FURTHER STUDIES ON THE "PHARMACOLOGY" OF PLACEBO ADMINISTRATION [1]

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The effects produced when presumably inert substances (*e.g.,* lactose and saline) are given to normal and diseased individuals are appreciated by many. Few physicians would deny the power of a placebo to influence pain, anxiety, or other "subjective" states in certain individuals; the ability of placebos to affect "objective" phenomena (such as vomiting) or to produce "side effects" of various sorts has also been reported (1–3).

This article is an attempt to describe certain lesser known aspects of the "pharmacology" of the placebo by depicting, in some detail, the ways in which the clinical use of inert substances may lead to effects which are usually considered to be the exclusive property of active agents. Certain implications of the data will be discussed.

METHODS AND RESULTS

Time-effect curve in single dose experiments

One of the basic indices of pharmacologic activity is the time-effect relationship. When an active drug is given to patients, a maximal effect is typically achieved at a certain point in time. It is not widely appreciated that placebos can also show this behavior.

In Figure 1 are plotted some data obtained in a study of the effects of aspirin or a placebo on postpartum pain. One hundred and twenty-eight patients were studied in an obstetrical ward during the five day period following delivery. Identical appearing capsules were administered at random to any patient requesting medication for pain. All patients were interviewed by the same technician under double blind conditions immediately prior to medication, and at stated intervals after medication, and asked how bad their pain was. Four arbitrary pain categories were used; "very severe," "severe," "moderate," and "slight," plus another category for "no pain." Data were obtained at one-half, one, two, and three hours after medication. The average pain relief scores were obtained as follows: Each patient was given a pain relief score for each interview after medication. If a patient described no relief at all at a given interview, a score of zero was recorded; if a decrease in pain was reported, a score of one, two, three or four was given, depending on the degree of relief reported. Thus, a change from "very severe" to "severe," or from "severe" to "moderate," or from "slight" to "no pain" counted as "one"; a change from "very severe" to "moderate," "severe" to "slight," or "moderate" to "no pain" counted as "two," and so forth. The sum of scores for all patients at a given interview point was then divided by the number of patients to give a mean pain relief score for the one-half hour point, the hour point, and so forth. These data are plotted in Figure 1. The general similarity in the shape of the curves for those patients receiving aspirin and for those receiving placebo is evident, although the two treatments differ considerably in efficacy. A total pain relief score was obtained for each subject by adding the relief scores at each interview point. A mean total pain relief score was then calculated by averaging all such scores for each drug. The mean total pain relief score for aspirin over the first three hours after medication was 5.91 with a standard error of 0.35; for placebo, 3.45 plus or minus 0.44. This difference is significant at the 0.01 level. In analyzing the placebo curve to see whether there was indeed changing efficacy with time, a two-tailed sign-test (4) was applied to the 23 patients who showed different degrees of relief at the one-half hour and one hour points. Of these, 20 showed a greater degree of relief at the one hour point than

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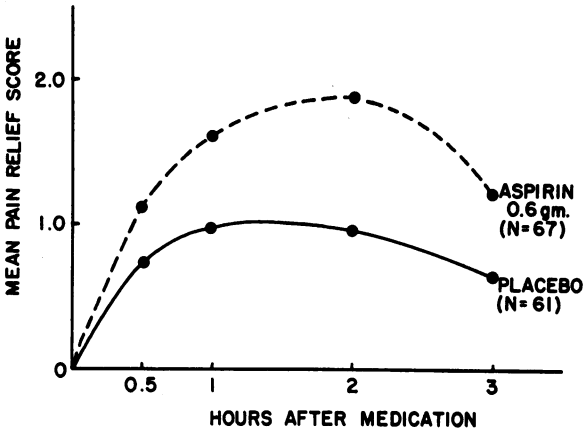

FIG. 1. MEAN PAIN RELIEF SCORES AFTER PLACEBO OR ASPIRIN IN PATIENTS SUFFERING FROM POSTPARTUM PAIN

at the half-hour interview, a difference significant at the 0.01 level. Although the mean score for placebo relief is somewhat lower at three hours than at one hour, this difference is not statistically significant.

"Cumulative" effects of placebos

A second basic type of pharmacologic study is the delineation of the effect of repeated doses of a drug. This is often considered to be a reflection of increasing concentration of drug in the blood or body. It is not generally appreciated that placebos can also show a "build-up" in effect, and that there may be a "carry-over" after cessation of placebo therapy.

Presented in Figures 2 and 3 are the data from two separate experiments. In one experiment, 34 patients suffering from tuberculosis, and on anti-tuberculosis drugs, were given a yellow tablet daily for seven days, having been told that the tablets would increase their "appetite" and improve their "pep and energy." [2] They were asked to indicate their status each day on sheets, as shown in Table I. For four days after medication was stopped, additional observations were made. The results, shown in Figure 2, indicate that the placebo therapy was associated with gradual rises in subjective reports of both appetite and pep. The levels achieved were maintained after cessation of placebos. In order to provide a baseline against which the reliability of the changes could be tested, the nine ratings before placebos were begun were averaged. A comparison of the mean of the first three ratings made under placebo with this baseline showed a rise in appetite scores from 2.51 to 2.93, which was statistically significant at the 0.01 level [sign-test, two-tailed (4)]. For pep the change was from 2.72 to 2.91. This change was not statistically significant. For both variables the curves continued to rise, however, as the placebo therapy continued. Appetite rose from 2.93 to 3.45 and pep from 2.91 to 3.34, if the means of the first three days' ratings on placebo are compared with those of the last three of the placebo therapy. Both of these changes are significant at the 0.01 level. The curves did not drop following the end of placebo therapy, the rating four days later being 3.53 for appetite, 3.50 for pep.

Figure 3 illustrates similar data on a population of 31 hospitalized patients suffering from various chronic illnesses. Here there was a short pre-placebo period of three days, a placebo period of six days, and a post-placebo period of two weeks. (There was, however, a lapse of five days during the post-placebo period when no interview data were obtained.) Once again there appears to be a cumulative beneficial effect over the period of placebo administration, with a partial return to pre-placebo status in the case of "pep" two weeks after stopping placebos. The mean ratings for the pre-placebo period were 3.05 for

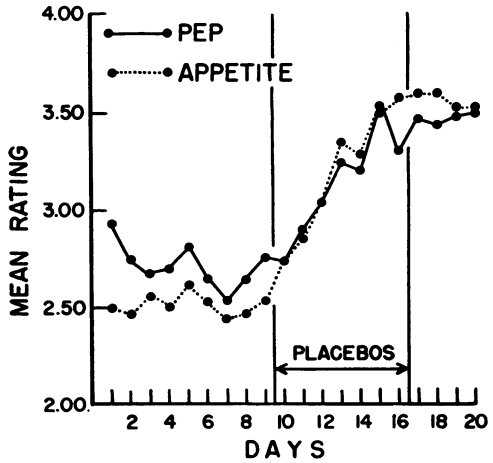

FIG. 2. PEP AND APPETITE RATINGS IN 34 TUBERCULOUS PATIENTS TREATED WITH PLACEBO

[2] It should be emphasized that the responses dealt with here are *verbal reports*. The extent, *e.g.*, to which food intake would have been correlated with "appetite" is an interesting but different question.

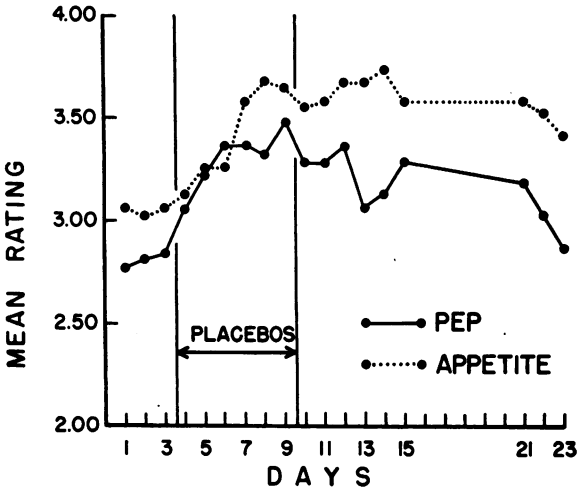

FIG. 3. PEP AND APPETITE RATINGS IN 31 PATIENTS HOSPITALIZED FOR VARIOUS CHRONIC DISEASES AND TREATED WITH PLACEBO

appetite and 2.78 for pep. Both rose to a mean of 3.22 for the first three days on placebo. Sign tests showed that only the change for pep was significant ($p < 0.01$). The ratings rose further to means of 3.63 and 3.39 for appetite and pep, respectively, for the last days of placebo therapy. The increase for appetite is statistically significant at the 0.01 level. As in the first study, the ratings remained at substantially the same levels after placebos were withdrawn. The mean ratings over the next six days were 3.64 for appetite and 3.24 for pep. Two weeks after the stopping of placebos, pep had shown a decrease to a mean of 3.03 for the last three ratings available. This drop differs significantly from the 3.39 of the last three days on placebo. The ratings for appetite did not show such a decrease, with a mean for the last three days of 3.51.

Effectiveness of placebos in relation to severity of disease

Another general characteristic of drugs is the inverse relationship of their efficacy to the severity of a given complaint. The same relationship for placebos has been apparent in some of our own data. In a study on the efficacy of morphine and injected saline on postoperative pain (2), an inverse relationship existed between the number of doses of medication required postoperatively and the efficacy of morphine or placebo (see Table II).

TABLE I

Questionnaire

A) How is your appetite today? (Check one of the following)
   1. No appetite at all
   2. Poor appetite
   3. Fair appetite
   4. Good appetite
   5. Very good appetite

B) How is your pep and energy today? (Check one of the following)
   1. No pep or energy at all
   2. Very little pep or energy
   3. Fair pep and energy
   4. Good pep and energy
   5. Very good pep and energy

If the average severity of pain of a group of patients can be gauged by the ability of a given dose of morphine to relieve their pain, it would appear that the patients requiring the largest number of doses of medication had more severe pain and were less relieved by morphine and placebo. In any case, there is an interesting parallelism between the performance of morphine and the performance of placebo.

Figure 4 also bears on this point. These data were collected in the previously described postpartum study, and are a breakdown of the data on complete relief of pain observed after placebo into those observations collected on patients describing their pain initially as "very severe" or "severe" as contrasted with those obtained on patients with pain initially described as "slight" or "moderate." The percentage of patients reporting complete relief of pain at any given time after medication is higher in the case of the "slight-moderate" group than in the "very severe-severe"

TABLE II

*Pain relief with morphine or placebo in patients suffering from postoperative pain**

Group	No. of Pts.	Morphine	Placebo
I (2 doses/pt.)	12	92%	58%
II (4 doses/pt.)	21	75%	40%
III (6 doses/pt.)	15	61%	40%
IV (8 or more doses/pt.)	15	58%	15%

* The patients are stratified according to number of doses of medication required during entire postoperative period.

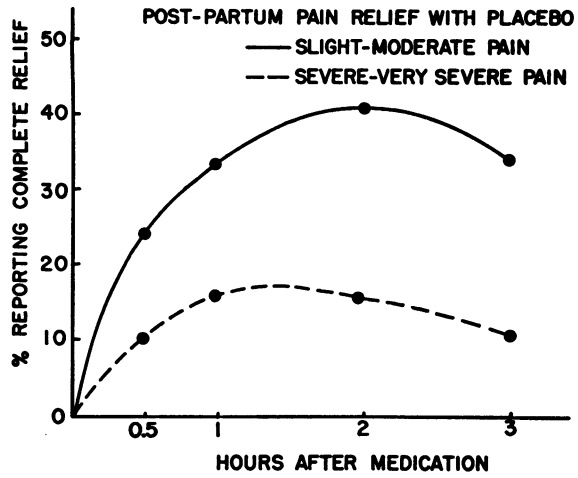

FIG. 4. RELATIONSHIP BETWEEN REPORTED SEVERITY OF PAIN AND ANALGESIC EFFICACY OF PLACEBO

group. The percentage of patients reporting complete relief of pain at some time during the three hour interval post-placebo was 21 per cent in the case of the "very severe-severe" group (n = 19), and 57 per cent in the case of the "slight-moderate" group (n = 42). This difference is significant at the 0.01 level. These data seem most easily interpreted as a less effective handling of the greater therapeutic challenge by placebo. The aspirin data from this study have been similarly analyzed and also indicate a similar lessened efficacy in patients with greater pain.

DISCUSSION

There are certain implications in these data. First of all, uncontrolled studies that claim a new or old drug to have shown unequivocal therapeutic benefit, merely because of "peak effects" or "cumulative effects" or persistent benefit after cessation of treatment, must be interpreted with considerable caution. A placebo effect is obviously not an "all or none" phenomenon, and such effects are not necessarily turned off or on, like an electric light bulb. Secondly, the time-effect relationships of placebo phenomena may be extremely important in deciding upon the times when data are to be collected in controlled trials. It is conceivable, for example, that in a certain situation the effects of suggestion are rapidly obtained, but also wear off fairly rapidly. In another situation the effects may require longer to wear off (5). A failure to collect data at points other than the placebo "peak" may give a misleading notion about the efficacy of an active drug being compared against placebo. Thirdly, it appears likely [as suggested in an earlier paper (2)] that the use of patients presenting severe therapeutic challenges may, at least on occasion, render placebo controls less necessary or less important.

Several questions are raised by the data presented. How can one explain the "cumulative effects" experienced by the patients receiving placebos? At times, patients interviewed on the first few days on placebos volunteered the information that, "You know, it takes a while for these drugs to take hold, Doc." The desire not to "disappoint" a doctor who is presumably eager for the patient to show improvement may increase progressively with the passage of time, as may the degree of reinforcement for a patient who feels that a "correct" answer (*i.e.*, improvement) will result in the doctor taking a greater interest in him.

In regard to the "carry-over" described, we can only speculate. One possibility is that patients who are improved on placebos may feel (at least temporarily) that the placebo has achieved a "cure" and that further medication is not needed. It must be difficult for a patient to believe that a doctor who had observed significant benefit in a patient from the administration of a small pill would stop or withhold such a pill if a continued need existed. One might also interpret the placebo reaction in terms of simple learning theory. Typically, in learning experiments, the abrupt withdrawal of the cue for response (here the administration of pills) is not followed by immediate cessation of response. Instead, one usually sees a gradual and irregular decline. It would be of great interest to see studies of the effectiveness of prolonged placebo therapy in various clinical situations.

It is evident that these studies give no proof that the results described were *caused* by the placebos, and would not have occurred in the absence of their administration. In regard to the pertinence of the data in recommending caution in uncontrolled experiments, such demonstration is not necessary, of course. Nevertheless, it seems unlikely that such data as presented in Figures 2 and 3, with similar curves in different populations, are really due to chance improvement unrelated

to the giving of placebos. These groups were chosen because of the relative stability of their surroundings and their illness at the time of our studies.

These data on severity of complaint and placebo efficacy are somewhat at variance with those reported by Beecher (6), who found that patients studied early in the postoperative period (where pain is presumably more severe than later) are handled almost as well by placebo as by morphine, whereas later in the postoperative course morphine performs much better than placebo. The results were interpreted as showing that placebos work most effectively when the stress is greater. However, it is of interest that Keats has found (in similar patients studied by a similar technique) placebo and morphine yielding pain relief in 27 per cent and 60 per cent, respectively, of patients early in the postoperative course, and 55 per cent and 80 per cent, respectively, late in the postoperative course (7). Keats' findings are thus in agreement with those in the present report.

SUMMARY

Data are presented to indicate that subjective responses to placebos can mimic certain characteristics of "active" drugs, such as "peak effects," "cumulative effects," "carry-over effects," and varying efficacy depending on the severity of the complaint being treated. Certain implications of these facts are discussed.

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