*, 1958; Kurland, 1957; Lasagna *et al.*, 1954; Samuels and Edisen, 1961; Tibbetts and Hawkings, 1956). Sex also fails to differentiate response, as predicted; although women are reported to respond more frequently in some studies (Abramson *et al.*, 1955; Gliedman *et al.*, 1958), neither Lasagna *et al.* (1954), nor Samuels and Edisen (1961) found any sex difference.

Contrary to expectation, duration of illness is related to response. No such association was found by Hargreaves *et al.* (1958) or by Samuels and Edisen (1961). The only previous example of a duration-placebo response relationship was reported by Tibbetts and Hawkings (1956) who examined the characteristics of 41 neurotics assigned to control groups in carbon dioxide and acetylcholine trials. The mean duration of illness before referral of patients recovering after placebo treatment was 3·5 months, of those making a definite improvement, 6·9 months and of those showing no improvement, 19·8 months. According to the authors, this relationship would be anticipated; but they offer no explanation.

Out of the four positively phrased hypotheses, two—those concerned with extraversion and attitudes—are supported at a statistically significant level. Extraversion in particular consistently predisposes to a favourable response. This conflicts with the results of Morison *et al.* (1961), who are alone in finding an association between introversion and placebo response; however, the reliability of their data is open to question (Black, 1965). Although Joyce's (1959) medical student responders were not significantly extraverted on the MPI, they were rated as more sociable by their class-mates. Sociability also characterized consistent subjective responders (Muller, 1965) and patients whose post-operative pain was often relieved by placebos (Lasagna *et al.*, 1954; Lasagna, 1955). In a factorial study Eysenck and Eysenck (1963) have shown that sociability is a component trait of extraversion. Knowles and Lucas (1960) obtained a significant correlation between extraversion and number of placebo responses when nurses were tested under individual (but not under group) conditions. Linton and Langs (1962) found their responders to be less introspective and Gartner's (1961) were significantly extraverted.

Attitudes significantly discriminate response in two of the six analyses; and in every one, patients with the least favourable attitudes showed the least improvement. A similar relationship has been found following placebo treatment of persistently fatigued university students (Knowles and Lucas, 1962), chronic schizophrenics (Gorham and Sherman, 1961) and, with one exception (Sheard, 1964), of patients with depressive illnesses (Gorham and Lasky, 1962; Honigfeld, 1963).

The predictions about the differential effects of confidence in doctors and concern with health are not supported by the results. Confidence in doctors, using the same measure, was found to characterize placebo responders in a previous study of anxious out-patients (Black, 1959). However, these patients had been attending the clinic for some time, and their expression of confidence in doctors was probably a more valid reflection of their attitudes, since it was based on their actual out-patient experience, than the replies of new out-patients in the present investigation. The latter's views may pertain more to their reactions to their general practitioners' referring them to hospital than to outcome of further treatment.

Preoccupation with body function charac-

terized the placebo responders studied by Lasagna *et al.* (1954). In normal subjects, too, responders report significantly more fear and worry about their bodies (Linton and Langs, 1962), while Joyce (1959) found that awareness of autonomic activity discriminated between reactors and non-reactors. It is possible that failure to confirm the hypothesis about concern with health is due to poor choice of criterion, since agreeing with items on the Cornell Medical Index Health Questionnaire does not necessarily denote excessive concern over these symptoms.

Although Tibbetts and Hawkings (1956) regarded the relationship between duration of illness before referral and response to placebo treatment as virtually self-evident, it is by no means self-evident why duration should also be related in a similar ways to long-term outcome of neurotic disorders. Pollitt (1960) followed up 101 patients treated for obsessional states, for an average of $3\frac{1}{2}$ years. He noted, "The most profound influence on prognosis was the duration of illness before the patient sought psychiatric advice." Patients who were symptom-free at follow-up had a mean duration of illness before referral of 3·0 years: for those who showed no improvement the duration was 8·1 years ($p < 0{\cdot}05$). More recently, Giel, Knox and Carstairs (1964) reported a five-year follow-up of 93 new out-patient cases of neurosis. Out of 17 variables recorded initially, "the only consistent prognostic indicator was duration of illness before the first psychiatric consultation . . . of 24 cases with a history of less than three months' illness, 22 had a good outcome; this was significantly better than for those with a longer history." ($p < 0{\cdot}02$).

These findings suggest that there is something in common between whatever factors are responsible for the difference in outcome and those that influence the time when a patient is referred to a psychiatrist. From interviews with general practitioners it seemed that their decision about referral was mainly influenced by the patient's failure to respond to treatment (Rawnsley and Loudon, 1962). If so, it is possible that patients who have been ill longer before seeing a psychiatrist are the more resistant to treatment, whether at the hands of the general practitioner or the psychiatrist; and that in fact, they form part of a chronic psychiatric population whose prognosis is much the same with or without treatment. On the other hand, reasons other than failure to respond to treatment must account for many referrals, the more so the earlier in their illness patients are referred. Although duration of illness on referral appears to be a consistent prognostic variable, it cannot therefore operate as an index of susceptibility to treatment in all cases; and it is difficult to see how it can itself determine response to placebo, let alone long-term outcome. An economical, if over-simplified explanation would be that all these phenomena are consequences of patients' differing along a single continuum. Certainly we know little about the factors which determine, or at least relate to duration of neurotic illness, although Shepherd and Gruenberg (1957) have emphasized the importance of such information.

It seems reasonable that these factors derive partly from constitutional and personality characteristics. The finding that extraverted patients respond significantly better to placebo than introverted patients is consistent with this supposition. Moreover, if in fact introverts have been ill for longer before referral and they have persistently failed to respond to medical treatment, one might well expect them to be pessimistic about further treatment; that patients with the least favourable attitudes also improve less is compatible with this expectation. Of course, substantiation of these speculations depends on showing that the above variables co-vary in the manner suggested; their interrelationships will be explored more fully in another report.

Finally, the relevance of these findings to diagnosis should be mentioned. Like most psychiatric diagnoses, that of anxiety state is based on an assessment of symptoms and signs and, to a lesser extent, on history and personality. It is essentially a descriptive exercise and provides little guide to prognosis, treated or untreated. In a somewhat neglected paper, Walker (1959) treated expectantly 111 out-patients with carefully defined anxiety states, and at follow-up classified them by outcome, mode of onset and course of illness. Only the

28 patients with a good prognosis showed a well-delineated pattern: instantaneous onset and an episodic course without precipitation. Although commonly diagnosed and accepted as anxiety states, Walker felt that the clinical picture in this group was best described as depression with episodic anxiety; in personality they were independent and energetic. These findings emphasize that the diagnosis of anxiety state, as currently made, is inadequate for prognostic purposes. Although it is not justified to equate the independent, energetic personalities of the good prognosis cases with the extraverted patients who respond to placebo, the parallel is worth noting. The results of the present investigation support the inference from Walker's study that the diagnosis of anxiety state cannot be regarded as a homogenous classification: it contains meaningful sub-groups whose prognoses differ significantly, at least as far as short-term outcome is concerned. If confirmed, these differences would need to be taken into account in selection for and evaluation of psychotherapy and drug trials.

Summary

1. Forty-four new out-patients with an agreed diagnosis of anxiety state were treated by the same doctor for three weeks; the first 29 received placebo and the next 15, sodium amylobarbitone. Progress was recorded weekly on Hamilton's Anxiety State Rating Scale (ASRS); placebo patients also returned self-ratings twice weekly.

2. For both sets of patients it was predicted that age, sex and duration of illness before referral would not be related to response; and those who expressed more confidence in doctors, favourable attitudes to hospital, psychiatry and psychiatric treatment, more complaints about their physical health and were more extraverted, would show the better response.

3. In both treatment samples there is a significant linear correlation between initial and third week ASRS scores; a regression correction was therefore applied to yield individually adjusted final scores. Their validity is indicated by a significant correlation with patients' self-ratings.

4. Among patients treated with placebo, the predictions concerning age, sex, attitudes and extraversion are confirmed. Contrary to expectation, duration of illness differentiates response to a significant extent, patients being ill for less than a year showing the most improvement.

5. The pattern of results for patients treated with sodium amylobarbitone is identical to that for the placebo sample, although only extraversion differentiates response at a statistically significant level.

6. The two samples do not differ significantly on any of the independent and dependent variables. Analysis of the pooled sample provides no further support for the two unconfirmed hypotheses.

7. It is concluded that patients can be independently classified in a way that also differentiates their response to placebo. The question whether the same classification will differentiate their response to active medication cannot be answered by the present data, since there is no indication that a specific drug effect was achieved.

8. The results confirm in one sample those that have usually been reported singly in previous studies.

9. Duration of illness before referral differentiates short-term outcome and has also been shown by others to be a long-term prognosticator. One explanation is that these three variables represent various manifestations of a single constitutional or personality factor.

10. The existence of independently defined sub-groups with different prognoses suggests that patients diagnosed as anxiety states do not constitute an homogenous population.

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