

THE PLACEBO RESPONSE

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IN recent controlled trials, conducted by the authors (1956), we were interested to note the proportion of patients improving with the administration of placebos. A placebo is defined in the *Shorter Oxford Dictionary* (1944) as "A medicine given more to please than to benefit the patient". It is presumed that, implicit in this definition, is the qualification that the doctor is aware of the relatively inert qualities of the substance, whilst the patient is not. There is, of course, a type of patient who derives considerable benefit mainly by virtue of the fact that he has been pleased. In spite of the discovery of increasing numbers of drugs with specific properties, the prescription of placebos is still common practice. Dunlop *et al.* (1952) analysed over 17,000 prescriptions of which about one-third were tonics, stomachics or sedatives; although barbiturates cannot strictly be called placebos, the spirit in which they are prescribed frequently puts them near to this category.

The definition in the *American Illustrated Medical Dictionary* (Dorland, 1951)—"An inactive substance or preparation, formerly given to please or gratify a patient, now also used in controlled studies to determine the efficacy of medicinal substances"—is more comprehensive and embraces modern usage. The usefulness of the placebo in controlled therapeutic trials is now generally acknowledged: this is nowhere more true than where psychiatric practice is concerned, because a substantial proportion of emotionally disturbed patients show favourable responses to any therapeutic effort which combines enthusiasm, impressiveness and benevolence. This apparent platitude is justified by a study of psychiatric publications, which will at any time demonstrate how frequently the principle involved is overlooked.

The work of Stewart Wolf and his collaborators (1950) has stimulated a more sophisticated and precise interest in the subject. They performed interesting experiments on the patient Tom, who had a gastric fistula. It was possible to demonstrate by direct observation that the effects of some drugs (Urogastrone, Benadryl, Pyribenzamine and Posterior Pituitary extract) on the gastric function were directly dependent on Tom's emotional state. For instance when Tom was relaxed, administration of Urogastrone caused cessation of gastric function but when Tom was already provoked the same substance increased gastric activity. An injection of sterile water enhanced gastric blood flow. In another experiment a patient suffering from nausea and vomiting of pregnancy (usually associated with flaccidity of the stomach) was given 10 c.c. of syrup of ipecacuanha and told that it would reduce her nausea. This it did and the stomach resumed activity within 20 minutes. The responses with prostigmine were comparable. Tom, too, was given prostigmine, which produced abdominal cramps and diarrhoea; when this was followed by the administration of lactose and tap water the same results were obtained. Wolf's conclusions were that the important factors are the state of the end-organ at the time of administration, the setting (i.e. the route, presence of experimenters, etc.), and conditioning circumstances.

In another paper Stewart Wolf and Pinsky (1954) report their observations on 31 out-patients who acted as their own controls. They were anxious, tense patients, some of whom had psychosomatic complications such as peptic ulcer and migraine. The results with mephenesin tablets and an inert placebo showed that in either case 20–30 per cent. were better, 50–70 per cent. unchanged and 10–20 per cent. worse. More surprising was the fact that minor side-reactions such as light-headedness, drowsiness and anorexia occurred frequently with both mephenesin and placebo and in three cases there were major reactions. Administration both of mephenesin and placebo was followed in one case by overwhelming palpitations, weakness and nausea, in another by a diffuse erythematous rash and in a third by epigastric pain, watery diarrhoea, urticaria and angioneurotic oedema. Other interesting examples of placebo responses are quoted by the authors.

The concept of the “placebo reactor” (Beecher *et al.*, 1953; Lasagna *et al.*, 1954) is a useful one and has carried enquiry a stage further. Lasagna and his collaborators studied 162 patients who had undergone surgical operations. They devised a method of studying the effects of morphine and of saline on post-operative pain. In this way they were able to differentiate between “placebo reactors” and “non-reactors”. The reactors were on the whole five years older but there was no sex differentiation. Reactors on the whole tended to be more expansive, co-operative and uncomplaining; they were more regular Church-goers, had less formal education, and their reactions to stress were more readily translated into somatic form.

In a controlled clinical trial comparing the effects of carbon dioxide treatment with inhalation of compressed air, the authors (1956) found that about 50 per cent. of patients improved irrespective of whether they had carbon dioxide or the inert substance. Similarly in a controlled trial (1956) comparing the effects of intravenous acetyl choline and sterile water, about 60 per cent. of the patients improved, again irrespective of whether the pharmacologically active or inert substance was administered. The slightly better results in the latter trial are probably explained by more discriminating case selection, as judged by premorbid personalities and the duration and phasic quality of the illness.

The patients used as controls received substances which are unquestionably inert and we regard those deriving benefit as placebo reactors. Since no difference could be shown between results in the treated and control series, it seems reasonable to believe that cases responding to “treatment” were also showing a placebo response.

In the combined control series there are 43 patients in all. One of these gave up treatment at an early stage and another was worse after treatment. Some of the features of the remaining 41 patients are analysed in the Table.

Estimation of improvement was based on clinical impression by the assessor (who was ignorant as to which patients were in the treatment or control series), on practical capacity and on the patient’s own statements, usually amplified by independent statements of a friend or member of the family. Patients were divided into three groups. In Group I recovery was virtually complete; in Group II definite improvement was seen and in Group III there was no material change. We are not concerned at this stage with follow-up figures since immediate response is what is under consideration; no doubt the follow-up, which we intend to undertake, will show a significant number of relapses.

The numbers are small and justify impressions rather than firm conclusions. It would seem that youth, if anything, favours placebo response. Sex distribution

is similar but the presence of previous neurotic traits and hysterical or inadequate features in the personality militate against a positive placebo response.

TABLE I

The Placebo Reaction

Factor			I	II	III
Total	13	10	18
Age	..	Minimum	22	28	28
	..	Average	32	38	42
	..	Maximum	42	59	55
Sex	..	Male	7	4	10
	..	Female	6	6	8
Neurotic traits	..	Childhood	3	1	6
	..	Adult	2	2	8
Personality noted as	..	Over anxious	6	4	4
	..	Obsessive	4	4	9
	..	Hysterical	..	2	8
	..	Inadequate	3
Intelligence	..	Below average	..	1	2
	..	Average	9	8	14
	..	Above average	3	1	3
Work record	..	Stable	13	10	15
	..	Unstable	3
Environmental problem	5	4	8
Duration of illness	..	Minimum	0.5	1.0	0.7
	..	Average	3.0	5.7	8.7
	..	Maximum	7.0	14.0	50.0
Pattern of illness	..	Phasic	7	4	4
	..	Non-phasic	6	6	14
Severity of illness	..	Moderate	10	9	14
	..	Severe	3	1	4
Diagnostic group	..	Psychic anxiety	10	5	..
	..	Somatic anxiety	3	2	2
	..	Anxiety depression	..	1	1
	..	Anxiety hysteria	..	1	4
	..	Conversion hysteria	..	1	6
	..	Depressive conversion	3
..	Obsessional neurosis	2	

Nothing useful emerges from a consideration of intelligence and work record. We had expected that the presence of an obvious contemporary environmental problem would prejudice placebo reaction but this does not seem to be the case. As would be anticipated, a greater duration of illness prior to treatment and an unremitting pattern of illness both lead to smaller numbers of positive placebo responses. On the other hand severity seemed to have little effect on improvement.

The fallacies attendant on diagnostic sub-groups are fully appreciated and it is well known that independent clinicians will use different criteria, depending

on their experience and persuasion. The nature of the clinical sub-divisions used by us has been described in the reports of our acetyl choline and carbon dioxide therapeutic trials. Not only in the combined control series but in each of our groups of patients, totalling 220, whether treated by acetyl choline, carbon dioxide or inert substances, one trend stands out clearly and consistently. This trend is to the effect that patients with unelaborated anxiety are those most likely to respond in a positive manner to a placebo administered under the circumstances described. Somatic elaboration with a physiological basis does not greatly prejudice this response, but hysterical conversion affects it adversely. The fuller the conversion, the more resistant is the patient. The three patients in the controlled series, in which hypochondriacal symptoms proved to be based on depression, were non-reactors, as were also two obsessional neurotics.

It would seem to us inescapable that the placebo reaction must be a manifestation of suggestion, using this term in its broadest sense. If indeed this is so, our findings concerning its relation to hysterical conversion are at variance with popular belief. The notion of a special relationship between hysteria and suggestibility originated in France during the last century and though hysteria had then a somewhat different meaning from its contemporary one, this idea has had universal influence up to the present day. Such a relationship is certainly assumed by many workers in assessing the results of new treatments, so that greater efficiency in non-hysterics is regarded as evidence that the substances do not act by suggestion. Such has been true of the two methods under review at present, namely carbon dioxide inhalation therapy and acetyl choline therapy. Concerning the former Meduna (1950) says—"of the whole group of patients my treatment of whom I am reporting, hardly 3 per cent. were conversion hysterics, the par excellence suggestible group", while Sargant (1952), writing of acetyl choline therapy, would seem to have much the same in mind when he says "we have not so far found that it helps the hysterical patient more than any other new treatment with a highly suggestive value".

Approaching the problem of suggestibility from the standpoint of tests claimed to measure this trait, psychologists were able to produce little evidence of any correlation with hysteria. The relevant literature has been well reviewed by Eysenck (1947) who also reports on extensive experimental work conducted with various colleagues. He describes two quite uncorrelated and independent factors operating in the tests customarily used; primary suggestibility which concerns the suggestion of movements, and secondary suggestibility which concerns the suggestion of sensations or perceptions. Prestige suggestibility, he thought, might perhaps be a third factor. He showed primary suggestibility to be related both to ability to be hypnotized and to "neuroticism" as this is understood by him, but to be in no way positively related to hysteria. In fact, dysthymics were if anything more suggestible than hysterics, with suggestibility in hysteria tending, as Bleuler (1924) has suggested, to operate in a negative direction. It is difficult to see in what relationship this somewhat abstracted type of suggestibility stands to the reactions so far described in this paper or to suggestion as it is generally met with in the clinical sphere. Certainly, however, Eysenck's findings are more in keeping with our own than with the popular view.

To explain his data Eysenck invokes the concepts of aptitude and attitude. In the case of primary suggestibility aptitude is a tendency for the thought of a movement to be accompanied by an incipient movement of the muscles involved. In practice this aptitude is influenced by attitude, the desire of the

subject to resist or not to resist the suggestion. Of the two it would seem to us that attitude is likely to have greater clinical significance. In this respect there is undoubtedly a striking difference between the test and clinical situations. Whilst in tests the suggested material is essentially neutral in type and attitude may be determined mainly by instructions given, clinically patients are being asked to modify meaningful symptom patterns.

If neurotic illness is viewed from this standpoint it would seem possible that a positive attitude towards symptomatic improvement may more usually be associated with dysthymic than with hysterical illness, since in the latter powerful motives of secondary gain militate against progress. Other things being equal, it is then perhaps reasonable to expect that therapeutic suggestion might prove more effective in the dysthymic group, and our own results with the mild implied suggestion of inert placebos do indeed indicate that this may be so.

What then of the customary view of the association of hysteria and suggestibility, which must surely refer to some observable phenomenon? We believe our confirmatory finding of what Meduna (1950) termed "pseudo-improvement" is of significance here. This consists of dramatic symptomatic relief in the very early phases of treatment followed a little later by relapse. By contrast with the more gradual sustained response, this occurred almost exclusively in hysterical patients and is of course much more reminiscent of what frequently happens after treatment by hypnotic suggestion. Being a striking phenomenon it might well account for the conventional view. This also could be principally a matter of attitude. What for the dysthymic might appear to imply a showy, shallow, and superficial process, could seem dramatic and exciting to the hysteric. As treatment progresses, more fundamental attitudes, perhaps as we believe influenced by subtle modifications of family attitude, are likely to prove of greater importance.

We have not, as yet, made a systematic study of domestic influences, but hope to do so later. The sort of mechanisms we have in mind may, perhaps, be made clearer by an example. A woman may develop an anxiety state with headache and vasomotor disturbance. She has real symptoms, but is told by her general practitioner and by a physician at the hospital that her trouble is "all due to nerves". The husband, either from impatience or because he believes it to be in his wife's interests, adopts a stern and coercive attitude. This is interpreted by the patient as due to lack of sympathy and may lead to symptoms of a more florid kind. If then, the patient is referred to a psychiatric out-patient clinic and treatment is "by talking", the husband will regard this as confirmation of his view that the symptoms are "imaginary". If on the other hand the patient is directed to attend regularly for injections or inhalations involving unconsciousness, the implication is that real suffering is involved. Family attitudes change; the patient's self-esteem is bolstered by facing and surviving repeated physical ordeals and morale is stimulated by the camaraderie of a clinic where others are doing the same. The scene is set for improvement. We believe that we have observed processes of this kind many times.

Administrative, economic and academic reasons should prompt us to establish so far as possible how the results of treatment with a placebo contrast with those following psychotherapy and to what extent they are enhanced by psychotherapy. This cannot be an easy task because there are so many variables contained in the term psychotherapy. These include intensity and circumstances of treatment, personality of the therapist and even possibly the dogma to which he subscribes: and psychotherapy, using the term in its broad rather than its restricted sense, is bound to be implicit in regular clinic attendance however

far deliberate suggestion, abreaction and explanation are avoided. We believe that Meduna and many others have underestimated the importance of the psychological changes brought about by such attendance.

The findings of Harris (1954) are interesting in this connection. In the Out-patient Department of the Maudsley Hospital 120 psychoneurotic patients were divided into two groups, allocation depending on the spin of a coin. One group was treated by psychotherapy, the other by carbon dioxide inhalation, following the Meduna technique. On assessment a year later no significant difference between the two groups was found. Frank (1953), in his interpretation of 238 cases, found no significant differences in the results where psychotherapy was undertaken in association with carbon dioxide treatment as compared with those series of cases in which it was not. The findings of Atoynatan *et al.* (1954) are slightly at variance with those of Frank. They treated 48 anxious patients, 26 receiving nitrous oxide inhalations followed by carbon dioxide, whilst 22 patients received nitrous oxide alone. The difference in improvement was not statistically significant. The patients were grouped further into the "permissive" in whom discussion with a therapist was allowed and a "non-permissive" group in which it was not. In the permissive group the greater improvement as compared with the non-permissive group was of statistical significance. The authors' conclusion that the therapeutic setting contributes more to improvement than the gas involved is in line with our beliefs. One would certainly expect from general experience that opportunity to discuss the treatment and its effect on symptoms would favour improvement; but "permissiveness" is not the same thing as formal psychotherapy.

This paper has not been presented in any spirit of iconoclasm. What we have attempted to do is to indicate that, in our opinion, a more critical attitude is needed towards novel physical treatments. Some of these will prove, in time, to have almost specific properties and we believe that E.C.T. comes in this category; others, of which insulin coma treatment may be an example, have intrinsic but not specific value. The majority are likely to prove to be placebos, producing temporary improvement in something like 40–70 per cent. of patients. Even so it may be that they have their place. If future findings do justify the enlightened use of the more elaborate placebo, one difficulty is anticipated; it is hard for a team to maintain its enthusiasm about the use of an inert substance unless that enthusiasm is fired and maintained by a specific objective, such as a research project; and it may well be that enthusiasm is one of the more effective ingredients of the therapeutic situation.

Certainly recognition of the mode of action of a treatment is vital for real advance. Without this knowledge unnecessarily complex and even hazardous treatments may continue to be used and the results of treatment may mislead physiologists and pharmacologists in developing their theories. Similar observations could well apply to formal psychotherapy. It still has to be shown that psychoanalysis has specific advantages and, for instance, that patients treated by Freudian methods do better than those submitting themselves to Jungian analysis or, indeed, better than those treated intensively, enthusiastically and sensibly by a heretic.

Whether or not the placebo has a place in psychiatric treatment, it is certain that its use in an uncritical manner cannot be justified. Used in that spirit, it could make for laxity of diagnosis, a static approach to treatment and general stultification of effort. Perhaps the same can be said for psychotherapy.

SUMMARY

(1) Reference is made to some of the literature relating to placebo response and to suggestibility.

(2) The authors' findings with controlled groups receiving intravenous acetyl choline, carbon dioxide inhalation and inert substances are considered in relation to placebo response.

(3) Differential factors favouring placebo reaction are discussed.

(4) A more critical attitude, both to the use of physical methods and of psychotherapy, is advocated.

REFERENCES

- ATOYNATAN, T. H., GOLDSTONE, S., GOLDSMITH, J., and COHEN, L. D., *Psychiat. Quart.*, 1954, **28**, 641.
- BEECHER, H. K., KEATS, A. S., MOSTELLER, F., and LASAGNA, L., *J. Pharmacol.*, 1953, **109**, 393.
- BLEULER, E., *Textbook of Psychiatry*, 1924. New York: Macmillan.
- DORLAND, W. A. N., *The American Illustrated Medical Dictionary*, 1951. Philadelphia and London: Saunders.
- DUNLOP, D. M., HENDERSON, T. L., and INCH, R. S., *Brit. med. J.*, 1952, *i*, 292.
- EYSENCK, H. J., *Dimensions of Personality*, 1947. London: Routledge & Kegan Paul, Ltd.
- FRANK, J. A., *Amer. J. Psychiat.*, 1953, **110**, 93.
- HARRIS, A., *J. Ment. Sci.*, 1954, **100**, 718.
- HAWKINGS, J. R., and TIBBETTS, R. W., *J. Ment. Sci.*, 1956, **102**, 43.
- Idem*, *Ibid.*, 1956, **102**, 52.
- LASAGNA, L., MOSTELLER, F., VON FELSINGER, J. M., and BEECHER, H. K., *Amer. J. Med.*, 1954, **16**, 770.
- MEDUNA, L. J., *Carbon Dioxide Therapy*, 1950. Springfield, Illinois, U.S.A.: Charles C. Thomas.
- SARGANT, W., *Proc. R. Soc. Med.*, 1952, **45**, 515.
- The Shorter Oxford English Dictionary*, 1944. Oxford University Press.
- WOLF, S., *J. Clin. Invest.*, 1950, **29**, 100.
- Idem* and PINSKY, R. H., *J. Amer. med. Ass.*, 1954, **155**, 339.