EXPERIMENTAL STUDIES OF THE PLACEBO RESPONSE

By

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THE critical evaluation of new drugs or remedies against inert substances or non-specific procedures has led to the recognition that responses to a placebo are important in their own right. Such responses may be dramatic and persistent and they can be associated with quite definite physiological changes (Wolf and Pinsky, 1954). The placebo response may well be an important component of many established treatments both physical and psychological, and does in itself constitute a means of therapy (Roberts and Hamilton, 1958; Gliedman *et al.*, 1958).

Most placebo responses have been studied during the course of a clinical trial or hospital treatment. These studies have defined some of the features of the placebo response, and some of the characteristics of the placebo responder. This literature has been reviewed by Trouton (1957). The experiments here reported are an attempt to reproduce similar responses in healthy volunteers under experimental conditions in order to investigate specific aspects of the placebo effect. Our aims were twofold. (1) To assess the effect of varying the conditions of administration upon the number and type of placebo responses and (2) to determine some of the personality correlates of the placebo responder.

The placebo, a small white lactose tablet, was introduced as an active preparation in the following way. "The drug to be administered is a substance which is being tested experimentally in the Research Department. Many effects have been reported following its administration and it will help us greatly to have the benefit of your personal experience."

In all the experiments the placebo response was measured by the subject ticking off one or more of 26 possible drug effects which were listed in alphabetical order on a duplicated form handed to the subject before he was given the placebo. Many of the effects were those described by Beecher (1955) as toxic side-effects of a placebo. The total list could be classified into 13 "pleasant" and 13 "unpleasant" effects. Each subject was asked to tick only those effects which he or she thought were due to the action of the drug; particularly marked effects could be double ticked. Further, the time at which this tick was made was to be recorded.

To assess the effect of varying the conditions under which a placebo is taken the placebo was administered under two conditions, "individual" and "group". Under "individual" conditions each subject sat alone, was given the placebo, and was asked to report on the check list the effects of the "drug" during a 30-minute period. Under "group" conditions three subjects seated together in the same room were similarly asked to report effects. They were unobserved

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and free to talk. By administering the placebo to groups of individuals we hoped to produce a situation analogous to that sometimes operating during treatment in hospital wards or out-patient departments.

To determine some of the personality correlates of the placebo responder the subjects were asked to complete the Maudsley Personality Inventory (M.P.I.) (Eysenck, 1959) which gives measures of "neuroticism" and "extraversion" as defined within Eysenck's personality theory. This choice was determined not only by the considerations of ease and speed of administration but also because these measures have been related to aspects of learning and of suggestibility (Eysenck, 1947, 1957), psychological processes thought to be particularly relevant to placebo research (Gliedman, Gantt and Teitelbaum, 1957; Kurland, 1957; Trouton, 1957).

To facilitate presentation, results are reported for experiments carried out under "group" or "individual" conditions rather than in their chronological order. Two of the experiments were under "group" and two under "individual" conditions.

Placebo Responses of Subjects Tested in Groups

Group Conditions: Experiment I

In the first experiment under "group" conditions 12 subjects, mostly nursing staff (11 of them female) were randomly allocated to four groups of three. Eight of these 12 subjects reported experiencing one or more effects over the thirty-minute period following the administration of the placebo. In all, 28 responses were recorded, 12 (42·9 per cent.) of which were pleasant and 16 (57·1 per cent.) were unpleasant.

When each of the personality measures was correlated with the number of placebo responses (both pleasant and unpleasant) the correlation with neuroticism was highly significant ($r=0·89$, $p=<·01$). The correlation with extraversion, however, was not significantly different from zero ($r=0·20$).

To confirm this finding of a close association between neuroticism and placebo responding, a further four groups were tested under "group" conditions.

Group Conditions: Experiment II

A group of 13 hospital nurses who had volunteered to participate in this study were ranked in order of their neuroticism scores. Initially subjects 2–13 were then placed in four groups of three by taking successive numbers. Our intention was to obtain four groups which could be ranked in order of their mean neuroticism scores, the prediction being that the total number of placebo responses recorded for each group would show an identical rank order. However, because of conflicting duty hours we were unable to maintain these original groupings. This had two unfortunate effects. Firstly, two of our groups had mean neuroticism scores which were almost identical and secondly, the previous balance of extraversion scores was upset. In view of the unsatisfactory grouping the data were analysed by correlating scores on neuroticism and extraversion and the total number of placebo responses recorded by each of the 12 subjects. The correlation with neuroticism is again positive ($r=0·37$) although significantly lower than that previously found. The correlation with extraversion on this occasion is significant ($r=0·69$, $p=<·05$).

Three of the groups gave 25 responses between them, the fourth group failed to respond at all. The behaviour of this fourth group was strikingly different to that previously experienced and we believe that this failure to

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respond may perhaps be accounted for by the behaviour of two student nurses being inhibited by the presence of a ward sister who was the third member of the group. The lack of response in this group had the effect of diminishing the correlation with neuroticism and of slightly increasing the correlation with extraversion. When this fact is allowed for the correlations for the remaining 9 cases are 0·52 and 0·66 for neuroticism and extraversion respectively.

Since in these two experiments the subjects and conditions of administration are relatively constant, the correlations between the personality factors and the number of placebo responses have been combined to give the best estimate of these correlations under "group" conditions of administration. The correlations show a close relationship between neuroticism and placebo responding under "group" conditions ($r=0\cdot65$, $p=<\cdot01$). On the other hand, there appears to be little association with extraversion ($r=0\cdot38$, $p=>\cdot05$). When the atypical group in the second experiment is omitted from the calculations the correlation with neuroticism is increased to 0·74, the correlation with extraversion remains unchanged.

An alternative way of expressing the relationship between neuroticism and placebo responding is shown in Figure 1. The regression line giving the best prediction of the number of placebo responses given scores on neuroticism was calculated from the data of both experiments. In view of the uncharacteristic

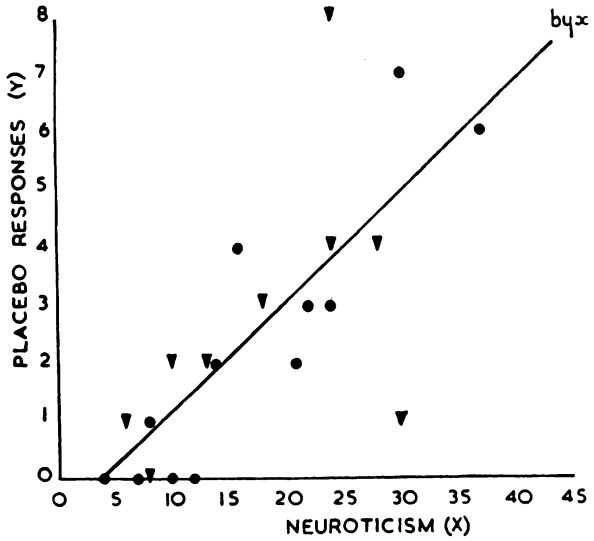

FIG. 1.—Placebo responses under "group conditions" plotted against scores on neuroticism with the regression line calculated from these data. (n=21.)
●=Experiment 1. ▼=Experiment 2.

behaviour of one of the groups in Experiment II, it seemed justifiable to omit them from this calculation and from Figure 1. The number of placebo responses given by the remaining 21 subjects in our two experiments have been plotted against their scores on neuroticism. It can be seen from Figure 1 that there is little scatter about the regression line and that the subjects in both experiments are alike in this respect.

In conclusion, it would appear from our two experiments that when subjects are seated together in a group, neuroticism, but not extraversion, has a close association with the degree of response to a placebo.

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Placebo Responses of Subjects Tested Individually

Whereas in the two previous experiments the subjects were seated in groups during the thirty-minute observation period, in the two experiments to be reported now, the individuals were asked to record effects whilst sitting alone.

Individual Conditions: Experiment I

Eleven subjects (7 of them female), mostly nursing staff, were used in the first of these experiments. Each completed the M.P.I. and was introduced to the placebo in the manner previously described.

Seven of our 11 subjects reported experiencing one or more "drug" effects. These seven subjects gave 27 responses between them; this figure is almost identical to those previously reported under group conditions. Thus, changing the conditions of administration apparently made no difference to the total number of placebo responses recorded. However, whereas under "group" conditions pleasant and unpleasant effects are almost equally represented in this experiment, pleasant effects predominated significantly (81·5 per cent., $p = < \cdot 002$).

The correlations between the personality factors and the total number of placebo responses show striking deviations from those reported under "group" conditions. The correlation with extraversion is positive and significant ($r = \cdot 63$, $p = < \cdot 05$), but the correlation with neuroticism is virtually zero ($r = \cdot 07$).

The predominance of pleasant effects recorded in the record sheets of the subjects, and the high correlation with extraversion, suggested to us the hypothesis that this correlation was a function of differences in "set" between introverts and extraverts; the extraverts being more prone to attribute relatively normal changes in mood, etc., to the action of the "drug".

This hypothesis was tested in a second experiment. This also provided an opportunity to confirm our findings regarding the neuroticism factor.

Individual Conditions: Experiment II

The design of this experiment was based on the observation that introverts "carry out tasks slowly but accurately" whilst extraverts "tend to do them quickly and inaccurately" (Eysenck, 1946). It was postulated that accuracy in observing subjective changes and, therefore, in discriminating them from drug effects, would be an attribute of introverts, whilst for extraverts the converse would be true. However, by stressing the importance of accuracy in our instructions to the subjects it was thought that the set that the introvert adopted as a matter of course could be imposed upon the extravert. In other words, if such instructions brought about a homogeneity in set, then the number of reported placebo effects should be the same for both introverts and extraverts under these conditions.

Procedure

The placebo effect was measured after two types of instructions had been given. The first was comparable to that given in the first experiment; the subject was merely asked to report effects that he thought were attributable to the drug ("no stress" conditions). The second opened with a statement to the effect that the experiments were highly important and crucial; and the importance of accurate reporting was stressed throughout ("stress" conditions).

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In testing this hypothesis four groups of theological students were taken from a group of 46 according to whether or not they scored high or low on the E factor. There were two matched groups of introverts and two matched groups of extraverts; the mean E scores were approximately 16 and 31 respectively. Analysis of variance indicated no significant differences in neuroticism between these four groups. One group of introverts and one group of extraverts were tested under "no stress" conditions, the other groups being tested under "stress" conditions. The allocation of "stress" and "no stress" conditions to the groups and the order of testing was random.

Specifically the predictions were:

(*a*) That under "no stress" conditions the extraverts would give a significantly greater number of placebo responses than the introverts: a prediction based upon our earlier finding.

(*b*) That under "stress" conditions the extraverts would show a significant reduction in the number of responses (the effect of set) whereas the introverts would remain relatively stable.

Results

The results (Table I) have been analysed by non-parametric techniques (Siegel, 1956). The introverts under "no stress" conditions give more responses than do the extraverts, but this difference was shown to be insignificant by the Mann-Whitney U Test ($U=7\cdot0$, $p=\cdot09$). Under stressed conditions there are more responses and the two personality groups behave alike. From the data it appeared that there could be an interaction between personality and type of instruction, i.e. the extraverts tending to respond more when accuracy was stressed. Thus there is no support for either of our predictions.

To test the significance of the observed interaction, difference scores were obtained by noting the discrepancies in scores for the matched pairs under the two experimental conditions. These two sets of scores were then compared by means of the Mann-Whitney U Test; this test indicated no significant difference ($U=14\cdot5$, $p>\cdot5$) and thus there is no real difference in the change of score between the two groups.

TABLE I

The Total Number of Placebo Responses Given by the Extraverted and Introverted Groups Under the Two Experimental Conditions

	Extraverts		Introverts	
	No Stress N=6	Stress N=6	No Stress N=6	Stress N=6
No. of placebo responses	3·0	19·0	12·0	17·0

In view of this finding the scores for introverts and extraverts were combined to see whether there was a significant increase in scores when the instructions were altered. Wilcoxon's matched-pairs signed-ranks test showed this increase just failed to reach significance at the 5 per cent. level ($p=\cdot07$).

This increase in score probably reflects an increase in interest in the experiment, an interpretation similar to that given by Glaser (1953) who found that when three drugs and a dummy were given in random order at seven-day intervals, questionnaire responses gradually declined until the fourth and last administration when there was a significant increase.

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The correlations between personality and placebo measures were computed for the "no stress" conditions. The correlation with neuroticism is again found to be positive but low and insignificant (r=0·17); this confirms our earlier finding for individuals. The correlation with extraversion is, however, negative (r=—0·39) rather than positive as in our previous study, although with this size of sample it does not reach statistical significance.

Summary of Findings, and Conclusions

The experimental procedures enabled us (1) to compare the number and type of placebo responses, and (2) to determine some of the personality correlates of the placebo responder under the two conditions of administration, "group" and "individual".

Regarding the first of these we have found that the total number of placebo responses under the two kinds of administration are remarkably uniform (Table II). The only exception is the second experiment under "individual" conditions where it has already been noted that instructions stressing the importance of the experiments and accurate reporting markedly increased the placebo scores of the students. Again except in one case (Experiment I, "individual" conditions) the number of pleasant effects reported is approximately equal to the number of unpleasant effects under both "group" and "individual" conditions. We conclude, therefore, that varying the conditions of administration as between "individual" and "group" makes no difference to the number or type of placebo responses.

Table II

Total Number of Placebo Responses Classified as "Pleasant" (P) or "Unpleasant" (U) in Each of the Four Experiments

Placebo Responses	Group Administration				Individual Administration					
	Experiment I N=12		Experiment II N=12		Experiment I N=13		Experiment II No Stress N=12		Experiment II Stress N=12	
Experiment										
Type ..	P	U	P	U	P	U	P	U	P	U
Number ..	12	16	13	12	22	5	8	7	18	18
Total ..	28		25		27		(Mean=25·5)			

Concerning the personality correlates of the placebo responder some interesting findings have emerged (Table III).

Table III

Correlations Between Total Numbers of Placebo Responses and Neuroticism and Extraversion Under Group (Combined Data) and Individual Conditions

Administration	Neuroticism	Extraversion
Group: N=21	0·74*	0·38
Individual: N=11	0·07	0·63†
N=12	0·17	—0·39

* p=<·01 † p=<·05.

It would appear from our experiments that the relationship between personality dimensions and placebo responses is to some extent dependent upon the conditions under which the placebo is administered. This interpretation is clearest for neuroticism; under "group" conditions the correlation is highly

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significant but under "individual" conditions the correlation is not significantly different from zero. The finding for extraversion is less clear-cut. Under "group" conditions the overall correlation is positive but does not reach significance. Under "individual" conditions, that is, when the individuals were tested in isolation, we obtained contrary findings. When the subjects were nurses the correlation was positive and significant; when they were theological students the correlation was negative but insignificant. A possible explanation for these discrepant results is discussed below.

The actual findings in terms of symptoms reported are detailed on the symptom check list which is reproduced below.

The Symptom Check List together with the Number of Times each Effect was Reported by the Subjects in all Four Experiments (N=59)

Symptoms		Symptoms	
Able to see more clearly	0	Energetic	2
Able to think more clearly	3	Gay	7
Aches and/or pains	7	Less tired	8
Agitated	2	Lethargic	6
Alert	4	More comfortable	2
Apprehensive	2	More tired	7
Attentive	3	Confused thinking	5
Calm	11	Blurred vision	4
Clearheaded	6	Pleasantly detached	3
"Couldn't care less"	4	Relaxed	20
Depressed	0	Restless	3
Distractable	0	Strange and unreal	3
Drowsy	12	Thick headed	7
			131

Information regarding the distribution of scores on neuroticism and extraversion for the four experimental groups for which correlation coefficients were calculated is given below in Table IV.

TABLE IV

The Mean Scores and Standard Deviation for Neuroticism and Extraversion for the Experimental Groups Under the Two Conditions of Administration for which Correlation Coefficients have been Calculated

Experiment	Neuroticism Mean	Neuroticism S.D.	Extraversion Mean	Extraversion S.D.
Individual conditions:				
Experiment I (N=11)	19·82	9·45	28·27	7·52
Experiment II (N=12)	25·83	11·92	24·00	9·29
Group conditions:				
Experiment I (N=12)	17·08	9·97	27·42	11·31
Experiment II (N=12)	18·42	7·79	28·50	7·45

DISCUSSION

Following administration of a placebo 66 per cent. of our 59 subjects reported experiencing one or more effects which they attributed to the action of a "drug". This high figure, similar to that previously reported by Glaser and

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Whittow (1953) indicates that we were successful in our attempt to reproduce a placebo effect under experimental conditions. Whether or not the placebo responses we described are analogous to those under clinical conditions has yet to be shown, and thus it would be unwise to generalize from our selected populations. There are obvious and no doubt important differences between nurses and students volunteering for experiments with new "drugs" and patients seeking relief from often debilitating symptoms. The similarities are, however, no less clear; effects attributed to an active substance are experienced, despite the absence of any pharmacological action.

Many of the reported effects were mild, for example, feeling "relaxed", "calm", "drowsy". Some, however, were quite striking. One theological student complained of pain on the top of his head which radiated on to his face and lower jaw. One nurse complained of extreme nausea and developed a marked pallor; another noted marked blurring of vision.

Many writers have loosely attributed the placebo effect to "suggestibility". Such statements, however, are of little value unless suggestibility itself is clearly defined, for Eysenck and Furneaux (1945) and Stukart (1958) have shown that tests commonly employed to measure this attribute can be referred to more than one factor after factor analysis. Eysenck's original description of primary (or ideo-motor) suggestibility (Eysenck, 1943) has recently been confirmed by Stukart (1958) who also expanded the concept of secondary suggestibility of Eysenck and Furneaux (1945) in a way particularly relevant to our own study.

This factor of secondary suggestibility is characterized by the influence of such subjective factors as expectation or "set", and the need for conformity upon the individual's perceptions, memory, and judgments. Further, Stukart showed that neurotics were more suggestible when tests of this type were employed. In these cases the suggestion was not only of the "indirect" kind (Eysenck and Furneaux, 1945) but came also from the personal pressure of the examiner and from rehearsed co-judges. This finding confirmed his hypothesis that "neurotics are more suggestible than normals in situations where an element of personal pressure, activating the need for conformity of the subjects, is inherent in the suggestions . . . " (*op. cit.*, p. 124).

In our studies on groups such personal pressure could have come both from the direct suggestion of the experimenter that the inert tablet was a drug under investigation, and from other members of the group whenever they made a response. We found that in many cases there was a marked concordance in the times at which identical or similar "symptoms" were noted by different members of the group, a finding which strongly supports this interpretation.

Joyce (1959) found with healthy medical students working in pairs, that placebo responders were, among other things, "more sensitive to social influences", and more particularly, were found to be less "dominant" and less "self-confident" on the Bernreuter Scale. He also found evidence for emotional lability in the reactor group as shown by greater variability in pulse rate. From the known inter-correlations of the individual Bernreuter scales (*cf.* Vernon, 1953) Joyce's results indicate higher neuroticism of the reactors, a finding in agreement with our own for groups.

Our finding that there is virtually no correlation with neuroticism under "individual" conditions is not necessarily inconsistent with the above argument, for under these conditions the personal suggestions were restricted to the opening remarks of the experimenter. The low and insignificant correlation between neuroticism and placebo responding was found on both occasions when the subjects, nurses and theological students, were tested individually.

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This finding needs to be confirmed with patients before its implications are fully explored. However, accepting the evidence as it stands the effect of a placebo on a neurotic population is likely to be enhanced if the person treated is one of a group attending an active out-patient department. For example, the high level of placebo response obtained by Hawkings and Tibbetts in their trials of acetylcholine and carbon-dioxide therapy (1956a, b) were obtained in a setting of which particular features were social mixing before and after treatment and the presence of a high proportion of patients receiving benefit from E.C.T. giving rise to "high group morale and a great sense of therapeutic optimism".

Under "individual" conditions our results showed that the correlation with the extraversion factor was positive for nurses but negative for the theological students. A possible explanation is that on account of their different background and their consequent lack of sophistication in regard to drug effects, the theological students could not discriminate as clearly as could nurses between spontaneous changes in mood and sensation, and likely drug effects. The student who wished to be accurate (our hypothesis was that such a set characterized the introvert) would therefore, attribute these changes to the action of the drug. In contradistinction the nurse who also wished to be accurate would discount them.

It is possible, therefore, that personality factors operate against a background of knowledge and experience, and that where this is different, responses that are apparently contradictory in their relation to personality dimensions may occur. This hypothesis obviously requires confirmation, but it is probably in accordance with findings such as Lasagna's. He found marked differences in attitude—presumably a reflection of experience—between his placebo responders and non-responders (Lasagna *et al.*, 1954).

Summary

Four experiments are reported in which the effect of a placebo in healthy subjects has been studied. The placebo was a small white lactose tablet which was administered orally and introduced as a drug with potential effects. For thirty minutes following the administration of the placebo the subjects recorded symptoms on a check list of 26 items, half of which were pleasant and half unpleasant.

In two of the experiments the subjects spent the thirty-minute observation period sitting alone (individual conditions) and in the other two, subjects were seated in groups of three (group conditions).

Before each experiment all the subjects completed the M.P.I.

Sixty-six per cent. of the subjects (N=59) reported one or more effects. Analysis of the data led to the following conclusions:

1. The total number of responses reported remained constant despite altering the conditions of administration (i.e. "individual" and "group").
2. The proportion of pleasant to unpleasant responses remained approximately one-half throughout the experiments.
3. The relationship between placebo responding and personality varied according to the conditions of administration. This was clearest for neuroticism where the correlation was high ($r = \cdot 74$) under "group" but insignificant under "individual" conditions.

The interpretation of the correlations with extraversion was less clear. When homogeneous samples were tested the pattern of correlations was the converse for

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that of neuroticism, i.e. significant correlation under "individual" but insignificant under "group" conditions. However, when theological students, as opposed to nurses, were tested, the correlation became negative. A possible explanation was discussed.

4. "Stress" administration in which the importance of the research and the necessity for accurate observations were emphasized, increased responses.

The findings, and their relation to those previously reported, were discussed in detail.

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