

# Nonblind Placebo Trial

*An Exploration of Neurotic Patients' Responses to Placebo  
When Its Inert Content Is Disclosed*

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## Introduction

THE PLACEBO effect, that is, the effect obtained when a presumably inert substance is given to normal or diseased individuals, has been the object of many studies in the last decade. A considerable amount of attention has been paid to the psychological factors underlying this effect, and many workers in the field would subscribe to what Gliedman et al<sup>6</sup> write: "The so-called placebo effect should be looked upon as an epiphenomenon of complicated psychological processes, which are far more important than the disarmingly simple means utilized for its realization."

What is the nature of these processes? Kurland<sup>15</sup> states that ". . . the placebo reaction is generally accepted to be a manifestation of suggestion . . ."; in this framework, one common assumption is that the patient should believe he is taking an active drug.<sup>22</sup> Throughout the vast literature on the placebo effect there is a consensus on one basic factor which Hampson et al<sup>7</sup> state as follows:

The high value which our culture places on pills and medicine may be involved in this phenomenon whereby even inert substances become endowed with physiological potency when they are presented to the patient as therapeutic agents.

Lieberman<sup>16</sup> has attempted to conceptualize and systematize many factors of the placebo phenomenon following the analysis of communication research by Hovland et al.<sup>8</sup> He resolves the placebo effect into three interacting components: (1) the observable doctor-patient therapeutic stimuli; (2) the predispositional factors in the patient; and (3) the internal mediating processes that are fed by the

therapeutic stimuli and the predispositional factors.

While the "internal mediating processes" can be probably only the object of theoretical consideration, the "predispositional factors" as well as the "therapeutic stimuli" have been widely studied. Lasagna et al<sup>14</sup> have described such "predispositional factors" which distinguish experimental subjects as placebo reactors and placebo nonreactors. Knowles and Lucas<sup>11,12</sup> classified such predispositions as neuroticism and extraversion, while Tibbetts and Hawkins<sup>22</sup> found unelaborated anxiety to play a key role. Knowles and Lucas<sup>11</sup> examined some of the situational factors in the patient's "predisposition" and found that if the experimental participants were in groups of three the response was different than when the experimental subjects were isolated.

The observable doctor-patient therapeutic stimuli have been examined in terms of the personal characteristics of the doctors by Uhlenhuth et al<sup>23</sup> and in terms of the doctor's behavior by Joyce<sup>10</sup> and by Fisher et al.<sup>2</sup>

The role of the stimulus, "pill," has also been studied, particularly in terms of side-effects, via the so-called active placebo which Haas et al<sup>6</sup> suggest should be called "fake placebo" (Kaschiertes Placebo). Lipman et al<sup>17</sup> have used atropine for this purpose.

We were unable to find mention in the literature of any experiment testing the assumption that a prerequisite for the placebo effect in a neurotic patient is unawareness of the real nature of the substance received. We therefore designed and carried out the study reported here, with the hypothesis that patients can be willing to take placebo and can improve despite disclosure of the inert content of the pills.

The study was conducted with adult neurotic outpatients who were clearly not alcoholic or suffering from neurological disorder and who

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presented signs of anxiety. The number of subjects was limited due to the exploratory nature of this unusual and "paradoxical" experiment in which neurotic outpatients asking for help were requested to take capsules containing no medication. A safeguard was introduced by suggesting to each patient that placebo would be prescribed for one week, after which further treatment could be offered. Obviously, this safeguard was another variable in the study, but it was felt that the possibility was still present of obtaining valid and significant results. The restriction of subjects to neurotics presenting signs of anxiety was based on the findings reported by many authors that symptoms related to subjective feelings of apprehension and helplessness are significantly helped by drugs and placebos.<sup>1,5</sup>

### Method

This study took place from June to August, 1963, in the Outpatient Department of the Henry Phipps Psychiatric Clinic, a service for adolescents and adults who cannot afford private care. The patients selected were 15 newly admitted neurotics ranging in age from 19 to 67 years, but only one patient was above 50 years of age. The mean age of the sample was 35 years. Thirteen patients were female and nine were white.

Each patient was seen twice. The first visit involved a complete evaluation, followed by prescription of placebo; the second visit took place a week later and consisted of two separate interviews aimed at assessing change and making further disposition. Two psychiatrists participated, one as therapist for eight patients and the other for seven patients. Each interview was observed through a one-way screen by one of the psychiatrists, who also recorded the session on tape and interviewed the patient at the end of the second session.

At the initial visit, each patient was evaluated for approximately an hour, following which his case was discussed at the regular intake conference. The patient was then seen again for 15 to 30 minutes, during which time the placebo was introduced. A script was prepared and carefully enacted as follows :

"Mr. Doe, at the intake conference we discussed your problems and your condition, and it was decided to consider further the possibility and the need of treatment for you before we make a final recommendation next week. Meanwhile, we have a week between now and your next appointment, and we would like to do something to give you some relief from your symptoms. Many different kinds of tranquilizers and similar pills have been used for conditions such as yours, and many of them have helped. Many people with your kind of condition have also been helped by what are sometimes called "sugar pills," and we feel that a so-called sugar pill may help you, too. Do you

know what a sugar pill is? A sugar pill is a pill with no medicine in it at all. I think this pill will help you as it has helped so many others. Are you willing to try this pill?"

The patient was then given a supply of placebo in the form of pink capsules contained in a small bottle with a label showing the name of the Johns Hopkins Hospital. He was instructed to take the capsules quite regularly, one capsule three times a day at each meal time. He was also asked to discontinue any tranquilizer, antidepressant, or sedative he may have been taking at the time. The importance of keeping the next appointment was stressed, and the patient was asked to return the bottle at that time with any pills left over. The statement that the pills had helped many others was usually repeated again, especially if the patient asked questions concerning the treatment, conveying doubtful attitudes about its possible effectiveness.

The second visit consisted of a brief interview focused on the symptoms present at that time and on any changes noticed since the first visit. The alternate psychiatrist then proceeded to further explore with the patient the changes noticed, the opinions and feelings of the patient about the treating doctor and the treatment received, and his desires concerning further treatment.

The following improvement measures were used:

A. *Overall Change.* This is measured by a 7 point scale ranging from 7, "very much worse," through 4, "no change," to 1, "very much better," rated by the patient immediately prior to the second visit, in terms of how he had felt during the past week compared to how he felt prior to his initial visit. The rating was also made by the doctor at the end of the second visit.

B. *Symptom Checklist.* This is a 65-item modified Hopkins Symptom Checklist. The patient was asked how much the symptoms bothered him in the past week in the categories, "not at all," "a little," "quite a bit," and "extremely," scored from 0 to 3. The patient filled out this checklist at the initial interview just prior to introduction of placebo and again immediately prior to the second visit.

C. *Target Symptoms.* To obtain this rating, the treating psychiatrist also filled out a Symptom Checklist on the patient immediately after the initial interview. He was instructed not to infer symptoms but to check a "not elicited" category for any symptoms not actually mentioned by the patient. Target Symptoms were defined at the first interview as any complaint checked as present by both doctor and patient. In order to rate change, these Target Symptoms were then scored from the Symptom Checklist filled out by the patient at the second visit.

D. *Pathology.* The treating psychiatrist rated each patient on a scale ranging from 1, "no pathology," through 8, "extreme pathology," at each visit, making this rating on the basis of the patient's illness as compared to experience with other outpatients.

### Results

*Measures.* Of the 15 patients who started the study, only one indicated definite reluctance

TABLE 1.—Patient and Doctor Mean Improvement Ratings\*

Patient Ratings	Initial Score	Final Score	Change	No. Pt. Improved
Symptom Checklist (per item)	1.04	0.61	0.43	13
Target Symptoms (per item)	1.78	1.01	0.77	14
Overall change			2.07	13
Doctor Ratings				
Overall change			1.79	14
Pathology	3.79	2.43	1.36	12

\* N equals 14 completed patients.

to take the pills at the conclusion of the first visit. Fourteen patients were completers, ie, they kept the second appointment. Pill counts revealed that only one of these 14 completing patients had deviated from prescribed dosage by more than one third, having taken 11 of 21 pills.

As shown in Table 1, the average initial Symptom Checklist score for the 14 completing patients per item initially was 1.04, "just a little," with an average improvement per item of 0.43. Thirteen of the 14 patients showed improvement, eight improving by at least 10 raw-score points and 11 by at least 5 points. One patient, whose husband had made a suicidal attempt during the study week, had a final score 10 points higher than at her initial visit. This 41% decrease in symptoms for the population is statistically highly significant and is actually more than the score reduction which has occurred with groups of patients on drugs or placebos in other drug studies we have conducted using the same measurements.\* However, expected length of treatment may have been an issue here. In the other studies duration was not clearly spelled out, whereas in the present study patients were informed they could improve on placebo in one week.

On the Target Symptoms, all 14 completers were improved, the average initial patient score per item of 1.78, approximately "quite a bit," reducing by 0.77 (43%) to an average post-treatment score of 1.01, "just a little." (As would be expected, selecting from the total symptom checklist those items of greater im-

\* Unpublished results, NIMH-PSC Outpatient Studies.

portance to the individual patient gives a higher initial score than for the total list. The higher score and larger improvement as indicated by the target symptom method is representative of our clinical impression.)

The average Patient Overall Change score at completion of the study was 2.07, "quite a bit better," with 13 patients indicating improvement and one patient indicating no change.

On the Doctor Overall Change ratings, the average patient score at the end of treatment was 1.79, closest to "quite a bit better," with all patients improved on this measure.

On the Pathology ratings, the average patient score at the initial visit was 3.79, with a pathology decrease of 1.36. This was a 36% improvement, with 12 patients rated as improved, one as unchanged, and one patient as a point worse.

In summary, there is very strong statistical evidence, on the basis of both doctor and patient ratings, that the completing patients as a group felt considerably improved. Eleven patients were rated as improved on all five measures. One patient was improved on all measures except for the Pathology Score, for which there was no change. One patient improved on all measures except for the Patient Overall Change score, for which there was no change. There was only one patient for whom any measure indicated an increase of symptomatology or pathology; for this patient there was a slight increase of scores on the Total Symptom Checklist and the Pathology rating, and improvement was indicated on the other three measures.

The one patient who did not return for the second appointment was seen by a social worker. Her Symptom Checklist showed a 10-point raw score increase in symptoms, and the Target ratings showed a 5-point increase. She estimated no change on the Overall Change Measure. Other ratings were not obtained.

There were no significant differences in improvement scores of patients seen by one or the other doctor,

*Interview Content Evaluation.* Table 2 is based on opinions elicited from the patients during the second visit; their opinions of the capsule content are compared with their interpretations of the key factors causing improvement. The average Symptom Checklist change score for each group of opinions is also

TABLE 2.—*Patient Interpretations of Pill Content and Factors in Improvement\**

Patient Opinion of Capsule Contents	Patient Interpretation of Chief Factors in Improvement			Av Symp Checklist Chg Score per Item
	Pill	Doctor	Self	
Placebo (no doubts)	A †	B	C	0.80
Placebo, (minimal doubts)	D,E	F		0.31
Placebo (definite doubts)	G		H	-0.05
Drug (definite doubts)	P,Q,R		S	0.12
Drug (no doubts)	T,U			1.08

\* N equals 14.

† Each patient is identified by a letter.

given. All 14 completing patients are listed, since in the interviews they all indicated there was at least minimal improvement.

A most important finding is that improvement occurred in patients believing placebo was administered, "in spite of" such belief. There was no difference in improvement ratings between those eight patients who believed the pills contained placebo and the six patients who believed an active drug was involved.

It can be seen from Table 2 that only three patients had absolutely no doubts that the capsules contained an inactive ingredient. As a result of the use of the term "sugar pill" three patients, P, Q, and R, wondered during the treatment week if the capsule contained a "special sugar" of some sort.

Table 2 also shows that the five patients who felt without any doubt the pills definitely contained placebo or definitely contained drugs were rated as a group to be more improved than the other patients. This was significant by the Mann-Whitney U-Test ( $P < 0.05$ ).

It can be noted from the table that nine of the 14 patients felt the pill was the major factor in their improvement. It is quite interesting that not only five of the six patients who felt the pills probably contained medicine attributed improvement to the pills, but also four of the eight patients who assumed they probably contained placebo also attributed the major beneficial effects to the pills.

Table 3 compares patient interpretations of the chief factors causing improvement with interpretations, jointly reached by the two doc-

tors, of the interview transcript data. The doctors judged the relative importance for improvement of prior treatment experiences with doctors and drugs versus the present treatment experience. The five patients included in the former classification tended to have previous positive experiences with doctors and drugs and relatively stereotyped responses to the study. In general, they did not indicate that they perceived anything unique about the treatment program, and they responded to the paradoxical pill statements by "ignoring" them, simply taking prescribed pills and improving. At the final interview, they all felt the pill was the major factor in their improvement; four of them thought the pills contained drug. In other words, this group saw the improvement as caused by a pill which contained a drug.

It may be added that "side-reaction" information also suggests the role of previous drug experiences. Of the six patients who thought the pills contained drugs, three had "side-reactions" they attributed to the pills. None of the eight patients who thought the pills were placebo had reactions they attributed to the pills, although two of them had symptoms which could have been considered such. Of the three patients with the "definite" side-reactions, two had previously experienced identical side-reactions on active drugs (dry mouth).

For patients in the present treatment experience classification, the treatment or doctor tended to have a special meaning to the extent it was felt improvement would have been sig-

TABLE 3.—*Patient and Doctor Interpretations of Factors in Improvement\**

Doctor Interpretation of Major Factors in Improvement	Patient Interpretation of Chief Factors in Improvement			
	Pill	Doctor	Self	
1. Prior learning experiences with doctors and drugs	D †			
	P †			
	Q †			
	R †			
	U †			
2. Present study experience				
	A. Relationship with doctor	G †	B †	
			F †	
	B. Meaning of pill + relationship with doctor	A †		C †
		E †		H †
		T †		S †

\* N equals 14.

† Indicates patient believes capsules contain placebo.

‡ Indicates patient believes capsules contain drug. (Each patient is identified by a letter.)

nificantly less without this unique element (see case summaries). The majority of these nine patients thought they were helped chiefly by placebo, by themselves or by the doctor. They tended not to report prior gratifying experiences with drugs and doctors.

Although there is an apparent relationship between symptomatic improvement and strength of conviction as to the nature of the pill, as indicated in Table 2, there is no suggestion of a relationship between change and patient or doctor interpretation of major factors in improvement.

Four patients volunteered at the final appointment that the study pill was the most effective ever prescribed for them.

*The Study Experience.* We think it may be illuminating to describe the study experience of some of the patients. Patients A and C are examples of patients who were convinced the capsules contained placebo.

Patient A was a 20-year-old married female who complained of crying spells and irritability of several months' duration; a history of suicidal gestures was reported. The symptoms were related to her feelings of inadequacy concerning difficulty coping with the demands of a mentally retarded 20-month-old child. In the past, the patient had tended not to use doctors or medications for relief of psychological distress; she shied away from medicines for fear that she would become addicted, although she had taken "Nervine" as a self-prescription. When placebo was introduced, the patient indicated no concern about the pills. At the subsequent visit, she reported she was feeling better, with a marked decrease in irritability and an increased tolerance of stress. There were no side-reactions. She was quite convinced the pills contained no medicine, yet found they had been more helpful than Nervine. She felt that the pill was the effective agent in her treatment, remarking that when it had been prescribed she had assumed without question it would help "ease my mind." The prescription of a "helpful" capsule containing no drug, by a doctor to whom she reacted positively, had a special meaning because she was fearful of becoming addicted to drugs. The patient wanted to continue with the same doctor and with the placebo subsequent to the study.

Patient C was a 28-year-old married female, mother of five children, who complained of extreme tension, shortness of breath, trembling, crying spells, insomnia, suicidal thoughts, and poor appetite with weight loss. She indicated her symptoms centered around interpersonal relations with her husband, who somewhat sadistically provoked her with acting-out behavior. She had previously received medication for her symptoms,

with no improvement. When pills were again prescribed, the patient said that she needed something really strong; on the other hand, she was quite hesitant about taking medicine because of her identification with a mother who had frequently carried out suicidal gestures with drugs. As soon as it was clear to her that these pills were inactive, she dropped her objections and eagerly agreed to take the pills. She reported at that point, "I do feel better today, I'll be honest with you. Before I came in here I was very upset and when I was talking with you before I was very upset." At the subsequent visit the patient reported she had been doing "fine." "I've had more control and I've felt better." Her somatic symptoms had almost completely disappeared. She made it clear that she never considered the pills to be anything but placebo and reported no side-reactions. Commenting on the factors accounting for her marked improvement, the patient remarked that if a person takes a pill "in the right frame of mind," she may feel improved because the pill gives her "moral support." She also felt that the doctor was quite reassuring. Finally, the patient stated, "I think that I had a lot to do with it myself, to be honest. By knowing myself that I had to control myself to keep myself in the right frame of mind." She then indicated that the most important factor in her improvement was that she helped herself. Our feeling was that the patient did help herself but that she was able to do this only after the placebo gave her an alternative solution to that chosen by her mother in such situations. The patient wanted to continue seeing the doctor, but unfortunately, was not asked whether she wanted to continue with the pills.

There were two patients, T and U, who were absolutely positive we had prescribed capsules containing active medication.

Patient T was a 45-year-old, rigid, influence-resistant, and somewhat paranoid, divorced male with chief complaints of severe insomnia, loss of appetite and weight, restlessness, feelings of despair, death wishes, and various somatic symptoms. He had strong repressed dependent strivings, and he was quite distressed that he could not control his conflicted obsessive preoccupations with a lady friend with whom he had been involved five years; he reported that because of this he was unable to think clearly most of the time. It was felt that the patient was on the verge of an agitated depression. He had previously taken tranquilizers and sedatives, without help, except for minimal symptomatic improvement on amitriptyline (Elavil); he reported that the drugs had given him a side-reaction of dry mouth. At the second visit the patient immediately stated, "It wasn't sugar, it was medicine!" He reported a marked reduction in all symptoms except for poor appetite. He was impressed with the diminished preoccupation with the lady friend and stated that since the first day on the pills he had been able to think very clearly. This marked reduction in symptoms was accompanied by a strikingly different pattern of thinking about his interpersonal difficulties. "I have for five years had 99% of my thoughts and hopes and ambitions all concentrated and all around this woman.

ü Sodium bromide, potassium bromide, and ammonium bromide.

I have accepted that there is a possibility that it might not be, and if it isn't going to be, I'm not going to kill myself, I'm not going to fall apart. I'm going to continue working, I'm going to try to live a normal life. If it's to be by myself, that is, without a wife, it will be without a wife." The patient reported there was clear evidence he was receiving a drug. Not only did he improve markedly more than on any other pill, but he noted side-reactions 30 minutes to one hour after each dose, consisting of dry mouth, along with butterflies in the abdominal area, lasting about one hour. He felt that perhaps the doctor had told him he was receiving placebo so that he would think that he was helping himself, when actually the drug was the factor.

What factors account for this patient's marked improvement on placebo? It was noted that he had a strong positive reaction to the therapist, who presented a combination of optimistic confidence and relative absence of authoritativeness; the doctor prescribed a pill which he definitely expected would help and vividly demonstrated avoidance of advertising his powers, simultaneously playing down the dependency issue, by describing the pill as inactive. The patient responded to this noncommittal, yet confident approach, and at one point stated, "I know that you spell your name C-O-V-I and not G-O-D."

Patient U was a 24-year-old married female who dated the onset of her present illness to the birth of her third child five months prior to evaluation. She complained of insomnia, anorexia, irritability, tension, and was clearly depressed. She also reported writing a letter about death during a dissociative episode and wondered if she was on the verge of a "nervous breakdown." The patient had considerable previous experience with drugs, having worked both for a drug manufacturer and for a prescription pharmacy. One of her comments on introduction to placebo was, "Well, when I worked in the pharmacy we used to laugh at them; they really thought they were getting help," referring to patients on placebo. She reported quite positive experiences with doctors and drugs and had taken both meprobamate and chlordiazepoxide hydrochloride (Librium) without experiencing side-reactions. When placebo was introduced, the patient was very skeptical, asked whether the doctor felt people can be helped just by the idea of taking pills and suggested it would have been better if she had not been told the nature of the pills. When the doctor pressed the point he expected the pills would help her to feel a good deal better, she stated, "And if they did, then I wouldn't have to have any help?" clearly indicating her confusion. At the return visit the patient entered the interview room saying, "They're not sugar pills." Upon questioning about this, she stated, "Because they worked." She also reported that this medicine was somewhat better than the other medicines she had received for emotional symptoms. When asked why the doctor would prescribe a drug and describe it as placebo, she stated, "Maybe he wanted to see how I reacted to it. I don't know about psychiatrists, I've never been around them. I've been around a lot of

doctors, 22 in the last seven years, but not psychiatrists."

We feel there are a number of factors involved in the patient's response to placebo but that the relatively outstanding feature was her previous experience of responding positively to the act of taking pills prescribed by doctors. As an indication of the pill-taking experience, the patient reported that each time she took a pill she was accustomed to thinking about how she felt, whether she was feeling better or not, and that these thoughts had a clearly positive flavor. A further question to be answered is why the patient was helped more by the placebo than by the tranquilizers she had taken previously. The fact that the therapist reminded her of her grandfather may have been an element. In addition, she seemed quite gratified to have grasped the paradoxical treatment situation by concluding we had given a drug. The patient was very satisfied with the idea of continuing with the same doctor and pills.

Following are brief excerpts of the study experiences for patients F, H, and S, who had doubts about the nature of the capsule contents. When "sugar pills" were introduced to patient F, she wondered if they worked in some way as a treatment for diabetes, mentioning her sister had this disease. Although it was clearly explained that there was no medicine of any sort in the capsules, the patient's last question in the initial interview was whether the medication would make her too drowsy. At the time of her final appointment, the patient reported she was markedly improved, feeling better than she had in over 20 years. She stated that although she believed she had been receiving placebo, she had noted that the contents of the capsules tasted sweet. The contents were actually tasteless. The patient indicated that she was quite suggestible, and she thought the treatment had been effective through a form of "hypnosis" because she had been told so many times she would improve.

Patient H was a 28-year-old man with a rather rigid personality pattern and little insight, who complained of irritability and temper outbursts for several months. At the first visit he indicated that placebo could not help. When he returned for visit two, the patient became aware of changes in his condition only as he was able to furnish satisfactory explanations for such change. Initially, he reported that there was essentially no improvement, stating that only ineffectual "hypochondriacs" are influenced by such pills. When questioned about specific symptoms, he became aware that he was less irritable, with fewer temper outbursts; he pointed out that improvement had actually started even before he came to see us. He subsequently thought of two further explanations for improvement during the treatment week. The first was that he had helped himself. Also, he stated the pills might well contain a "mild tranquilizer," commenting that the doctor could have told him that they were placebo simply to make sure that he would take them. (He had a history of avoiding medication, having never taken pills in the past except for vitamins.) He categorically stated that if the pills were placebos they didn't help him, and if they were tranquilizers, perhaps

they did; the explanation of the pills was basic to his grasp of the experience. In discussing these possible explanations for change which did not conflict with self-esteem, the patient recalled that for the first time in his marriage he had given his wife the "silent treatment" during a fight rather than losing his temper and that this brought a definite positive response on her part. He then realized that his obsessive, anxious preoccupation with a girl friend had been completely absent during the week of treatment. Finally, the patient was asked if taking the pills had reminded him to work on his problems, and he had an immediate "Aha!" reaction, reporting, "Every time I took a pill I thought of my doctor and how I'm doing. It just reminds me that you are trying to change yourself." At the end of the interview, his overall conclusion was that he had chiefly helped himself. It was noted that throughout this second interview, patient H was considerably more expressive and interactive than at the first appointment, with more affective and intellectual insight.

Patient S was a 32-year-old woman with Raynaud's disease who complained of tension symptoms which she attached to inability to stop smoking. She reported having taken a nonprescription type of drug which was supposed to help her to stop smoking but which only caused dry mouth. When placebo was introduced, she asked, "Why would it help, because for people, each time they take a pill, it's a symbol or something of someone caring about you, thinking about you three or four times a day?" When she returned for the second visit, the patient reported considerable improvement with regard to her anxious and apprehensive feelings, although she had been able to cut down only slightly on the smoking. She had noted considerable dry mouth during the treatment week, which she attributed to the pills. She felt the pills did not contain medicine in the usual sense, although they probably contained something "like a liniment." "I consider medicine something that will alleviate your symptoms, but this didn't alleviate the symptoms, just the desire to smoke." "Well, it's like these liniments that you rub on, the skin gets hot and makes the pain go." In further discussion, she indicated that the prescription by a psychiatrist of a pill containing nothing to help the anxiety symptoms brought to her awareness the thought that she could help herself. As a result of this, she made a number of changes in her environmental situation, which was quite at variance with her usual passive approach to problems.

Finally, the patient who dropped out of treatment, an anxious, depressed 45-year-old married woman, reported to the social worker at follow-up that she generally accepted the placebo and was feeling improved, primarily as a result of seeing the doctor, but that she became quite upset and discontinued the pills after her husband ridiculed and verbally attacked her for wasting her money on "sugar pills." At first she was angry with the husband, but subsequently she became increasingly depressed. There were no side-reactions to the pills. At follow-up, she expressed an interest in continuing the pills and in returning to the

clinic but did not keep an appointment. It appeared that she was caught in an impossible bind between the hospital's approach and that of her husband.

### Comment

From this study, we have learned that neurotic outpatients can be willing to take placebo even when the inert content is disclosed, at least in a situation presenting certain safeguards to them. In fact, many of the 15 patients appeared satisfied with the treatment; at least five patients desired to continue the placebo treatment and two felt no need of further treatment. One patient dropped out of treatment, but she manifested regret for having been talked out of continuing by her husband.

The study has shown that unawareness of the inert nature of the placebo is not an indispensable condition for improvement on placebo. It may here be argued that some general factors may have had a powerful influence in determining improvement "in spite of" the disclosure. An important consideration is the size of the sample, small enough to present the chance that a large percentage of individuals would be included who would have improved markedly under any treatment or even spontaneously. As Lasagna<sup>15</sup> points out, placebos, among other factors, "control naturally occurring, that is, spontaneous, changes in the course of disease" and "such a situation can be appreciated only if one contrives an experiment so that there are control periods (for groups) when nothing of any sort is given and which may be compared with the placebo-treated period (for group)."

In the analysis of results, it has been shown that 6 of 14 patients did not believe the capsules did not contain active drug, with three of them experiencing "side-reactions" they attributed to the pills. This was apparently related to the force of prior experiences, which at times induced patients to disregard or to disbelieve the doctor's assertion, and even played a role in determining physiological effects of taking the pills. This opens an important question regarding the limits of the capability of the experimenter, therapist, or teacher in influencing or changing established concepts in his trainees. The awareness of these limits is probably one foundation for the assumption that the patient should be led to believe the potency of placebo is due to chemical nature of a supposedly active

drug. Jongbloed and Van Goor<sup>9</sup> were able to convince sportsmen who were inhaling- bottled air that oxygen was administered to them and obtained better effort performances; then they administered pure oxygen to the sportsmen, telling them that it was simply air, and performances dropped. Of course, we do not know whether these authors would have obtained superior performances also if they had tried to convince the sportsmen that bottled air alone could improve such performances. The present study indicates this possibility.

The finding that the patients who had the most definite opinions as to the nature of the pills also showed the most improvement does not necessarily mean that a definite concept of the nature of treatment leads to a good response, since these same patients also came into the study with higher initial distress. Recent studies, including that of Uhlenhuth and Park,<sup>24</sup> have demonstrated that patients with higher initial distress improve more (law of initial value). The findings of Beecher<sup>1</sup> that "the effectiveness of placebos is far greater when stress (pain) is greater than when it is less" may also be seen to indicate this trend. A possibly appropriate description for our findings may be that patients with higher initial distress and who show relatively marked improvement often develop quite definite ideas about the nature of treatment perhaps as the result of some need for a clear-cut frame of reference. The definite nature of these beliefs may be more important than their direction; it can be questioned how necessary it is for patients always to develop "correct" insight, insofar as "correct" insight is usually understood as the therapist's concept of the situation. The implication here is that a "faith" of some sort rather than a verifiable rationale is in some instances a more essential part of therapy, as has been illustrated by Frank.<sup>3</sup>

What general factors involved in the present study account for the fact that those patients who believed the pills were placebo improved as much as those who believed they were drug? Gliedman et al<sup>4</sup> write: "When placebos are employed, the achieved change in a patient's status may reflect his response to the particular doctor, or the doctor as symbolized by the medication, regardless of whether the medication was phar-

macologically active or not." The doctor may elicit "salutary changes in patients with appropriate prior experience," changes which "are probably transmitted by means of placebo." The treating doctors were quite enthusiastic about the study, optimistic in their statements, and at the same time quite anxious about telling patients that they would receive placebo. This combination of enthusiasm and alertness must have had a strong positive impact on the patients. It is also significant that Whitehorn<sup>25</sup> suggests:

... To designate as "placebo" effects all those psychological and psychophysiological benefits or detriments which quite directly involve the patient's expectations and depend directly upon the diminution or augmentation of the patient's apprehension by the symbolism of medication or the symbolic implications of the physician's behavior and attitudes.

Under this viewpoint, the expectations of further and possibly different treatment at the end of the week of experimental treatment with placebo may be seen as a part of the placebo therapy.<sup>19</sup> Gliedman et al<sup>4</sup> point out:

The animal learns to raise his leg because this has become a means for having food produced. Similarly, a patient may decide to meet his doctor's expectations because of anticipated rewards from him such as approval, respect, understanding, etc, provided the doctor meaningfully arouses him, ie, creates an appropriate central excitatory state. The use of placebo in these circumstances might function to reinforce symbolically such a doctor's effect in terms of the rewards the patient receives for modifying himself in accordance with his doctor's implied or direct recommendations. Patient changes ensuing after the use of placebo may obscure the role of the doctor, though it may be his presence, actually or symbolically, which makes these changes possible.

It would appear that the formulation of placebo effect as a response to the belief active medication is prescribed involves too narrow a view. A more comprehensive assumption would be that the basic requirement is general belief a situation defined as treatment might help, whatever its specific details.

The present placebo treatment could be viewed as having some affinity to psychotherapy not only in a manner similar to the "non-specific form of psychotherapy" which Rosenthal and Frank<sup>21</sup> describe as "produced by the patient's faith in the efficacy of the therapist and his technique." Two major characteristics of accepted psychotherapeutic techniques<sup>18</sup> were present: on the one hand, support and reassur-



ance were given, while, on the other hand, the responsibility for improvement was thrown back to the patient by means of the paradoxical statement that he needed treatment but that he could improve with a capsule containing no drug. How the combination of these two elements, support and autonomy, could benefit even a very distressed individual was dramatically illustrated in the case of patient T. His very positive response to the pills suggests the possibility that a negativistic, treatment oriented yet influence resistant patient might respond quite well to a doctor who prescribes a paradoxical treatment. Patient E had a similar experience. For patient H, a psychologically rigid individual, the ambiguous situation introduced broader thinking and feeling in much the same fashion as the posthypnotic experience or lysergic acid diethylamide (LSD-25) influences certain individuals. For patients C and S, statements that a pill with nothing in it might help brought to their awareness the thought they could help themselves. Finally, one patient responded favorably to a pill which could not be addicting (A) and another to the safety from suicidal risk (C).

The methodological issue of nonblind versus double-blind research can be raised with regard to the present study. The wealth of fascinating material gained by intensive evaluation of individual responses to information not presented to patients in double-blind psychopharmacological research speaks in favor of the study of the individual, in addition to statistical evaluation of checklists, and also strongly suggests the value of careful nonblind research. Human subjects are uniquely different from other research subjects in that they can judge and report, and this talent is frequently wasted in controlled studies. It is important to consider patients as part of the research team and to develop refined methodology for educating them to report valid data.<sup>19</sup>

### Summary

Fifteen anxious, neurotic outpatients were placed on placebo treatment for one week after being informed the pills contained inert material. Fourteen patients took the pills and returned for the subsequent appointment, with all 14 reporting improvement; there was also over-

all marked improvement by doctor and patient ratings on several measures.

Eight patients stated at the subsequent appointment that they believed the pills were placebos, although only three patients were absolutely certain of this. Six of the returning patients thought the pills contained drugs, with two patients absolutely certain. Improvement was not related to belief in the nature of the pills but did appear related to certainty of belief.

The five patients dealing with the treatment situation in a relatively stereotyped manner patterned on previous doctor and medicine experiences tended to believe they were helped chiefly by an active drug. The other nine patients tended to believe they were helped by placebo, by themselves or by the doctor. For some of these latter patients, the paradoxical combination of verbal support with deliberately withheld medicinal support had psychotherapeutic implications.

The primary finding is that patients can be willing to take placebo and can improve despite disclosure of the inert content of the pills; belief in pill as drug was not a requirement for improvement. Methodological limitations and theoretical implications of these findings were discussed.

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### Generic and Trade Names of Drugs

Amitriptyline hydrochloride ◊ Elavil Hydrochloride.  
Meprobamate ◊ Equanil, Equanil L-A, Wyseals,  
Meprospan, Mepro tabs, Miltown.  
Chlordiazepoxide hydrochloride ◊ Librium.

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