Recent advances in the identification and characterisation of dental stem cells and in dental tissue-engineering strategies suggest that bioengineering approaches may successfully be used to regenerate dental tissues and whole teeth. As clinically relevant methods for generation of bioengineered dental tissues and whole teeth continue to improve, interest in the application of tissue regeneration increases. This paper describes dental derived stem cells and their characterization.
Using a microfluidic device to investigate the role of the furry (FRY) gene in Dictyostelium discoideum.

The landmark technique remains a safe alternative to ultrasound guidance for performing a Fascia iliacus block: A cadaveric study

How does addiction occur?

The diagnostic work-up of stable chest pain at a large university teaching hospital

Interview with Professor Laurence Kirmayer, Director of Cultural Psychiatry
Introduction

The World Journal of Medical Education and Research (WJMER) (ISSN 2052-1715) is an online publication of the Doctors Academy Group of Educational Establishments. Published on a quarterly basis, the aim of the journal is to promote academia and research amongst members of the multi-disciplinary healthcare team including doctors, dentists, scientists, and students of these specialties from around the world. The principal objective of this journal is to encourage the aforementioned, from developing countries in particular, to publish their work. The journal intends to promote the healthy transfer of knowledge, opinions and expertise between those who have the benefit of cutting edge technology and those who need to innovate within their resource constraints. It is our hope that this will help to develop medical knowledge and to provide optimal clinical care in different settings. We envisage an incessant stream of information flowing along the channels that WJMER will create and that a surfeit of ideas will be gleaned from this process. We look forward to sharing these experiences with our readers in our editions. We are honoured to welcome you to WJMER.
How Does Addiction Occur?

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Introduction
Addiction imposes enormous social and economic burdens on the individuals, their families, and on society as a whole. Illicit drug addiction, accounts for approximately 2% of the total burden of disease in Europe, with estimates for tobacco and alcohol at around 12 and 10% respectively. The economic costs of alcohol addiction alone in the UK are estimated to exceed £25 billion per year including health, crime-related costs and losses in productivity. For centuries people have tried to define addiction and understand its nature, in the hope of developing therapeutic solutions. Addiction has been described as a sin, crime, bad habit, moral weakness, disease and, most recently as a disease of the brain. Many factors have been identified that prompt people to experiment with illicit substances, however, taking a drug is not synonymous with developing an addiction. The question of addiction specifically concerns the processes by which drug-taking in certain individuals, evolves into compulsive patterns of drug-seeking and drug-taking that takes place at the expense of most other activities, and is characterised by the inability to cease.

Throughout the years, the understanding of this phenomenon has changed dramatically. Addiction was originally described in the context of drugs causing physical dependence and withdrawal symptoms, i.e. heroin and alcohol. Later, it became clear that other substances, such as tobacco, which do not cause physical dependence, are still strongly addictive. This uncovered the existence of both physical and psychological components of addiction. Thereafter, the concept of addiction kept evolving with its inherent association with drugs, i.e. medicines or other substances which have a physiological effect when ingested or otherwise introduced into the body. It has become apparent that it is not only drugs that one can develop an addiction to. Stimuli and activities such as gambling, internet use, shopping and sex can become strong addictions.

Due to the vast variety of addictive substances and stimuli, the development of a universal theory of addiction, encompassing all of its ‘faces’ is extremely challenging. A successful theory should enable prediction of circumstances in which addiction is more likely to occur and give insights into how it can be prevented, controlled and treated. It might seek to predict whether a given substance or activity will be addictive, who will be at risk of developing an addiction if exposed to particular stimuli, or whether changes in social factors will lead to an increase in the prevalence of particular forms of dependence.

Discussion
In thinking about the problem of addiction and the models of addiction, it is important to bear in mind that many people experiment with potentially addictive substances or stimuli, but most do not get addicted. Indeed, the factors responsible for experimental or casual drug use may not be relevant to the problem of addiction as the drug-taking and drug-seeking behavior in the addict may involve factors that are qualitatively different from those that motivate the non-addict.

One of the earliest theories of addiction is the positive reinforcement model, which postulates that addicts are motivated by the euphoric or hedonic effect that the drug produces. However although the pleasure effect associated with drug taking may be one of the factors prompting the experiment with drugs, in the addict the association between the hedonic consequences of drug consumption and the
ability of drugs to motivate behaviour often become
dissociated⁴. Firstly, drug-taking may increase
dramatically over time as an addiction develops, but
the pleasure induced by a given dose of a drug is not
reported to increase. Secondly, it has been reported
that even a 50% decrease in the subjective effects
of cocaine did not reduce it’s use by addicts⁴. Thirdly, it
has been shown that people will work for low doses of
morphine or cocaine that produce no subjective
pleasure at all ⁴. Finally, the positive reinforcement
theory implies that the addiction liability is directly
proportional to the drug’s euphorogenic power, but
then alcohol, which is a mood depressant, can cause
addiction. The positive reinforcement model is
strongly opposed by Khantzian⁵, who clearly states
that patients do not take drugs for the pleasure.
Indeed, clients of the addiction services themselves
often say they ‘hate taking drugs, drinking or smoking’
or even ‘feel disgusted by it’, but yet, cannot stop.

After the realisation that hedonic effects of the drugs
could not explain the phenomenon of negative reinforcement,
the focus shifted to the model of negative reinforcement,
which postulates that addicts are driven by withdrawal
avoidance. However, this model proved to have
considerable limitations too. Firstly, drugs that do not
produce strong withdrawal syndromes, such as
psychostimulants, can be highly addictive. Conversely,
some drugs that do produce tolerance and withdrawal,
such as tricyclic antidepressants or anticholinergics, do
not support compulsive patterns of use⁴. Furthermore,
the fact that there are only two drugs which produce
physical dependence and withdrawal symptoms, alcohol
and heroin, shows significant limitations of the negative
reinforcement model. Finally, the prolonged cessation of
the physically addictive drugs and the decay of
withdrawal symptoms are not synonymous with a cure
and relapse to compulsive use, even long after recovery
remains a major problem in addiction. Therefore,
although there are circumstances when the desire to
avoid withdrawal is undoubtedly a potent motive for
drug use, the urge to alleviate withdrawal symptoms is
neither necessary nor sufficient to account for
compulsive drug-seeking and drug-taking behaviors
or the problem of relapse.

In the search for a more comprehensive explanation
of addiction, the psychological and neurobiological
perspectives were combined resulting in the ‘incentive-
sensitisation’ model. Its core paradigm is that
potentially addictive drugs share the ability to produce
long-lasting adaptations in neural systems,
which render the brain reward systems hypersensitive
or ‘sensitised’ to drugs and drug-associated stimuli.
When sensitised, the incentive salience process
produces compulsive patterns of drug-seeking
behaviour. Through associative learning the enhanced
incentive value becomes focused specifically on drug-
related stimuli, leading to increasingly more
compulsive patterns of drug-seeking and drug-taking
behaviour. The persistence of neural sensitisation is
hypothesised to leave addicts susceptible to relapse
even long after the discontinuation of drug use⁴. The
involvement of the associative learning and
conditioning in addiction has also been proposed by
the ‘cognitive schemata model’ as well as the theory of
‘addiction as an excessive appetite⁵.

The biochemical component of the ‘incentive-
sensitisation’ model, i.e. the involvement of the brain
reward system and the neuroadaptations produced
by drug use have been further studied with the hope and
objective of finding a neurobiological explanation of
addiction. Betz and colleagues⁶ suggested that a common
mechanism might underlie addictions to otherwise
apparently unrelated drugs and hypothesised that, as
proposed by the ‘incentive-sensitisation’ theory, the
neurotransmitter dopamine might play a central role in
the molecular mechanism of at least some addictions.

This is consistent with Ross and Peselow’s⁷ study which
postulates that addiction occurs due to neurobiological
changes to the natural reward and adaptive behaviour
and proposes a common biochemical model of addiction.
According to this model, drugs of abuse corrupt the
motivational and learning neurocircuits and by doing so,
alter how an addicted individual interacts with salient
environment stimuli that come to predict reward,
whether it be biologically orientated or drug conditioned
stimuli. The mesolimbic dopaminergic pathway mediates
the acute rewarding aspects of drug intake and
conditioned learning associated with craving and relapse.
Adaptations in the mesocortical and cortifugal
glutamatergic pathway mediate the conscious aspects of
drug intake, such as craving, loss of inhibitory control,
and continued drug-acquisition behaviours at the
expense of biologically relevant ones and despite
catastrophic negative consequences. Several other
mechanisms have also been identified as involved in the
development of addiction ¹⁰. These findings are in line
with the conclusions reached by Hou and colleagues ¹¹ in
their study concerning imaging of the dopaminergic
system in drug addiction. The neurobiological theory of
addiction, if viable, offers potential for future
pharmacological therapies for addiction.

The discovery that the addicted brain is different in its
neurobiology from the non-addicted brain⁸ gave the
basis to the development of the theory that addiction
is a disease. More precisely, it is viewed as a chronic
disease of pathological learning with a relapsing
remitting course. This claim has met with fierce
criticism. Foddy\textsuperscript{12} argues that changes in brain structure and function are not enough to constitute a disease and that plasticity is a normal and largely beneficial characteristic of human brains. Indeed, in childhood, in the case of injury to the brain, the neuroplasticity allows for the function of the damaged parts to be taken over, to some extent, by others. Hence, one can argue that plasticity is simply an adaptation to changing circumstances, whether it be loss of a particular part of the brain, or chronic presence of a substance. Furthermore, Foddy\textsuperscript{12} insists that there are important practical consequences to defining something as a disease. Among other things, people are normally not held morally or legally responsible for the symptoms of a disease, even when it is self-inflicted. Here, some inconsistencies are highlighted - addiction is officially regarded as a disease, yet, the official application of the disease label has not freed the addicts from moral or legal responsibility. Moreover, unlike many other diseased people, they are denied disability payments and protection against workplace discrimination. Finally, the disease label transforms drug-taking from an autonomous, responsible choice into an external phenomenon, something which happens to the addict against his or her will. This approach would indeed question the rationale behind currently used and effective psychotherapies, which promote individuals' choice and will to be free of addiction. Despite the contra arguments, the concept that addiction is a neurobiological disease is now the official position of both the National Institute on Drug Abuse (NIDA) and the World Health Organisation (WHO).

Despite its wide evidence base, the biochemical model of addiction has been challenged. One of the major criticisms is the limitation to drugs and lack of consideration of addictive non-drug stimuli or activities such as gambling, internet use or shopping addiction\textsuperscript{5}. However, Ross and Peselow subsequently showed possible neuropathway involvement in addictive activities. The opioidergic and serotonergic systems have been implicated in impulse control disorders such as pathological gambling, a discovery which could lead to the development of potential pharmacological therapies for addiction. Another criticism of the biochemical model of addiction is its neglect of the social component\textsuperscript{5}. Similarly, Dingel and colleagues\textsuperscript{13} argue that the main potential harms of focusing on biological etiology of addiction stem from a concept of addiction that is dissociated from social context. Focusing on genetic testing and brain scans may lead one to overemphasise pharmaceutical ‘magic bullet cures’ and underemphasise, and underfund, more traditional therapies and public health prevention strategies that have proven to be effective. Genetic research on addiction may fundamentally change our conception of deviance and our identities and may thus transform our susceptibility to substance use into something isolated in our biology, not embedded in biosocial context. This point of view is supported by the effectiveness of currently used psychosocial therapies, such as e.g. cognitive behavioural therapy, intuitive recovery or meetings of alcoholics anonymous. Furthermore, the importance of the biosocial context is stressed by the ‘incentive-sensitisation’ model, which clarifies that sensitisation is not an inevitable consequence of exposure to potentially addictive drugs. It is not a simple pharmacological phenomenon and both the expression and the induction of sensitisation can be powerfully modulated by non-pharmacological factors, including environmental and (presumably psychological) factors associated with drug administration. It was evident in animal studies, which showed that sensitisation occurred more readily when a drug was given in a novel environment rather than in the animal’s home cage\textsuperscript{4}. The same conclusion was reached by the observations outlined by Kalant\textsuperscript{14} of American veterans of the Vietnam War who had returned to the United States as heroin addicts. A surprisingly high proportion of those who became abstinent during treatment remained abstinent since returning to their home environments. This is in striking contrast with the observations of addicts who had long been free of withdrawal symptoms and drug craving during their confinement in the hospitals, but relapsed abruptly on the return to the environments associated with their previous drug use. This phenomenon is often observed in patients recovering from drug addiction who admit that moving away from the environment previously associated with drug use greatly reduces their craving and chances of relapse. Moreover, interestingly, self-administration of the drug seems to play a crucial role in the development of addiction or lack of thereof after drug use. Physical dependence can be produced by large doses of an opioid analgesic administered therapeutically by a health care professional to a patient with severe pain; yet, such patients rarely become compulsive drug-seekers. The situation was different for wounded veterans of the American Civil War, who were issued syringes and morphine tablets for self-administration. Many of them did become victims of what was later known as a ‘soldier’s disease’, i.e. became addicted\textsuperscript{14}. Both groups described took the same drug for the same purpose of pain relief. The factor that was different for the group that developed compulsive drug-seeking behaviours was the self-administration of the drug. The fact that
sensitisation and gene expression are affected by environmental and contextual factors, as well as by the drugs that are self-administered, means that addiction cannot be conceptualised exclusively in terms of the interaction between the drugs and the biological constitution of an individual. Hence, the neurobiological model, despite providing valuable insight into the physiology of addiction which can yield helpful therapeutic solutions in the future, is in itself not sufficient to account for the development of addiction. A variety of elements of the environmental context must also be taken into account.

Another alternative explanation for addiction is the psychodynamic model. Similarly to the biochemical model, it describes addiction primarily as a disorder of self-control or self-regulation, but ascribed to social and environmental variables. According to Khantzian, individuals with addictions suffer because they cannot or do not regulate their emotions, self-esteem, relationships and their behaviour. Therefore, they self-medicate the distress and pain associated with self-regulation difficulties. Despite the possible temporary relief provided by short-term use of addictive substances, in the long run, the illicit substances erode the existing human capacity to cope, further increasing the person’s vulnerability to addictions. This theory is supported by the effectiveness of psychological treatments which focus on addressing and modifying the above-mentioned vulnerabilities which the psychodynamic model identifies as precipitating and maintaining factors for addictive behaviour. Individual and group therapies guided by understanding and empathy, provide powerful antidotes to the alienation, dysphoria and anguish, which are part of substance use disorders.

As outlined, the biological and psychosocial approaches to addiction have numerous differences, yet, they share a common view that addiction is characterised by a compromised ability of self-control and compulsive behaviour. Interestingly, this central paradigm of addiction has been challenged by the philosophical perspective on addiction. Addictive behaviours have been defined as compulsive for several reasons. Firstly, addicts appear to act compulsively because of their insensitivity to the costs of their drug use. Secondly, they appear compulsive because they regret their drug use, but still fail to reduce it. Thirdly, they appear compulsive because they report experiencing strong desires which they feel unable to control. Finally, neuroscientists have claimed that addicts behave compulsively because their actions have identifiable neurological processes as their root cause. Foddy argues that none of the reasons identified would be considered uncontroversial proof of compulsion within philosophical discourse. He states that neither regret, nor strong desire, nor imprudent choices, nor changes in brain biology can establish without further argumentation that addicts behave compulsively in the sense that these would diminish their responsibility for their choices. A philosophical mistake is made with important practical and scientific ramifications when the above reasons are taken to be sufficient proof that addicts lack control. Indeed, the question of control or lack of thereof in the context of addiction is of paramount importance. At the heart of this problem is the question whether we give to our strongest desires voluntarily or whether we have capacity for willpower which can fail in the face of a powerful urge, making these actions involuntary. Currently, there is a lot of controversy in this area. Various theories of addiction are based on the principle of impaired self-control and clients often admit they want to break their addiction, but cannot control themselves. Yet, the therapies used are centred on being in control and having strong will. Moreover, they are very effective and many clients recover proving they can be and are in control. This shows that much remains to be learned about the intricacies of self-control and its role in addiction.

The models described in this article provide valuable insight into the biological changes in the brain caused by addictive stimuli and ways in which these alterations further enhance appetitive behaviour as well the psychosocial mechanisms that fuel addiction and relapse. Nonetheless, a question remains unanswered of why the great majority of people who experiment with potentially addictive substances and activities do not become dependent whereas some individuals do. The search for an answer to this important question has directed both, biologically and psychosocially orientated research, towards identifying potential factors that can increase a person’s vulnerability or risk of developing an addiction. Based on the observation that addiction often runs in families, it has been hypothesised that inherited biological neuroadaptations could be responsible for the increased susceptibility of some individuals to develop an addiction. Ersch and colleagues recently investigated whether the prefrontal deficits measured in cocaine-dependent individuals are induced by chronic cocaine use or whether they are pre-existing, heritable traits. To approach this problem, cocaine-dependent individuals were compared with their drug naïve first-degree relatives and with unrelated drug-naïve volunteers by measuring impaired inhibitory control, a well-known phenotype among the cocaine addicts. Interestingly, equivalent behavioural impairments in inhibitory control as well as reduction in the prefrontal and striatal volume were found in the cocaine-dependent group and their biological siblings with no history of drug abuse, compared with unrelated relatives. The model of pre-existing biological predisposition and vulnerability to addiction was further investigated and confirmed in
subsequent animal studies. Different strains or genetically modified mice showed marked distinction in drug use and relapse and the ‘impulsive’ animals more readily acquired and intensively self-administered cocaine.

These studies suggest that heritable traits in the form of brain structure and consequent impulsivity are crucial to understanding risk and resilience in addiction. However, the fact that the genetically susceptible siblings of the investigated cocaine addicts did not develop addictions suggests that genes alone cannot account for addictions and other factors, such as the environment and social circumstances must play a role. These factors and their potential to increase one’s vulnerability to addictions were discussed by Khantzian as part of the psychodynamic model. He pointed out that the ability of humans to self-regulate their emotions, self-esteem, relationships and behavior was governed less by instincts and more by coping skills and capacities acquired from the caretaking environment, suggesting that inadequacy of the conditions that one grows up in can affect their susceptibility to addictions. This is where the psychodynamic model overlaps with attachment theory of addiction implying that individuals suffering from attachment difficulties in childhood may not have acquired adequate self-regulation mechanisms from their home environment, which can make them more vulnerable to developing an addiction. These findings strongly suggest that the power of addiction resides in the interaction of the drug with the internal terrain (the biological and psychosocial context) of the person who uses it. This highlights the complexity and multidimensionality of addiction and, hence, the need for a multidisciplinary approach in uncovering its nature.

**Conclusion**

It is concluded that addiction is an extremely complex phenomenon involving an interaction between an addictive substance or activity and an individual user, including their biological and psychosocial habitus. Molecular neurobiology studies have given valuable insight into the neuronal mechanisms and adaptive changes occurring in addiction as well as genetic predisposition to developing addiction. Moreover, behavioural responses such as conditioning have been implicated. There is also abundant evidence that psychological and social factors, such as self-regulation or attachment capacity, play a role in both predisposition to as well as development of addiction. However, none of the theories alone can fully account for the process of addiction. This suggests that understanding of this phenomenon in its entirety requires appropriate integrative multidisciplinary approaches of study, involving neurobiology, pharmacology, psychology, philosophy and sociology working towards a common goal.
References:


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