THE POWERFUL PLACEBO

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Placebos have doubtless been used for centuries by wise physicians as well as by quacks, but it is only recently that recognition of an enquiring kind has been given the clinical circumstance where the use of this tool is essential "... to distinguish pharmacological effects from the effects of suggestion, and ... to obtain an unbiased assessment of the result of experiment." It is interesting that Pepper could say as recently as 10 years ago "apparently there has never been a paper published discussing [primarily] the important subject of the placebo." In 1953 Gaddum 1 said:

Such tablets are sometimes called placebos, but it is better to call them dummies. According to the Shorter Oxford Dictionary the word placebo has been used since 1811 to mean a medicine given more to please than to benefit the patient. Dummy tablets are not particularly noted for the pleasure which they give to their recipients. One meaning of the word dummy is a "counterfeit object." This seems to me the right word to describe a form of treatment which is intended to have no effect and I follow those who use it. A placebo is something which is intended to act through a psychological mechanism. It is an aid to therapeutic suggestion, but the effect which it produces may be either psychological or physical. It may make the patient feel better without any obvious justification, or it may produce actual changes in such things as the gastric secretion. Dummy tablets may, of course, act as placebos, but, if they do, they lose some of their value as dummy tablets. They have two real functions, one of which is to distinguish pharmacological effects from the effects of suggestion, and the other is to obtain an unbiased assessment of the result of experiment.

One may comment on Gaddum's remarks: Both "dummies" and placebos are the same pharmacologically inert substances; i.e., lactose, saline solution, starch. Since they appear to be differentiable chiefly in the reasons for which they are given and only at times distinguishable in terms of their effects, it seems simpler to use the term placebo, whose two principal justifications are well stated in Professor Gaddum's last sentence quoted above. Finally, I do not understand how a dummy tablet could be prevented from having a psychological effect that, if pleasing, would make it a placebo. One term seems to fill the bill. If it falls a bit short of precision, perhaps the language will have to grow a little to include the new use.

To the increasingly well-recognized uses of the placebo I would add its use as a tool to get at certain fundamental mechanisms of the action of drugs, especially those designed to modify subjective responses. This use will be illustrated here. Strong evidence will be presented to support the view that several classes of drugs have an important part of their action on the reaction or processing component of suffering, as opposed to their effect on the original sensation.

The opportunities opened up by the placebo are unique, for it cannot possibly enter into any process by virtue of its chemical composition. It has, so to speak, neither the reactivity nor the physical dimensions required of an "effective" drug. It does not matter in the least what the placebo is made of or how much is used so long as it is not detected as a placebo by the subject or the observer. Thus the placebo provides an indispensable tool for study of the reaction or processing component of suffering. This will be referred to later on in this paper. I have discussed it extensively elsewhere. 2

REASONS FOR USE

Reasons for the use of the placebo can be indicated by summarizing, then, its common purposes: as a psychological instrument in the therapy of certain ailments arising out of mental illness, as a resource of the harassed doctor in dealing with the neurotic patient, to determine the true effect of drugs apart from suggestion in experimental work, as a device for eliminating bias not only on the part of the patient but also, when used as an unknown, of the observer, and, finally, as a tool of importance in the study of the mechanisms of drug action. Moreover, as a consequence of the use of placebos, those who react to them in a positive way can be screened out to advantage under some circumstances and the focus sharpened on drug effects. For example, Jellinek (1946) in studying 199 patients with headache found that 79 never got relief from a placebo, whereas 120 did. His data for these numbers can be tabulated as follows: While differences between A, B and C do not emerge in the "mean success rate," it appears in the placebo-nonreactor group that A is definitely more effective than the other agents (table 1). He thus demonstrated (validated with statistical methods) that when the placebo reactors are screened out more useful differentiations can be made than otherwise is the case. Jellinek is not on such sure ground when he seems to dismiss the placebo reactors as those having "imagined pain, psychological headaches." From work on postoperative wound pain done by me and my associates it appears that placebos can relieve pain arising from physiological cause. (Certainly the reverse is true: psychological cause in promoting a flow of gastric juice can produce ulcer pain, etc.) This matter of the place of reaction to unpleasant sensory phenomena has been discussed elsewhere. 2

We can take an example from our own work where placebos have relieved pain arising from physiological cause (surgical incision) and show how useful the screening out of placebo reactors can be. I, with Keats, Mosteller, and Lasagna, 3 in 1953, administered analgesics by mouth to patients having steady, severe postoperative wound pain, and we found that when we took all patients and all data we could not differentiate between

From the Anesthesia Laboratory of the Harvard Medical School at the Massachusetts General Hospital.

Read before the Section on Surgery, General and Abdominal, at the 104th Annual Meeting of the American Medical Association, Atlantic City, June 7, 1955.


certain combined acetylsalicylic acid data and narcotic (morphine and codeine) data; however, when we screened out the placebo reactors, a sharp differential emerged in favor of the acetylsalicylic acid administered orally as opposed to the narcotics administered orally. Observations of this kind were enough to give us an interest in the placebo reactor as such. We made a study of him and of the placebo response in 1954 in a group of 162 patients having steady, severe postoperative wound pain. We found that there were no differences in sex ratios or in intelligence between reactors and nonreactors. There are however significant differences in attitudes, habits, educational background, and personality structure between consistent reactors and nonreactors. These have been described in the report of this study. (There was a significantly higher incidence of relief from morphine in the placebo reactors than in the nonreactors.)

Lasagna, Mosteller, von Felsinger, and 1 found in a study of severe postoperative wound pain that the number of placebo doses was correlated highly with the total number of doses of all kinds. Fifteen patients with one placebo dose showed 53% relief from the placebo; 21 patients with two placebo doses got 40% relief from the placebo; in 15 patients with three placebo doses 40% gave relief; and of 15 patients with four or more placebo doses 15% gave relief. There was a significant correlation between number of doses and percentage relief. This same study gave an opportunity to examine the consistency of the placebo response. Sixty-nine patients received two or more doses of a placebo. Fifty-five per cent (38 patients) of these behaved inconsistently, that is to say, sometimes the placebo produced relief and sometimes not. Fourteen per cent (10 patients) were consistent reactors, that is, all placebo doses were effective. Thirty-one per cent (21 patients) were consistent nonreactors; the placebo doses were never effective. It is impossible to predict the efficacy of subsequent placebos from the response to the initial dose of saline. It must not be supposed that the action of placebos is limited to "psychological" responses. Many examples could be given of "physiological" change, objective change, produced by placebos. Data on this will be presented below.

**MAGNITUDE OF THE THERAPEUTIC EFFECT OF PLACEBOS**

Notwithstanding the keen interest of a number of individuals in placebo reactors and the placebo response, there is too little scientific as well as clinical appreciation of how important unawareness of these placebo effects can be and how devastating to experimental studies as well as to sound clinical judgment lack of attention to them can be. This problem exists in many laboratories and in many fields of therapy. Its size and pervasiveness can best be illustrated by quantitative data from the studies of others as well as our own. Fifteen illustrative studies have been chosen at random (doubtless many more could have been included) and are shown in table 2. These are not a selected group; all studies examined that presented adequate data have been included. Thus in 15 studies (7 of our own, 8 of others) involving 1,082 patients, placebos are found to have an average significant effectiveness of 35.2±2.2%, a degree not widely recognized. The great power of placebos provides one of the strongest supports for the view that drugs that are capable of altering subjective responses and symptoms do so to an important degree through their effect on the reaction component of suffering.³

**TOXIC AND OTHER SUBJECTIVE SIDE-EFFECTS OF PLACEBOS**

Not only do placebos produce beneficial results, but like other therapeutic agents they have associated toxic effects. In a consideration of 35 different toxic effects of placebos that we had observed in one or more of our studies, there is a sizable incidence of effect attributable to the placebo as follows: dry mouth, 7 subjects out of 77, or 9%; nausea, 9 subjects out of 92, or 10%; sensation of heaviness, 14 subjects out of 77, or 18%; headache, 23 subjects out of 92, or 25%; difficulty concentrating, 14 subjects out of 92, or 15%; drowsiness, 36 subjects out of 72, or 50%; warm glow, 6 subjects out of 77, or 8%; relaxation, 5 subjects out of 57, or 9%; fatigue, 10 subjects out of 57, or 18%; sleep, 7 subjects out of 72, or 10%. The effects mentioned were recorded as definite but without the subject's or observer's knowledge that only a placebo had been administered.

Wolf and Pinsky ⁵ reported in 1954 on an interesting study of placebos and their associated toxic reactions. They found, in studying a supposedly effective drug and a placebo (lactose) in patients with anxiety and tension as prominent complaints, that these symptoms were made better in about 30% of 31 patients. It is interesting to observe that the improvement rate was greater on the subjective side as just given than it was when objective signs of anxiety such as tremulousness, sweating, and tachycardia were considered. In this case (objective signs) about 17% were made better.

In these patients of Wolf and Pinsky there were various minor complaints, but 3 of the 31 patients had major reactions to the placebo: one promptly had overwhelming weakness, palpitation, and nausea both after taking the placebo and also after the tested (therapeutically ineffective) drug. A diffuse rash—itchy, erythematous, and maculopapular—developed in a second patient after the placebo. It was diagnosed by a skin consultant as dermatitis medicamentosa. The rash quickly cleared after the placebo administration was stopped. Since the

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placebo was a small quantity of lactose taken orally, it is hardly possible that it could have produced a real dermatitis. In a third patient, within 10 minutes after taking her pills, epigastric pain followed by watery diarrhea, urticaria, and angioneurotic edema of the lips developed. These signs and symptoms occurred twice more after she received the pills and again when the batch of pills was shifted; thus she had the reaction after both the (therapeutically ineffective) drug as well as after the placebo. These powerful placebo effects are objective evidence that the reaction phase of suffering can produce gross physical change.

**TABLE 2.—Therapeutic Effectiveness of Placebos in Several Conditions**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Study</th>
<th>Placebo</th>
<th>Patients, (No.)</th>
<th>% Satisfactorily Relieved by a Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beecher and others (1935)</td>
<td>Lactose</td>
<td>P. O.</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Lasagna and others (1944)</td>
<td>Lactose</td>
<td>P. O.</td>
<td>49</td>
</tr>
<tr>
<td>Pain from angina pectoris</td>
<td>Evans, W., and Hoyle, C.: Quart. J. Med. 2:312-328, 1953</td>
<td>Sodium bicarbonate</td>
<td>&quot;Placebo&quot;</td>
<td>38</td>
</tr>
<tr>
<td>Headache</td>
<td>Jellinek (1946)</td>
<td>Lactose</td>
<td>P. O.</td>
<td>22</td>
</tr>
<tr>
<td>Seasickness</td>
<td>Gay and Carlinne (1940)</td>
<td>Lactose</td>
<td>P. O.</td>
<td>22</td>
</tr>
<tr>
<td>Anxiety and tension</td>
<td>Wolf and Pinsky (1954)</td>
<td>Lactose</td>
<td>P. O.</td>
<td>22</td>
</tr>
<tr>
<td>Experimental cough</td>
<td>Hills (1952)</td>
<td>Lactose</td>
<td>P. O.</td>
<td>22</td>
</tr>
</tbody>
</table>

* I. V., intravenous; S. C., subcutaneous; P. O., oral.

**OBJECTIVE EFFECTS OF PLACEBOS**

Abbot, Mack, and Wolf found in 13 experiments with placebos on a subject with a gastric fistula that the gastric acid level decreased in eight experiments, increased in two, and was unchanged in three. Whereas, in a second group of 13 experiments with no agent used, the gastric acid level increased in one case, decreased in 4, and remained the same in 8. The gastric acid level fell apparently about twice as often when a placebo was used as when no agent was administered. In the section above on toxic effects, reference was made to the patients of Wolf and Pinsky who developed objective toxic signs following placebo administration: palpitation, erythematous rash, watery diarrhea, urticaria, and angioneurotic edema. Wolf has pointed out "... placebo effects include objective changes at the end organ which may exceed those attributable to potent pharmacologic action."

During work with narcotics, Keats and I observed that 7 subjects out of 15, or 47%, were recorded as having constricted pupils, believed at the time (using "unknowns" technique) to be a drug effect, although later it was found that a placebo had been used. Even though this observed effect possibly might not have been related to the placebo administration in this case, it illustrates the kind of error that can get into uncontrolled drug experiments.

Cleghorn, Graham, Campbell, Rublee, Elliott, and Safran studied the adrenal cortex in psychoneurotic patients where anxiety requiring hospitalization was the most prominent feature. They found that a placebo (isotonic sodium chloride) injection produced a response in patients with severe anxiety similar to that given by corticotropin (ACTH) in normal patients. (As criteria of adrenal cortical activity they used the following indexes: increase in circulating neutrophils, decrease in lymphocytes, decrease in eosinophils, increase in the ratio of uric acid to creatinine. And more recently they
have added: potassium, sodium, 17-ketosteroids, and neutral reducing lipids determinations.) The amount of change was recorded in several types of experiments on normals (labeled O) as well as on patients. The patients have been divided arbitrarily into three categories, mild effect (labeled \( \frac{1}{2} \)), moderate (labeled 1), marked (labeled 2) and the numerical range limits for these groups set down. The label numbers in a given case were added together to give a composite index of adrenal cortical activity. Normal subjects who received a small dose of corticotropin always reacted more than the \( \frac{1}{2} \) class; class 1 was the range of change never observed in normal controls but was common in stress and with corticotropin; class 2 presented a degree of change that was unusual for doses of corticotropin not exceeding 25 units. The response increased with the dose of corticotropin. Twenty-five of the subjects received a saline placebo injection. From the data it is evident that the patients with the severest anxiety states have a greater disturbance of their adrenal cortical activity by the placebo than is true of patients with less anxiety.

These objective changes show that placebos can set off the adrenals and mimic drug action. They also show that the severer the disease state the greater is their effect. (This is in line with our long-standing thesis that, for sound information concerning the effectiveness of certain drugs designed to alter subjective responses ordinarily arising in disease, it is sounder than otherwise to go to the pathological situation for answers as to drug effectiveness.)

In work in progress I have found strong evidence that placebos are far more effective in relieving a stressful situation (early postoperative wound pain) when the stress is severe than when it is less so. Thus subjective and objective (Cleghorn and others) data both support the view of a differential effectiveness of placebos.

**COMMENT**

An interesting discussion of the use of the placebo in therapy was presented by Gold and others in one of the Cornell Conferences on Therapy in 1946. Gold was one of the very earliest investigators to understand the use and significance and importance of the placebo. Not enough attention has been given to his sensible comments over the years. At this particular conference, DuBois commented that, although scarcely mentioned in the literature, placebos are more used than any other class of drugs. He objected to the definition of a placebo as an agent designed to pacify rather than to benefit and held, reasonably enough, that to pacify is to benefit. DuBois recalled that Fantus claimed that the lower the intelligence of the patient the more he is benefited by a placebo. Gold strongly disagreed and provided support for his disagreement. We agree with Gold on the basis of our own evidence. Wolff pointed out that the placebo as a symbol of the doctor's care as effect "I will take care of you." Diepholz suggested that the person reacts to suggestion because what is suggested becomes to him reality. He believes it and consequently the expected result occurs. (In believing, the expected reaction takes place.) Gold made a strong plea for "pure" placebos; i.e., placebos that do not contain any element that could conceivably have a direct effect on the body's cells, otherwise the physician is likely to deceive himself. He comes to believe that these unlikely agents are nevertheless, by virtue of the specific drug included, effective, when really all the power they have is as a placebo.

In studies of severe, steady postoperative wound pain extending over a considerable number of years we have found that rather constantly 30% or more of these individuals get satisfactory pain relief from a placebo. The effectiveness of a placebo does vary in this work as shown in table 2, from one group to another, but is always at an impressively high level, generally above the 30% mentioned. Certainly in these and the other studies shown in table 2 the validity of the thesis presented here (namely, that the placebo can have powerful therapeutic effect) hinges largely on the definition of "satisfactory relief." In each study referred to this has been carefully defined. For example, in our pain work satisfactory relief is defined as "50 per cent or more relief of pain" at two checked intervals, 45 and 90 minutes after administration of the agent. (This is a reproducible judgment patients find easy to make.) Each author has been explicit, and some have required even greater success than indicated above. For example, Gay and Carliner (1949) required, for a positive effect, complete relief of seasickness within 30 minutes of administration of the placebo. The important point here is that in each of these representative studies, patients and observers alike, working with unknowns (usually "double blind" technique) have concluded that a real therapeutic effect has occurred. The implication of this for an uncontrolled study is clear.

The constancy of the placebo effect (35.2 ± 2.2%) as indicated by the small standard error of the mean in a fairly wide variety of conditions, including pain, nausea, and mood changes, suggests that a fundamental mechanism in common is operating in these several cases, one that surely deserves further study.

With placebos having an average high effectiveness of 35% (table 2) in the variety of conditions dealt with here, it should be apparent that "clinical impression" is hardly a dependable source of information without the essential safeguards of the double unknowns technique, the use of placebos also as unknowns, randomization of administration, the use of correlated data (all agents are studied in the same patients), and mathematical validation of any supposed differences. These safeguards are essential when matters of judgment enter into decision. Many "effective" drugs have power only a little greater than that of a placebo. To separate out even fairly great true effects above those of a placebo is manifestly difficult to impossible on the basis of clinical impression. Many a drug has been extolled on the basis of clinical impression when the only power it had was that of a placebo.

Not only does the use (and study) of placebos offer much of practical value, but it is important to recognize that use of this tool promises to give access to an understanding of certain basic problems of mechanism of action of narcotics and other agents that modify subjective responses. A detailed discussion has been given else-

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where of the two phases of suffering: the original pain sensation, for example, and then the reaction to it or the processing of it by the central nervous system. The evidence for the importance of the reaction phase as the site of drug action has been assembled, and in that account the effectiveness of placebos stands as one of the principal supports of the concept. We can learn still more from placebos along this line. Consider the following statement: If, against all of the evidence to the contrary, one were to hold the view that the placebo is a feeble or useless therapeutic agent, then the placebo should appear most effective when the test condition is mild and less effective when pitted against severe conditions. There are two kinds of evidence, subjective and objective, referred to above, that just the opposite is the case: placebos are most effective when the stress (anxiety or pain, for example) is greatest.

Two other views fit well with these findings. For some years we have held to the working hypothesis that subjective responses must be studied in man where they arise in pathology, that they cannot be usefully contrived experimentally in man. There is considerable factual evidence to support this view. We believe the reason for this is that in pathology the significance, the reaction, is greatest and of a kind and degree that cannot adequately be produced experimentally. Where the significance is greatest, one can expect the greatest reaction, the greatest (more extensive) processing of the original sensations, and, in a parallel way, the greatest response to therapy both of "active" drugs (like morphine) and of placebos insofar as they act on the reaction phase. This may explain why morphine fails to block the experimental pain of the Hardy-Wolff procedures. The greater effectiveness of the placebo where the stress and reaction are greatest, taking into account that the placebo can only act on the reaction facet, supports the view that placebos being chiefly effective as indicated when there is great significance, great reaction, do indeed act by altering the reaction.

Placebos provide an opportunity for attacking problems not possible of study with specifically effective drugs (like morphine on pain), since with these drugs one can never be sure that the original sensation was not altered by drug action. The placebo effect of active drugs is masked by their active effects. The power attributed to morphine is then presumably a placebo effect plus its drug effect. The total "drug" effect is equal to its "active" effect plus its placebo effect: 75% of a group in severe postoperative pain are satisfactorily relieved by a large dose of morphine (15 mg. of the salt per 70 kg. of body weight), but 35% are relieved by the placebo.

SUMMARY AND CONCLUSIONS

It is evident that placebos have a high degree of therapeutic effectiveness in treating subjective responses, decided improvement, interpreted under the unknowns technique as a real therapeutic effect, being produced in 35.2 ± 2.2% of cases. This is shown in over 1,000 patients in 15 studies covering a wide variety of areas: wound pain, the pain of angina pectoris, headache, nausea, phenomena related to cough and to drug-induced mood changes, anxiety and tension, and finally the common cold, a wide spread of human ailments where subjective factors enter. The relative constancy of the placebo effect over a fairly wide assortment of subjective responses suggests that a fundamental mechanism in common is operating, one that deserves more study. The evidence is that placebos are most effective when the stress is greatest. This supports the concept of the reaction phase as an important site of drug action.

Placebos have not only remarkable therapeutic power but also toxic effects. These are both subjective and objective. The reaction (psychological) component of suffering has power to produce gross physical change. It is plain not only that therapeutic power of a drug under study must in most cases be hedged about by the controls described below but also that studies of side-effects must be subjected to the same controls.

When subjective responses, symptoms, are under study, it is apparent that the high order of effectiveness of placebos must be recognized. Clearly, arbitrary criteria of effectiveness of a drug must be set up. Preservation of sound judgment both in the laboratory and in the clinic requires the use of the "double blind" technique, where neither the subject nor the observer is aware of what agent was used or indeed when it was used. This latter requirement is made possible by the insertion of a placebo, also as an unknown, into the plan of study. A standard of reference should be employed for comparison with new agents or techniques. Randomization of administration of the agents tested is important. The use of correlated data (the agents compared are tested in the same patients) is essential if modest numbers are to be worked with. Mathematical validation of observed difference is often necessary. Whenever judgment is a component of appraisal of a drug or a technique, and this is often the case, conscious or unconscious bias must be eliminated by the procedures just mentioned. These requirements have been discussed in detail elsewhere.


Machine Age Overtakes Medicine.—As year succeeds year, some new physical or chemical technic and some new and elaborate machine are applied to the study of disease; great claims are always made for the precision of the answers yielded by these technics and machines. One of the greatest struggles that a practicing doctor has is to keep up-to-date with advances of this kind. No sooner has he mastered one than another is upon him. Moreover, the machines or technics are often so complex that he cannot understand them. He has to take what they tell him on trust. . . . There is a growing tendency for doctors to rely on the information given by such technics and machines in preference to the information which they gain themselves from the history and physical signs. I am extremely doubtful if this is in the interests of good doctoring, and for three reasons. First, the errors and limitations of these new technics are not at first appreciated. . . . Second, a thorough clinical examination, which will be carried out only by doctors who appreciate its worth, is the best method of establishing that spirit of mutual understanding and good will which is the core of the doctor-patient relationship. Finally, to rely on data, the nature of which one does not understand, is the first step in losing intellectual honesty. The doctor is particularly vulnerable to a loss of this kind, since so much of therapeutics is based on suggestion. And the loss naturally leaves him and his patients the poorer.—G. W. Pickering, M.D., Disorders of Contemporary Society and Their Impact on Medicine, Annals of Internal Medicine, November, 1955.