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Physical dependence type 2

INTRODUCTION

In 1954, Olds and Milner discovered that there appeared to be pleasure spots in the brain (see Olds[8]. Implanting electrodes in certain areas of the brain, and enabling a rat to stimulate that area by pressing on a lever that activated an electric current, produced in most brain areas nothing of note. In some brain areas, however, the rats seemed keen on the effects of self-stimulation; in some cases, if left to heir own devices, they would self-stimulate to the exclusion of all else – this was most likely to happen in a degraded environment devoid of stimulation.

As mentioned, noradrenaline was discovered in the brain in 1954. In 1959, a second catecholamine, dopamine, was identified. This was shown to be deficient in patients with Parkinson's disease. Replacement therapy, using the dopamine precursor L-dopa, brings about substantial benefits to sufferers of this disease.

The later mapping of dopamine-containing neurones showed that they originated in a discrete area – the ventral tegmentum. Some of these neurones run to strictly motor areas of the brain and constitute the nigrostriatal system. It is the loss of nerve cells in this pathway that leads to Parkinson's disease.

Other dopamine-containing neurones run to higher areas of the midbrain and to cortical areas. It appears that these are centrally involved in what is termed incentive learning – the kind of learning that occurs when an animal encounters a biologically important stimulus such as food or a potential sexual partner.

The ventral tegmental system seems to be closely associated with the pleasure systems discovered by Olds and Milner. However, the picture has become far more complicated. It now seems that, far from there being pleasure hot spots in the brain, there are areas of the brain that respond to familiar signals pleasurably and unfamiliar signals with displeasure. Pleasure seems to be at least in part a function of the familiarity of the message being relayed through the system.

CRAVING

Why do so many alcohol or opiate users return to their addiction after detoxification? If the terror of withdrawal were such a significant factor in producing chronic abuse, it might be expected that anyone with the least bit of wit would keep well clear of further involvement. What perversity or self-destructive impulse is it that leads to further abuse?

The traditional response to this problem was to distinguish between physical dependence and psychological dependence. It is usually argued that the latter is a state of mind, one that may stem from deep-seated psychological difficulties. It is this state of mind that some people see as the real problem with the addictions. While it is relatively easy with modern technologies to take

in drug addicts and ‘dry them out’, it is a much more difficult problem to ensure they remain drug free.

When asked why they return to their habits, the usual response from sufferers is in terms of cravings. The notion of cravings seems to suggest a depravity or perversity in keeping with the social opprobrium accorded to addicts. It suggests some weakness on their part that fits in with the idea they have psychological difficulties. Current research suggests that this picture is quite wrong.[9]

It seems, increasingly, that cravings are a very tangible physical reality and that the form of dependence that is characterised by cravings is in fact a physical dependence of another sort. In favour of this argument is the fact that not all drugs of abuse cause cravings. Cocaine, the amphetamines, nicotine, alcohol and the opiates notably do, but LSD, phencyclidine, the psychedelic drugs generally and the benzodiazepines, antidepressants and antipsychotics do not.

BEHAVIOURAL SENSITISATION

Experimental work on drug effects on the brain has revealed that continued administration of certain drugs, far from leading to tolerance, appears to produce just the opposite effect, even when the environment is held constant. Indeed, in a mirror image of the production of tolerance, the holding of the environment constant, in these experiments, appears to facilitate the production of increasingly enhanced effects in response to certain drugs.

This phenomenon is called behavioural sensitisation.[3,10] Certain drugs induce it, others do not. Morphine is capable of inducing both sensitisation and tolerance within the one animal: the animal develops tolerance to some of the effects of morphine, such as analgesia, and sensitisation to others – one of which is the fact that continued intake becomes increasingly pleasurable.

Initial experiments suggested that morphine produced behavioural inactivity and was somewhat unpleasant. Animals who were linked to electrodes connected to the so-called pleasure spots in the brain were less likely to self-stimulate themselves when given morphine. This ran contrary to the popular belief that opiates are pleasurable, and in fact it can be noted that the experience of many people trying opiates for the first time is that they are not very pleasant.

Subsequent experiments demonstrated that morphine becomes increasingly pleasant to take. Chronic exposure to morphine in experimental animals gradually brings about increases in activity and self-stimulation. There is an odd aspect to this, which is that such increases are at their height some 3 hours after morphine administration, in contrast to analgesia which is at a maximum 1 hour after administration. Maximal brain levels of the drug also occur 1 hour, and not 3 hours, after administration. Furthermore, analgesia and the respiratory depression brought about by morphine can be antagonised by morphine antagonists, such as naloxone, but the pleasurable effects of the drug are not antagonised by these agents.

APPETITES

What is happening? It appears that morphine, alcohol, cocaine and the amphetamines feed into the brain systems responsible for the generation of and satisfaction of appetites, of which the ventral tegmental system outlined above is a component part. A moment's reflection should indicate that the last thing an appetitive system could do with is tolerance to the sight of food, drink or sex, for example – rather, just the opposite. In contrast to the effect of environmental cues in helping to bring about tolerance because they signal the non-threatening, or insignificant, nature of what is happening, environmental cues might be expected to lead to increased effects where appetites are concerned. That is, we will become increasingly sensitive to aspects of an environment that indicate the possibility of food or sex or drink. Such cues should lead to

increased rather than decreased interest. Typically, however, we do not notice the accumulation of environmental prompts pushing us toward the consummation of an appetite, unless we have been removed from the environment artificially for a while. Try dieting, seriously, and you will become aware of all the prompts to eat in the environment – advertisements in magazines, smells of food, cooking, etc.

The effect of public houses and the cultures surrounding both drink and drugs provide a host of small prompts, each of which prime an appetite that has already been created. This can even extend to having one's appetite aroused by the sight of needles.

Once stimulated, appetites, while not imperative, have a way of grabbing attention. It is natural to bend our minds to the satisfaction of our appetites, when they require satisfying. As the weight of cues to indulgence builds up, we typically come closer and closer to behaving on automatic pilot. We less and less regard alternative cues in the environment. Thus the hacking cough is not registered as we light up another cigarette, or the number of meals and amount of food we take are not realised as we sit down for a little soothing snack, and the children's Christmas presents get forgotten until the drink runs out.

The establishment of such appetites can be blocked. For example, giving morphine accompanied by dopamine-blocking drugs (antipsychotics) or naloxone does block the development of behavioural sensitisation. However, once appetites have been established, they cannot easily be extirpated. Neither opiate antagonists nor antipsychotics abolish cravings for opiates once they have become established.

It does not make sense that appetites could be abolished – controlled, perhaps, but not abolished. It is possible to manage one's appetite. For example, the amount of food habitually taken bears some relation to the amount of food felt to be needed. Thus eating a lot creates a big

appetite. Decreasing one's intake can lead to reduced cravings. Similarly sexual appetites are to some extent set by the frequency of indulgence. The notion that some of us are born with greater sex drives than others has little solid evidence in its favour. However, even in the case of total abstinence, we would not expect our sexual appetite to vanish entirely.

However, while appetites, once established, may not readily be abolished, the notion of craving should not be taken to imply that something has been created that is insatiable and beyond human resources to combat. For example, opiate-induced craving, while a real phenomenon, does not appear to be uncontrollable. Rather, as the experience of American GIs returning home from Vietnam suggests, the vast majority of regularly indulging individuals can put aside the habit when they are removed from social situations conducive to it. Once removed from the environmental cues that prompt cravings, only a minority of individuals have overwhelming difficulties.

Current therapeutic strategies are increasingly leaning toward the management of cravings on the model of managing appetites for food, when these are disordered as in bulimia or anorexia nervosa. The issue is often one of helping the individual set a reasonable management strategy rather than having them insist on complete self-control. For example, subjects with bulimia will often plan to eat only one meal a day. This leaves them liable to be overcome by hunger pangs on some other occasion, leading to guilty and rushed snacks, which are unsatisfying and lead in turn to eating more and more food and feeling even more guilty afterwards. Management aims at recognising when an appetite has been stimulated and how to handle it at that point, in a manner that allows the individual to bring into play the usual controls we all have where appetites are concerned, but regarding which we do not normally need to be aware.

PHARMACOLOGICAL MANAGEMENT OF APPETITES

The first treatment for alcohol problems was disulfiram (Antabuse). This operates on a behavioural principle and aims to abolish an appetite or help with its control. Alcohol in the body breaks down to an aldehyde compound and then to an acid. Disulfiram blocks the conversion of the aldehyde to the acid. This leads to an unpleasant increase in the amount of the aldehyde in the bloodstream, so that after a drink or two subjects taking disulfiram may feel extremely nauseated and/or have a severe headache. This experience is supposed to deter them from taking any more alcohol. In practice, if individuals want to drink, they simply do not take their disulfiram that morning.

A similar approach has been taken with opiate users. It is common in a number of centres for opiate users who have been detoxified to be put on maintenance naltrexone. This is supposed to block the pleasure that they would get from their drugs. There is some debate about how well it does this, but there is some evidence it can help[5]. Naltrexone can cause dysphoria, which, in the case of an opiate user, might make them liable to seek out relief. In all cases the use of naltrexone should be delayed until the user has been opiate free for at least 5 days because of the risk of precipitating withdrawal effects. The initial dose of naltrexone is 10 mg per day, increasing to 150 mg over 2 weeks. The effects of naltrexone last up to 3 days, and therefore dosing needs to be only every 3 days thereafter.

However, another use for naltrexone has emerged recently, which stems from the probable role of brain opioid systems in the genesis of appetites. A number of trials have now indicated that the use of naltrexone after alcohol detoxification reduces the risk of relapse, probably by reducing craving.[4] This has led to it being licensed for this purpose.

Another drug licensed for the management of relapse in alcoholism is acamprosate[11]. This acts on the g-aminobutyric acid (GABA) system on which the benzodiazepines act. Whether it produces a direct anticraving effect or reduces cravings by being in some way anxiolytic is less clear. Naltrexone and acamprosate seem to work best for different patient groups. There is, however, very little clinical work aimed at mapping out which groups of patients will respond to which agent. This is not the kind of work that drug companies are likely to be inclined to do, as it would mean settling for a restricted segment of the market.

There are two further drugs marketed for cravings. Bupropion, a dopamine and noradrenaline reuptake inhibitor, with antagonist effects at nicotinic receptors, marketed as an antidepressant in the United States (Wellbutrin), is also licensed under the trade name Zyban for smoking cessation. In so far as this works it seems to do so, in part at least, by minimising cravings for nicotine and cigarettes. Another agent, varenicline (Chantix) also acts on nicotinic receptors among other sites and has been licensed for smoking cessation. It supposedly reduces the pleasure in smoking and alleviates cravings. Both buproprion and varenicline have been linked to an induction of suicidality. The respective companies blame smoking cessation for the suicidality but the degree of suicidality on treatment seems out of all proportion to naturally occurring difficulties on withdrawal.

There is every reason for believing that each of these agents may in fact work for particular individuals, rather than for different conditions such as alcohol, opiate or nicotine dependency. Judicious clinical trials of each, even in the conditions for which they are not licensed, are appropriate. The rationality with which these drugs are used would be further enhanced by studies that pay heed to how takers who find the drugs effective say they are working.

PSYCHOLOGICAL FACTORS IN SUBSTANCE ABUSE

The induction of appetites and cravings used to be seen as psychological dependence. If it is, in fact, just as much a physical process as the dependence and tolerance that underpin withdrawal, is there any other psychology involved?

There almost certainly is.[1] For example, LSD, phencyclidine and many of the new designer drugs do not cause either physical dependence or craving, yet they are abused – and increasingly so. Despite evidence that phencyclidine, for example, led to a considerable number of deaths and despite the fact that it did not lead to any obvious euphoria, during the 1980s it became for a period the second most common drug of abuse in the USA. Why?

Common to many of these drugs is the fact that they alter consciousness. As a result, they are interesting to take. They permit an escape from reality. This suggests that two factors in their use will be a certain amount of playful activity and a need to escape reality.

As regards playfulness, there are two aspects to this. First, there is the notion that people will try something new simply because it is there, just as they will climb mountains or run across continents. Allied to these things 'simply being there', there is the matter of our innate curiosity. The other aspect to playfulness is that it is a means to handle boredom. For want of something better to do, humans will turn to virtually anything, no matter how dangerous it may be. Even Russian roulette, as Graham Greene confessed, may be tried as a way of livening things up or structuring them. Indeed, it can often seem that everything that happens is just a game to counteract boredom, from intrepid mountain climbing to scientific endeavours, the writing of books or the taking of the most recently designed drugs.

When we are bored, we do things: we eat or shop. New clothes, books or records often seem to restore a sense of purpose to things. One of the central problems of treating alcohol and

opiate dependence, aside from physical dependence of both types, is the question of what will the individual now do to structure their time. Frequently it turns out that keeping an alcohol-dependent individual away from pubs also means abolishing their entire social life at a stroke. What are they to do with the yawning hole that opens up where their social life used to be?

From this perspective, the question of drug abuse becomes, to a large extent, a matter of accident, which stems from the fact that, at various points in life, some of the activities available to be sampled cause physical dependence and others produce cravings – just as it is an accident that some of the pursuits available to be taken up, such as motorcycling, have a high fatality rate.

Just as with motorbikes, it seems that if one can get through an experimental stage between the ages of 15 and 25 years without having been too involved in high-risk pursuits or in taking of drugs with a high dependence potential, then one is not likely to be killed accidentally or to become substance dependent accidentally. It is not that playfulness diminishes after this age, so much as that the burden of commitments and responsibilities restricts for most of us the opportunities to participate.

DISINHIBITION

Along with the fear that drugs may cause dependence, there is a fear that they may change personalities by either abolishing the normal personality of an individual or by liberating demons from the unconscious. The adage *in vino veritas* is often taken to mean something like this. Both alcohol and benzodiazepines are supposed to disinhibit people. What is happening?

One thing that may happen, but which is relatively rare, is that these compounds, like almost any other drug that gets into the brain, may cause dissociative reactions. These are outlined in Chapters 2 and 4.

The more usual disinhibition on alcohol is socially disinhibited behaviour, which may involve an inappropriate pinching of bottoms or, more seriously, violence towards one's partner. In such cases, it is typically argued that alcohol is a general depressant that depresses brain inhibitory pathways first. Accordingly, with an inhibition of inhibitions, there is supposedly a brief period of disinhibition before increasing levels of alcohol blot out all behaviour in a general stupor. The supposed inhibitory tracts that are especially sensitive to the effects of alcohol, benzodiazepines or barbiturates are rarely specified. If pushed, advocates of this position tend to suggest that activity of the frontal lobes of the brain is the first to be affected by alcohol, this being a brain region that has general executive or inhibitory control over all other brain regions. However, there is little evidence to support this idea other than the popular presumption that something like this must be the case. But must it?

There is no question that alcohol discoordinates and slurs speech. This can be demonstrated reliably in experimental situations and can be correlated precisely with the actions of alcohol on coordination centres, such as the cerebellum. Alcohol and benzodiazepines also reverse the inhibition that fear may cause, enabling someone to go on stage and give a lecture, for instance. However, in the case of someone behaving outrageously in a public situation, who then gets some troubling news such as their house is on fire, they are liable to 'sober up' instantly – although they may still remain less than perfectly coordinated as they set about getting home. Or the social disinhibition that I show one evening may be quite different to the disinhibition I show the following evening, in contrast to the discoordination, which will be approximately the same.

An alternative account of what is happening is that, misled by the very real effects of alcohol on gait, coherence and anxiety, we also put other changes in behaviours down to the drug

that are more properly seen as a function of the social situation in which it is taken. In general, there is a gap between our knowledge of what drugs reliably do and our difficulties in explaining the complexities of social interactions that can be exploited by both substance abusers and those who would put down societal ills to such abuses.

There are a number of factors that almost compel such an identification. There is, first, our tendency to seek an explanation for what is happening to us. This shows up well in placebo-controlled studies of drugs generally. It is the common experience of many investigators that a not inconsiderable number of subjects have to be withdrawn from such studies because of intolerable side effects from what turns out to be placebo.

A probable explanation for this is that, of 100 subjects who enter a study, a number of them are bound to get obscure aches or physical complaints of some sort, on at least one occasion anyway. Such discomforts are borne none too happily in the normal course of events. We put up with them because it is not clear what the cause is and accordingly we have little option. If they occur during a week when we are taking some new pill, it may be very difficult to believe that the pill is not responsible.

Applied to alcohol, such arguments yield the following picture. That alcohol itself does not disinhibit. That alcohol is commonly consumed in situations where the usual rules of restraint are altered. That alcohol, by altering the physical state, provides a cue that a certain state has been entered in which the subject has learnt that the usual rules of accountability do not apply. Thus, if after drinking I go home and beat my wife, I know that my friends, who know me for a basically decent sort, will not attribute what has happened to me, but rather to the drink they saw me having. This, it should be noted, is not an *in vino veritas* argument.

These issues also play a considerable part in the abuse of other drugs. In the case of cannabis, it is quite clear that takers have to ‘learn’ to get stoned. Initial taking of the drug produces the effects on perception that are typical of cannabis, but not ‘stoned’ behaviour. It is subsequent smoking in the company of others who are ‘stoned’ that brings about stoned behaviour.

When it comes to the abuse of street drugs, generally, the analysis of urine samples indicates that users are often taking mixtures that contain a wide variety of white powders – and perhaps none of the particular white powder they think they are getting. Some of these extras may be other stimulants, such as strychnine, but the behaviour the users display will be behaviour appropriate to the culture surrounding the drug they think they are on.