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Factors Contributing to Unexpected Reactions in two Human Drug-Placebo Experiments¹

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In the experimental investigation of a drug, the administration of a placebo is an attempt to deal with psychological phenomena associated with the taking of medicines. The effects common to both drug and placebo subjects are subtracted, so to speak, from the total effect, in order to isolate the supposed drug action (see, for instance, BEECHER [1955], HAAS *et al.* [1959], KURLAND [1960]).

It is not with the experimental prudence of this measure with which we will deal in this discussion, but with the explanations offered for the occurrence of placebo reactions. Of several broad alternative explanations, we have chosen to develop one in discussing the case history of two subjects who showed rather clear effects. To anticipate the discussion somewhat, we have viewed the reactions of our subjects primarily in cognitive terms: as the efforts of a complex information-processing organism to come to terms with comparatively complex sources of information. We believe that the development of this construction is a fruitful contribution to the placebo problem.

Procedures

The subjects, two healthy males of 34 and 37 years of age, had been observers in a visual acuity test over a period of several weeks. At weekly intervals, certain drugs were administered; the subjects knew that they would receive either a placebo or one of several drugs, including one of several "psychotomimetic" drugs. Both had had psychological training and had read of the latter drugs or observed other subjects who had been given them. Neither had taken such drugs

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before. The episodes of interest occurred on the two occasions when one of the subjects was given d-lysergic acid diethylamide (LSD 25)³ while the other received a placebo.

At the time of the first LSD 25 experiment both subjects had been administered, on two previous occasions, 15 and 30 mg d-amphetamine sulfate; both had accurately recognized the drug effects and distinguished the drug from placebo.

The visual task under investigation at the time was the recognition of the orientation of a thin opaque line on a blank, uniformly illuminated circular screen (REED [1963]). The subjects knew that the line had been placed in one of six orientations determined by the experimenter's throw of a die. Each subject was required to guess or to report the position of the line as the screen was brought closer to him in prescribed stops.

All procedures took place in a virtually dark room to which the subjects had adapted for visual testing. They each acted sometimes as experimenter and sometimes as observer in the visual experiments and, on occasions of drug administration, were able to communicate with each other and with the administrator of the drug.

The person who administered the drug stayed with the subjects, taking notes of their conversation and recording his own observations. From time to time he asked whether the subjects felt anything unusual or whether they thought they had received a drug. In the case of the LSD 25 experiments, an additional observer was brought into the experimental room at one point; he was asked to observe the subjects and surmise which substance each had received.

On the day following all drug experiments, and before discussing the experiment retrospectively, the subjects were required to write a summary of the experience of the preceding day and to make a further judgment about the nature of the substance given to them.

Observations and Reports of the Subjects

Experiment 1

Subject A received 0.1 mg LSD 25 in 10 ml distilled water by mouth, subject B received simultaneously 1 mg quinine in 10 ml distilled water by mouth.

³ We are grateful to Dr. RUDOLF BIRCHER from Sandoz Pharmaceuticals for giving us samples of the drug.

Extract from observer's report on subject A:

After 85 minutes A reports "I have been so occupied with nausea, a most unpleasant feeling. With eyes closed I see a shimmering membrane like looking through the wings of a dragon fly. With eyes open I make errors of judgment, all perceptions are accurate, no images interfere. I enjoy it not." His voice drifts off, becomes unintelligible... laughter. An unsteady gait can be observed. After 4 hours and 28 minutes, following 100 minutes of rest, he reports very lively dreams like: "T. came in and after you had remarked yesterday that he looked ill he looked to me so terribly ill and... I dreamt of a ball, all were dancing, all were animals, rather piggish." Rambled on rather incoherently. "The drug is wearing off but there are still effects, I feel rather maudlin, sentimental. I see my grandmother's hands."

Extract from observer's report on subject B:

After 15 minutes B reports that he feels very relaxed. After 85 minutes "I feel quite detached from the rest of the place here, quite relaxed, a little bit shaky and jittery, but otherwise nothing." "The images appear in quite burning colours, almost an explosion, purple is floating around in my visual field, some quite distinct images of people". "If I close my eyes for a time it is much more, my coordination is off, speaking is only very slowly, I can't seem to hear myself clearly". An unsteady gait was observed. After 4 hours and 47 minutes B reports: "Right now I feel extremely relaxed, somewhat detached, things are not quite real to me as if I had taken a nap, it is not unpleasant, I think you have a weekly patient in me for your drug". "I don't see anything special at the present time, everything is slightly changed. I was impressed by the brightness of things, the distortion of distant objects, they seemed much farther away, things are distorted in space". "I was aware that things were there but not in the right position". "A lot of strange shapes and brilliant colour, after images, as if I looked through pebble finished glass, particularly this morning. Especially this morning colours were more brilliant than I have ever experienced." "Voices were at times somewhat in the distance along with a feeling of not being in a real situation, a dream kind of state, time is distorted, goes rather slowly, an hour is only 10 or 15 minutes when I look at my watch". Laughter.

From observer's report on A and B:

After 5 hours and 30 minutes the observer asked each subject whether he believed that he got the same drug as the other and, assuming that they had the same drug, whether one had a higher dose than the other. The answer from both, after having weighed evidence for and against the same drug, was that they did not know. However, both agreed that they had no evidence that one got a higher dose than the other.

About one hour and a half after application of the drug a second observer stayed for several minutes with the two subjects in the dark room. When he came out and was informed by the first observer that only one subject had received the drug, he showed great surprise and was not sure which one had had the drug.

Extract from subject A's report:

I first noticed some effects of the drug after what seemed about 15 to 20 minutes. We had set me up in the phoropter and I was trying to concentrate on the test, but found it increasingly more difficult to do so... Sitting there on the floor I began to have those thoughts which I'd heard about, and which I had always taken as misevaluations of one's own thinking. On the basis of some fleeting experience, an epigrammatic summary would pop into my head. For instance, it seemed to me a rather profound thought that men invents things by thinking, and gets into trouble because of his inventions. He is always inventing something new, both to his advantage and to his distress... I was now in a dreamlike state in which it was very difficult to keep my eyes open... Colours outside the room seemed more brilliant, but not strikingly so. I had been in semidarkness for a long time. The walk downstairs was difficult. The motion of my walking changed the image of the stairs, the corridor and floors as I passed... In a kind of half-sleep dreaming lying on my couch downstairs, I began a period of emotional, sentimental thinking. At first I had a series of dreams which all became progressively ridiculous, and I was surprised awake to hear myself laughing. One of the dreams was a gold and white ball-room in which animals in eighteenth century costumes danced. The fat bulges of pigs showed through silk stockings... People who had come in during this time struck me strangely. I was aware of signs of aging in their faces. I thought that there must be a time when men

come to look like their fathers, or rather like their fathers were as mature old men... I couldn't move or write smoothly. I was uncertain of my judgment and noticed that time relations seemed intact until I took some active part in events.

Subject B's report:

Within two to three minutes of ingestion there appeared a subjective feeling of warmth, a feeling of slight rise in body temperature, which passed within a minute or so. At 10 minutes there began a feeling of lightheadedness similar in quality to medium alcohol intoxication which lasted in essentially the same degree for 6 to 8 hours after the administration of the drug. Accompanying the feeling of lightheadedness was a pronounced nausea and general stomach discomfort which lasted for about one hour with fluctuations from mild to quite severe. Attention was particularly difficult to maintain during the first hour after administration, and coordination seemed to be impaired (difficulty in writing, manipulating equipment, moving about in general). From one to two hours after administration of the drug there was a period of "shakeyness" and weakness with mild chills and general malaise. During the second hour, there were observed a series of vivid after-image-like illusions with the eyes closed. These images were not related to previously observed objects (as in a true after-image) but consisted of an array of very beautiful coloured displays in blues and purples which seemed to fill the entire visual field and were quite long in duration (several minutes). During this second hour in particular, and generally for the first 6 hours after administration, there was a strong tendency to doze or nap and during these "naps" quite vivid dreams were experienced such as conversations with individuals, progressions of faces and thoughts of past events. During the third hour after administration no physical discomfort persisted and it was possible to eat lunch with no adverse effects. From this period of time through the remainder of the first 12 hours there was little or no change in the sensations perceived. During this time there were feelings of mild to medium strong intoxication, slowed judgment, and a sleepiness which led to a rather pleasant lethargic state when not resisted. For 12 to 24 hours stomach cramps, accompanied by headache and restlessness were evident (not like alcoholic "letdown"). These feelings were accompanied by feeling of gen-

eral fatigue and some tension (musculature) and restlessness. In summary: After the initial feeling of general physical illness had passed (within the first hour) there were feelings of living in a "just awakened" or semi-dreamlike state, where things often did not seem as if they were really happening. Visual stimulation seemed overly intense at times. Judgment and concern over one's activities were generally impaired (such as realization of slowed speech without any concern over it, and poor judgment of distances, and size of objects).

Subject A found the visual task extremely difficult to perform. The few trials in which measurements were taken do not permit a clear inference about the level of performance. Subject B achieved his usual level of visual acuity.

Experiment 2

The same subjects as in experiment one were used in experiment two. The experiment was performed one week later and both had been informed about the medication they had received a week earlier. Subject A received now 10 ml distilled water containing two drops of acetic acid and subject B received 10 ml distilled water containing 0.1 mg LSD 25 by mouth.

Extract from observer's report on both subjects:

After 15 minutes, 30 minutes, 40 minutes and one hour 23 minutes both subjects volunteered or answered on inquiry that they did not feel anything out of the ordinary. After 4 hours subject A reported on questioning that he felt rather tired, but not more than normal. "I guess I got a drug because the display seemed different, there were not as many illusory lines, I was kind of subdued, did poorly, but that is not unusual". Subject B reported that "he felt normal in almost every respect". During the following hours both subjects stated repeatedly that they felt a little tired, but not unusually so.

Both performed the visual task at accustomed level of proficiency.

Subject A's report:

Apart from a slight fatigue noted between 11 and 12 o'clock there was no marked effect of the drug and a note I made on my calendar

says that the fatigue was lessening. When S. ran me for his experiment, I slept during part of the music... During the night I slept well in contrast to every other occasion when I have had a drug.

Subject B's report:

no effect—just extreme fatigue.

Discussion

It seems a fair summary of events to say that in experiment 1 both subjects showed effects characteristic for LSD 25 (though only A had received the drug), while in experiment 2 neither showed the characteristic LSD 25 effects despite the fact that subject B had received the drug in an usually highly effective dose (ISBELL *et al.* [1956]).

What interpretation of these results is to be made? There seem to be several broad categories.

The first interpretation would seek explanation in variation in the bodily chemical milieu. It is known, for instance, that by producing anticipatory fear, a significant rise in blood free fatty acids and other metabolic products can be stimulated (see for example in MALLOV and WITT [1961]). A drug introduced into the body at such a time would encounter a changed chemical milieu in which its reaction would be altered. Explanation along such lines might be of assistance as a possible clue to subject B's failure to exhibit LSD 25 effects in experiment 2; one could hypothesize a transient or enduring resistance to the drug, rendering it ineffective. However, the interpretation is less helpful in accounting for his behavior in experiment 1, unless one were to surmise the presence of a concurrent fatigue, illness or other bodily state. It is also made less likely through the results of the preceding d-amphetamine experiments: here, in a comparable psychological and metabolic situation, drug and placebo effects could clearly be distinguished in both subjects.

A second set of alternatives is less helpful. This interpretation would attribute the appearance of placebo effects to "suggestibility" or to a personality idiosyncrasy of the subject. Since the basis and the justification for each such inference lies in the same set of phenomena, the explanation is circular: The subject is "suggestible" because he manifests a drug effect in the absence of a drug, and the appearance of the effect is attributed to the characteristic of being "suggestible".

The ad hoc nature of such an explanation is made apparent by considering the failure of LSD 25 effects to appear in experiment 2; it would be necessary to imagine the subject as being suggestible to the non-appearance of drug effects. ASCH [1952] has analyzed experiments on suggestion in terms which we will find useful later in the discussion.

While there are doubtless individual differences in responses, to attribute these differences to "personality differences" seems simply to rename the phenomena. Our two subjects might be distinguished from each other in multitudinous ways; even preliminary attempts at explanation require more precise identification of the pertinent variables than an indication that they are to be located in that catalogue of differences.

There seems to us to be merit in reminding ourselves that the human subject in a drug experiment is an active information-gathering and information-processing organism. It has been observed that placebo effects are dependent upon the relationship between experimenter and subject and that they are consequences of (perhaps subconscious) expectations and anticipations (HEIMANN [1963]). It is interesting that a similar proposal has been made for hypnosis (BARBER [1961], ORNE [1962]). We will adopt this tradition of analysis to the extent that it refers to a perceiver possessing hypotheses and expectations, and evaluating sources of information for news to guide his conduct.

Consider the condition of subject B in experiment 1. He is aware that subject A is experiencing something other than the drug effects previously encountered, and knows that a hallucinogenic drug might have been given to one or both subjects. He is asked whether he feels or notices anything, and is required to examine his perceptual field for potentially observable events. He will weight certain events more than he would ordinarily, both because they might assist in anticipating the appearance of effects and because the subject intends to comply with the experimenter's implicit requirement to omit no significant detail. Imagery and bodily states not ordinarily given attention may now be brought into awareness. Subject B's report in experiment 1 falls into this category, including the visual imagery. The imagery occurs in fact when eyes are closed, a circumstance under which a suitably attentive subject would become aware of entoptic phenomena.

Beyond the matter of bringing potentially available data into awareness lies the possibility that the search for such data produces its own imagery. Just such a phenomenon occurs in the visual task

employed in the experiment. As has been previously reported (REED [1963]), practiced subjects in this task have observed the appearance of an image of the line in several positions on the face of the screen. The appearance of this hallucinatory line seems to require knowledge of the object of search, and may represent an attempt to match some sort of central representation of that object to the minimal data being received. We may speculate whether this experimental visual phenomenon has its counterparts in other visual search tasks and in the interpretation of sensory data generally. If this phenomenon is a paradigm for subject B's experience, we may interpret his reports of vivid imagery as consequences of his search for some sort of definite data. As a matter of fact his report being formal and without specific content, suggests just this in contrast to the report of subject A. This seems less a matter of verbal habit than a reflection of the different tasks confronting the two subjects.

There are not only competing messages from the sensory systems, but there is "noise" in the sensory apparatus. The manner in which a signal is extracted from the several sources of noise is complex and subject to error. Modern psychophysical experiment has shown that the probability of occurrence of a signal and the relative importance of false negative and false positive reports are factors in accurate detection of the signal (GALANTER [1962], LUCE [1963]). Even in apparently simple detection tasks, a subject's state of information and motivation enters into his reported experience. Both subjects in the drug experiment were given a task at once vaguer and more complex than the detection of a physical stimulus. They were required to report on the sensory apparatus itself, on the means of getting information. The difficulties of interpretation of subtle events seem compounded in this instance.

Up to this point we have examined information other than that which the subjects got from the reports of other people including each other. ASCH, in his analysis of the concept of suggestion, has pointed out the importance of such sources especially when direct sources of information are limited. For instance SHERIF (see ASCH p. 495) in his studies of the autokinetic phenomenon (the apparent movement of a small stationary light source in a dark room) found an interpersonal effect. While subjects alone in the situation quickly established a relatively constant level of judgment with a consistency sufficient to distinguish their responses from those of other subjects, when pairs

of subjects were consequently brought together their judgments began to converge. ASCH interprets this effect not as a consequence of suggestion but as the reasonable effort of subjects to establish some consensus in their judgments when the available information was severely limited. Similarly, in our experiment, the behavior of the other person is a potential clue to the condition in which the subject finds himself. Subject B, in a dark room with restricted sensory input observing the nausea and early discomfort of subject A, alerts himself to the onset of such symptoms in himself and finds certain bodily states which may be so interpreted.

Finally, a fourth source of information for the subject lies in the record of his immediate and remote history, e.g. in his prior sensitizations or habituations to bodily events. Previous experience may cause a shift in the subject's receptivity to one form of stimulation or another. He may be impelled to review or revise his own experience. The fact that subject B reports his unusual visual images only retrospective in the afternoon points towards the influence of observing A. Such a shift occurs in our experiment 2 also in the embarrassment of subject B in discovering that he was wrong in believing he had received a drug in experiment 1. He was clearly not eager to exaggerate any of his impressions or experiences in subsequent trials. He did not wish to appear foolish. The power of this consideration overriding the expected results of the drug in experiment 2 is impressive. It seems not simply the case that he neglected to tell what he was experiencing: while the performance of the visual task for subject A when drugged was difficult and too brief to obtain clear data, subject B (under drug influence in experiment 2) seemed competent to perform the task at his usual level.

In conclusion, we have proposed an analysis of a placebo effect in terms of the cognitive demands placed upon the subject by the experiment. Rather than the somewhat pejorative assigning of personality idiosyncrasies, such an interpretation recognizes the complex matrix of hypotheses, fears, knowledge and states of adaptation into which the drug or placebo enters as a new datum. Such consideration make comprehensible the hazard in predicting a drug effect in a *single* individual. Our initial surprise at the dramatic effects of the appearance of drug symptoms in a non-drugged subject and the absence of symptoms when he did have the drug yielded to attempts to understand the phenomena.

Summary

An attempt is made to interpret a "drug reaction" in a human subject who received no drug and a "placebo reaction" in a subject who was given LSD 25, by viewing the experiment in cognitive terms. The following are identified as factors which might contribute to the reaction: (a) in the special situation potentially available data are brought into awareness, (b) imagery is produced in the search for anticipated data, (c) the second subject who has actually received the drug supplies data for the placebo reactor, and (d) the past history is used as another important source of information for the present situation.

Zusammenfassung

Die Verfasser versuchen die «Medikament-Reaktion» in einer Versuchsperson, die kein Medikament bekommen hatte und die «Placebo-Reaktion» in einer Versuchsperson, die LSD 25 erhalten hatte dadurch zu deuten, daß sie das Experiment vom erkenntnistheoretischen Gesichtspunkt aus betrachten. Sie finden, daß wahrscheinlich die folgenden Faktoren zu der Reaktion beigetragen haben: a) in der besonderen Situation sind latente Informationen ins Bewußtsein getreten, b) Vorstellungen sind in Erwartung kommender Ereignisse produziert worden, c) die zweite Versuchsperson, die das Medikament erhalten hat, liefert dem Placebo-Reaktor Informationen, und d) die Versuchsperson benutzt vergangene Ereignisse als eine wichtige Informationsquelle für die Beurteilung der gegenwärtigen Situation.

Résumé

Les auteurs essayent d'interpréter la réaction médicamenteuse d'un sujet qui n'avait pas reçu un médicament et la réaction placebo d'un sujet qui avait reçu LSD 25 par examinant l'expérience au point de vue cognitif. Ils trouvent que probablement les facteurs suivants ont contribué à la réaction: a) dans la situation spéciale d'informations latentes sont entrées dans la conscience, b) des images se sont produites en recherche des événements anticipés, c) le deuxième sujet qui a reçu le médicament fourni des informations au réacteur placebo, et d) l'histoire passée est utilisée comme source d'information importante pour la situation présente.

REFERENCES

- ASCH, S.: Social psychology (Prentice Hall, New York 1952).
- BARBER, T.X.: Physiological effects of "hypnosis". *Psychol. Bull.* 58: 390-419 (1961).
- BEECHER, H.K.: The powerful placebo. *J. amer. med. Ass.* 159: 1602-1606 (1955).
- GALANTER, E.: Contemporary psychophysics. *New directions in psychology*, pp. 89-156 (Holt, Rinehart & Winston, 1962).
- HAAS, H.; FINK, H. and HAERTFELDER, G.: Das Placeboproblem. *Progr. drug Res.* 1: 279-454 (1959).
- HEIMANN, H.: *Pharmakopsychologie und Psychiatrie. Akt. Fragen Psychiat. Neurol.*, vol. 1, pp. 295-319 (Karger, Basel/New York 1964).
- ISELL, H.; BELLEVILLE, R.E.; FRASER, H.F.; WIKLER, A. and LOGAN, C.R.: Studies on lysergic acid diethylamide. *Arch. Neurol. Psychiat.* 76: 468-478 (1956).
- KURLAND, A.A.: Placebo effect. *Drugs and behavior* (Wiley, New York 1960).
- LUCE, R.D.: Detection and recognition. *Handbook of mathematical psychology*, pp. 103-189 (Wiley, New York 1963).
- MALLOV, S. and WITT, P.N.: Effect of stress and tranquilization on plasma free fatty acid levels in the rat. *J. Pharmacol.* 132: 126-130 (1961).
- ORNE, M.T.: On the social psychology of the psychological experiment. *Amer. Psychol.* 17: 776-783 (1962).
- REED, C.F.: Illusory images consequent to search in a visual task. *Confin. Psychiat.* 6: 65-70 (1963).

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