INTOXICATION AND SOCIETY
PROBLEMATIC PLEASURES OF DRUGS AND ALCOHOL

ADDITION AS A DISEASE STATE

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The idea that drug and alcohol addiction might or might not be a state of disease has been in flux over the past 200 years. Nineteenth century physicians clearly recognised alcohol addiction to be an uncontrollable craving for alcohol but distinguished it from alcoholism by pathological change, as might be observed in the liver, this latter definition being derived from that provided by Giovanni Morgagni in *De Sedibus et Causis Morborum*, his classic work published in 1761. Little changed until the mid-1940s when Morton Jellinek published a paper on “Phases in the drinking history of alcoholics” (Jellinek, 1946). In this paper, he described alcoholism as a disease, a category reserved for those individuals who exhibited tolerance, withdrawal symptoms, and either ‘loss of control’ or ‘inability to abstain’ from alcohol. Importantly, Jellinek considered features of the disease, such as inability to abstain and loss of control, to be shaped by cultural factors and that prevention or treatment of alcoholism would require complex cultural, political, and economic issues to be addressed.

In parallel with Jellinek’s remarkable insight, a flurry of activity presaged the contemporary view of addiction being a disease that could be medically treated or at least controlled to some extent. In the early 1990s, the frequency of relapse to drug use in individuals addicted to narcotic drugs led to the establishment of narcotic clinics that could legally provide heroin and morphine as maintenance therapy. The clinics failed dismally as they did not lead to abstinence. These clinics were eventually closed by a legal interpretation of the 1914 Harrison Act, which controlled the production, importation and distribution of opiates. This interpretation prevented medical personnel from providing maintenance therapy to addicts and this prohibition lasted from the early 1920s until 1965. At that time Vincent Dole and Marie Nyswander made a simple but critical observation. They discerned that long-term maintenance was virtually impossible using short-acting narcotics but could be achieved with narcotics that had a long duration of action (Dole and Nyswander, 1965). By using methadone, a synthetic opiate with a duration of action averaging 24 to 36 hours, as compared to 10 minutes for heroin, they could block the euphoria experienced by injecting heroin. We now know methadone, being a partial agonist, exerted very little effect on the brain opiate receptors but blocked the action of morphine or heroin, which are full agonists with very strong effects. Remarkably, however, Dole and Nyswander did not arrive at the idea of using methadone on a receptor-based theory of pharmacology. In contrast, they relied on a metabolic theory developed mainly by Vincent Dole (Dole and Nyswander, 1967).
Dole argued that as individuals became addicted to narcotics they ‘underwent a permanent metabolic change,’ a state not unlike that for which a diabetic requires insulin.

Harry Collier, an English pharmacologist, had a different view to the metabolic hypothesis proposed by Dole. He suggested the effect of addictive drugs to be mediated by a cell receptor-based mechanism (Collier, 1965). Collier based this idea on the writings of Paul Ehrlich (1854-1915). Ehrlich had proposed that chemical substances, or drugs, acted on a living system by becoming attached to particular sites on cells. In modern terminology, these sites are now termed receptors. Collier’s speculation, however, was much more sophisticated. In essence, he maintained that the continued presence of a drug acting on specific receptors in the brain caused an adaptive change in the numbers of those receptors and that this effect caused tolerance to the drug. Secondly, and as a consequence of the increased number of receptors, removal of the drug allowed the physiological effects of the natural transmitter acting on the receptor to have a greater functional impact and that this change caused the drug withdrawal syndrome. Truly, this was a most remarkable insight. It was a flight of genius that pre-empted our current concepts of drug action and the mechanisms of addiction.

Inevitably, in 1973, Candace Pert and Solomon Snyder demonstrated the existence of opiate receptors in the brain. At that time the analgesic action of the opiate drugs was well-known and their relative potencies in relieving pain had been established. Pert and Snyder selected naloxone for their studies as this opiate potently blocks the analgesic actions of other opiates, such as morphine and heroin, and therefore might be expected to bind with great avidity to the putative opiate receptors in the brain (Pert and Snyder, 1973). Secondly, they attached a radioactive tracer to naloxone and used this labelled drug to directly measure its affinity for the brain receptors. Finally, they used other opiate drugs to displace the radioactive naloxone from the brain receptors to show that its binding was specific to the site at which the other opiates mediated their action. Of particular interest was the finding that the avidity of morphine for the opiate receptor was much greater than that of methadone, an observation that predicted their addicting potential. John Hughes and Hans Kosterlitz, working in Aberdeen, subsequently identified the brain’s natural neurotransmitter for the opiate receptor to be a family of small peptides, chains of amino acids linked together (proteins are very long peptides), that they termed enkephalins (Hughes et al., 1977). The brain system upon which addicting narcotic drugs exerted their action had been described. More importantly, this work had been carried out against the backdrop of Nixon’s presidency; a time of tumultuous social change in the USA with political and military problems in Vietnam and the identification of drug-related problems as one of the contributing sources of the crises facing the government. The funding paradigms supporting the science of addiction had been born.

This demonstration of opiate receptors and their transmitters in the brain fuelled optimism that addiction could be understood at the molecular level. The receptor sites of action for most
drugs of abuse have now been identified and this feat of molecular biology has allowed such drugs to be classified according to their action. This was a significant advance as drugs of abuse had previously been classified according to their physiological or psychological actions – stimulants or sedatives. Secondly, the idea that drugs of abuse impacted on normal brain neurotransmission, which is a highly controlled process, further reinforced the idea of addictive substances altering 'homeostatic' balance and this facilitated an understanding of the extremes of perception and behaviour observed in addicts.

Developments in the elucidation of molecular mechanisms for the action of drugs of abuse paralleled an increasing interest in the motivational and behavioural consequences of drugs of abuse and their relationship to states of addiction. Progress in this domain stemmed from a paper published by James Olds and Peter Milner in 1954 in which they described a phenomenon by which direct electrical stimulation of certain brain areas in rats evoked very specific behavioural effects (Olds and Milner, 1954). In order to receive such stimulations, Olds and Milner observed that animals would readily approach a circumscribed part of their environment. Clearly, animals actively sought the rewarding properties of these stimulations. Secondly, Olds and Milner found that animals would learn to perform a task, such as pressing a lever, in order to receive further stimulations. These stimulations could also produce behavioural reinforcement. It should be noted, however, that the terms used to describe each of these actions can have somewhat different meanings. Reward refers to the idea of pleasure and is used to describe those stimuli that are actively sought out by animals and humans. The term 'reinforcement' has its antecedents in the work of Edward Thorndike (1874-1949). He had observed that certain events strengthen a preceding stimulus-response. As in the work of Olds and Milner, electrical stimulation 'reinforced' the lever press task. This was Thorndike's connectionist hypothesis, an idea later significantly reworked by the psychologist Burrhus Frederic Skinner (1904-1990). He termed the phenomenon operant conditioning. Subsequent work demonstrated the ventral tegmental area to be the main region responding to intracranial self-stimulation. As this area provides a rich source of dopaminergic fibres to the nucleus accumbens, over time, the idea evolved that this brain circuitry and dopamine regulated the response to all of our natural biological rewards, such as food and sex (Stellar and Stellar, 1985).

There is now a vast literature on the role of dopamine in motivational processes of reward and reinforcement. The general principle established is that any actions enhancing the action of dopamine, such as drugs that mimic its action (agonists), increase the rewarding value of intracranial self-stimulation. Subsequently, drugs of abuse were found to augment the rewarding and reinforcing effects of intracranial self-stimulation and the effect showed a good correspondence with their abuse potential (Kornetsky et al., 1979). The idea that drugs of abuse might increase dopamine transmission in the nucleus accumbens was eventually demonstrated. Using a technique known as microdialysis, increased dopamine overflow in
the accum bens was observed to occur following administration of either amphetamine, cocaine, morphine, nicotine, and alcohol and this outflow was accompanied by locomotor activation (DiChiara and Imperato, 1988). The focal point of reward and reinforcement for drugs of abuse was now firmly linked to activation of the midbrain dopamine neurons (Koob and Bloom, 1988).

Further progress on understanding the role of dopamine in the neurocircuitry of the addicted state was only made possible by the significant advances achieved in the technology and methodology of brain imaging. This technology specifically advanced our capability of relating brain structure to function in conscious subjects. These imaging methods relied largely on indices of blood flow as measured with radioactive drugs (such as positron emission tomography – PET) or radio signals that differed according to the composition of tissue and provide detailed images of different brain regions (magnetic resonance imaging – MRI). Functional MRI (fMRI) measures the change in magnetic fields associated with the ratio of oxygenated to deoxygenated haemoglobin and thus can be used to visualise neural activities with high spatial and temporal resolution.

These imaging techniques have been widely embraced by neuroscientists as a means to understanding the neural mechanisms that sub-serve phenomena that range from cognition to consciousness and to the pondering of complex ethical conundrums. Frequently derided as a form of ‘mind-reading’ or ‘neophrenology,’ critics of these imaging techniques have been most vociferous in their condemnations. These extreme positions arise frequently from a poor understanding of the capacity and limitations of these imaging techniques. The overarching assumption is that the mind can be divided in modules and that their individual activities can be imaged. The concern with this viewpoint is that unified brain function does not operate by the activity of individual components. Another concern is that these imaging methods relied largely on indices of blood flow which is a surrogate signal for the activity of a heterogeneous group of neurons. Notwithstanding these concerns, the imaging techniques employed would appear to measure change in functional activity in defined populations of neurons, as these changes concur with the outcome of decades of studies relating discrete lesions and electrophysiological recordings to function (Logothetis, 2008).

Using PET studies in particular, most drugs of abuse when tested in humans have now been shown to produce significant increases in dopamine in the nucleus accumbens (ventral striatum) and that this is associated with the subjective perception of the drugs being rewarding (Volkow et al., 2009). The use of these technologies has further allowed Volkow and colleagues to suggest key circuits to be disrupted in states of addiction and that this dysregulation is associated with impaired dopamine function (Volkow et al., 2012). These circuits include a disrupted reward system in the nucleus accumbens, loss of control over motivation in areas of the prefrontal cortex, and impaired memory and learning in subcortical
structures termed the hippocampus and amygdala. In essence, Volkow and colleagues view addiction as a state of disease that centres on disrupted function in the prefrontal cortex that, in turn, leads to loss of inhibitory control and appropriate decision making in drug addicts. In turn, they believe this gives rise to addicts requiring immediate reward of the drug and loss of control over their intake. Moreover, Volkow and colleagues believe the greatest problem facing drug addicts is their lack of awareness of the disease and the need of therapeutic intervention. Elucidating the neurocircuitry underlying this dysfunctional insight of addicts is the goal they now aim to achieve (Goldstein et al., 2009).

**Literature cited**


