

"DRUGS AND BEHAVIOUR"

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In this paper, I would like to discuss a particular aspect of the relationship between drug treatment and individual behaviour. My purpose is to discuss some of the findings related to the placebo response and the implications of the findings for drug therapy.

It has long been known, of course, that the placebo response plays an extremely important role in an individual's reaction to a particular drug. This was very well shown in a study by Park and Covi (1965) who carried out an investigation in which placebos were given to a series of 15 neurotic patients newly admitted to the out-patients department of the Henry Phipps Psychiatric Clinic. This is a service for adolescents and adults who cannot afford private care. The mean age of the sample was 35 years, with an age range from 19 to 67, with years only one patient over 50 years.

Each patient was seen on two occasions. On the first visit, the patient was fully evaluated and a placebo was prescribed. On the second visit, which took place one week later, two separate interviews were held to assess change and decide on further treatment.

At the initial visit, the patient was prescribed a placebo in a standard way. The psychiatrists told the patient that his problem had been discussed and it was decided that the possibility for further treatment would be made one week later. In the meantime, he was told that he would be given a pill which might help. He was told that many people were helped by, what was called, a sugar pill and that this was "a pill with no medicine in it at all". He was told "I think this pill will help you as it has helped so many others. Are you willing to try this pill?" The patient was then given a supply of the placebo which consisted of pink capsules and told to take one three times a day at each meal. He was also told to discontinue any other medication which he might have been taking.

The findings for this study were extremely interesting. In the first place it was found that neurotic out-patients were willing to take a placebo even when the inert content was disclosed. Fourteen of the fifteen patients took the pills

and returned for the second appointment. All of the fourteen reported improvement, and there was, also, overall marked improvement according to the doctor and patient ratings on several measures. Of the fourteen patients, only eight stated at the second interview that they believed the pills were placebos and, of these, only three absolutely certain that this was the case. Six of the patients thought the pills contained drugs and two were absolutely certain that this was so.

These researchers concluded that "the formulation of placebo effect as a response to the belief active medication is prescribed involved too narrow a view. A more comprehensive assumption would be that the basic requirement is general belief that a situation defined this treatment, whatever its specific details."

This study is a most interesting and important one since it forces to acknowledge that the placebo effect is not a unitary phenomenon and is, in fact, a rather complex one.

It is also interesting to consider the effect of expectations from a placebo in psychiatrists and nursing staff. Loranger et al., (1961) gave placebos to 120 hospitalized psychiatric patients. Patients, psychiatrists and nurses were told that two drugs were being evaluated, one of which was a new tranquillizer and the other a new energizer. In actual fact, both drugs were inert. Uncontrolled and subjective methods of evaluation indicated that from 53 to 80% of the patients benefited from the new "drugs". When matched control groups and objective rating scales were used, it was found that a temporary improvement was caused by the tranquillizer but not by the "energizer". This study, the authors felt, "dramatically illustrates the dubious value of studies which do not employ double-blind and other controlled procedures". In addition to this, of course, it also indicated that the precise nature of the placebo response.

There is, of course, considerable interest in understanding the personality correlates of the placebo response. One study aimed at elucidating this question was carried out by Gelfand et al., (1965) These workers noted that a number of writers had suggested that the placebo phenomenon

could be viewed as one example of the social influence or persuasion process and that, therefore, one might expect that personality variables which correlated with general persuasability should also be related to placebo responsivity. One variable found to be negatively related to persuasability is self-esteem and it was, therefore, also hypothesized that low self-esteem would be associated with high placebo responsivity. Other workers found that placebo reactors were more likely to give socially desirable responses in an interview situation and that they were more likely to identify themselves as regular churchgoers and interested in church affairs. It has certainly been suggested by a number of writers that faith is an important element in placebo responsivity. Against this background, Gelfand et al. studied 25 paid volunteer female college students, aged 18 to 30. The placebo testing procedure involved the induction of pain using an ultra-sonic therapy unit. Subjects were told that the apparatus would cause warmth to the ball of the thumb at first, followed by a feeling of pain. They were told to indicate when the warmth turned to pain and then to remove their thumb from the apparatus when the pain became too uncomfortable. There were four trials before the inert substance was taken, followed by another three trials. The subjects were given a self-esteem test and a social desirability questionnaire. In addition, they filled in a religious belief-behaviour questionnaire after the experiment.

The result of this study indicated a positive relationship between placebo responsivity and religious behaviour and belief, but no relationship between any of the self-esteem measures and placebo responsivity. A significant finding was that religiosity and social desirability scores were related to the pain tolerance but not to the pain threshold placebo measure. It was felt that this supported previous work which indicated that pain threshold is more highly loaded with physiological and with psychological components, whereas pain tolerance is more highly loaded with psychological than physiological components.

Another study of considerable interest to the question of personality variables in the placebo response involved the investigation of the relationship between this response and suggestibility and hypnotisability. This study was carried out by Evans who studied two groups, each of 12 male volunteer undergraduates who were selected from the upper and lower 5% of the distribution of susceptibility to hypnosis. Definite changes in objective and subjective performance were found

following the ingestion of placebo in a modified double-blind study. The placebo response did not discriminate between subjects who were susceptible or unsusceptible to hypnosis and there were no strong relationships between measures of placebo response and measures of suggestibility. Thus, the suggested relationships between the placebo response and in the suggestibility of hypnotic susceptibility were not supported.

The studies which have been described make us conscious of the powerful effect of the doctor/patient relationship and the need to be aware of placebo factors in the course of pharmacologic treatment. Not only has it been shown that patients respond to inert substances but Vinar even described a patient who had become drug dependent on a placebo. Schapira showed that the colour of tablets played a significant role in the patient's response. They found that symptoms of anxiety were most improved with green tablets, whereas depressive symptoms responded best to yellow tablets. These colour preferences did not reach levels of statistical significance, except in the case of phobias as rated by the physicians' assessment.

Attention should also be drawn to the fact that not all placebo responses are positive ones. Lesse pointed out that negative placebo responses can occur, particularly in patients who had previous experience of similar drugs or have been associated with others who have taken these drugs and have reported untoward effects.

In conclusion, one may say that the placebo response is a much neglected aspect of drug therapy. Its complete elimination from every day treatment is not only impossible, but probably also undesirable. What is required is a proper understanding of the nature of the placebo response in order to make the better use of the placebo effect possible. Forrer has pointed out that "the placebo effect is a psychosomatic resultant of psychological processes which have become unconsciously attached to therapeutic endeavours. Symbolising as it does to the patient the gratification of infantile needs, the placebo can serve to relieve functional components of discomfort and disability. Placebos should be acknowledged as a potent force of our therapeutic armamentarium."

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INTRODUCTION

Because the pathophysiology of mental illness has not been made clear yet, psychotropic drugs are studied mainly for their possible therapeutic effects on the symptom and behaviour of men, especially patients. The predictive value of animal study is still uncertain. However, recent advances in the study of animal psychology and ecology may bring us useful information on the presumed effects and safety of new drugs. These studies also may contribute to the drug trial in men. Furthermore, if unexpected events should happen during the clinical trial, it would be necessary to "feed back" to the animal studies to clarify the cause. For this reason, the basic knowledge of clinical psychiatrists on the effects of psychotropic drugs on animal behaviour will be more and more required for the initial clinical trial of the safety and effects of new drugs.

For the interpretation of animal studies, the following two types of classification are tentatively made, based on the ecological and psychological aspects of behaviour.

1. Drug action on individual or group behaviour.
2. Drug action on conditioned or non-conditioned behaviour.

According to this classification, some known effects of psychotropic drugs will be mentioned.

1. Individual and Group Behaviour

Most laboratory experiments were performed in isolated environment which differed sometimes

from the usual living conditions of animals. Recently, Utena studied the effects of amphetamines by chronic administration to a group of Japanese monkeys and observed that the effects of drug on the intoxication symptoms varied according to the rank of each monkey in the colony. Furthermore, it is well known that the acute toxicity of amphetamine in isolated mice is ten times lower than in grouped mice. The relation between the two different species of animals, such as cats and mice, is common knowledge, and administration of a tranquillizer to the predatory cat suppresses its natural rat-killing behaviour. Recently, Ueki et al. studied the mouse killing behaviour (muri-cide) of rats after the administration of T.H.C. (active substance of marihuana). The aggressive behaviour of a cynomolgus monkey towards the experimenter was used to test the taming effect of minor tranquillizers which reduced aggression without impeding the spontaneous psychomotor activity.

2. Conditioned and Non-conditioned Behaviour

When we interpret the behavioural change in animals induced by drugs, the nature of basic behaviour should be at first analyzed. For this purpose, the classification into two different natures of behaviour, non-conditioned and conditioned, seems to be one of the most simple and convenient ways.

a) Non-conditioned behaviour

This included natural, instinctive behaviour acquired through heredity, and artificially induced (by men) behaviour. The pathologi-

cal criterion on normality and abnormality is the same as human clinical psychology.

i) *Normal behaviour*

The C.N.S. stimulants and depressants influence the spontaneous motor activity of animals when administered in certain dosages. However, it is almost impossible to interpret the action of drugs by phenomena only, because amphetamines and LSD may inhibit the ambulation of animals. In this respect, the after-effect of drugs should be carefully evaluated. Very often, so-called hang-over or rebound phenomena may be observed in the case of hypnotics, analgesics and alcohol after the disappearance of the drugs from the body.

The effects of psychotropic drugs on the feeding behaviour is well known. Amphetamine and related psychostimulants reduce appetite, and chlorthalidoxepoxide increases the food intake and body weight of animals when administered continuously. The sedative effect and polyphagia in animals after the administration of minor tranquillizers seem to be interesting in connection with specific pathology of Klein-Levin's syndrome (Hypersomnia-bulimia, i.e. periodic somnolence and morbid hunger).

The effects of psychotropic drugs on sexual behaviour were reported several times in human beings. We have not yet had enough information on whether these effects are direct or indirect. Most drugs may be influential on libido and/or potency in human sexual behaviour. Recently, there have been recurrent observations on increased sexual activity after L-dopa treatment in Parkinsonian patients. The sexual behaviour and brain monoamine were studied recently in animals. Parachlorophenylalanine (PCPA), which is a specific inhibitor of 5HT synthesis without affection on catecholamine, produces compulsive sexual activity in male rats, cats and dogs.

The homosexual mounting behaviour in rats can also be induced by the administration of L-dopa with peripherally acting decarboxylase inhibitor Ro4-4602. PCPA not only induces homosexual mounting behaviour, but markedly increases the percentage of male animals exhibiting

copulatory behaviour with females in estrus. The effect of PCPA is not only prevented by castration but strikingly potentiated by testosterone (Tagliamonte 1972)

The effect of psychotropic drugs on the sleep cycle, especially on the slow and paradoxical sleep, was reported very frequently in animals (Jouvet et al.). In this connection, the rebound phenomena of paradoxical sleep suppressed while the drug is effective were discussed in connection with hang-over phenomena and possible relation with drug dependency. However, there are still no conclusive findings.

ii) *Abnormal and pathological behaviour*

It is still almost impossible to produce or obtain any psychopathological phenomenon in animals which is similar to human beings. However, many efforts have been made to examine the drug effects on the abnormal behaviour of animals for the purpose of obtaining more specific and sensitive tests to be used in the screening of new drugs.

Some examples are cited as follows:

— *Hereditary characteristics abnormal behaviour.*

There are not so many reports on the findings of pathological phenomena in the same species of animals, i.e. hereditary neuro-psychiatric diseases. The audiogenic epilepsy in mice and the dancing mice (manic psychomotor excitation) will be one of the examples. The discussion on the existence of spontaneous schizophrenia-like state in monkeys is of permanent interest among the specialists, but most of all the hypothetical interpretation.

The species' specific abnormal behaviour (mainly interpreted by men) will be observed quite frequently. The photic epilepsy in African baboons was used for the screening of new anticonvulsants. The taming effects of benzodiazepine derivatives on the aggressive cynomolgus monkeys are very well known.

— *Chemically induced pathological behaviour*

The most difficult problem is to produce permanent abnormal behaviour, even after the direct effect of chemical substance disappears.

Nakajima H. and Thuillier reported in

1957 on the dancing-mice produced by short-term administrations of iminodipropionitril. The symptoms were similar to hereditary dancing-mice. This phenomenon lasted during the whole life of the mice.

The effects of major and minor tranquillizers, hypnotics, hallucinogens and amphetamine on these mice were studied and classified according to the actions which corresponded well with the clinical classification of Delay.

Ueki reported the long lasting abnormal behaviour of rats in isolated condition (muricide and catalepsy) induced by short-range administration of T.H.C. and studied the action of different psychotropic drugs.

The considerable amount of research on abnormal behaviour produced while the drug is active has been reported.

Catalepsy induced by neuroleptics and bulbocapnine is well known and used for the screening of anti-depressants and anti-parkinsonism drugs.

—Physically induced pathological behaviour

The rats whose limbic systems (septal, olfactory and amygdaloid) are destroyed have been used frequently for the screening of tranquilizers. The external noxious stimuli may modify animal behaviour. The fighting behaviour of mice by foot electroshock has been used also for the screening of tranquilizers.

— Abnormal behaviour induced by special situation

Generally, when mice and rats living in groups are isolated individually for some time, the aggressive fighting behaviour to

others will appear. This is used for the screening of tranquilizers.

b) *Conditioned behaviour*

Most integrated human behaviour is conditioned; but in the case of laboratory animals, the spontaneously conditioned behaviour does not always exist.

Therefore, the effects of drugs are studied in the following two directions.

— Effects on the formation of conditioning
For example:

* Learning procedure

* Drug intake behaviour (In this case, the drug is used as a kind of reward, i.e. reinforcement of conditioning).

— The effect on conditioned behaviour, especially in operant avoidance and escape.

The interpretation of the results obtained by animal conditioning experiments is sometimes different, especially on human conditioned behaviour formed in quite different procedures. Therefore, the analysis and interpretation of the data for clinical applications should be done extremely carefully.

CONCLUSION

The effect of psychotropic drugs on animal behaviour will supply useful and interesting information for the clinical evaluation of the safety and efficacy of drugs. However, it should be noticed that most of the results obtained in animals have only relative predictive value for human studies in the case of psychotropic drugs. Therefore, the needs of adequate and well-designed clinical studies should be more emphasized. In this regard, the comparative value to reference drugs (not only inactive control and positive control, but also negative control) will bring clinicians very useful suggestions for the application of drugs to human beings.

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In the last two decades, the introduction of psychotropic drugs which are pharmacologically potent and effective has changed the practice of psychiatry radically from what it used to be. It is

difficult I am sure, for the younger ones among us who have come into psychiatry during the era of psychotropic medication to imagine what the practice of psychiatry was like when, even at the best centres in the world, with the most eminent professors available and the best facilities at one's own disposition, all that psychiatrists had to offer was psychotherapy or long drawn-out psychoanalysis for neurotic disorders for patients who can afford the time and the expense, and institutional custodial care for the psychotics whose behaviour was socially unacceptable and therefore embarrassing to their relatives.

Modern Psychiatric Therapy

Although the millenium has not arrived yet when the aetiology of the major psychiatric disorders are known and radical cures are available most probably in the form of pharmacological substances, naturally occurring or synthetic, the options for therapy available to a young resident in psychiatry to offer his patients today is something that is vastly different from what they were twenty-five years ago when all one had to offer were electro-convulsive therapy, insulin shock-therapy and a couple of pharmacological compounds of dubious efficacy. By the same token, it is very difficult to imagine what the practice of psychiatry was like at the turn of the century. All one had to use on disturbed patients were the bromides and a few other sedatives. Of course there were the strait-jackets of leather or canvas and there was the padded-cell to fall back on in the last resort.

While taking a historical perspective, it is cogent to point out that the use of drugs to control the behaviour of human beings is not new to this part of the world. It is common knowledge that maidservants or *amaahs* of this part of the world who were left with the charge of unruly offsprings of upper and upper middle class families often resorted to substances like opium to keep the exuberance of their young charges within bounds. But at the more therapeutic level, the Ayurvedic physicians of India have been using the leaves of *Rauwolfia Serpentina* for the treatment of mental disorders for several centuries now. The use of this substance in the management of psychiatric disorder was brought to the attention of the medical world by Dr. R. A. Hakim of Ahrnabad, India, when he presented a paper on this subject for which he was awarded a gold medal in 1953. Nathan S. Kline took this up and was able to demonstrate in a successful therapeutic

trial on psychiatric patients in a state hospital in the United States. (Noyes & Kolb. 1958).

Social Changes

This wide availability of drugs in the last two decades, often referred to as the "pharmacological explosion" has influenced not only the behaviour but also the attitudes and life patterns of human beings both directly and indirectly. These drugs provide the relief, if not the cure for man's physical and psychiatric ills. The availability of the wide range of antibiotic drugs has completely changed the pattern of morbidity and mortality in many societies. This has many far-reaching sociological effects. The age structure of the population in the developed countries has changed significantly. People survive to an older age and therefore, the middle-aged and the elderly constitute a much larger proportion of the population than before, and social facilities and social institutions, therefore, have to be changed accordingly to cater for this sector of the population. The sexual behaviour and sexual mores of people in many societies have changed radically as a result of the availability of the oral contraceptives. For young people in urbanised societies sexual activity now becomes a practical proposition without the threat of the possibility of an unwanted pregnancy. This has of course been equated with promiscuity and decried as decadence by moralists, but decadence or not, oral contraceptives provide an answer of sorts to the problem of over-population.

The Drug Dependent Society

With the whole array of pharmacological compounds available, indeed one can even say that there are several alternative drugs available for each particular purpose. The life of human beings, one gets the impression, become so dependent on the use of drugs. Working in a university community, in a situation where great emphasis is laid on the passing of examinations, one sees students near examination time taking tablets so that they can keep awake to study and then taking tablets to go to sleep, in an attempt to counteract the effect of the stimulant tablets taken earlier and then waking up by the alarm clock to take other tablets in order to be able to stay awake again at lectures the following morning. It is no wonder that many of these students become drug-dependent. Just as the trade name "Aspirin" has become a household word to people now in their forties and fifties for the whole range of ills, anything from a headache that results from a disagreement

with one's spouse through the fever and vigor of a urinary tract infection so also now, to people in their late teens and twenties, the trade names of "Librium" and "Valium" have become household words in their own right as agents for the relief of any distress ranging from anxiety about the outcome of one's application for a job to the dejection following a failure in an important examination. Indeed Carstairs (1969) says that "...everyone nowadays expects to be happy. Pills have come to be regarded as a means of doing away with everyday anxieties and pains...". Indeed modern man will be quite lost and unable to cope if he finds himself in a situation where these pharmacological compounds become unavailable. Even inactive compounds are used e.g. Deer Horn and Essence of Chicken.

The Drug Dilemma

In a way one cannot help pointing a finger at oneself, the physician, for this state of affairs. Very often, a family doctor in his busy practice with his long line of patients waiting outside his consulting room to be seen, finds it a much easier way out than taking a little bit more time to talk to his patients, to resort to the use of anxiolytic drugs to help to tide the patients over various crises. Indeed, doctors often feel that the prescription of a drug for the patient is mandatory when in fact lending a sympathetic ear to the patient's problem for half an hour might be more efficacious in helping him to cope with it. Smith, (1966) in a study of drugs prescribed for hospitalised patients found that an average of eight drugs are routinely prescribed for hospitalised patients without infections while those with infections could be prescribed as many as 42. But on the other hand, in the practice of psychiatry, one is very often confronted with a schizophrenic patient in a state of relapse and the evidence is very clear that the relapse has come about as a result of this patient neglecting to take his medication. Indeed the physician has very carefully steered a course between the Scylla of over-prescribing and Charybdis of not prescribing at all. Imlah (1970) states, "Every doctor has a list of patients who wants drugs but should not have them, and another list of those who need drugs but do not take them."

There is, of course, the other school of thought which is very wary of the use of drugs, particularly in the control of human behaviour. Szasz (1957) stated that use of tranquillisers in the treatment of disturbed psychotic patients is nothing more than using "chemical strait-jacket" rather than using a canvas or leather one. Huxley (1932)

visualised in his "Brave New World" a society not very distant in time when the behaviour of the population can be controlled by the mass administration of various drugs through the water supply. This indeed is a frightening prospect which evokes rather paranoid fantasies of some of the population of every country to the extent that even the fluoridation of the water supply, a measure against dental caries in children, a fact for which there is strong scientific evidence to support, is regarded with suspicion and rejected in terms such as a measure in "compulsory medication". These are the very same people who have no compunction whatever to reach out for the bottles of Aspirin or Valium when they are in the least way distressed by any work problem they are faced with any day of the week. Such a controversy over the fluoridation of the water supply rages at this very moment in this country and every few weeks one sees a spate of letters from readers in the local newspapers on this subject-arguing the issue despite repeated assurances from the authorities.

Which for what?

Going on to a personal level, one feels that while the availability of psychotropic drugs is a boon to the practice of psychiatry, one has to be aware on the other hand that the vast array of compounds that are being produced and being marketed leaves one with a problem of which drug to choose and for what condition. Indeed keeping up with the journals on the reports of drug trials alone is a major occupation in itself. Indeed, there is evidence to show that many physicians have given up on this and depend on the representatives of various drug firms who visit their offices ever so regularly to digest this information for them. (Wilson, 1963).

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