

Concerning Things That Are Obvious

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Well over one hundred and fifty years ago Humphrey Davy was experimenting with his new discovery, nitrous-oxide. The following passage taken from Dunglison's *General Therapeutics*, 1843, describes one of Davy's therapeutic trials:

"Dr. Beddoes, having inferred that the inhalation of nitrous-oxide must be a specific for palsy, a patient was selected for trial and placed under the care of young Davy. Previous to administering the gas, Davy inserted a small thermometer under the tongue of the patient to ascertain the temperature. The paralytic, deeply impressed by Dr. Beddoes with a certainty of the success of the remedy, of which he knew nothing, no sooner felt the thermometer in the mouth than he declared he felt better. Nothing more was done, and the sick man was requested to return the following day. The same ceremony was repeated with the same result and, at the end of a fortnight, he was dismissed cured—no remedy of any kind except the thermometer having been used!"

Now no one would seriously believe that taking the patient's temperature would cure cerebral palsy. No, indeed! But the patient apparently did recover.

Today when the physician is confronted with a patient suffering severe pain he will, with little hesitation, prescribe 15 mg. (or if he is unfamiliar with the official system of drug dosage—grains $\frac{1}{4}$) morphine sulphate s.c. The patient obtains relief and no one is surprised because this effect is an expected one. Truly, it is easy to believe what is obvious and easier still to discount what is not obvious. However, in the two cases cited there may be a common factor at work and when this factor is finally brought into broad daylight it raises some rather embarrassing questions regarding our knowledge of drug action and the manner in which we apply scientific principles to obtain it. For this reason I always discuss the therapeutic actions of the placebo at the very end of the course in medical pharmacology.

Let me now paint for you a perfectly ridiculous picture: the physician sits in his office wrestling with a particularly difficult diagnostic problem when in comes a detail man (salesman) from one of the pharmaceutical houses (drug companies). He is obviously enthusiastic because he has left his bag with all the free samples (for clinical trial) in his car outside. As a matter of fact the only thing he has in his hand is a capsule and this he tosses onto the physician's desk with a triumphant gesture. (I suppose that in currently popular jargon this could be described as a therapeutic confrontation.) "There it is, Doc", he says, trembling with excitement, "there is the wonder drug of the age—our company's gift to medicine. Not only will it cure headache, toothache, acute pain, the common cold, cough, enteritis, angina pectoris, motion sickness and certain types of diabetes—but it is practically non-toxic, costs only a few cents a pound and comes in three convenient sizes". What painfully follows the outburst I will leave to your imagination.

Yet such a compound does exist and lest the reader gets the idea that the placebo-marketing business might be more lucrative than studying (or practising) medicine, let me advise him that he is too late. Perhaps the most bold venture in this regard that I know of concerns the drug known as ethylenedisulfide. During the 1940's

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HOW MUCH SHOULD A GOOD DRUG COST ?

Competition exerts a strong influence on the price of prescription drugs. Only rarely does one manufacturer's product offer the sole chemotherapeutic means of treating a particular condition. But if new and better drugs are to be widely and continually available, certain costs have to be met.

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this was marketed as a treatment for asthma and associated allergic conditions. Apparently no one read the fine print on the label: "ethylenedisulfide, one part in 10^{16} parts of triple distilled water". No purer form of water had ever been marketed, yet its injection had produced cures.

If the placebo—this "pharmacologically inert substance"—does everything it is claimed to do, how does it work—and how often would its use result in a successful outcome? In what situations does it work? Or is the whole thing to be dismissed as "psychological"? The answers to these questions are as yet incomplete, but those answers that we have are surprising.

The placebo reactor is a ubiquitous person. Judging from the frequency of positive placebo reactions he (or she) represents a little better than one-third of the population. This means that of one hundred individuals, thirty-five will react positively to both a drug and an "inert" substance. (The chances of success here are pretty high.)

As might be anticipated, the environment in which a therapeutic measure is undertaken may very materially determine the outcome. Thus the assessment of, let us say, analgesic action among a number of compounds may, when carried out on a population of medical students in the laboratory, yield very different results when carried out on a group of patients in hospital. In the latter environment the subject may not always need to be told what the outcome of therapy is expected to be. If he is suffering from pain or insomnia or cough, and is given some medicine, the reason for this is obvious. Suggestion here is automatic. In other situations a suggested outcome may modify or even reverse the usual pharmacological actions. (These still do exist.) It has even been recorded that the effects of a dose of alcohol known to be intoxicating were entirely without this effect when taken in belief that the substance was flavoured water. (I must say I cannot see the point in such an experiment; the reverse might have been more interesting and certainly cheaper; but I suppose most anything is justifiable in the cause of science.)

Granted that the placebo does possess very powerful properties, we might rightfully ask—how does it work?—what is its mechanism of action? This is a difficult question to answer because the action with which we are ultimately concerned cannot be adequately quantitated. The result is that we must resort to words, and words have an unfortunate property of not always permitting us to say exactly what we mean. Perhaps a clue as to the placebo's mechanism of action might best be gained from the following type of illustration: an experiment has been designed to test the effectiveness of a new anti-tussive (scientific word for cough drop). A number of patients suffering cough of pathological origin are instructed to count and record the number of coughs experienced during a specified number of 5-minute intervals. They then receive their medication—identified only by a code number, but which may be the new drug, a standard drug like codeine phosphate, or a placebo. As in the pre-treatment period, the subject is required to count the number of coughs experienced during subsequent 5-minute intervals. In a great majority of cases the patient will report a reduced incidence of cough during the post-treatment period regardless of which medication he has received. However, had we taken the precaution of having an observer (who should also be ignorant of the identity of the medication), to check on the cough counts, we might have found that whereas during the pre-treatment period both patient and observer agree as to the incidence of cough, during the post-treatment period the observer reports an unchanged incidence. In other words, the patient was coughing just as frequently after receiving medication but he was less aware of it. The same reduced awareness appears to be involved in analgesic action.

In seeking the reason why this is so, one rapidly approaches the realm of the unknown and some, less inclined to admit of man's ignorance of these matters, merely substitute words for words. "It's all in the mind" is one frequently used phrase to which I object strongly. Firstly, it implies that the answer is known when in reality it is not, and secondly, I do not believe there is such a *thing* as a mind. Mind is an activity of the brain in the same way that running is an activity of the body. It is unfortunate that the activity became identified by a noun rather than a verb. (And having resolved a fundamental problem that has been concerning philosophers for centuries, I will now return to the subject at hand.)

Whether or not the brain is identified as the causative agent, it is clear that the placebo action is not confined to this organ. For example, it was shown that in a group of patients an injection of saline resulted in changes in eosinophil counts and steroid electrolyte excretion comparable to that brought about by a dose of ACTH. Again in a study involving a number of diabetics who were readily controlled on oral drug therapy, the administration of a placebo accomplished satisfactory results in 63 percent of the cases, as judged by urine sugar and blood sugar, hematocrit, non-protein nitrogen and cephalic flocculation tests. The action of a placebo in cases such as these might very profitably be used to unearth the primary cause of such pathological states as diabetes, i.e., the placebo might turn out to be a very useful investigational tool.

If all that has been said leads one to be suspect of anything which is obvious, how does one avoid these therapeutic pitfalls? Before answering this question, one might raise the controversial issue of whether it is worthwhile avoiding them anyway because, whether or not a drug does "what it is supposed to do", that is, exert its pharmacological actions, is immaterial as long as it cures the patient. (If some-

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one at this point feels the urge to shout "heresy" or "ethics", let me urge him before doing so to recall the long history of medical treatment and to ponder the point as to how many therapeutic measures were likely to have been successful purely because of the placebo effect involved. Cures were wrought by these procedures; but were they unethical?)

If one does seek to distinguish pharmacological from placebo activity, then one must resort to the double-blind technique. A series of drugs which usually includes an unknown, a standard (such as morphine for pain or codeine for cough) and a placebo are tested on as uniform a group of subjects as it is possible to obtain. The individual drugs are identified by code name or number so that neither the patient nor the person making the observations knows the nature of the medication. Only when observations are completed and conclusions drawn is the code broken and the identity of the medication revealed. The double-blind technique is about the best method yet devised to eliminate bias, bias on the part of the subject and bias on the part of the observer. It should be appreciated that this method of testing is not designed merely to find whether a particular drug works; we already know that it is likely to work on at least 25 percent of patients. The information obtained allows one to judge whether or not a new drug is more potent than a standard drug, placebo effects having been taken into account.

Indispensable as it is to the determination of drug efficacy, the placebo is today in danger of being throttled by the metastases of governmental bureaucracy. Recent amendments to the U. S. Food, Drug and Cosmetic Act require "that experts using such drugs for investigational purposes (clinical trial) certify to such manufacturer or sponsor that they will inform any human beings to whom such drugs, or any controls used in connection therewith, are being administered, or their representatives, that such drugs are being used for investigational purposes and will obtain the consent of such human beings, or their representatives, except where they deem it feasible or, in their professional judgment, contrary to the best interests of such human beings". Thus in exercising his professional judgment the expert must decide how the best interests of the humans involved in the trial are to be weighed against the best interests of humanity in general. By law he is required to inform the patient of the nature of his medication and obtain his consent. This maneuver is designed of course to protect the patient, but in complying with this regulation the expert knows that the structure of the double-blind technique may be destroyed.

Quite understandably the experts object to such legislation and many of them have voiced their opinions in the press. No advance in therapy, they would point out, has ever been bought without involving a certain amount of risk. This is the price that has to be paid for knowledge. The regulations quoted above would seem to imply that knowledge has no price tag and undeniably this is true of certain kinds of knowledge, but is this the kind of knowledge that we seek? Sober reflection and the passage of time will probably pacify these troubled waters. In the meantime it should be clear that there is a great need to distinguish things that are obvious from things that are familiar. It is easy to decide that taking a patient's temperature, as Davy did, would not really cure palsy because these things are obviously not related; and it is just as easy to conclude that morphine obtunds pain because everyone is familiar with this analgesic action. Considering the importance of the placebo in the doctor-patient relationship, one starts to wonder who (unconsciously) has been pulling the wool over who's eyes?

REFERENCES:

For more detailed information on the placebo the reader is referred to:
Beecher, H. K., *Measurement of Subjective Responses*, Oxford Univ. Press, 1959.