Placebo Reactions in a Study of Lysergic Acid Diethylamide (LSD-25)

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There has been a recent upsurge of interest in the reactions of placebo subjects under a wide range of conditions.[3,9,10,16-19,22,24] Indications that, after administration of an inert substance, certain persons report relief of pain or other therapeutic responses, as well as a wide range of subjective and "psychosomatic" effects, form the main basis for this interest.[3,6,9,16,24] These observations are important both for studies of drug action and for more general studies of human functioning.

In a recent review of the pharmacology of placebos, Wolf[24] discussed the mechanism of placebo reactions and stated that "the fundamental stimulus is the meaningful situation." In keeping with this view, responses to placebo administration will be viewed by us as responses to the stimulus conditions in their totality, which we will refer to as "the placebo situation." There are many relevant factors which determine a person's response to this situation, the first being the over-all situation itself.[21] In this respect, studies of placebo effects may be divided into 2 broad types: research in a clinical setting in which the subject is a patient who anticipates therapeutic relief, and research in the laboratory, where there is a broader interest in the phenomenology of the subject's reaction. Unfortunately, there is little evidence as yet that observations made in one setting have any relevance to those made in the other,[4,12,21,24] although a definitive study of this problem has not been reported.

Within each of these 2 types, studies vary in other ways that make the comparison of findings difficult. For example, subjects have been studied individually[4,12] and in

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groups.[1,2] In the only report of a placebo study in which the same subjects were studied both individually and in groups, Knowles and Lucas [8] found that the relationships between 2 personality measures and placebo response were different in the 2 conditions. This study, done in a laboratory, substantiates the remarks of Wolf, who emphasized that consistent placebo responses and consistent "placebo reactors" are unlikely because of the many varied factors that determine the placebo response, such as long-term and current motivations, the nature of the test agent for which the placebo is used as a control, and the life situation of the subject.[24] In support of the latter point, Knowles and Lucas [8] obtained different results for nurses and for theology students.

Still other factors, as yet unexplored, are undoubtedly important. Differences in the physical settings, personnel, and theoretical orientation of different laboratories might be expected to cause variations in the placebo reaction. The use of the placebo in a study solely concerned with placebo effects [8] might also be expected to produce different responses from those obtained in a study in which the placebo serves as a control for the study of one or more active drugs.[1,2,6,26] Lastly, the instrument with which the placebo effect is measured varies greatly from one study to the next, further making it difficult to compare different studies. It is not surprising, then, that reports of placebo responses and the personality correlates of these responses, themselves measured in a variety of ways, have differed greatly. In view of this, the controversial question as to whether there exists a group of "placebo reactors," persons with certain specifiable personality features who consistently react more strongly than other people to a placebo, is certainly premature,[4,7,9,12,22,24] but we may review briefly the studies most relevant to this issue.

Lasagna and his co-workers [12] (cf. 22 for a critique of this study) examined the personality attributes of persons who reacted strongly to a placebo, studying a group of hospitalized postoperative patients who were given drugs or placebos orally for pain relief. The degree of relief afforded was rated by interviewers without knowledge of the substance ingested. The personality of the patients was assessed through the Rorschach Test and the observations of ward personnel. Those gaining most relief from placebos were found to be anxious, emotionally labile, narcissistic, preoccupied with bodily processes, dependent, and with less control over instinctual impulses. Low placebo reactors were found to show fewer deviations from normal, although they were viewed as rigid and emotionally controlled. Responses to the placebo were inconsistent from one occasion to the next in 55% of the persons studied, raising serious question as to the validity of the concept of "a placebo reactor."

A second study reported by this group [4] used similar personality assessment procedures, but took place in a laboratory setting and explored the subjective effects of a series of drugs, as well as a placebo. The personality findings reported are based on the assessment of subjects who reacted atypically to the drugs under study, since the authors felt that these findings were also applicable to the placebo response. It should be noted, however, that this contention is open to question.* The personality attributes of these subjects were: immaturity, impulsivity, inadequate controls over emotions, and tendencies toward depression, anxiety, and hostility.

Other research related to the question of whether there is a consistency in reactions to placebos is far from definitive; indeed, it is quite inferential. Jellinek,[7] for example, studied headache relief in 199 outpatients to whom 3 analgesic drugs and a placebo were

* Of their 20 subjects, 4 had both an atypical drug reaction and a high placebo effect, 4 had the atypical drug reaction only, 2 had a high placebo effect only, and 10 subjects had neither. Their claim that findings for the 8 atypical drug reactors are applicable to the 6 placebo reactors, on the basis of the overlap of 4 subjects, is rather questionable. We report their findings, with reservations, because of the paucity of published studies that have any bearing at all on the issues under discussion.

administered on a double-blind basis, every subject receiving each drug for 2 weeks. He found that most headache patients either gained no relief at all from the placebo or gained relief consistently; that is, the reaction to the placebo was highly consistent within a subject. Jellinek designated those who had consistent relief with the placebo as "placebo reactors" and found that they had a far more variable reaction to the actual analgesic drugs than the nonplacebo reactors, who tended to do consistently well on the analgesics. There was no personality evaluation.

Using an entirely different design and context, Wolf et al.[25] studied 27 students in a laboratory, inducing nausea with ipecac and offering a placebo for relief. Each subject had 7 trials. They found no consistency from trial to trial within individual subjects. No personality assessment was made, and it should be noted that no active antinauseant was given along with the placebo. On the basis of this study, Wolf concluded that one cannot speak of a consistent "placebo reactor."

Abramson et al.[1,2] administered a placebo to 33 subjects in a laboratory study of the subjective effects of lysergic acid diethylamide (LSD-25). A questionnaire was used to elicit subjective responses anticipated with the drug, consisting primarily of items dealing with somatic and perceptual reactions. Subjects were tested in groups of 2 to 5, with some subjects in each group receiving LSD-25 and others the placebo. As we have already noted, Knowles and Lucas [8] found evidence that findings differ for placebo subjects seen in groups and those seen individually. Slater et al.[20] have shown that the response to LSD-25 will also vary according to whether the subject is studied in a group of drug subjects or alone. The effects of combining both drug and placebo subjects might be expected to be considerable, but they have not been explored specifically.

In the study by Abramson et al.,[1,2] placebo subjects gave totals of from zero to 15 positive responses to the 47-item questionnaire in the course of 3 to 5 questionnaire administrations per subject. In their paper, they report in detail the questions that were accepted most often by their subjects and state that "these in general correspond to certain of the symptoms of the LSD-25 reaction." A limited effort was made to compare the extent of the placebo reaction with psychological data drawn primarily from the Wechsler-Bellevue Test and the Rorschach Test given under nondrug conditions. In the 12 subjects for whom these analyses were made, high placebo responders appeared to be ideationally oriented and more verbally adept, while low responders were found to be action-oriented and more stereotyped in their thinking.

The Abramson study presents data relevant to a further variable of the placebo response: variations in the reaction over time. Some placebo studies elicit responses on a single occasion [8] and identify the placebo response on that basis, while others, such as Abramson et al.[1,2] elicit responses several times and identify placebo reactors on the basis of a cumulative score derived from several questionnaire administrations. In addition, on the basis of questionnaires given hourly, Abramson et al. were able to examine the time curve of the group reaction. They found that the peak of the placebo effect occurred in the first hour. Lasagna et al.[11] also found that reactivity to placebos varied over time.

Abramson et al.[1,2] reported a wide range of somatic responses with placebo administration. This laboratory finding is in keeping with the many clinical studies in which somatic side effects have occurred in patients receiving placebos.[3,24,26] The mechanisms producing such effects have not been explored to any extent.

The present report, which is one aspect of an exploration of the effects of LSD-25 and the personality correlates of these effects, will focus on the data gathered from a placebo group by means of a 74-item questionnaire developed to monitor the LSD-25 and placebo reactions. It will describe the type of person who, within a selected sample and in a laboratory, reacts or does not react

to a particular placebo situation when subjective responses are studied individually over an 8-hour period. The questionnaire is described in detail elsewhere.[15] It contains a wide range of perceptual, cognitive, affective, and somatic items, and was designed to reflect the kinds of subjective effects reported by subjects under LSD-25 and in other altered states of consciousness. Within this context, we shall concern ourselves primarily with 3 issues: (1) Does the questionnaire successfully differentiate between drug and placebo subjects? (2) If the placebo reaction does not resemble the reaction to LSD-25, what is the nature of this reaction? (3) What are the variables of personality that are related to the strength of the placebo effect?

Method

The subjects were male professional actors. Thirty subjects were given LSD-25 and 20 were given a tap-water placebo. The selection and screening of subjects, the experimental conditions, the complete questionnaire, and the details of its administration and scoring are described elsewhere[15] and will not be repeated here. The questionnaire was given once on the pretest day and 4 times on the experimental day, at approximately one-half, 2, 5, and 8 hours after the "drug" was administered. For each administration of the questionnaire, a Total Questionnaire Score was obtained by giving one point to each item answered "yes" and a half point to each item that was spontaneously qualified (e.g., "a little," "slightly"). Each subject's performance on the experimental day was evaluated in 2 ways: (1) in terms of a hypothetical "Experimental Day Protocol," based on the items accepted by him *at any time* during the day, and (2) in terms of his "Peak Reaction," that is, the single questionnaire, for each subject, on which he obtained his highest single Total Questionnaire Score. It is possible that the content of the questionnaire suggested effects to placebo subjects. An attempt was made to counter this by telling subjects that individuals vary widely in their reactions and that they would not necessarily experience many of the effects described.

The personality variables cited below were derived from an assessment of each subject made by one or 2 staff members, based on extensive psychological test and interview data (cf. 15) and without knowledge of his behavior in the experiment. There were 142 variables covering broadly the areas of motives, defenses, thought processes, inner states, identity and interpersonal behavior; each was rated on a 9-point scale. Through correlational analysis, the 142 variables were later reduced to 73, many of them combining several of the original variables.

Results

Comparison of Placebo and LSD-25 Subjects.—The first question to be considered is whether the questionnaire successfully differentiated the placebo group from the LSD-25 group. Table 1 shows, first, that the 2 groups do not differ significantly in the Total Questionnaire Scores obtained on the pretest day. For the experimental day, however, the difference between the groups is very great for both the peak questionnaire and for the entire experimental day. The experimental day differences are not only highly significant statistically, but the 2 groups show little overlap. When the 2 groups are compared on the 74 individual items, the differences for the Peak Reaction are significant at the 0.01 level for 34 items, at the 0.05 level for an additional 17 items, and at the 0.10 level for an additional 9 items, leaving only 14 items that fail to reach the 0.10 level. When the Experimental Day as a whole is considered, the corresponding numbers of items are 49 at the 0.01 level, 11 at the 0.05 level, 4 at the 0.10 level, and

TABLE 1.—*Comparison of Total Questionnaire Scores of LSD-25 and Placebo Groups*

	Placebo (N=20)	LSD-25 (N=30)	*t*	*p*
Pretest Day				
Mean	3.6	4.8	1.1	n.s.
Sigma	3.2	4.3		
Range	0 to 13.0	0 to 16.0		
Peak Questionnaire-Experimental Day				
Mean	7.7	29.4	10.1	0.001
Sigma	4.8	9.9		
Range	0 to 15.5	11.5 to 43.0		
Experimental Day Total				
Mean	11.1	38.8	10.2	0.001
Sigma	7.4	11.4		
Range	0 to 21.5	15.5 to 56.5		
t: Pretest vs. Peak	3.1	12.3		
p	0.01	0.001		
t: Pretest vs. Exp. Day Total	4.1	15.0		
p	0.001	0.001		

10 that fail to reach significance. One-tailed probability values are cited, since the drug group was expected to accept more items.

While the 2 groups can be readily differentiated, as groups, ideally we might wish that it would be possible to place every individual subject correctly in either the LSD-25 or placebo group on the basis of his questionnaire responses. If we consider the peak questionnaire, 27 drug subjects (90%) have total scores higher than any placebo subject and 13 placebo subjects (65%) have scores lower than any drug subject. The range of overlap of the 2 distributions, therefore, includes 10 subjects, 3 from the drug group and 7 from the placebo group.

Three methods were used in order to learn whether a more detailed analysis of the questionnaire data could identify these 10 subjects correctly. The first method was a modification of the quantitative scoring. Questionnaires were rescored, using only those items on which the total drug and placebo samples differed at the 0.01 level (for a list of these items, cf. 15). The total score based only on these highly differentiating items correctly places all but one subject.† When we examine the protocol of the one placebo subject who is not placed correctly, it appears that the resemblance consists in his having reported many somatic reactions.

The second method was purely qualitative. The peak reaction protocols were read by 17 judges who were asked to guess the group from which each subject came.‡ The majority opinion was correct for all but one subject, in this case a drug subject who was considered by 53% of the judges to be a placebo subject. If we use the more stringent criterion that the number of judges who correctly placed each subject should exceed chance at the 0.01 level (binomial test), the results are less impressive, though still an improvement over the Total Questionnaire Score. By this rigorous standard, 5 of the 10 subjects in the overlap range (2 drug and 3 placebo) are correctly placed.

The third method used a quantitative approach to the qualitative data. All qualitative responses to the questionnaire items were coded, using scoring categories developed from the data. When only subjects outside of the overlap range were considered, there were a number of response categories used at least once for the 27 highest-scoring LSD-25 subjects and not for any of the 13 lowest-scoring placebo subjects. When the protocols in the overlap score range were then scored for these categories alone, it was found that all 3 of the drug subjects in this group gave some responses scored in the drug-specific categories (the numbers of responses so scored were 9, 12, and 28), while none of the 7 placebo subjects gave any.

We may conclude, then, that the questionnaire is a sensitive instrument for differentiating the reactions of subjects who have been given LSD-25 from those who have been given a placebo, not only in terms of group means, but for individual subjects as well. Clearly, therefore, the reactions of placebo subjects in the present study did not simulate the effects of the drug.

The Reactions of Placebo Subjects.—The Pretest Day: While we may now feel confident that it is justifiable to consider the placebo subjects without reference to the LSD-25 subjects, since their reactions were clearly different, it is necessary to differentiate the responses of placebo subjects on the experimental day from their pretest responses. The placebo group showed a significant increase ($p<0.01$) in mean Total Questionnaire Scores from the pretest to the experimental day, but there is a good

† This method is admittedly circular, since it merely demonstrates that the items that differentiate the groups also differentiate the individuals in these groups. It does, however, show that the items that differentiate extreme subjects also differentiate all but one of the subjects whose total scores fall into the overlap range.

‡ In order to have an approximately equal number of protocols from each group, 3 additional drug protocols were included. They were in the same score range, but did not represent the peak reactions of the subjects from whom they were obtained. The authors wish to thank the staff members of the Research Center for Mental Health for their help in judging the protocols.

deal of overlap in the range of scores; only 4 of the 20 subjects obtained Experimental Day Scores higher than the highest pretest score. Since we would like to interpret the scores on the experimental day as indicative of the effect of the total experimental situation on the placebo subjects, and to consider differences in those scores as reflecting individual differences in their reactions to the situation, we must rule out the possibility that those scores are merely an exaggeration of their reactions on the pretest day.

When the pretest Total Questionnaire Scores are correlated with the Experimental Day Scores we obtain a product-moment coefficient of 0.22 (0.18 with the Peak Reaction). Since this correlation means that pretest scores account for only 5% of the variance in Experimental Day Scores, we may conclude that there is no general "yes-saying tendency" that accounts for individual differences in placebo reactions on the experimental day.

Another possibility is that, even though the subjects with the highest scores were not the same on both days, the nature of the reaction was similar on the 2 days. This can be tested by examining the number of subjects who accepted each item on each day. When, over the set of 74 items, the number accepting each item on the pretest day is correlated with the number accepting the item on the experimental day, $r=0.49$. While this r is significant at the 0.01 level, it accounts for only 24% of the item variance. Furthermore, it is inflated by the large number of LSD-specific items that were not accepted by an appreciable number of placebo subjects on either day. If we compare the 15 items accepted most often (by 35% or more of the subjects) on the experimental day with the 13 items accepted most often (by 15% or more of the subjects) on the pretest day, we find that only 3 of these items are the same; by chance, 2.6 items in common would be expected. The pretest reactions were, then, different from the experimental day reactions.

Before considering the placebo reactions on the experimental day, we may describe briefly the nature of the pretest responses, since they represent reactions to a different kind of situation. Most of the items accepted by 20% or more of the subjects on the pretest questionnaire fall into 2 groups: those representing difficulty in concentrating on the tasks or in understanding and performing them (Items 10, 36, 39, and 22), and those expressing self-consciousness (Items 23 and 45). In addition, dizziness or grogginess was reported (Item 46a), generally with the comment "I'm not used to getting up this early."

The Temporal Course of the Placebo Response: When the pattern of placebo responses over time is examined, no consistent time curve can be seen in the Total Questionnaire Scores for the entire placebo sample. The means at the different hours after drug administration are: 3.40 at a half hour, 3.95 at 2 hours, 5.20 at 5 hours, and 3.82 at 8 hours; there are no significant differences among these means. If we consider individual subjects, 4 subjects had their peak reaction at a half hour, 7 subjects at 2 hours, 4 subjects at 5 hours, and 4 subjects at 8 hours (one subject had a zero score throughout and so had no peak). This is not significantly different from a chance distribution. Neither the time curve of the group means nor the distribution of Peak Questionnaires over time, then, show any clear maximum, and these 2 ways of viewing the temporal pattern have their maximal points at different times. This is in contrast to the LSD-25 group, where both the group means and the location of the Peak Questionnaires showed a significantly stronger reaction at 5 hours than at the other time periods. We may say, therefore, that the total placebo reaction did not follow any time pattern that was consistent for the group as a whole.

While the Total Score does not reveal any clear trend during the course of the day, different aspects of the reaction were more prominent at different times. Somatic symptoms and feelings of having lost control were strongest at a half-hour and declined steadily thereafter. By 2 hours,

feelings of having acquired new meanings and a general feeling of disinhibition became more prominent; these feelings persisted through 5 hours and dropped off by 8 hours. At the 5-hour period, difficulty in thinking reached its maximum, accompanied by some feelings of things having lost meaning and feelings of elation or silliness. Finally, loss of the sense of time, feelings of being inhibited and slowed down, angry or annoyed, and depressed increased steadily and reached their maximum at the end of the day.§

Consistency of the Placebo Response: Another question that may be raised is whether the placebo subjects reacted consistently during the experimental day. This can be answered by obtaining the 6 correlations between Total Questionnaire Scores on the 4 administrations of the questionnaire. When this is done, it is found that the 2-hour, 5-hour, and 8-hour scores are highly intercorrelated; the 3 correlations between pairs of questionnaires are 0.66, 0.63, and 0.70.|| The half-hour score, however, is only slightly correlated with the later ones, the correlation coefficients being 0.33, 0.47, and 0.11; while all 3 are positive, as we would expect, only the correlation with the 5-hour scores reaches the 0.05 level. We may say, then, that the reaction pattern that each subject will exhibit during the day was not clearly established by a half-hour after he received the placebo, but that subjects were individually consistent during the period from 2 to 8 hours after placebo administration, some having a generally strong reaction while others showed only a weak effect. These relationships enable us to speak of subjects as being "placebo reactors" or not, within the framework of the experimental day, although we have no evidence on the question of whether these subjects would react similarly in a different experimental setting.

§ It may be noted that, in general, this sequence is similar to that seen in the LSD-25 subjects,[15] although at a much lower level.

|| Rank-order correlations were used, since the scores of placebo subjects are strongly skewed. All 3 correlations are beyond the 0.01 level.

TABLE 2.—*Questionnaire Items Accepted by Placebo Subjects Significantly More Often on Experimental Day than on Pretest Day*

% of S's Accepting (N=20)			
Pretest	Peak Experimental Day		
5	25 ‡	35 †	4. Do you find yourself talking about personal things that you wouldn't usually talk about?
0	25 †	30 †	7. Have you felt occasionally that you have lost your sense of time?
10	35 ‡	45 †	11. Have you felt that certain things were especially clear to you or that you understood them better?
0	30 †	40 *	14. Has your body looked or felt strange in any way? (report of somatic symptoms)
10	15	35 †	15. Have you been especially happy?
5	25	45 *	16a. Have you been feeling silly?
0	5	20 ‡	19. Have events or experiences seemed illogical or disconnected?
10	25	35 ‡	21b. Has time been passing slower than usual?
10	30	50 †	29c. Have you been talking more than usual?
5	40 †	45 †	33. Have you felt angry or annoyed? (directed externally)
10	25	40 †	35. Do you think that your judgment and ability to evaluate have been different from usual? (report judgment improved)
			46. Have you had any of the following physical sensations?
20	45	50 ‡	a. Dizziness or grogginess?
5	20	35 †	b. Numbness or tingling?
0	20 ‡	25 †	i. Mouth dry or less saliva than usual?
0	5	20 ‡	j. Pressure or ringing in ears?
10	40 †	40 †	k. Felt weak physically?
0	15	35 †	l. Body felt lighter or like it was floating in space?

* Increase from pretest to experimental day significant at 0.01 level (one-tailed test).
† Increase significant at 0.05 level (one-tailed test).
‡ Increase significant at 0.10 level (one-tailed test).

The Nature of the Placebo Response: Table 2 presents the questionnaire items that the placebo subjects accepted more often on the experimental day than on the pretest day, at the 0.10 level or better (for the percentage of placebo subjects accepting each of the 74 items, cf. 15, Table 1). Significance levels for the differences between the 2 days are indicated; one-tailed tests of significance were used, since it was expected that the experimental situation would produce an increase in the number of items accepted. Two of the 74 items show an increase that reaches the 0.01 level, an additional 11 items reach the 0.05 level, and 4 more items reach the 0.10 level. The 13 items reaching the 0.05 level or better constitute a significantly higher number than the 3.7 items that would be expected to reach this level by chance (corrected $\chi^2 = 22.0$, $p < 0.001$). We may therefore consider it valid to interpret the obtained differences, and we will consider the 17 items that reach the 0.10 level as reflecting the most typical reactions to the placebo situation.

Seven of these items deal with physical symptoms: Placebo subjects tended to feel dizzy or groggy (46a), weak (46k), numb (46b), light (46l) and, to a lesser extent, to experience dryness of the mouth (46i) and pressure or ringing in the ears (46j), as well as reporting physical symptoms more often in response to a general question (14s). They reported that they were talking more than usual (29c), in many cases about things they wouldn't usually talk about (4). They felt both happy (15) and silly (16a). They tended to feel that their judgment was somewhat better than usual (35), and the qualitative answers indicate that when this occurred it was because they felt relaxed and at ease. At times they also reported that they understood certain things better than usual (11), but their responses indicate that this usually was because they were taking some of the tests for the second time (in contrast to LSD-25 subjects, who often felt that they had acquired new insights). They often reported that they had experienced some loss of the sense of time (7), and particularly that time was passing more slowly than usual (21b). They reported that some things seemed illogical or disconnected (19), which usually referred to the experimental procedures (while drug subjects tended to report dissociation of thought processes under this item). One of the reactions most frequently reported was anger or annoyance at the experimenters or the experimental situation (33).

The reactions of placebo subjects were, then, concentrated in somatic symptoms, changes in affect, and a certain expansiveness which was reflected in talking a lot and in a feeling of improved judgment. The areas covered by the questionnaire in which they showed virtually no effect deal with ego changes, feelings of merging into the environment, perceptual distortions, thought disorder, and loss of meaning.¶

Personality Variables Associated with the Placebo Reaction.—The relationships between the strength of the placebo reaction and the personality variables were evaluated by dividing the sample into strong and weak reactors. Since the intercorrelations of the 4 questionnaires administered on the experimental day show that the individually consistent reaction patterns were established after the half-hour questionnaire (see above), subjects were divided on the basis of the average of their Total Scores for the 2-hour, 5-hour, and 8-hour questionnaires. The 10 subjects above the median were considered strong placebo reactors, while the

¶ The questionnaire items were grouped, on an a priori basis, into 17 scales, each of which consists of items relevant to a specific area of functioning; the scales are described elsewhere.[15] The description of the areas in which placebo subjects showed no increase from their pretest scores is based on the lack of statistically significant increases for Scales I (Difficulty in thinking), V-A (Closer to environment), V-C (Ego changes, alienation), VI (Distortions of visual perception), and VIII-B (Old meanings lost). On all other scales their increase reached the 0.05 level with a one-tailed test of significance. It should be borne in mind, however, that for the LSD-25 subjects all scales showed an increase at the 0.001 level, while for the placebo group the increase on only one scale (XI-B, Somatic symptoms) reached this significance level.

TABLE 3.—*Personality Variables on Which Strong and Weak Placebo Reactors Differ*

t	*p*(Two-Tail)	
		Items Characterizing Strong Reactors
2.75	0.05	2 Bland and uncommunicative (tends to be quiet and uncommunicative; affect is bland or flat; lacks spontaneity and passion)
2.33	0.05	33 General passivity and passive resistance (longs for peace and quiet; needs relaxation and rest; hates exertion and effort [n Passivity]; refuses to become involved in things, withdraws into self or drags his feet rather than overtly rebelling)
2.24	0.05	35 Suggestible and dependent on others to take initiative
2.45	0.05	38 Failure of defense (becomes disorganized and unadaptive under stress, feels helpless)
3.40	0.01	40 Loose thinking [vs. clear thinking] (concepts tend to be loose, fuzzy, vague, poorly articulated and sloppily worded; does not communicate ideas clearly, effectively, and appropriately)
		Items Characterizing Weak Reactors (i.e., Strong Reactors Lack These)
2.44	0.05	4 Affect well-modulated, good-tempered (generally cheerful and good-tempered; affect expression is well modulated, flexible, spontaneous, but not fluid)
3.57	0.01	6 Is socially perceptive; responsive to interpersonal nuances
3.68	0.01	28 Often feels angry and impatient with himself
2.56	0.05	30 Goal-striving in the face of frustration (strives for his goals persistently and with endurance; counteraction—in the face of frustration, redoubles efforts to succeed, if injured strikes back directly at the source; when frustrated, does not withdraw cathexis from the goal)
4.27	0.01	43 Introspective and sensitive to minimal cues (introspective and self-examining; alert and sensitive to small differences and slight cues)
2.21	0.05	47 Analyzes a problem skillfully, actively, and accurately
2.69	0.05	53 Intellectualization and intellectuality (has the identity of an intellectual; intellectualization—seeks safety in information and knowledge, under stress gets distance and avoids anxiety by taking a "scientific" or "philosophical" attitude; values information for its own sake, wants to be well-informed)
2.84	0.05	54 Seeks creative outlets, strives for understanding (needs outlet for creative urges, eager to write, build, or create things or ideas [n Construction, Creative]; seeks explanations, wants to understand reasons for things, enjoys reading and study [n Understanding])
3.00	0.01	55 Sensitive, creative identity and philosophical concerns (has the identity of the sensitive, creative artist; concerned with abstract and philosophical problems, e.g., religion, values, the meaning of life)

10 subjects below the median were considered weak reactors. The difference between the 2 groups on each of the 73 personality variables was evaluated by the *t*-test, using two-tailed significance levels since no predictions were made. Table 3 lists the 14 variables on which strong and weak reactors differ at the 0.05 level of significance.#

The variables listed in Table 3 represent 4 major areas of personality.* In regard to activity-passivity (Variables 30, 33, 35, and 38), the strong placebo reactors tend to be more passive, more suggestible, and more poorly defended, while the weak reactors persist in striving for their goals, and redouble their efforts when frustrated. The 2 groups differ also in their expression of affect (Variables 2 and 4); strong reactors show a flattening of affect, while weak reactors tend to be good-tempered, with well-modulated and flexible affect expression.

The remaining 2 groups of variables are closely related to each other. The variables most strongly related to the strength of the placebo reaction (6, 28, 43, and 55) indicate that weak placebo reactors are more sensitive to both external and internal cues and conceive of themselves as sensitive. They are socially perceptive as well as self-examining; their impatience with themselves may reflect both self-doubt and the maintainence of high standards of achievement. The remaining variables (40, 47, 53, and 54) deal with intellectual functioning. Weak placebo reactors see themselves as intel-

These 14 variables exceed the chance value of 3.65 to a significant extent, if a χ^2 test (corrected for attenuation) is used; χ^2 is 28.0, while a value of only 10.8 is necessary to reach the 0.001 level. It should be noted that such a test is not, strictly speaking, valid, since the variables are not independent of each other; it is used, with this reservation, in the absence of a more valid test.

* The grouping of the variables is based on the patterning of the correlations among the variables. The resultant grouping, however, makes sense psychologically as well as statistically.

lectuals, are intellectually alert and curious, and function more effectively in intellectual tasks. They tend to use intellectualization as a defense; the context suggests that it is an appropriate and effective defense for them. The strong placebo reactors, in contrast, show thinking which is loose or vague and poorly communicated.

Personality Variables Associated with the Pretest Reaction.—The personality variables associated with the placebo reaction may be contrasted with those associated with a high pretest score.† High pretest subjects are characterized as being narcissistic with fluidity of affect and having a narrow range of interests. They are *lacking in* intellectualization, counterphobic or hypomanic tendencies, and persistent goal-striving in the face of frustration. They also lack a practical or "hard-boiled" self-concept, a wish for authoritarian roles or identification with authority figures, and fear of losing control over aggressive impulses. This pattern seems to depict a kind of person who would feel self-conscious at "being a guinea pig," and who would complain of difficulty in carrying out the required tasks rather than buckling down and doing them in a straightforward manner.

Patterns of Placebo Reaction.—An analysis of the specific questionnaire items accepted by different subjects led to the identification of 3 groups of subjects. These groups may be considered to represent the major patterns of placebo response found in the present study. While the number of cases in each group is too small to justify statistical treatment, they may be briefly described here.

Five of the 10 strong placebo reactors fall into Group A, while the remaining 5 each had somewhat disparate response patterns. The questionnaire responses and personality pattern of subjects in Group A resemble the strong reactor pattern already described.

Of the 10 weak placebo reactors, 3 are in Group B, 4 in Group C, and 3 are not in any group. Groups B and C, therefore, represent 2 different styles of weak placebo reaction. Subjects in Group B became bored, hostile, annoyed at the lack of any interesting effects, and somewhat suspicious of the whole procedure. In the personality assessment they were characterized as hostile, greedy, manipulative, concerned with status, bland, lacking in insight and, in contrast to many of the other subjects, strongly heterosexual. The subjects in Group C were minimally affected by the situation, and the only consistent effect shown by them was a feeling of increased understanding. They are characterized, in the personality assessment, as intellectual, creative, skillful in problem-solving, with well-modulated affect, curious about people and fond of gossip, and with a desire to help others. They are also described as orderly, obsessive, and having feelings of sexual inadequacy.

Comment

As has been noted, Wolf [24] has called the placebo reaction a "response to a meaningful situation." The placebo reactions reported here are a function of a number of aspects of the total situation, and we shall attempt to define those which seem most important. First, there is the administration of an inert substance, initially unknown to either subject or experimenter; second, there are the motivations and expectations of both subject and experimenter, and the interaction between those 2 persons; third, there is the experimental setting, which includes the room and the procedures performed throughout the day; fourth, there is the personality of the individual subject,

† Since very few subjects had pretest scores of any magnitude, the entire sample was dichotomized for this comparison. Ten high pretest scorers (7 drug and 3 placebo) were compared with the other 40 subjects, and *t*-tests performed for the 73 personality variables. Eight of these variables differentiate between high and low pretest scorers at the 0.05 level (two-tailed test). Since only 2 of these are among the 13 variables associated with a strong placebo reaction, while 1.4 would be expected by chance, we can conclude that the personality correlates of a high pretest score are not the same as the personality correlates of the placebo reaction.

and the limitations imposed by the measures utilized to assess it; and fifth, there is the instrument used to measure the placebo reactions—in this instance, the questionnaire. Of these factors, we will discuss those for which our data are most relevant.

Certain considerations stem from the use of the present questionnaire to monitor the placebo reaction, since the findings are inevitably limited by the questions asked. It should be noted that the questionnaire was designed primarily with the LSD-25 reaction in mind. Consideration of the placebo reaction in advance would have led to the inclusion of questions specifically designed to provide a clearer understanding of how the placebo subjects felt.‡ This is generally overlooked in studies where placebo groups are used primarily as controls and not given the separate attention they merit. The present questionnaire did, however, permit the report by placebo subjects of a wide range of subjective experiences relatively unexplored in previous placebo studies.[3]

The questionnaire proved to be highly successful in differentiating drug from placebo subjects. It is of interest that the qualitative data, that is, the remarks of the subjects, whether reviewed by judges or scored formally, differentiated subjects from the 2 groups even when quantitative scores were borderline. Abramson et al.,[2] who used only a quantitative scoring of their questionnaire, suggested that a positive response from a drug subject might not have the same meaning as a positive response from a placebo subject. The data reported here, as well as the qualitative data to be reported elsewhere, show that LSD-25 and placebo responses do indeed often have different meanings, so that the 2 kinds of reactions differ qualitatively as well as quantitatively.

Abramson et al.[2] state, as a general impression, that placebo responses resemble LSD-25 responses, but this may well be a function of the conditions of their experiment. Most of their questionnaire items dealt with somatic reactions, which we have found to be the class of reaction reported most often by placebo subjects, rather than the affective and cognitive reactions that we have found to be most effective in distinguishing between drug and placebo reactions. The apparent resemblance would also have been weaker if qualitative data had been obtained. To the extent that their placebo reactors did resemble drug subjects, the fact that they were tested in groups which also included drug subjects undoubtedly played a large part. Furthermore, their subjects expected to receive LSD-25, while our subjects did not know what drug was being studied and at no time observed the reactions of any other subject.

Comparison of the pretest and the placebo reactions can help to clarify the meaning of the placebo situation and reaction. On the pretest day no substance was ingested and subjects were asked about their everyday feelings or received tests of "normal functioning" to be used as baseline data. Subjects were seen in a normally lit office instead of the darkened experimental room used on the following day. The setting and instructions of the pretest day tended to induce a task-oriented attitude in the subject. In keeping with this, the responses of high pretest scorers reflected primarily their difficulty in maintaining a task-orientation, and their personalities seem appropriate for the kind of person who would have such difficulty. It should be noted that they were not assessed as being notably suggestible or passive.

It has sometimes been assumed that "placebo reactors" are essentially suggestible people who tend to say "yes" to many questionnaire items.[2,22] The fact that strong placebo reactors in the present study did not have notably high pretest scores, as shown by the negligible correlation of 0.22 between their Total Scores on the pretest and experimental days, shows that they are not people who are "suggestible" in a general sense of the term. Nevertheless, they were assessed as being passive and sug-

‡ Examples of such items might be: "Are you bored?" "Do you feel disappointed?" "Do you feel that you have been misled?" "Are you relaxed?" or "Are you drowsy?"

gestible. Consideration of the nature of the placebo situation, the personality attributes of strong placebo reactors, and the interaction between the two may clarify the specific ways in which suggestion operated.

Some of the personality characteristics of strong placebo reactors—their passivity, suggestibility, poor defenses, and lack of active goal-striving—have face validity. We would expect such people to be strongly affected by the experimental situation. It is, however, the variables dealing with sensitivity to both internal and external cues that are most strongly related to the strength of the placebo reaction. We may hypothesize that the greater sensitivity of the *weak* placebo reactors serves to minimize their reaction to the situation. Their more effective use of intellect may also be a factor. Subjects who are self-examining and self-critical should be those best able to evaluate their own reactions and to realize that they are not really experiencing anything out of the ordinary. Furthermore, their sensitivity to external cues, particularly interpersonal nuances, may have made them more sensitive to the experimenters' inevitable knowledge that they were placebo subjects. In contrast, the greater suggestibility of the *strong* placebo reactors combined with the fact that they tend not to look closely or critically at their own reactions, would make them more likely to accept the suggestion that they have received a drug and to interpret their own reactions accordingly.

It might be thought that the greater suggestibility of the strong reactors makes them more prone to believe that they have received a drug and to act accordingly, but they do not accept items indiscriminately, and the more psychotic-like items are scarcely accepted at all by placebo subjects. It seems rather that the anticipation of receiving a drug caused the strong placebo reactors to reinterpret their usual subjective reactions or to sanction reactions that they considered permissible under the influence of an imagined drug. Suggestibility does, then, play a part in producing the strong placebo reaction. It does not operate simply, however, but it is rather that various aspects of the suggestible subject's personality determine his reaction to the total situation. In regard to the failure of strong placebo reactors to show any marked "yes-saying" tendency on the pretest day, we may add that, while the experimental day produces the implicit expectation of abnormal reactions, the expectation on the pretest day is that normal reactions are being tested. If there is any suggestion involved in the pretest situation, then, it is the suggestion not to show an effect.

The pattern of personality variables that are associated with the strong placebo reaction in the present study resembles the pattern that has been found to underly susceptibility to influence in perception,[23] in the autokinetic situation,[13] and in response to written communications.[14] Subjects who were mostly easily influenced in these studies were found to be generally passive and relatively inadequate in coping with tasks unaided. They had a weaker self-image and were less introspective and self-examining, with a marked lack of sensitivity to cues from within.

The placebo reactions of some subjects may be determined by factors other than those that typify the strong reactors. The reaction may center on being told to expect a mysterious drug and then *failing* to experience the expected effects. The subjects in Group B, whose response emphasized boredom, annoyance, and suspiciousness, seem to have shown such an effect. These subjects may also have been responding to an awareness of the experimenters' reduced interest in a subject they realize has received a placebo. The fact that some of our subjects became angry on realizing that they had received a placebo indicates that disappointment over "receiving nothing," a factor often overlooked, should be considered in studying placebo reactions. The data further suggest the possibility that the experimental situation may arouse threatening drives such as anger, which are then covered up, in part, by feelings of boredom.[5] On the other hand, relief at not experiencing

potentially frightening drug effects may determine other reactions in placebo subjects.

Another aspect of the placebo reaction to be considered is its progress over time. For the group as a whole, there is an intelligible progression of reactions, with the somatic symptoms and feelings of loss of control at the beginning of the day probably reflecting an anticipatory anxiety, and the boredom, fatigue, and annoyance that became prominent at the end of the day best viewed as the consequence of lengthy testing. As to individual subjects, the most striking finding is that the tendency to be a strong or a weak reactor is established between a half-hour and 2 hours after receiving the placebo. After that point, there is great individual consistency in the strength of the reaction for the rest of the 8-hour day. Within this consistency, several different patterns appeared. The reactions of subjects in Group B, who were more bored and resentful, tended to build up as the day progressed. Subjects in Group C, on the other hand, seem to have perceived the situation well and reacted very little; the reactions they did have occurred almost entirely in the first 2 hours.

The prominence of somatic symptoms in the placebo reaction suggests that they served a function in adapting to the situation. As we have noted, the concentration of these symptoms at the half-hour period suggests that somatic channels may reflect anxiety or apprehension. The blurred vision and dizziness reported by Group B subjects suggest that physical symptoms may also reflect anger. The comparative physical inactivity of the experimental day may also have played a role. Our data support the frequent report of physical side-effects when placebos are administered for therapeutic purposes,[3,24,26] confirming Wolf's hypothesis that many body organs may participate in the placebo response.

It is of interest to consider how the strong and weak reactors differ in this area in everyday life. Two groups of items dealing with the body were selected from the MMPI, given in the initial screening. Strong and weak reactors do not differ in the number of MMPI items accepted that deal with actual physical symptoms, but strong reactors report significantly more fear and worry about their bodies ($t=2.18$, 0.05 level). The body is, apparently, a source of conflict to them, and it is noteworthy that the impression that they have received a drug encourages them to report physical symptoms even though they do not normally report an excessive number of symptoms. We also identified, within the LSD-25 group, subjects with the personality characteristics of strong placebo reactors (cf. Table 3). The drug reaction of these subjects is marked by a significantly greater report of physical symptoms than is given by other drug subjects ($r=0.49$, 0.01 level). This may, then, represent a component of their drug reaction that is similar in some respects to the reaction of strong placebo reactors.§

A comparison of the personality correlates of a strong placebo reaction in our study with those found in other studies may add to our understanding of the placebo response. Such comparisons, since they are based on somewhat limited studies, using diverse methods, must be considered tentative. The findings of Lasagna et al.[12] based on the use of the placebo for postoperative pain alleviation, resemble the present findings in that their high reactors were more dependent and had poorer impulse control. Their reactors were preoccupied with bodily processes; although our strong reactors were not assessed in this way, the worry about the body expressed in the MMPI and their greater number of somatic symptoms on the experimental day lend some support

§ Two points should, however, be noted. First, regardless of personality type, drug subjects consistently report more somatic symptoms than do placebo subjects, so that much of their physical symptomatology must be attributed to the effects of LSD-25. Secondly, drug subjects whose personalities resemble those of strong placebo reactors report about the same number of nonsomatic LSD-25 reactions as the other drug subjects, so that their questionnaires clearly identify them as having received the drug.

to this finding. Lasagna et al.[12] also reported that high placebo reactors were narcissistic and emotionally labile; this is not confirmed in our strong placebo reactors, though characteristic of our high *pretest* reactors. These authors reported that low reactors are more emotionally controlled, more likely to use intellectual defenses, and more rigid; our data confirm the first 2 fiindings, but not the rigidity.

The second study by this group,[4] though it resembles our study in that it used a laboratory setting and studied subjective reactions, must be considered cautiously because it confuses the atypical drug reaction with the placebo reaction (cf. footnote p. 370). Of special interest, however, is their report that high reactors were hostile and showed a striving for prestige and achievement, often beyond their capacities. While our strong placebo reactors did not show these tendencies, these attributes were typical of the subjects in Group B, who had a clearly definable, though restricted, placebo reaction. Had our questionnaire included more items specifically oriented to the placebo reaction, rather than being limited to the effects typical of LSD-25, these subjects probably would have received higher Total Scores and thus emerged as a second type of strong placebo reactor.

It is clear that further research is necessary into the consistency of placebo reactions within the same situation and across situations. If subjects do not react consistently, generalizations must be quite limited, and personality correlates, if they have any meaning at all, must be restricted to the particular conditions under study. The present study demonstrates individual consistency in response to a placebo in the course of one day where the conditions remain relatively constant, but it cannot deal with the question of the broader generality of the placebo response. Furthermore, the overlap of personality correlates in this study and in others is encouraging, but far from definitive, in view of the limitations of the data available for comparison. The present findings should, therefore, be validated by further investigations of both the consistency of the placebo response and its personality correlates.

Summary

In a double-blind study of subjective reactions to lysergic acid diethylamide (LSD-25), a 74-item questionnaire was used to monitor the reactions of 20 subjects given a tap-water placebo orally and 30 subjects given the drug. The questionnaire was highly successful in differentiating placebo subjects from those receiving LSD-25, using either quantitative or qualitative measures. The placebo reaction is viewed as a reaction to a specific situation, as shown, in part, by the differences from pretest behavior. The placebo reaction is characterized by somatic, affective, and limited cognitive changes. Three distinct patterns of placebo reaction are reported: (*a*) succumbing to the situation, (*b*) becoming bored and hostile, and (*c*) hardly reacting at all. The course of the placebo reaction over time is also described.

Significant personality differences between strong and weak placebo reactors are described. Strong placebo reactors are passive and poorly defended, comparatively insensitive, and unintellectual, with loose thinking and flattened affect. Weak placebo reactors tend to be sensitive to internal and external cues, self-examining and intellectually curious and to function well intellectually. They see themselves as creative and intellectual, tend to use intellectualization as a defense and have generally more effective defenses, with persistent goal-striving in the face of frustration.

The present findings are discussed in relation to those of previous studies. The concepts of suggestibility, "the placebo situation," and "the placebo reactor" are discussed in particular.

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REFERENCES

1. Abramson, H. A.; Jarvik, M. E.; Kaufman, M. R.; Kornetsky, C.; Levine, A., and Wagner, M.: Lysergic Acid Diethylamide (LSD-25): I. Physiological and Perceptual Responses, J. Psychol. 39:3-60, 1955.

2. Abramson, H. A.; Jarvik, M. E.; Levine, A.; Kaufman, M. R., and Hirsch, M. W.: Lysergic Acid Diethylamide (LSD-25): XV. The Effects Produced by Substitution of a Tap Water Placebo, J. Psychol. 40:367-383, 1955.

3. Beecher, H.: The Powerful Placebo, J.A.M.A. 159:1602-1606, 1955.

4. Felsinger, J. M. von; Lasagna, L., and Beecher, H. K.: Drug-Induced Mood Changes in Man: II. Personality and Reactions to Drugs, J.A.M.A. 157:1113-1119, 1955.

5. Fenichel, O.: On the Psychology of Boredom, in The Collected Papers of Otto Fenichel: First Series, New York, W. W. Norton & Company, Inc., 1953.

6. Fisher, H., and Dlin, B.: The Dynamics of Placebo Therapy: A Clinical Study, Amer. J. Med. Sci. 232:504-512, 1956.

7. Jellinek, E. M.: Clinical Tests on Comparative Effectiveness of Analgesic Drugs, Biometrics 2:87-91, 1946.

8. Knowles, J. B., and Lucas, C. J.: Experimental Studies of the Placebo Response, J. Ment. Sci. 106:231-240, 1960.

9. Kurland, A.: The Drug Placebo—Its Psychodynamic and Conditional Reflex Action, Behav. Sci. 2:101-110, 1957.

10. Kurland, A.: Placebo Effect, in Drugs and Behavior, edited by L. Uhr and J. Miller, New York, John Wiley & Sons, Inc., 1960.

11. Lasagna, L.; Laties, V. G., and Dohan, J. L.: Further Studies on the "Pharmacology" of Placebo Administration, J. Clin. Invest. 37:533-537, 1958.

12. Lasagna, L.; Mosteller, F.; Felsinger, J. M. von, and Beecher, H. K.: A Study of the Placebo Response, Amer. J. Med. 16:770-779, 1954.

13. Linton, H. B.: Rorschach Correlates of Response to Suggestion, J. Abnorm. Soc. Psychol. 49:75-83, 1954.

14. Linton, H. B., and Graham, E.: Personality Correlates of Persuasability, Personality and Persuasability, Yale Studies in Attitude and Communication, Vol. 2, edited by C. I. Hovland and I. L. Janis, New Haven, Yale University Press, 1959.

15. Linton, H., and Langs, R.: Subjective Reactions to Lysergic Acid Diethylamide (LSD-25): Measured by a Questionnaire, Arch. Gen. Psychiat., this issue, p. 352.

16. Rosenthal, D., and Frank, J.: Psychotherapy and the Placebo Effect, Psychol. Bull. 53:294-302, 1956.

17. Shapiro, A.: The Placebo Effect in the History of Medical Treatment (Implications for Psychiatry), Amer. J. Psychiat. 116:298-304, 1959.

18. Shapiro, A.: Attitudes Towards the Use of Placebo in Treatment, J. Nerv. Ment. Dis. 130:200-209, 1960.

19. Shapiro, A.: A Contribution to a History of the Placebo Effect, Science 5:109-135, 1960.

20. Slater, P. E.; Morimoto, K., and Hyde, R. W.: The Effect of Group Administration Upon Symptom Formation Under LSD, J. Nerv. Ment. Dis. 125:312-315, 1957.

21. Starkweather, J. A.: Individual and Situational Influence on Drug Effects, in A Pharmacologic Approach to the Study of the Mind, edited by R. M. Featherstone and A. Simon, Springfield, Ill., Charles C Thomas, Publisher, 1959.

22. Trouton, D.: Placebos and Their Psychological Effects, J. Ment. Sci. 103:344-354, 1957.

23. Witkin, H. A.; Lewis, H. B.; Hertzman, M.; Machover, K.; Meissner, P. B., and Wapner, S.: Personality Through Perception, New York, Harper & Brothers, 1954.

24. Wolf, S.: The Pharmacology of Placebos, Pharmacol. Rev. 11:689-704, 1959.

25. Wolf, S.; Doering, C. R.; Clark, M. L., and Hagans, J. A.: Chance Distribution and the Placebo Reactor, J. Lab. Clin. Med. 49:837-841, 1957.

26. Wolf, S., and Pinsky, R.: Effects of Placebo Administration and Occurrence of Toxic Reactions, J.A.M.A. 155:339-341, 1954.