Self-medication with mood-changing drugs

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The aim of this article is to examine some of the consequences of the recent advances in neurobiology in terms of the ability of drugs to manipulate the mind. Most laymen are totally ignorant of the general mechanism underlying the brain-mind relationship and therefore of the action of mind-altering drugs. Professor Grahame-Smith considers that one of the intrinsic evils of man's neurobiological make up is that a prime motive of the brain seems to be to bring comfort, security and pleasure for itself. Therefore it is not surprising that drugs – notably the barbiturates and more recently the benzodiazepines (tranquillizers) – have been prescribed to give to the brain that peace of mind that it seeks. However, it can be argued that such drugs cannot replace anxiety with peace of mind or unhappiness or depression with happiness. The action of such drugs upon the molecules of the brain is negative – a placebo effect.

'And if ever, by some unlucky chance, anything unpleasant should somehow happen, why, there's always *soma* to give you a holiday from the facts. And there's always *soma* to calm your anger, to reconcile you to your enemies, to make you patient and long-suffering. In the past you could only accomplish these things by making a great effort and after years of hard moral training. Now, you swallow two or three half-gramme tablets and there you are. Anybody can be virtuous now. You can carry at least half your morality about in a bottle. Christianity without tears – that's what *soma* is.'

ALDOUS HUXLEY *Brave New World*

Aldous Huxley in the *Brave New World* had the social order partially preserved by '*soma*', an apparently effective, fairly non-toxic, inexpensive drug substitute for present-day alcohol, nicotine, soccer violence, pop idols, pornography and bingo, and infinitely more effective. Two tablets would bring happiness for a weekend.

To many laymen there is a void, about which many are completely ignorant and some do not even recognize, between the taking of an aspirin and the relief of a headache. Most people do not ask, 'How does the aspirin relieve the headache?' They take pills for symptoms in the same way as I bang the television set when the picture flickers, a totally mindless exercise which nevertheless some-

times works. We cannot, however, afford to ignore how the present mind-altering drugs act or the general mechanisms underlying the brain-mind relationship.

I know of nothing (yet!) which makes me believe like Koestler, that there is a 'ghost in the machine'. Neither Koestler, nor anyone in his book, *The ghost in the machine* (1967), actually comes out and lays their cards on the table as to why, apart from ignorance about how the brain works in relation to the mind, they believe that there is a non-physical force at work. While admitting ignorance of the precise brain mechanisms underlying mood, feeling, anxiety, thinking, consciousness, pleasure, perception, creativity and so on I am not prepared to substitute mysticism for ignorance. I believe that there is likely to be a biological basis in the brain for every function of the mind.

The brain is at one and the same time extremely simple and extremely complex. Its simplicity lies in the fact that there are a limited number of things it can do, albeit that each of these things is a complex phenomenon, and that these limited functions can be manipulated by drugs on the one hand and by environment and experience on the other. Considering all the states of mind produced by drugs there is not one, as far as I can tell, which has not been experienced in the normal run of things, or by disease, fasting, physical or mental exhaustion, prolonged stress, fear, mystical medication or religious fervour. Drugs appear to 'turn on' or 'turn off' the same brain mechanisms as other processes turn 'on' or 'off', that is, they can act only on the biological substrates available to them.

Brain biology and mood

Certain general principles appear now to be sufficiently well established to make certain statements which bridge the gap which has so long existed between those whose views relied entirely upon psychological factors, such as the effect of the environment, learning and experience, as being the sole factors involved in the production of mind, states to the exclusion of brain biology, and the new era of psychopharmacology beginning in the early 1950s with the use of chlorpromazine and reserpine, since when some have placed almost complete reliance upon manipulation of mind and feeling with drugs for therapeutic purposes. It would be

fallacious to pretend that we understand what mood, peace of mind and feeling are, and what their precise biological basis is, but it is not too speculative to presume that at one level at least those functions of the brain related to mood depend upon the integrated function of certain neuronal tracts within the brain, probably situated phylogenetically at a fairly primitive level. Moore (1971) puts it succinctly: 'Highly integrated neural functions, such as those involving thought processes, which are generally considered to take place in cortical structures, may be modified by primitive, tonically active, subcortical systems (eg, limbic and reticular activity systems). Accordingly, a dysfunction of these delicately balanced primitive systems may result in derangements of mental processes and behaviour.' That the function of such neuronal mechanisms can be manipulated with drugs is undoubted and there is ample evidence to show in animals, at least, that experience, environment and learning can equally alter the biochemical and pharmacological functioning of the brain and thereby behaviour. To a neurobiologist it is not surprising that psychical experiences can be induced on the one hand by either meditative or environmental means and on the other by drugs such as LSD and mescaline. A word of warning, however, before it is assumed that everybody's brain is the same. Certainly biochemical differences in the brain can be found between different strains of the same species of animal which behave differently under various experimental psychological procedures, and it is not unreasonable to suppose that certain fundamental characteristics of the individual personality depend upon unique neuroanatomical, neurobiochemical and neuropharmacological factors differing between individuals. These may be partly determined by experience and the totality of environment and they may also be partly genetic. Thus people might be expected to behave or feel differently in response to mind-altering drugs, and indeed such is the case in regard to alcohol, morphine, amphetamine and marijuana. This individual variation must be taken into account when considering the problems of self medication. It is, for instance, quite possible that there is something different about the biology of the brain of the alcoholic or of that of the nicotine, amphetamine or heroin addict which has made that individual more prone to addiction. If this is the case then in the future such individuals might be recognized somehow and warned just as one warns people with asthma not to smoke cigarettes.

Long-term effect of drugs on brain function

Another neurobiological phenomenon in regard to drugs is the long-term effect in changing brain function. One of the functions of the brain is to record experience. To do this structural and func-

tional changes occur within brain tissue. There are several drugs which when given to animals and then stopped cause a change in the responsiveness of those animals, days or weeks later, in response to other drugs. The most obvious example is the effect of opiate antagonists to produce withdrawal symptoms in opiate addicts. Recently Green and I (1975) have shown that rats chronically pretreated with chlorpromazine become much more sensitive to behavioural excitation when the chlorpromazine is stopped. In addition, the prolonged, intermittent administration of thyrotrophin-releasing hormone (which has actions in the brain distinct from its actions on the pituitary) and recurrent electroconvulsive shock produce in the rat a greatly increased sensitivity to a number of behaviourally excitant drugs (Green and Grahame-Smith, 1975). In other words, on the first exposure to the drug changes have occurred in the brain which remain after the drug has been stopped which alter subsequent responses to various stimuli. Just as experience alters our future behaviour so do drugs. Many people appear to think that the individual remains more or less unchanged after using drugs, say pot, or the successfully weaned heroin addict, but I think that animal experiments and the writings of many previous drug users show that profound alterations in the brain can occur which change the individual for life and cannot be eradicated, for example, in regard to the use of amphetamines in minimal brain dysfunction in children (Sproufe and Stewart, 1973). If rats are anything to go by, these children's brains may be changed for life. Drugs which alter the brain and therefore the mind are having such marked effects on brain structure and function that there is just the possibility that they may alter the 'aging' process of the brain. They may slow the process down, but, knowing in general what drugs do, it would be better to assume that they have no effect or speed up the process. It might take 50 years to make sure that any drug does not have this effect and children treated with amphetamines will have to be followed up carefully.

Tranquillizers and their effects

Now to turn to some of the terms used in the context of this paper. The term 'tranquillizer' is relatively new and fashionable, replacing 'sedative' when the benzodiazepines (Valium and Librium) largely began to replace the barbiturates in the symptomatic treatment of anxiety states during the 1960s. Although one is not on very strong ground it is common human experience that the mere absence of anxiety does not produce a tranquil or a peaceful mind. The benzodiazepine group of drugs and barbiturates undoubtedly relieve anxiety to some extent, or at least lessen its impact on the state of mind. Although the benzodiazepines do this without as great a sedative effect as the barbiturates,

both benzodiazepines and barbiturates are hypnotics and no drug is yet available which completely separates sedation from anxiety-relieving effects. But I believe that there is a positive quality about tranquillity and peace of mind which transcends mere absence of anxiety and this cannot at present be achieved with drugs without altering the level of consciousness. In considering the present, particularly in terms of the benzodiazepines, which are currently the most favoured of drugs used as tranquillizers to take the edge off anxiety, it must be emphasized that they possess a general sedative quality, that they have demonstrable deleterious effects on reaction and reflex times, motor co-ordination and decision taking. I believe that these neurological and psychological toxic effects make these drugs quite unsuitable for true self medication. The toxic, let alone the social, implications would be vast. Other drugs – such as the barbiturates, meprobamate and various mixtures containing methaqualone – are even more toxic and subject to misuse.

There is little evidence that physical addiction to benzodiazepines is important though undoubtedly in maladjusted individuals psychological dependence may occur, but by and large with the benzodiazepines this is not a great problem. A greater problem with all mind-changing drugs of the type we are discussing is that because they are used by unhappy, anxious people an overdose is a way out and these drugs tend to be the ones used to attempt to commit suicide.

No one is going to take a drug that produces depression, sadness and dysphoria. It is of interest to note that even in informed and pharmacologically knowledgeable people the knowledge that a pharmacologically induced mood has been produced chemically in no way lessens its impact on the mind and feeling as the effect of alcohol or reserpine bears witness. Telling a patient that his depression is due to reserpine does not make him feel any better!

Effect of antidepressive drugs on patients and normal subjects

Many lay people tend to think that the drugs used in the treatment of depression are mood-changing drugs which relieve everyday depression in non-psychiatrically disturbed people. This is not so. Tricyclic antidepressants and the majority of monoamine oxidase inhibitors, which are more or less effective in relieving certain well defined depressive illnesses, have very little effect in producing euphoria, elation and contentment in people with normal mood swings. In fact the few anecdotal studies which have been done show that these drugs, like most drugs, make 'normal' people feel worse than usual: they certainly do not elevate mood. In addition, the tricyclic antidepressants and monoamine oxidase inhibitors are very slowly

acting in depressive states, their effects taking a week or more to become apparent. In addition both groups of compounds are really highly toxic when considered in the context of self medication. They would never be suitable, even if they were effective, for the manipulation of normal mood swings.

Lithium salts have recently been introduced and are now routinely used for the prevention of manic depressive disease, and, in some quarters, for recurrent severe endogenous depression. I have seen no data about the effects of lithium salts on normal mood and I do not believe that any experiments have been done. From what I know about the drug, however, it seems extremely unlikely that lithium salts will really allow or even induce a fairly sustained level of happiness. It is interesting to note that there are many anecdotes being told of the effect of lithium to suck creativity out of artistic manic-depressive people, many of whom apparently rely on their mood swings for either creativity or productivity.

There is no doubt that we do not have safe or even very effective drugs for manipulating normal mood swings and producing tranquillity of mind. All the current tranquillizers, antidepressives, hallucinogenics, opiates and amphetamines are potentially too dangerous.

Self medication

There are two types of self medication: the first, the situation in which you walk into the chemist's shop and buy the drug over the counter without prescription. The other form of self medication which society has evolved for itself is by manipulating the medical profession. This is what might be called prescription 'on demand'. This is the actual situation with the contraceptive pill but all around the world there are millions of people who go to see their doctor with straightforward psychological disturbances, such as anxiety and mild depression and their psychosomatic expression (I exclude severe anxiety and severe depression) who are treated with tranquillizing and mood-changing drugs; in many situations these act as placebos. In a very recent study workers in the psychopharmacology research branch of the National Institute of Mental Health in the USA surveyed the international use of tranquillizers (Balter, Levine and Manheimer, 1974). In Belgium, Denmark, France, Germany, Italy, The Netherlands, Spain, Sweden, the United Kingdom and the USA the proportion of persons who used these drugs on one or more occasions during the previous year was 17 per cent in Belgium and France, 10 per cent in Spain and 14.2 per cent in the United Kingdom. In every country the percentage of women having taken a tranquillizer during the previous year was higher than that of the men, and a very high proportion of drug users in all countries were 55 years of age

or older. When Balter and his colleagues looked at the use of tranquillizing agents taken on a regular daily basis for one month or more in these countries the United Kingdom actually came top of the list with 9 per cent of the population studied taking the drugs regularly, but followed closely by Denmark, The Netherlands and Belgium with Italy and Spain fairly low at about 4 per cent. So at the moment there is a situation where at the lowest estimate some 10 per cent of the population from the age of 15 onwards will have taken some tranquillizing agent prescribed by their doctor in any year and probably some 5 per cent regularly. This study also questioned respondents as to their attitudes to tranquillizers, and roughly half thought that they did more harm than good and the other half the reverse. In the United Kingdom 34 per cent thought that they did more harm than good, though 15 per cent of the users thought that they did more good than harm, and 37 per cent of the non-users thought that they did more harm than good. That really is not a surprising conclusion. There must be very few doctors engaged in primary medical care who are satisfied that the benzodiazepines are really effective in helping people to cope with their daily anxieties. But the phenomenal prescribing rate of these drugs is probably due to several factors:

- 1 Patients are conditioned into believing that medicine will do them good when prescribed by the doctor. That is the effectiveness of the placebo.

- 2 Doctors are relatively few, their time is short, they do not have the time to listen to the patient's problems and to help them to sort them out in a social and psychotherapeutic way. A prescription is a quick way out of this dilemma.

- 3 Doctors are also conditioned to their medicines being beneficial. The great virtue of the benzodiazepines is that doctors believe in their effectiveness because undoubtedly they have potent pharmacological actions and there is no more effective placebo than one in which both doctors and patients believe.

I am going to consider this 'prescription-on-demand' kind of self medication to illustrate how society's attitude towards medicine, and, for that matter, the medical attitude towards society, can be used by society to meet its needs. It is not absolutely necessary to have the 'over-the-counter' form of self medication in order to have a large proportion of the population taking a particular form of medication. Medical prescription, however, is very costly because it involves doctors' time but it does to some extent avoid gross misuse of such drugs and probably to some extent limits their toxic effects.

A digression on 'pot'

I am forced to deal briefly with one very important

point raised by the controversy over 'pot' which applies to any self-administered, mind-altering drug. This is the matter of the freedom of the individual to do what he wants. In our society at present freedom is constrained in many ways both to protect the individual from unacceptable risks (heroin) and to benefit the community (taxes). Society, through its various agencies to which it delegates responsibility, decides the constraints on this freedom and imposes them by legislation. It is often said that because, in spite of the law, thousands smoke pot, the law should be relaxed. But thousands thief, drink while driving, avoid tax and exceed the motoring speed limit. Mass law breaking in itself is no good reason for changing the law. However, if we could be sure that pot smoking of the taking of some drug was completely harmless to the individual and to society then obviously the law is unjust and unreasonable. But I know of no drug which is completely harmless, particularly those which alter states of mind. The hazards of nicotine and alcohol are well known. In our present state of knowledge it seems very likely that any drug capable of producing a pleasurable state of mind will be subject to considerable use by millions of people who can afford it (alcohol, nicotine) and of course considerable abuse (again alcohol and nicotine) with resulting psychological and physical toxic effects. Society has to decide whether the individual and collective benefits outweigh the risks. In regard to pot, I must be honest and say that I do not think we have sufficient evidence on either the benefits or the risks on which to base a definitive decision (Maugh, 1974a and b). It could turn out that our fears concerning the risks are groundless or that the benefits are exaggerated in comparison with the risks which are known.

Problems of drug research

The problems of doing research on the scale required are enormous and are similar to those posed by the introduction of any new medical drug which will be widely used. These problems can be summarized as follows.

- 1) We have to learn, within the scope of present knowledge, something about how the drug exerts its effect from studies in experimental animals and in man.

- 2) We have to study in great detail the effects of the drug on the target organ and on other physiological systems in animals and in man.

- 3) We have to build up knowledge of the likely side effects.

- 4) We have to find out how the body deals with the drug, whether it accumulates in the body, and whether it is converted by the body to compounds which themselves may be toxic.

- 5) We must run tests, acute (one dose) and chronic (many doses usually over a period of

months) on animals to see whether there is unexpected toxicity and toxicity has to include animal teratology and carcinogenicity. At this point the drug goes into small-scale clinical trials which involve its administration to selected 'patients' with the condition for which the drug appears indicated. These patients are carefully monitored for the beneficial effects and any toxic effects on various organ systems. If the drug appears beneficial and toxicity does not appear to be much of a problem then similar extended clinical trials with monitoring for efficacy and toxicity are carried out. If all is still well then the drug may be released for general medical use, when the real difficulties begin. All the studies so far have involved very few people, perhaps at the most one thousand or so. If the drug is for use in a common condition, say infection or arthritis, it may be given to millions. If for example, a particularly nasty toxic reaction only occurs once for every 10 000 people receiving the drug then in the initial phase no such toxic reaction may be seen. However, when the drug gets into the population then for every million people receiving it there may be 100 people who suffer severe illness due to that drug. Because most side effects of drugs present a picture which can mimic spontaneous disease it can be very difficult to pick up isolated toxic effects of a drug. If the toxic effects are delayed and appear only in the long term it requires a major epidemiological study to unearth them. An example is cigarette smoking.

Should 'pot' and socially used drugs be subject to clinical trials?

It seems to me that those wishing to introduce pot or any socially used drug for unrestricted use owe it to society, and society owes it to itself, to demand equally stringent monitoring of the effects of the substance. Fanciful though it might be, such studies could be carried out, although not under the present law. They would take about ten years and cost a great deal of money and even then one might not produce all the answers. Such studies would be required for any 'soma' type drug. Imperial Chemical Industries reckon that the background research and clinical testing that go into producing an important innovative drug costs in the region of 20-30 million pounds. And at the end of the day one can never be certain that the drug will really be effective, will prove to be an important therapeutic advance, or that overall its benefits will outweigh its risks. It is all a very expensive gamble.

Controlled investigation of mind-altering drugs

I have no doubt that any mind-altering drug considered for self medication by the general population will now have to undergo these stringent

controlled investigations but who will pay for them? It would be an interesting development if commercial pharmaceutical houses began to take an interest in this area. Ultimately, however, the problem is so vast that the final responsibility would be with the state and government. I can see grave difficulties in persuading government to spend very large amounts of money with good will in studying potential mind-altering drugs with a potential for self medication. Yet this is a logical conclusion which is reached when considering how to proceed toward producing and marketing a 'soma' and ensuring its safety.

Drugs potentially capable of altering capacity for enjoyment

I believe that we may have so far only just touched the possibilities for mind altering by drugs and that all the agents we have been considering are fairly non-specific, pharmacological agents. For instance, it is widely assumed by many psychiatrists that the capacity for enjoyment is necessarily linked with mood, but I am not sure that I entirely agree with this view although accepting that a depressive mood saps capacity for enjoyment. Animal experiments have established that there are so-called 'reward' systems in the brain, which function in such a fashion that the animal will perform in such a way either to achieve reward or presumably to experience a pleasurable sensation. While man will perform to achieve material comfort, at a social and cultural level he performs to achieve pleasurable sensations. It is common experience that capacity for enjoyment in a particular situation varies from time to time without any obvious involvement of mood, and it is not too far fetched to speculate from animal experiments and to presume that such capacity for enjoyment depends on the functioning of systems similar to the reward system in animal brains. I believe that besides the tranquillizing and mood-changing drugs we should be considering drugs that alter capacity for enjoyment. Perhaps this approach rather than any venture towards producing vague states of euphoria and peace of mind is more realistic, and alcohol and marijuana possess this property for some people.

Social implications of mind-altering drugs

For every state of mind manipulated by drugs there are new social implications. At the present rate of progress in neurobiology we are poised in the 21st century for some very real strides in psychopharmacology and that new, non-sedative, anxiety relieving agents, anti-aggressive drugs, really effective antidepressants and antipsychotic drugs, ie, anti-schizophrenia, true sleep inducers (which our present hypnotics really are not), reward

producing agents, concentration-producing agents, memory-improving agents, agents for combating senile mental change, may be with us by the turn of the century. This is not because people are actively looking for all of these but that as brain mechanisms are uncovered so the means for manipulating them become apparent; these means are a natural corollary of neurobiological progress. I think that in the present state of our knowledge it is impossible to predict whether agents which fulfil some inner need will perforce be addictive. I think it is likely that some individuals will always be so affected as we already have enough experience to know.

The prospect that the behaviour of man and his future development could be changed by mind-altering drugs, of a power and selectivity compared with which alcohol, nicotine and marijuana fade into significance, is at one and the same time frightening and challenging. Just as the nuclear bomb was an inevitable outcome of nuclear physics research so these agents will be an inevitable outcome of neurobiological research. Society should set up the means for dealing with the problem before it happens and mankind should be educated to realize that, at least at one level, his mind, personality and spirit are the result of molecules

interacting one with another, that these interactions can be altered by drug molecules, and that the 'ghost in the machine' may one day be challenged by the 'spanner in the works'.

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