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Executive Summary

Drug dependence is a serious personal and public health issue in developed countries, such as, Australia, the European Union, the UK, and the USA. It is also becoming a serious problem in developing countries. Many forms of drug dependence are difficult to treat because we lack effective psychosocial or pharmacological treatments.

There is strong research evidence that many addictive phenomena have a neurobiological basis. These include: the fact that psychoactive drugs act on brain neurotransmitters; evidence of a genetic contribution to vulnerability to addiction; the neural mechanisms of tolerance and withdrawal; and the discovery of the neural basis for the rewarding and dependence-producing effects of the major drugs of addiction.

The major potential benefit from an improved understanding of the neuroscience bases of addiction is improved treatment. An improved understanding of the neuroscience basis of addiction requires animal studies of drug effects and drug dependence; experimental studies in humans of drug effects and the neurobiological consequences of drug dependence; clinical trials of new pharmacotherapies for drug dependence; and possibly trials of pharmacological and immunological interventions that aim to prevent addiction.

After a century of debate about the ethics of biomedical animal experimentation, a regulatory compromise has been reached between two sets of competing views. On the one hand, there are those who would abolish all animal experimentation (e.g. proponents of animal liberation and animal rights). On the other, there are those who accept human dominion over animals, according to which animals either have no interests or human interests should always prevail over animals' when their interests conflict. This regulatory compromise has reduced the amount of animal experimentation that is done by restricting the species on which research can be done; using invertebrates where possible, and minimising animal pain and suffering. Under this compromise, animal research is publicly accepted, including neurobiological addiction research on rats and mice. Proposals to develop primate models of addiction to provide a better model of human addiction may challenge this consensus.

Human experimental studies of the neurobiological basis of addiction raise a number of ethical issues. One is the capacity of addicted persons to give free and informed consent to participate in

such studies. So long as participants are not intoxicated or suffering acute withdrawal symptoms at the time they give consent, there is no compelling reason why persons who are drug dependent cannot give free and informed consent. The risks of drug administration, and the use of neuroimaging methods in these experiments, generally do not pose as serious a risk to participants as provocation studies in disorders such as schizophrenia.

The ethical issues raised by clinical trials of new pharmacotherapies have been extensively debated and a consensus has evolved on the conditions that must be met. These include free and informed consent; an acceptable risk-benefit ratio; and protection of participant privacy and confidentiality. Trials with drug dependent persons require special attention to informed consent to ensure that persons are not intoxicated or experiencing withdrawal symptoms when deciding to participate in trials. Placebo comparisons may be ethically acceptable in such trials *if* there is no effective pharmacotherapy and *if* participants are also offered good quality psychosocial care.

Preventive pharmacological interventions for addiction do not yet exist and are likely to be highly controversial if they are developed. It is a possibility that looms larger with the development of interventions that have a potential preventive use, foremost among which are drug vaccines. The ethical issues raised by these approaches need to be debated. The risks of stigmatisation and discrimination that are raised by any preventive intervention that identifies high risk subjects will need to be dealt with. So too will issues of consent in minors and the potential risks to participants of immunological interventions.

Neuroscience research on addiction will also affect the long running debate between moral and medical models of addiction by providing a causal explanation of addiction in terms of brain processes. According to one influential version of this approach, addiction is a "brain disease" that results from the flick of a metaphorical switch in the brain produced by chronic drug use. This perspective undermines the moral view that addiction is wholly a matter of individual choice that is best dealt with by punishment and imprisonment.

Medical models of addiction may not be a wholly positive development if they lead to simple-minded social policies. They may, for example, lead to the seductive simplification that if we identify the minority that is genetically and biologically vulnerable to drug dependence, then the rest of the population can use drugs with impunity. They can also lead persons with addiction to abdicate responsibility for their behaviour and to a preoccupation with individual explanations of

behaviour, to the neglect of social policies for reducing addiction, including drug control policies. The challenge for the addiction neuroscience community will be to develop an understanding of addiction that gives biology its due without depicting addicts as automatons under the control of receptors in their brains.

The use of pharmacotherapies and drug vaccines under legal coercion is likely to be contentious. It is an arguably ethical policy if the process is under judicial oversight and if offenders are offered constrained choices of (a) whether or not to accept treatment and (b) the type of treatment that they accept. Any coerced use of a cocaine vaccine should be done cautiously and only after considerable clinical experience with its use with voluntary patients. It should be trialed and its safety, effectiveness and cost-effectiveness rigorously evaluated. Such an evaluation also needs to examine any adverse social or ethical consequences.

The most immediate benefit of work on the neuroscience and genetics of addiction may be more effective drugs to assist addicts to stop using their drugs of choice. It may also allow better matching of addicts to treatments. Population screening for multiple genes of small effect that increase susceptibility to drug dependence are unlikely to be practical.

Neuroscience research on addiction is not likely to reduce the need for public health drug control policies. It is much simpler, cheaper and more efficient to discourage the whole population from smoking tobacco, for example, than it is to attempt to make smoking safer by identifying those at highest risk of nicotine addiction or smoking-related disease. The same is arguably true for alcohol and illicit drugs.

The preventive use of a drug vaccine is speculative and ethically contentious. Any trials of their preventive use should be preceded by extensive clinical experience with a vaccine in voluntary patients who are cocaine dependent. A higher standard of safety would be required if it was used preventively and important ethical issues would be raised, such as, consent to its use by minors, the protection of privacy, and the prevention of discrimination.

Introduction

In this paper we consider the ethical and human rights issues that are raised by neuroscience research on the addictions, that is, research that investigates the biological processes in the brain that underlie the behavioural phenomena of addiction, such as tolerance, withdrawal, and compulsive drug use. Neuroscientists seek explanations for addictive phenomena in the chemical activity that occurs when psychoactive drugs act on neurotransmitters which in turn act on molecular receptors in the synapses between neurones, activating specific neural circuits in the regions of the brain that subserve motivation, memory, cognition and behaviour (*1,2*). A detailed neuroscientific understanding of addiction promises to lead to the development of drugs that can be used to treat, and perhaps to prevent, addiction.

We have approached our task as follows. First, we briefly describe the burden of suffering and disability that addiction imposes before outlining the promise of neuroscience research in improving our understanding of addiction and our capacity to more effectively and humanely respond to those who become addicted to the widely used psychoactive drugs in our community, namely, alcohol, nicotine, cannabis, sedatives, opioids, cocaine and amphetamines. We also describe the major types of animal and human research that neuroscientists undertake on the addictions. Second, we briefly outline our approach to the analysis of ethical and human rights issues raised by neuroscience research. Third, we analyse ethical issues raised by the following types of neuroscientific research: experimental research on animals; experimental laboratory studies on humans; epidemiological studies of patterns of drug use and correlates of drug dependence; clinical trials of pharmacological treatments for addiction derived from neuroscience research; and trials of pharmacological approaches to the prevention of addictive disorders. Finally, we consider the ethical and human rights implications of neuroscience research on addiction, addressing the following questions: How will neuroscience research affect the way that we understand addiction? How will it affect the way that we treat persons who are addicted to drugs? What implications will it have for the prevention of addiction?

1. Why Undertake Neuroscience Research on Addiction?

1.1 The Burden of Addiction

Addiction to drugs like alcohol, tobacco and illicit drugs is common in the adult population of many developed societies. Epidemiological surveys in the USA (*3-5*) and Australia (*6*) show that in any year around 25% of adults are dependent on tobacco, 7% are dependent on alcohol and 2% are dependent on illicit drugs. The prevalence of addictive disorders has not been as well studied in developing countries, but there are indications from data on drug use and drug-related problems like HIV that addictive disorders are a substantial problem there (*7*).

Addictive disorders also make a substantial contribution to the global burden of disease in terms of premature deaths and years of life lived with disability (*8*). This is true for estimates of the contribution to disease burden in the developed and developing world. These findings have been confirmed by more detailed estimates of disease burden in Australia (*9*) where tobacco, alcohol and illicit drugs contributed to approximately 9.7%, 2.2% and 1.8% respectively of the burden attributable to disease and injury in 1996. Addictive disorders also cause substantial individual suffering to persons afflicted by addiction, and their behaviour adversely affects their families and the community in which they live through motor vehicle accidents, violence, assault and crime, and impaired work performance and parenting (*10*).

1.2 The Promise of Neuroscience Research on Addiction

Neuroscience research promises to improve our understanding of addiction, our ability to treat those afflicted by drug dependence, and possibly our ability to prevent addictive disorders (*10,11*). There are three main reasons for believing this to be the case. First, there is substantial evidence that genetics contributes to vulnerability to addiction. The most plausible hypothesis is that this genetic vulnerability is expressed in differences in neurotransmitter function in key brain regions (*10*). Second, psychoactive drugs have been shown to exert their effects by acting on key neurotransmitter systems in specific brain areas. Their chronic use produces changes in these brain systems that may explain many of the phenomena of addiction, including the rewarding effects of drugs, tolerance, withdrawal, and relapse to drug use after abstinence (*11*). Third, neuroscience research is beginning to explain the effectiveness of many currently used pharmacotherapies, some of which (e.g. methadone) were introduced before recent advances in

neuroscience. Current research promises to provide more effective pharmacological therapies for the treatment of addiction (*11*).

1.2.1 Genetics

Work on the genetics of addiction indicates that people may inherit an increased likelihood (*vulnerability*) of developing drug dependence. Family studies of alcohol and other drug use disorders suggest that these disorders cluster in families (*12-15*). Adoption studies suggest that there is a significant genetic factor that influences adoptees' vulnerability to alcohol use disorders (*16,17*). Research with twins also finds that there is a significant genetic component (*heritability*) that increases the likelihood of dependence on a range of substances (*13,17-19*). Recent research involving male twins suggests that there is a common genetic vulnerability to substance misuse (*18,20*). The most plausible explanation of the genetic data is that there are genetic differences between individuals in genes controlling neurotransmitter systems. It is most likely that either multiple genes with small effects, or a small number of genes with incomplete penetrance, influence susceptibility to addiction (*13,21*).

1.2.2 Drugs of Addiction and Neurotransmitters

Alcohol, nicotine, heroin and cocaine act on neurotransmitter systems in the brain and on receptor molecules that respond to endogenous substances in the brain. Alcohol, for example, increases inhibitory transmission at gamma-amino-butyric acid (GABA-A) channels, increases serotonin (5HT-3) function, dopamine release and transmission at opiate receptors, and reduces excitatory transmission at the NMDA subtype of the glutamate receptor (*22,23*). Nicotine increases transmission of the neurotransmitters acetylcholine, norepinephrine, dopamine, serotonin, glutamate and endorphin (*24*). Cannabis acts on a cannabinoid receptor system that is distributed in brain regions subserving mental functions that are affected by cannabis, such as, memory, cognition and motor function (*25*). Opiate drugs act as agonists at three major opiate receptor subtypes (*22,26*). Cocaine binds to dopamine, noradrenaline and serotonin transporters (*22*), but exerts its reinforcing and stimulant effects by blocking dopamine re-uptake (*27*).

The chronic use of these drugs changes brain functioning. Users develop tolerance, requiring increasingly larger doses of drug to produce the desired psychoactive effect. Withdrawal symptoms, or an abstinence syndrome, may occur when drug use is abruptly discontinued, and

may contribute to a resumption of drug use. These phenomena are attributed to neuroadaptation (*28*): changes that occur in the brain that oppose a drug's acute actions after repeated drug administration. When drug use is discontinued, the adaptations are no longer opposed and so the brain's homeostasis is disrupted (*28*).

Different drugs of addiction act on different receptor systems, but they all act on brain systems in the medial forebrain that are mediated by the neurotransmitter dopamine (*28,29*). The mesolimbic-fronto-cortical dopamine system is a critical final pathway in the brain that controls reward (*28,29*). Dopamine has been implicated in the reinforcing effects of alcohol, with alcohol use resulting in the direct stimulation of dopamine and also an indirect increase in dopamine levels (*22*). The behavioural rewards of nicotine, and the basis for nicotine dependence, appears to be linked to the release of dopamine in the mesolimbic pathway (*23,24*). Similar findings have also been reported for cocaine, heroin and cannabis (*28*).

1.2.3 Pharmacological Treatments of Addiction

The major practical benefit of neuroscience research on addiction is likely to be improved treatment of addiction. The hope is that an improved understanding of the biological processes of addiction will enable persons who are drug dependent to be more effectively withdrawn from drugs and initiated into treatment that will reduce the likelihood of their relapsing to drug use and dependence. A longer term prospect is an improved capacity to prevent addiction.

The development of effective pharmacological treatments of addiction (such as, methadone maintenance) preceded the neuroscience research that now explains their effectiveness. In the case of the opioids, for example, the longer acting opioid methadone was shown to be effective in withdrawing and treating opioid dependent persons before opioid receptors were identified. Methadone can be administered orally in decreasing doses to achieve withdrawal from shorter-acting opioids like heroin (*30*). It can also be given in maintenance doses to prevent withdrawal symptoms, reduce craving and stabilise an addict's life to enable them to disengage from heroin use (*31*). Subsequent research has shown that methadone and other opioids (e.g. buprenorphine and LAAM) act on the same neurotransmitter systems as heroin and prevent heroin from exerting its effects by occupying the same receptors.

Neuroscience research on the neural mechanisms underlying alcohol's effects have identified agents, such as, naltrexone and acamprosate, that attenuate the rewarding effects of alcohol and reduce craving for alcohol in abstinent persons who were alcohol dependent (*32*,*33*). When given to abstinent alcoholics, both drugs reduce rates of relapse to dependent drinking. Nicotine replacement therapy has long been used to assist tobacco smokers to quit (*24*). Recently, the antidepressant bupropion has been found to substantially increase abstinence rates in nicotine dependence (*24*). We have had much less success in finding an effective pharmacological treatment for cocaine dependence. Despite several decades of research, we do not have pharmacological treatments for cocaine dependence that are as effective as methadone maintenance treatment is for heroin dependence (*34*). Recent research on a cocaine vaccine has suggested that immunological approaches may improve the outcome of treatment for cocaine dependence (*35*).

2. Types of Neuroscience Research on the Addictions

We have classified neuroscience research on addiction into four broad categories. These are: animal experiments; epidemiological research on addiction; human experiments; and clinical trials of pharmacological treatments for dependence and trials of preventive pharmacological interventions.

2.1 Animal Experiments

Animal experiments investigate the biological processes underlying addiction using animal behavioural models of human addictive behaviour. A popular animal model for studying human addiction is the self-administration paradigm in the rat. In this paradigm, a rat is taught to press a bar that delivers a dose of a psychoactive drug (such as nicotine or cocaine) via a syringe or canula into the animal's blood stream or into specific brain regions. This paradigm has been used to assess: the abuse liability of new psychoactive drugs; the effects of chronic administration of addictive drugs on behaviour; the addictive phenomena of tolerance and withdrawal; the effects of antagonist drugs on the rewarding effects of addictive drugs; and the neurochemical changes that are produced by chronic drug administration (*10*). The major reasons for doing these studies are that much greater experimental control is possible with animals, and more invasive experiments can be done on animals than would be permitted in humans. This research often results in animals acquiring an addiction to a drug and the animals are usually killed to permit the direct study of the effects of drug administration on neurotransmitter function.

2.2 Epidemiological Research on Addiction

Epidemiological research on drug addiction includes a range of studies whose boundaries are not sharply defined. It could be taken to include surveys of patterns of licit and illicit drug use in the community in that these define the populations of persons who are at risk of addiction because of exposure to drug use (e.g. *36*). These studies also identify the characteristics of regular drug users among whom would be included those who are drug dependent. Longitudinal studies of characteristics that predict the initiation and maintenance of drug use also bear upon addiction (*36*,*37*). Epidemiological research also includes studies of the prevalence and correlates of drug dependence in the general population (e.g. *3*,*5*,*6*). It also includes observational studies of treated populations who are followed up long after treatment to examine mortality, morbidity and

abstinence among drug dependent persons (e.g. *38*). The longer such treated populations are followed up, the less these studies are studies of treatment outcome. We take all of these types of studies to be included under the heading of epidemiological research. There is nothing that is specifically neuroscientific about these epidemiological studies, but their findings must be explained by credible neuroscience theories of addiction. In future, the inclusion of genetic and biological markers of risk in epidemiological studies will mean that their findings more directly contribute to neuroscientific research on addiction.

2.3 Human Experimentation

Human neuroscience experiments typically involve laboratory studies under controlled conditions of the effects of chronic drug exposure on current brain function or the acute effects of exposure to drugs, drug analogues, or drug-related cues (e.g. injecting equipment) on behaviour and brain function (*11*). An increasingly common type of study involves the use of brain imaging technologies (such as PET, SPECT and fMRI) (*39,40*) to study the acute effects of drugs and the neurobiological consequences of chronic drug use and drug dependence (e.g. *41-43*).

Human neurobiological experimental research offers little prospect of direct benefit to study participants. The major benefits of these studies are to future patients through an improved understanding of the aetiology and treatment of addiction. Such studies often involve some risk of harm to participants. In the case of brain imaging this may include exposure to weakly radioactive substances that are used to monitor brain processes. There are also some risks from exposure to drugs of addiction, other drugs that produce similar effects on brain function and potentially therapeutic substances such as antagonists, all of which act on the central nervous system.

2.4 Clinical Trials of Pharmacotherapy for Addiction

Clinical trials of pharmacotherapies for addiction compare the effects of different drug treatments, and sometimes placebos, on the drug use, health, social adjustment and well-being of persons who are drug dependent (*44*). The drugs that are trialed are increasingly identified as potential treatments for drug dependence as a result of neuroscience research on the biological mechanisms of addiction. These may include trials of: drugs that assist in completing withdrawal from a drug of dependence; drugs that are intended to reduce relapse to dependence after

withdrawal; and drugs that are intended to provide long-term maintenance of abstinence or psychosocial stability.

Clinical trials differ from experimental studies in one key respect: participants in clinical trials have some chance of benefiting from their participation in the study (*44*). This may be by obtaining access to good quality treatment for drug dependence (in the event of their receiving standard treatment or a placebo), or access to a promising experimental treatment for drug dependence (if they are assigned to the new treatment). As with participants in experiments, they may also be exposed to risks of the drug treatment, such as drug side effects and toxicity (*44,45*).

2.5 Trials of Pharmacotherapies to Prevent Addiction

Preventive trials involve controlled evaluations of pharmacological treatments that aim to prevent the development of drug addiction. This might be achieved by using a drug to treat a condition that increases a person's risk of developing drug dependence (e.g. attention-deficit hyperactivity disorder). It could conceivably involve the administration of a drug vaccine (e.g. against nicotine or cocaine) to young people who are at risk of addiction in order to reduce their chances of developing drug dependence, if they use nicotine or cocaine.

Trials of preventive pharmacotherapies are more a prospect on the horizon than a major undertaking at present. They nonetheless need to be discussed because two research developments suggest that such trials may soon be advocated. One is the development of vaccines against cocaine and nicotine. The initial motive for developing these vaccines has been to reduce relapse to drug use in persons who have been treated for dependence (*35*). However, these vaccines could be administered to children and adolescents with the intention of reducing their likelihood of becoming drug dependent. The second development has been "early interventions" with persons at high risk of developing schizophrenia. These involve a combination of psychosocial and pharmacological interventions. Because this work has been controversial in psychiatry, neuroscience researchers in the addictions would benefit from a discussion of issues that may arise in trials of preventive pharmacological treatments for addiction.

3. Our Approach to Ethical Analysis

There is a bewildering array of competing ethical theories that purport to rationalise common moral rules and allow us to decide what conduct is right or good or which course of action ought to be pursued in problematic cases (*46*,*47*). These theories include: utilitarianism or consequentialism, which judges individual actions or moral rules by the net effects for good and ill that they have on all who are affected by them (e.g. *48*); deontological or duty-based theories that derive obligatory rules for moral conduct from over-arching general ethical principles (e.g. *49*); rights-based theories (e.g. *50*); and the more recent and yet to be elaborated communitarian ethics (e.g. *51*). There is no consensus on which of these is the "best" ethical theory.

In the absence of consensus on a theory of ethics, ethical analyses of neuroscience research on addiction cannot rely upon the deduction of moral rulings from categorical imperatives or the use of a utilitarian calculus to select that action from all conceivable actions that produces the greatest good for the greatest number. This does not mean, however, that rationality has no role in ethics or that ethical analysis is a matter of arbitrary individual taste about which there is little point in arguing.

Ethical analysis does not always achieve consensus but the range of morally acceptable behaviour is often narrowed by ethical debate. A dialectical discovery process emerging from debate and discussion can identify common moral rules and shared justifications for particular courses of moral action. This process has been described as the method of "reflective equilibrium" (*49*). It involves testing ethical principles (that may be derived from one or more ethical theories) against widely shared moral rules that have been called the "common morality" (*46*). The process aims to reduce the discrepancies between our moral principles and our understanding of the "common morality", and by a process of iterative adjustment, works towards achieving an equilibrium between our principles and our shared moral judgements (*44*).

Over the past 30 years or so, an influential set of moral principles has emerged in Anglo-American analyses of the ethics of biomedical research (*44*,*52*). These are the principles of autonomy, non-maleficence, beneficence, and justice (*46*). They have also been included in influential international statements of ethical principles for medical research, such as, the Helsinki Declaration and the statements of United Nations organisations (*44*). For our purposes these can be regarded as a moral baseline for the ethical analysis of neuroscience research on the

addictions, with the proviso that they may need to be supplemented to deal with newly emerging issues.

3.1 Principles of Biomedical Ethics

3.1.1. Respect for Autonomy

Respecting autonomy means that we respect and do not interfere with the actions of rational persons that have a capacity for autonomous action, that is, adults who are able to freely decide upon a course of action without influence, coercion or force (*46*). The ability to make autonomous choices is based on self-deliberation, self-determination and self-governance, which some moral theories regard as a requirement of being a person ("personhood"). A being is said to be a person if and only if he or she has the capacity for autonomous action and has the ability to suffer. In the context of biomedical research, the principle of respect for autonomy is usually taken to require: informed consent to treatment or research participation, voluntariness in research participation, and maintenance of confidentiality and privacy of information provided to a researcher (*46*).

3.1.2 Non-Maleficence

The principle of non-maleficence simply means, "do no harm" (*46*). Following the principle of non-maleficence requires us to refrain from causing harm or injury, or from placing others at risk of harm or injury. In the biomedical research context, the principle of non-maleficence requires researchers to minimise the risks of research participation (*44*,*46*).

3.1.3 Beneficence

Beauchamp and Childress have identified "positive beneficence" and "utility" as two elements of the principle of beneficence (*46*). Positive beneficence requires us to perform actions that result in a benefit. Utility requires us to ensure that the benefits of our actions outweigh the burdens they impose upon others. The principle of beneficence therefore requires that an action produces benefits and that its benefits outweigh its burdens. In the context of biomedical research, this means that the benefits of the research to society should outweigh its risks to participants and also that, in the case of individual participants, the benefits of participation exceed the risks.

3.1.4 Distributive Justice

Justice is probably the most controversial of the four moral principles. For the purpose of our discussion, "justice" refers to "distributive justice" rather than retributive (criminal) or rectificatory (compensatory) justice (*46*). In bioethics, the principle of distributive justice has been central to debates about how to ensure equitable access to health care and to reduce unequal health outcomes. In the case of research, the principle of distributive justice refers to the equitable distribution of the risks, as well as the benefits of research participation (*44*). A fair and just research policy would aim to achieve a distribution of the benefits and burdens of research participation that is as fair and equitable as possible.

3.2 Human Rights

In 1948, the Universal Declaration of Human Rights (UDHR) set out an international set of human rights that would be honoured by all nations that signed the declaration (UN General Assembly, 10 December, 1948). The UDHR recognised that all people have rights by virtue of being human and that these were universal in the sense of applying equally to all people around the world, regardless of who they are or where they live (*53,54*). The UDHR enjoined nations to treat all people as equal and to promote and protect the right to life, liberty and security of person. It included "negative rights" such as the rights not to be enslaved or kept in servitude, and not to be tortured or subjected to cruel, inhuman and degrading treatment or punishment. It also obliged signatory states to afford people equal treatment before the law and the equal protection of the law without discrimination, by requiring that everyone charged with a penal offence should be presumed innocent until proved guilty according to law in a public trial with access to "all the guarantees necessary for his defense" (UDHR, 1948, article 11).

Ethical principles in medicine and human rights both embody injunctions to behave in specific ways but they differ in to whom they apply (*55*). Ethical principles typically apply to individuals, usually health care workers and researchers, whereas human rights impose obligations on states and governments to promote and protect the rights of their citizens from infringements by the state or others (*55*). Human rights are most relevant to the way in which treatments and interventions derived from neuroscience research are used to treat and prevent addiction. This is

because treatment and prevention may involve the use of the coercive powers of the state to threaten the human rights of persons who are addicted to drugs (*56*).

4. Ethics of Animal Experimentation in Neuroscience Research

4.1 General Justification of Animal Experimentation

The use of animals in biomedical research has traditionally been justified by a utilitarian argument that the harm inflicted upon animals in the course of research is outweighed by the gains in scientific knowledge to humans (and animals) (*57*). This defence has been generally accepted by the scientific community but it has received more qualified support from the public as a result of media reporting of controversial examples of animal experimentation (*44*).

For some researchers, animal research presents no ethical issues. Such an unreflective view often indicates an implicit belief that human beings have a special moral status that sets them apart from other animals. This is an unconscious residue of the theological doctrine of special human creation (*58*) that not only conflicts with the evolutionary origin of animals and humans; it also undermines the major rationale for biomedical research on animals, namely, that it will illuminate the causes of human health and disease because of the similarities between the biology of humans and other animals. As Rachels argues, it is inconsistent to accept the Darwinian theory of evolution and to believe that humans have unique biological and psychological characteristics that make their interests more important than those of other species (*58*).

4.2 Arguments Against Animal Experimentation

A number of different arguments have been raised against the use of animal subjects in scientific research. One objection is that the benefits gained from animal experimentation have been greatly exaggerated (*59*). Resnik rejects this statement, observing that animal research has provided some significant benefits to humans, for example, animals have been used in epilepsy research to examine the mechanisms that cause the disease, and to improve treatments (*60*). In any case, even if we accept that the benefits of animal experimentation have been exaggerated, this does not invalidate animal experimentation so long as there are some benefits. It may create a moral obligation to eliminate unnecessary animal research that is of doubtful benefit to humans.

A second objection to animal experimentation is that animal studies are unnecessary because there are alternatives to animal models, such as, tissue cultures and computer simulation (*57*). Although these technologies may provide useful alternatives to some types of animal

experimentation (e.g. product testing), they cannot replace the use of animals in neuroscience research because:

> "[t]issue cultures cannot develop depression, alcoholism…social abnormalities, or other psychologically relevant problems. To be useful, computer simulations have to be based on knowledge obtained from live behaving organisms, and therefore, cannot substitute for studies of live animals" (*61*).

A third criticism of animal experimentation is that the animals used do not provide good models of human biology, physiology and psychology (*57*). This criticism seems to have particular force when applied to neuroscience research. For example, research has shown that cortical organisation varies between species and that some non-human primates lack characteristics found in humans (*62*). It has also been argued that the psychology and neurobiology of addiction are not well-modelled in commonly used animals such as mice and rats (*57*). Thus, non-human primate models are "…desirable because the cortical anatomy and behavioural repertoire of primates more closely resembles those of humans" (*10*). However, much of the current knowledge regarding the neuroscience of addiction has come from animal experimentation using a number of different species. For example, 'knockout' mice have been used to identify initial targets for drugs, such as the CB_1 cannabinoid receptor, and biochemical pathways involved in cocaine metabolism have been investigated in the fruit fly *Drosophila melanogaster* (*63*).

The fourth and most influential and radical challenges to animal experimentation are the moral objections raised by some philosophers and ethicists, notably Peter Singer and Tom Regan. Both believe that animals are over-used in research, and often suffer unnecessarily. As a utilitarian, Singer argues that non-human animals have the capacity for suffering and enjoyment, and therefore, their interests must be viewed in equal consideration with those of humans (*64*). Anything less than this, Singer says, amounts to speciesism, which he equates with racism and sexism as an arbitrary and unjustified moral preference in favour of the interests of one's own species (*48*).

Singer does concede that some animals have a greater capacity for suffering than others, namely 'self-conscious' species such as mammals. In Singer's view, these self-conscious animals have future desires and a better understanding of what is happening to them during experimentation. Singer reasons that self-conscious non-human animals are more intelligent and aware of pain

than “humans with severe and irreversible brain damage” (*64*). He argues that researchers should not perform experiments on these animals that they would not perform on disabled humans. As a preference utilitarian, Singer agrees that an experiment that causes the death of one animal but saves the lives of thousands is justifiable. However, he argues that in most animal experimentation the benefits for humans do not outweigh the harm done to animals (*48*).

A more uncompromising view is taken by Regan who argues that experimentation on animals contravenes their moral right not to be harmed (*68*). He argues that no individual, animal or human may be harmed for the benefit of others, and so rejects the utilitarian justification for animal experimentation (*65,66*). Regan opposes all animal experiments designed to benefit humans, and rejects the use of animals in experiments designed to increase basic knowledge (*67,68*). He maintains that the risks of research experiments cannot be placed upon animals because they are unable to consent to their involvement (*66*).

4.3 A Policy Compromise

If the arguments of Singer and Regan were accepted, most, if not all, animal experimentation in psychology and neuroscience would have to stop. Their views have not been generally accepted by the community but their advocacy has reduced animal experimentation and increased the protection of animals from painful experimentation. Varner suggests that a societal compromise has been negotiated between those who oppose animal experimentation and those who deem it necessary (*67*). The moral objections to animal experimentation have increased the burden of proof that defenders of research must meet (*67*). This is a reasonable outcome as long as the burden of proof is not insurmountable.

Resnik has suggested that we accord moral status to animals on the basis of their ‘cognitive and emotive features’ (*57*). In his view, animals at the ‘high’ end of this scale, such as humans, have moral rights and duties in addition to their moral status. Animals at the other end of the scale have no such duties, but still have some moral status. Experiments involving animals at the ‘high’ end of the scale thus require more rigorous justification than those involving animals at the ‘low’ end of the scale. This gradation of moral status fits with the moral intuitions of researchers and the general public about what is permissible in animal experimentation. Most people who do not oppose animal experimentation in principle, for example, would probably agree that experiments involving non-human primates require greater scientific justification than those involving mice

(e.g. *59*).

The animal welfare and animal rights movements have had a significant influence on the regulation of animal experimentation in many countries. Government legislation now generally takes the interests of experimental animals into account by controlling the type of experiments that can be undertaken, the animal species that can be used in experiments, and the number of animals that can be used. Legislation in most countries recognises species distinctions by discouraging experiments on higher order vertebrates, especially when other vertebrates or invertebrates can be used instead (*44,69*).

In most countries, legislation adopts one of two perspectives that each acknowledges the need for animal experimentation while placing restrictions on the practice (*44*). European and American legislation takes a 'human priority' position in which animal suffering and loss are minimised but the interests of humans take precedence over those of animals when they conflict (*44*). In contrast, legislation in the United Kingdom and Australia is based on a 'balancing' position in which the interests of humans are generally regarded as more important than those of animals but they can sometimes be over-ridden in order to protect animals (*44*). Unlike legislation in Europe and America, UK and Australian legislation requires that during the ethical review process, the benefits of the proposed experiments be weighed against the harms that will be inflicted on the animals (*44*).

4.4 Special Issues in Neuroscience Addiction Research on Animals

Restrictions on animal experimentation have not prevented neuroscientists from undertaking research on addiction using animal models, such as, the rodent self-administration paradigm. There are no indications that public sentiment will change in ways that will threaten the continuation of this research. There may be more objections, however, to neuroscience animal research if we were to follow the recent recommendation of addiction researchers that animal models be developed that more closely resemble human addiction by undertaking experiments on addiction in non-human primates, such as, rhesus monkeys (*10*). The argument for conducting experiments that harm primates creates a moral dilemma, as Rachels has noted:

> "If the animal subjects are not sufficiently like us to provide a model, the experiments may be pointless…But if the animals are enough like us to provide a

> model, it may be impossible to justify treating them in ways we would not treat humans" (*58*).

The current legislation in many developed countries implicitly recognises this view by being more restrictive in the use of mammals (such as cats, dogs and primates) than in the use of mice or rats in biomedical research (*44*). This attitude may reduce the capacity of neurobiological addiction researchers to develop primate models of addiction phenomena, such as, self-administration paradigms. If they wish to do such research, they will need to persuade the public and legislators that this research is essential.

5. Ethical Principles in Human Biomedical Research

Since the Nuremberg trials of German medical researchers after World War II, a consensus has developed about the basic ethical requirements for biomedical research on humans (*44,52*). In most developed countries, national ethical codes set out ethical obligations that investigators must adhere to if their research is to be ethically and scientifically legitimate. Although specific conditions for ethical approval may differ from country to country, the same basic set of ethical principles is found in most national guidelines (*44*). These include independent ethical review of research proposals, respect for patient privacy, informed consent to participate in research, and protection of privacy and confidentiality of information (*44*). These are outlined before we discuss special issues raised by neuroscience research.

5.1 Independent Ethical Review of Risks and Benefits

In order for any human research to gain approval, investigators must obtain ethical approval from an independent ethical review committee, usually an institutional ethical review committee. An external review of a study protocol provides an independent assessment of whether the benefits of the proposed trial outweigh any risks that it poses to participants (*44*).

5.2 Informed Consent

Informed consent to participate in a research study is usually a matter of asking the research subject to consent to their participation after a detailed discussion of what their participation will entail and a description of any adverse events that may occur (*44*). The participation of persons under the age of eighteen would normally require the consent of a parent or guardian, along with the *assent* of the participant. Any uncertainty about the risks of participation must be accurately communicated, and there must be close monitoring of any adverse events, with medical care promptly provided for any adverse outcomes. The inclusion of cognitively impaired persons in a study may require special consideration. Consent may need to be obtained from a surrogate who makes a decision on behalf of the impaired research subject (*44*).

All forms of consent must be given after the participants are informed of what their involvement in the research will require of them. Research participants should have time to reflect on and consider their obligations at each stage of the consent procedure. Ideally, the consent process

would include a third party, usually a clinician not involved in the study, to ensure the integrity of the consent process. Participants must be allowed to withdraw at any time and this option must be given to participants at all stages of the research. A research subject's decision to withdraw must be respected, and subjects must be informed that they will not suffer any consequences upon withdrawal, such as, refusal of routine counselling or medical care (*44*). The data collected from a participant must be omitted from the final results if they withdraw from the study.

5.3 Subject Recruitment

The conditions under which persons are recruited into a study must not involve any form of coercion or use excessive inducements to participate (*44*). In recent years, it has become more common to reimburse participants for their involvement in some research studies. The most common justification is that reimbursements maximise initial recruitment and retention of participants in a study. Small reimbursements are offered to compensate participants for the time spent participating in a trial or for their travel expenses. Reimbursements may be interpreted by some potential subjects as rewards for participation and by researchers as a way of increasing the number of trial participants. Ashcroft argues that inducements are ethically acceptable if the inducement serves to recompense a participant for the inconvenience so long as it is *not* seen as a payment for any harm caused (*70*).

5.4 Privacy and Confidentiality

Researchers are obligated to protect the privacy of study participants. The participant's personal information must not be divulged to any individual or group of individuals without the participant's direct consent, and individual participants should not be identifiable from the published results of the study (*44*). These rules are especially important when study participants have a stigmatised condition like a mental illness or drug dependence.

6. Emerging Ethical Issues in Neuroscience Research

6.1 Research on Vulnerable Persons

Research involving persons who are cognitively or physically impaired requires special ethical consideration (*44*). A major ethical issue is whether vulnerable persons are capable of providing informed consent, specifically whether they are able to: (1) understand the rationale behind a clinical trial, (2) understand exactly what is required of them and why, and (3) give their free and informed consent to participate in the study (*71*).

We use the term "vulnerable" in three senses, following Roberts and Roberts (1999). Such persons may be vulnerable for one or more of the following three reasons: personal limitations to their freedom (intrinsic), environmental factors that limit their freedoms (extrinsic), and limitations on their freedom by virtue of a relationship with another person or group (relational) (*72*).

A generally accepted model of practice is one that recognises, caters for and protects the individual's special needs and minimises or eliminates any potential harms associated with the study (*44*). Moreover, an ethical requirement for IRB approval of research on vulnerable persons is that the proposed study benefits the individual and that any prescribed medical treatment is either the only or the best form of alleviating disease-related symptoms. One of the most ethically defensible frameworks used in trials involving vulnerable groups is the *protection model*.

Usually, there are three major elements inherent in the ethical approach used by researchers recruiting vulnerable persons for research participation. First, vulnerable participants must usually benefit from the trial, that is, the treatment offered to vulnerable persons must include some benefit to individual participants. Second, vulnerable participants must not usually be exposed to more than a minimal risk of harm. Third, the treatment must be more effective than any already available treatment options. A requirement that these three elements be met is one version of a protection model for research participants who are considered to be vulnerable (*71*).

Concern about research on vulnerable persons has been most pronounced in experimental and clinical studies of persons with schizophrenia (*72,73*). Critics of specific research studies, including patient advocates and carers (e.g. *74*), have advocated stringent standards for obtaining

informed consent in cognitively impaired persons. These include independent review by IRBs that include patients or patient advocates among their members (*74*). Some researchers have criticised these types of protection for being overly paternalistic and denying the mentally ill the right to make decisions on their own behalf (*75*). Proxy decision-making has been described as cumbersome, and some have argued that these restrictions will prevent important research into the causes and treatment of a serious cause of suffering (*72*).

6.1.1. Are Drug Dependent People Vulnerable Persons?

Do persons who are drug dependent have an impaired capacity to consent to participation in research? There has not been a great deal of discussion of the issue in the addictions field (for exceptions see *11,45*). Most of the recent controversy about neuroscience research on vulnerable populations has been about research on persons with schizophrenia (*73*) and stroke (*76*). In these cases, there are serious doubts about the capacity of some patients to give free and informed consent because they are intermittently or chronically cognitively impaired. We consider analogies between these cases and issues in experimental research on persons who are drug dependent.

Addiction per se does not impair in the same way or in the same degree as acute schizophrenia. Nonetheless, drug dependent persons may be vulnerable to coercion and inducement to participate in research when they are intoxicated or when they are experiencing acute withdrawal symptoms (*11,45*). Persons who were severely intoxicated by alcohol and cocaine, for example, suffer similar impairments to a person who is acutely psychotic. Similarly, a drug dependent person who was experiencing acute withdrawal symptoms could be induced to consent to participate in research studies by the offer of their drug of dependence, or medication to relieve their withdrawal symptoms (*11,45*).

Intoxicated persons would normally be excluded from experimental studies on the grounds of good research design, apart from the ethical problems with their inclusion. Intoxicated persons would also not be allowed to enter treatment trials until their intoxication had subsided and they had either completed drug withdrawal (as a precondition of entering abstinence-oriented treatment) or they had been stabilised on maintenance medication if maintenance treatment was to be trialed. Issues of informed consent would arise in conducting controlled trials of drugs that are used to treat symptoms of drug toxicity or overdose. In such cases where a person is unable to consent, proxy consent review may be required.

It can be argued that consent to participate in research studies should not be sought from persons who are experiencing acute symptoms of withdrawal. This may be an issue in experimental studies of acute drug effects into which only current drug users can be recruited because drug naïve subjects are excluded on ethical grounds (*11*). In such cases, the offer of drugs of dependence may be seen as an inducement to participate for drug-dependent persons in withdrawal. To avoid this problem, such studies should probably assess the severity of withdrawal symptoms when screening for subject suitability and before obtaining informed consent to participate in the study (*11*,*45*).

6.2 The Risks of Provocation Studies

Some research on schizophrenia has raised strong ethical concerns because it involves exposing persons whose capacity to consent is impaired to potentially serious risks. Such studies are called provocation studies. Drugs such as ketamine and amphetamine are administered to persons with schizophrenia with the aim of provoking symptoms of the disorder. These studies have their analogues in addiction neuroscience studies of the effects of drug administration on brain function. We begin by outlining the debate in the field of schizophrenia before examining the relevance of this debate to neuroscience research on the addictions.

Psychiatric Symptom Provocation Studies (PSPSs or "medical challenge studies") involve giving psychoactive substances (e.g. amphetamine) or exposing subjects who have mental disorders (e.g. schizophrenia, anxiety disorders) to stimuli (combat videos) in order to study the underlying pathophysiology of the patient's disorders (*77-79*). The responses produced by pharmacological provocation may eventually be used to: (1) select treatment, (2) provide preliminary assessments of the efficacy of new drug treatments, and (3) predict treatment response (*77*,*79*). Provocation studies have aroused greatest controversy in studies of schizophrenia because of the seriousness of relapse in this condition (*79*).

The most commonly used symptom provocation studies in medical science are the treadmill cardiac stress test and the glucose tolerance test. Analogies have been drawn between these diagnostic procedures and psychiatric symptom provocation studies. The argument is that just as the cardiac stress test (which began as an experimental procedure) has become a widely used diagnostic procedure, so too symptom provocation methods may eventually prove useful in

treatment selection and prediction of relapse (*77*). The main ethical issues raised in these papers concern informed subject consent, subject selection, short and long-term risks of provocation studies, and their scientific merit.

Informed Consent: The capacity of subjects to consent to the provocation procedure is central to the debate. Views differ between patient advocates and researchers on the capacity of schizophrenic patients to consent to such studies. D'Souza et al. suggest that the following improvements are required to the consent process: (1) family involvement, (2) involvement of an independent clinician to monitor the consent process, (3) video recordings of the consent process to enable independent assessments to be made of its adequacy, and (4) more readable consent forms (*77*). Similar suggestions have been made by some patient advocates (*74*).

Subject Selection: There is agreement that the risks of the provocation procedure should be minimised by excluding from such studies persons with severe mental illnesses, especially those with a history of violence, suicidal or homicidal behaviour, and prolonged relapses (*77,80*).

Scientific Merit: The scientific merit of some symptom provocation studies has been questioned by D'Souza et al. (*77*). Avila et al. defend such studies in principle, but concede that other types of study may be more effective in achieving scientific goals without causing patients distress (*79*). D'Souza et al. argue that studies that aim solely to provoke symptoms are unjustifiable unless they also serve the more serious scientific purpose of providing new insights into the pathophysiology or treatment of the disorder (*77*).

Risk: The risk to participants is the major ethical concern raised by patient advocates and carers. Proponents of provocation studies argue that the symptom exacerbation produced is transient, lasting between a few minutes and a few hours (*78*). D'Souza et al. argue that risks to the individual may be more serious and include: extreme psychotic symptoms, prolonged period of relapse, suicidal or homicidal behaviour, hospitalisation, loss of work or benefits, and disruption of family life (*77*). There are anecdotes of cases in which symptom provocation has produced prolonged relapses into psychosis. There are, however, very few studies that have examined the long term risks of participation in these studies. The lack of such information is a serious issue because symptom provocation studies generally do not offer the participant any prospect of benefit, such as, improved treatment or alleviation of symptoms.

The vulnerability of research subjects and the possibly serious risks that they entail raise serious doubts about the ethical justification of symptom provocation studies in severe mental illnesses such as schizophrenia. Their continued use requires strong justification and more serious ethical debate (*77,80*). In the meantime, such studies should be undertaken sparingly, and only after careful external scrutiny, preferably with the involvement of patient advocates on IRBs.

6.2.1 Provocation Studies in Neuroscience Research on Addiction

Provocation studies in neuroscience addiction research often use neuroimaging to study the effects of a psychoactive drug on brain function in drug users and drug dependent persons. For example, heroin dependent persons may be injected with a radioactive labelled substance, placed in a PET or SPECT scan (e.g. *39*), and then given an opioid drug or exposed to drug-related stimuli with the aim of identifying sites in the brain at which the drug acts (e.g. *41-43*). These provocation studies involve little or no prospect of therapeutic gain to participants. Their most likely benefits are an improved understanding of addiction that may benefit future patients by improving treatment outcome.

Informed consent procedures for provocation studies in the addictions need to make clear to potential participants the absence of any therapeutic gain and the risks of participation. Subjects who were seeking treatment should be actively referred to a treatment service (*45*). Steps also need to be taken to ensure that the capacity to give voluntary consent is not impaired because subjects are intoxicated or experiencing withdrawal symptoms. This may require screening for symptoms of drug dependence and withdrawal at the time of recruitment (*11*).

The risks of provocation studies in the addictions field would seem to be lower than those involving subjects with schizophrenia. Drug administration in these studies is a good deal less risky than drug use that occurs outside the laboratory setting. Much lower doses of pharmaceutically pure drug are used in laboratory studies, in the absence of concurrent drug use as occurs in the community. It is also administered under medical supervision with protocols in place to deal with any adverse events (*11*). Risks of drug administration can be further reduced by screening out persons who have experienced adverse effects from drugs such as the psychostimulants. The use of stimuli associated with drug use is much less invasive and poses fewer risks than exposure to drugs. The radioactively labelled substances used in some forms of

neuroimaging pose very little risk to subjects and the newer imaging methods, such as functional magnetic resonance, do not involve exposure to radiation or radioactive substances (*40*).

Symptom provocation studies in the addictions are more likely to meet ethical standards required by IRBs than those involving schizophrenia. They may be ethically acceptable and scientifically useful if subjects give free and informed consent to participate and no unfair inducements are used (e.g. offering drugs of dependence to patients suffering acute withdrawal symptoms). The risks of the procedure do not seem to be high, and are certainly much less than those in provocation research on schizophrenia that have been so controversial.

7. Ethical Issues in Epidemiological Research on Addictions

Epidemiological research on patterns of drug use and drug dependence is not usually seen as part of neuroscience research because it usually relies upon self-reported information on drug use and drug-related problems. Such research includes: surveys in the general and special population of drug use and drug dependence (e.g. *3,5,6*), twin studies of the genetics of addiction (e.g. *17*), and longitudinal studies of drug use and its consequences among young people (e.g. *36,37,81*) and among persons who have been treated for drug dependence (e.g. *38*). The findings of such research inform neuroscience research by describing addictive phenomena that need to be explained by neuroscience theories, such as, the individual characteristics that predict drug use and the development of drug dependence and other drug-related problems, and the genetic epidemiology of drug dependence found in twin studies. The distinction between epidemiological and neuroscience research on the addictions is also likely to become blurred when epidemiological studies include biological measures, such as, DNA from which specific susceptibility genes can be tested and other biological markers of risk.

The major ethical issues in epidemiological research are ensuring that participants give free and informed consent and protecting participants' privacy and the confidentiality of any information that is collected. Since no experimental procedures are involved, the major risks that subjects face arise from the possible use to their detriment of information that they provide. This may potentially include social ostracism and stigmatisation, if their drug use becomes known to family, friends or neighbours, and criminal prosecution if any information that they provide about illegal drug use or other criminal behaviour becomes known to the police in a way that can be linked to the individual.

7.1 Free and Informed Consent

Free and informed consent to participate in epidemiological research does not present any special problems for adults who can understand the nature of their participation and can freely decide to be involved or not. It presents more of an ethical issue for epidemiological studies of adolescents, which are increasingly being done because adolescence is the period when drug use often begins. The participation of adolescents in any form of research usually requires parental consent and adolescent assent (*44*). Obtaining such consent can be cumbersome in school-based surveys of drug use (an efficient way of doing surveys of drug use). It requires that the adolescent takes

home a consent form, asks his or her parents to complete it, and then remembers to bring the form back to school in time to participate in the survey. The result is typically low response rates, which is likely to be differential because it is more likely to lead to the exclusion of adolescents whose parents do not speak the majority language and adolescents who are at risk of drug use because of frequent absence from school. This has prompted researchers to use "passive parental consent", that is, to inform parents that a survey is to be done via a circular that invites parents to object to their child's participation. It is then assumed that the absence of parental objection means that the child can be included in school surveys. This approach requires more ethical justification and community discussion.

The payment of subjects for research participation may also raise issues of consent, especially in studies of drug users. In Australia, for example, it has been common practice since the early 1980s for drug researchers to pay drug users AUD$20 if they participate in research interviews. The money is intended to compensate participants for their time, travel and inconvenience. This method was used in studies of criminal behaviour among drug users in the early 1980s, and in national studies of AIDS and the health of drug users as part of the ANAIDUS studies that were conducted nationally in 1988/89. Payment of subjects is also standard practice in drug research in the USA.

The rationale for this practice is that compensating drug users for the inconvenience of being interviewed enlists the cooperation of drug users who are not enrolled in treatment services or in prison. AUD$20 is not a large sum of money, and for much of the period it was well below the street price of most illicit drugs. The inconvenience involved in most interviews is considerable, with typically an hour or more of the person's time taken. In addition, they usually travel from their homes to be interviewed.

In Australia, this strategy has proved to be a successful way of recruiting illicit drug users for research studies of among other things: needle-sharing and sexual behaviour for HIV transmission among drug users; risk factors for the transmission of hepatitis C and other infectious blood-borne diseases; patterns of illicit amphetamine use, including injecting use, the reasons for making the transition to injecting, and the prevalence of psychological and health problems caused by injecting amphetamine use; the prevalence and correlates of drug overdoses among heroin users; and national monitoring of trends in illicit drug use since 1996.

The information collected in these studies could not be obtained in any other way. Interviewing drug users in treatment, for example, would be of limited use because many drug users do not seek treatment, and those who do usually do so after several years of problem drug use. Obtaining information in this way provides advance warning of emerging trends in illicit drug use. It also provides an opportunity to provide drug users with information about the risks of their drug use, e.g. pamphlets, leaflets. Such information helps in the design of educational campaigns aimed at illicit drug users. The findings of these studies are also regularly presented to drug and alcohol treatment staff to alert them to problems emerging among persons seeking their help.

A concern expressed by critics of this practice is that the money will serve as an inducement because it will be used by drug users to buy drugs. The first question is whether drug users have the same rights as anyone else to be compensated for the time and inconvenience of being interviewed. The money may well be used to pay for tobacco, alcohol or illicit drugs, but so is any income that drug users obtain by employment, social welfare, or property crime. In terms of the daily drug use pattern of most injecting drug users, $20 buys a very small amount of the street drugs that they use per day. This issue remains unresolved.

7.2 Confidentiality, Privacy and Legal Hazard

Protecting the privacy of participants and the confidentiality of the information that they provide is critical in such research. The use of some drugs (e.g. cannabis, cocaine and heroin) is illegal, as is the use of alcohol by persons who are under the minimum legal drinking age. Drug use surveys may also ask about illegal drug use and the commission of other illegal acts, such as driving while intoxicated, selling illegal drugs or engaging in theft, fraud or violence to finance drug use. If such data were linked to an identified individual and given to the police, then the participant could face criminal charges. In the USA, certificates of confidentiality can be obtained by researchers that provide subjects with an assurance that this will not happen. The legal situation in most other countries is much less clear.

Confidentiality is much less of a problem when data are collected in a single cross-sectional interview. The information provided usually does not contain the subject's name or other identifiers because this information need not be collected. Confidentiality becomes more of an issue if interviews are recorded (e.g. on tape) because this could be used in a court of law.

Confidentiality becomes a potentially serious issue in longitudinal studies in which individually identifying data (e.g. name and address, and the names and addresses of family and friends) are collected so that individuals may be recontacted for further interviews at a later date. A standard precaution is to securely store names and identifiers, and to keep these separate from the survey data. Confidentiality will become an even more important issue when DNA samples (or biological tissues from which DNA can be obtained) are collected, because DNA provides a unique way of identifying all individuals (except identical twins). When linked with questionnaire or interview data, DNA permits information on self-reported illegal acts to be reliably linked to an individual. Special precautions will therefore be necessary to protect privacy in epidemiological studies of illegal drug use that also collect biological samples. This may require legislation similar to that which applies in the USA.

7.3 Distributional Justice

Justice and the criteria for good epidemiological research are in agreement in requiring that a representative sample of the population at risk is recruited into studies of patterns of drug use and drug dependence in the population. There may be issues raised by poorer retention in longitudinal studies of the indigent, homeless and poor, who may be at higher risk of developing drug dependence. Justice may also be an issue in studies of persons who have been treated for drug dependence if there is a preponderance of studies of persons entering publicly funded addiction treatment and a lack of representation of persons who are treated by private health services or private specialist physicians and psychiatrists.

8. Ethical Issues in Clinical Trials of Pharmacological Treatments for Addiction

Clinical trials of new therapeutic drugs are required for drug registration in most developed countries, and are now a widely accepted part of medical practice. There is international agreement that the criteria for the ethical conduct of such studies include: free and informed consent by study participants; an acceptable risk benefit ratio for participants; and protection of patient privacy and confidentiality (*44*).

8.1 Independent Ethical Review of Risks and Benefits

In order for any clinical trial to proceed, investigators must obtain ethical approval from an independent ethical review committee. The committee provides a disinterested and independent assessment of whether the benefits of the proposed trial outweigh any risks that participation poses to subjects.

8.2 Informed Consent

Informed consent to participate in a clinical trial is mandatory under international ethical codes for biomedical research (*44*). It involves asking the research subject to give consent to participate after they have been given a detailed discussion of the study protocol and the events that will occur during the trial (e.g. assessment, randomisation, treatment, and follow up). They also need to be told about any adverse events that may occur. The participation of persons under the age of eighteen would require the consent of a parent or guardian and the assent of the minor. Care would need to be taken to ensure that subjects were not at the time of giving consent under the influence of any drugs that may hinder rational decision-making.

All forms of consent must be given after the participants are informed of what their involvement in the research will require of them. Research participants should have time to reflect on and consider their obligations *before* providing written consent. A trial must allow participants to withdraw at any time without affecting their treatment. This option must be given to participants at all stages of the research. A subject's decision to withdraw must be respected and subjects must not suffer any consequences upon withdrawal, such as, refusal of routine counselling or medical care. The data collected from a participant must be omitted from the final trial data set if they withdraw from the study.

8.3 Subject Recruitment

Small reimbursements are offered to compensate participants for the time spent participating in a trial or for their travel expenses. Ashcroft argues that inducements are ethically acceptable if the inducement recompenses a participant for the inconvenience of participation and it is *not* seen as a payment for any harm caused (*70*). Because drug dependent persons are arguably a vulnerable social group, it would not be ethical to offer large financial or other in kind inducement to participate in a clinical trial. The use of smaller reimbursements to attend for follow up interviews is more defensible.

8.4 Privacy and Confidentiality

The privacy of trial participants is an important ethical obligation for all treatment trials involving persons who are drug dependent. The participant's personal information must not be divulged to any individual or group of individuals without the participant's direct consent, and participants' identities should not be identifiable from the published results of the study. These rules are accepted as necessary components of ethical clinical trials by experienced investigators; they are especially pertinent when studying a stigmatised disorder like drug dependence.

8.5 Trial Design

A randomised controlled trial (RCT) is widely accepted as the "gold standard" for treatment evaluation in medicine because it minimises bias in determining which patients receive which treatments (*82*). Random assignment to treatment is ethically acceptable if there is genuine uncertainty about the comparative worth of the two treatments, if trial participants are aware that they will be randomised, and if they are informed about the type of treatment to which they may be assigned (e.g. active or placebo) and risks of these treatments in the course of obtaining their informed consent to participate in the trial.

The choice of a comparison condition for a RCT raises an ethical issue: When is it ethically acceptable to compare the effectiveness of a new drug treatment for addiction with a placebo? Some authors have argued that it is unethical to provide only a placebo treatment, if there was an existing treatment that was effective for the condition (*44*). This argument is relevant in the case

of drug dependence, some forms of which can be life-threatening in the absence of treatment. It would be ethically acceptable, however, to use a placebo comparison condition if there was no effective pharmacotherapy for the condition, and if both treatment groups received the best available psychosocial treatment (*45*). In this case, the clinical trial would answer the question: does adding a pharmacotherapy to good psychosocial care improve outcome by comparison with adding a placebo to good psychosocial care? Since it is likely that any pharmacotherapy will ultimately be used in combination with good psychosocial treatment (*35*), this is usually the most relevant question to ask in a RCT of a new pharmacotherapy for drug dependence.

8.6 Distributive Justice

Justice and the criteria for good clinical trials agree in requiring that a representative sample of the population is recruited into such studies (*44*). Special efforts may need to be made to ensure that women, children and minorities are included in clinical trials to ensure that they have access to the benefits of research participation and that the results of research studies can be applied to these groups if drugs that are trialed are eventually approved and registered for clinical use (*44*).

8.7 Conflict of Interest

An ethical issue of increasing significance, given the extent of pharmaceutical company funding of clinical trials, is ensuring public confidence in the results of clinical trials (*83,84*). Public trust has been undermined by investigators who have failed to disclose their personal financial interests in the outcomes of clinical trials (e.g. as a result of being paid large consultancy fees for promoting pharmaceuticals or shares in pharmaceutical companies). This has become a larger problem as public funding for medical research and universities has been replaced by research funding from pharmaceutical companies. Conflict of interest is a special concern when research funded by pharmaceutical companies is conducted by contract research organisations with the pharmaceutical company sponsors controlling publication of the data (*83,85*).

No matter how scientifically rigorous and ethical a study is, its findings are of limited use if the public is not confident about their validity (*83,84*). Policies have been implemented by editors of leading medical journals in an effort to restore trust in clinical research. One has been the requirement by editors of leading medical journals that authors disclose funding sources, potential conflicts of interest, and assert that they have had complete control over the study data

and its analysis (*83*,*84*). A register of clinical trial protocols has been established to minimise the suppression of unfavourable results or ex post facto selection of results and methods of analysis to make a drug look its best (*86*).

Additional policy recommendations that have not so far been implemented include: independent monitoring of compliance with the study protocol, especially the reporting of adverse events experienced by participants; and a requirement that investigators and the sponsors of a trial commit to publishing its results within 2 years of data collection as a condition of the study being approved by an ethics committee (*87*). The latter seems well based given that the major ethical justification for undertaking research studies is to contribute to scientific knowledge (*44*), and that this cannot happen if trial results are not published (*87*).

9. Trials of Preventive Pharmacological Interventions for Addiction

Psychosocial and educational interventions have been widely used with the aim of preventing young people from using drugs (*88*). Universal interventions are aimed at all young people; indicated, targeted or selective interventions are aimed at those young people who are identified as being at higher risk of initiating drug use. The impact of both universal and selective educational interventions on rates of drug use has often been modest (*89*).

Psychosocial preventive interventions raise ethical issues. Universal interventions (those directed at all children) raise concerns about unintended adverse consequences, such as, encouraging drug experimentation in young people who may not otherwise have done so. Targeted or indicated interventions (those addressed to children at increased risk) raise additional ethical issues because they require the identification of young people who are at increased risk of using drugs. Their consent and that of their parents is required for them to participate in preventive interventions. In the process of obtaining such consent, the parents and their children may be acquainted with their risk status. Participation in trials of preventive interventions may also expose them to social stigmatisation and discrimination, if their participation in such interventions becomes known to their teachers, peers and their peers' parents. For example, parents whose children are judged to be at "low risk" may actively discourage their children from associating with "high risk" children, or they may agitate for high risk children to be excluded or removed from schools.

The same ethical issues of stigmatisation and discrimination are also raised by pharmacological or immunological interventions that aim to prevent drug addiction. We discuss two such interventions: early pharmacological interventions with persons at risk of addiction that may be inspired by similar efforts to prevent psychoses (e.g. *90*); and the preventive use of vaccines against drug effects to reduce risks of addiction (*91*).

9.1 Early Intervention Studies

Early intervention studies in schizophrenia identify persons who are at increased risk of developing schizophrenia because they have a family history of the disorder or they have psychological symptoms that may be early or "prodromal" symptoms of the disorder. Advocates of this approach aim to prevent the development of schizophrenia by a combination of good psychosocial care and low doses of the neuroleptic drugs that are used to treat schizophrenia

(*90*). Studies in Australia and the USA have shown that it is possible using standardised criteria to identify a group of young people who have a high risk (30-40%) of developing schizophrenia in the ensuing 6 to 12 months (*90,92*). A number of quasi-experiments and randomised trials suggest that the combined intervention reduces the rate at which schizophrenia occurs and reduces the severity of the disorder in those who develop it (*90*).

Critics of these studies have raised a number of ethical issues (e.g. *93,94*). These include the fact that there is a high false positive rate: 60% of those who are identified as being at risk do not develop the disorder. There is also the potential for stigmatisation and discrimination against those who are identified as being at risk. Even if there is no discrimination, there is the possibility that there will be adverse effects on individuals of being labelled as at risk of developing schizophrenia. There is also concern about the capacity of children and adolescents to consent to participate in such studies, and doubts about the acceptability of using proxy parental consent. Long term treatment with neuroleptic drugs can produce neurological disorders such as tardive dyskinesia. McGorry et al. have countered that the potential benefits (the prevention of schizophrenia and early treatment of cases that do occur) outweigh the potential risks of neuroleptic medication and stigmatisation, both of which they suggest (on the basis of controlled studies) have been exaggerated (*90*).

Analogous approaches could be taken to early intervention for addiction, although to date no trials have been explicitly undertaken with the aim of using pharmacotherapies as preventive interventions for addiction. Stimulant drugs, such as methylphenidate and dexamphetamine, have been used to treat children and adolescents with Attention Deficit and Hyperactivity Disorder (ADHD), an intervention that is controversial (*95*). Since ADHD in combination with conduct disorders increases the risks of developing substance use disorders (e.g. (*96*), and stimulant drugs reduce symptoms of ADHD (*97*), an unintended by-product of stimulant medication may be the prevention of addictive disorders. However, no one has so far argued for the use of psychostimulant medication to prevent addiction. It is unlikely that anyone would do so. Public concern about the long term use of stimulant drugs to treat ADHD suggests that any such proposal will be opposed; support for the chronic use of drugs in late childhood or adolescence to prevent the development of drug dependence would seem to be even less likely. Public sentiment is likely to pose a considerable obstacle to trials of preventive pharmacological interventions for addiction in childhood and adolescence.

There are additional ethical concerns about preventive pharmacological interventions for addiction. They would need to identify adolescents who were using drugs in ways that put them at high risk of becoming drug dependent. This could, in principle, be done by urine screens of children who displayed other behaviours that predict drug use, such as, truancy, conduct problems at school, and minor delinquency. Children identified in this way could be given antagonist drugs or vaccines to reduce rewarding effects of drugs that they may use. This is still a possible scenario rather than a serious proposal, but the ethical issues raised by this approach need to be carefully considered before it is implemented. We do so next when considering the use of drug vaccines to prevent addictive disorders.

9.2 Preventive Use of Drug Vaccines

Animal studies have shown that it is possible to use complexes of drugs and proteins to induce the formation of antibodies to drugs such as cocaine (e.g. *98,99*). These antibodies in the blood combine with the drug to prevent it reaching the brain to exert its effects (*99*). Animal studies show that antibodies against cocaine markedly attenuate its stimulant effects and block self-administration in rats (*100,101*). Human trials of its use in relapse prevention among cocaine dependent persons are being planned (*102*). If cocaine vaccines prove safe and effective in treating cocaine dependent persons, they could be used to prevent cocaine dependence in adolescents and young adults. Such a possibility has been raised and so is briefly discussed (*91,103*). Similar arguments will no doubt arise with the proposed preventive use of nicotine vaccines.

The preventive use of cocaine and nicotine vaccines would be ethical in the case of adults who voluntarily decided to use them after being informed of any risks. The vaccines would need to be shown to be safe and effective for this purpose, with higher standards of proof generally required for the safety and efficacy of preventive measures (*104*). The foreseeable risks of using the vaccine would have to be communicated to the person, who would have given informed consent to its use, and steps would need to be taken to protect the person's privacy. Under these conditions, the voluntary administration of a cocaine vaccine to a consenting adult who adjudged themselves to be susceptible to cocaine dependence would be ethically acceptable (*104*). Such use, however, is likely to be unusual.

The preventative vaccination of children and adolescents against cocaine dependence is a much

more ethically complex issue. Children would presumably be immunised against cocaine dependence at the request of their parents. Their parents would consent on behalf of their children who, as minors, would not be legally able to give informed consent. Parents already make choices on behalf of their children that affect their lives as adults (e.g. their diet and education). Some have argued, therefore, that immunisation against cocaine dependence would simply be another decision that some parents would make for their children (*91*). On this argument, a parent would have the right to immunise their child against cocaine dependence in much the same way as they have the right to vaccinate a child against measles or infectious disease (*105*).

Cocaine use may start in adolescence. Adolescents under the age of majority are able to reason and have sufficient capacity to be involved in decisions about their future, such as, whether they want to be immunised against cocaine dependence. Even if it is ethically acceptable for parents to consent on behalf of their children, the assent of an adolescent or an older child should be sought. Their failure to give assent should rarely be over-ridden and only if there is a strong moral reason for doing so (*44*).

Given the limited evidence and clinical experience with cocaine vaccines, we believe that it is too early to consider using cocaine vaccines to prevent cocaine dependence in adolescents. This does not mean that such a policy is unethical; only that it should not be implemented without much more careful ethical analysis and community consultation and debate. And any trials of this use should only occur after considerable experience has been obtained with the use of a cocaine vaccine in freely consenting adults.

10. Implications of Neuroscience Research for Models of Addiction

There has been a long running competition between moral and medical models of addiction (*106,107*). A moral model of addiction sees it as largely a voluntary behaviour in which people freely engage. On this account, addiction is an excuse for bad behaviour, one that allows some drug users to continue to take drugs without assuming responsibility for their conduct (*108*). Drug users who offend against the criminal code are therefore to be prosecuted and imprisoned if found guilty (*108*). A medical model of addiction, by contrast, recognises that, while many people can use some drugs without losing control over their use, a minority of users does lose control over their use and develops a mental or physical disorder – an addiction – that requires specific treatment if the sufferer is to become and remain abstinent (e.g. *107*).

The neurosciences promise to provide a causal explanation of addiction in terms of brain processes. The thesis is that addiction is a "brain disease" that results from the flick of a metaphorical switch in the brain that occurs as a result of chronic drug abuse (*107*). This perspective undermines the simple view that addiction is wholly a matter of individual choice and hence that drug users are best dealt with by punishment and imprisonment.

Medical models of addiction may not be a wholly positive development if they lead to simple-minded social policies. For example, the idea that addiction is a categorical disease entity lends itself to a seductive simplification in the case of alcohol, namely, that if we identify the minority of people who are genetically vulnerable to alcohol dependence then the rest of the population can use alcohol with impunity (*109*). This view ignores the adverse public health effects of alcohol intoxication. It is also at odds with the dimensional nature of alcohol and drug use and symptoms of dependence, and with the genetic evidence that multiple genes are involved in susceptibility to alcohol and drug dependence. It can also lead to an abdication of responsibility for one's behaviour (*110*) and to a preoccupation with individual explanation of behaviour and a neglect of remediable social causes and social policy options for reducing the prevalence of addiction, including drug control policies.

The implications of a neuroscience view of addiction for drug control policy (discussed below) are also not as simple as they may seem. Exposure to drug use remains a necessary condition for the development of addiction so societal efforts still need to be made (whether by criminal law or public health measures) to limit access to drugs by young people (*107*). Social disapproval also

remains a potent way of discouraging drug use. We can hope that neuroscience explanations of addiction may temper societal stigmatisation and ostracism of drug dependent people, especially young people who have made unwise choices about the use of drugs. Demonstrations of the greater cost-effectiveness of treatment than imprisonment may also provide an economic justification for a more humane, as well as a more effective and efficient, societal response to addiction.

The challenge for the addiction neuroscience community is to explain addiction in ways that give biology its due without depicting addicts as automatons under the control of receptors in their brains (*111*). This means seeing addiction as the result, in part, of choices that are made by individuals, not always wisely in the case of young people who operate with a short time frame in view, a sense of personal invulnerability and a scepticism towards their elders' warnings about the risks of drug use. It will also mean seeing loss of control over drug use as a matter of degree, with dependent drug users retaining the capacity to choose to become abstinent and to seek help to do so. It would be wise to encourage the community to see pharmacological drug treatments as prostheses for an impaired will, a kind of Ulyssian self-binding against temptation, rather than as the *sine qua non* of addiction treatment. It will also acknowledge that pharmacological treatment is only the beginning of the process of recovery and reintegration of the drug dependent person into the community. And it will require attention to a broader range of social policies in seeking to prevent drug use by our youth (*88*).

11. Implications of Neuroscience Research for the Treatment of Addiction

11.1 Improved Treatment of Addiction

The most likely benefit of neuroscience and genetic research on addiction is an improvement in cessation rates among persons who are drug dependent. This may happen in a number of ways.

First, a better understanding of the genetic and neuroscience basis of drug dependence may lead to more effective drugs to assist in cessation of drug use (*10,107,112*). These may include drugs that act on key neural reward pathways or affect drug metabolism. Such drugs may have fewer adverse side effects than existing ones. There may also be drug vaccines to help former addicts remain abstinent by preventing their drug of choice from acting on receptors in their brains.

Second, genotyping of addicts may better match patients to existing pharmacological treatments for addiction, such as, bupropion and nicotine replacement in the case of smoking (*112,113*); acamprosate and naltrexone in the case of alcohol dependence; and opioid agonists and antagonists in the case of opioid dependence. If, as seems likely, individual genes only modestly predict response to pharmacological treatments, then actuarial methods (such as multiple regression) will be needed to select treatment. Given the expense of genotyping (even with an anticipated reduction in cost with technological improvements, such as, high throughput testing using DNA microarrays), pharmacogenomic treatment selection will need to improve upon simpler methods of treatment matching, such as using behavioural measures (e.g. measures of dependence, or the number of previous unsuccessful quit attempts). It would also need to do better than the simpler policy of offering all patients the most effective treatment (averaged across genotypes) (*114*).

We will also need to consider disadvantages of giving drug dependent persons information about their genetic vulnerability to drug dependence. There is the possibility that it may encourage them to believe that their drug dependence is intractable (*115*). To avoid this outcome we will need to provide better education to overcome the mistaken belief that a genetic contribution to the causation of behaviour means that it cannot be changed. We need easily understood examples, such as, the fact that spectacles can correct short-sightedness which is under partial genetic control (*114*).

11.1.1 The Role of Drug Vaccines

If a controlled clinical trial demonstrates that nicotine and cocaine vaccines are safe and effective treatments of these types of drug dependence, then their use in the voluntary treatment of drug dependent adults needs to address a number of ethical issues (*91,104*).

The first ethical issue would be ensuring that patients freely consent to receive a vaccine with full knowledge of any risks that its use entails (*104*). Free and informed consent requires that patients are informed about the benefits and potential risks of the treatment and that they are not coerced into or unfairly induced to participate in treatment. The question of whether coercion is permissible and if so, under what conditions, is taken up below. These ethical requirements apply to existing pharmacological treatments for opioid dependence; they would not present any unique problems for the use of passive immunisation against nicotine or cocaine.

A potentially unique feature of active cocaine vaccination is that it may, in principle, have long-lasting consequences, namely, creating antibodies that can be detected in the blood of treated patients for some months. These antibody levels may not be sufficiently high to be therapeutic, but the fact that they could be detected raises the ethical issues of privacy and discrimination (*91*).

Of special concern is the possible loss of privacy by recovering cocaine addicts if employers and insurance companies had access to this information. Employers and insurance companies often obtain detailed personal medical information and, on occasion, blood samples from potential employees or clients. Because the community strongly disapproves of cocaine dependence (*91*), the loss of privacy by a recovering cocaine addict may lead to embarrassment, at best, and to social stigmatisation and ostracism by people in their social environment and in the wider community. As a result, former cocaine users could be discriminated against in the workplace or community (*91*). In the future, increasing social stigmatisation of smokers, and the possibility of discrimination by employers and the health insurance industry, may raise similar issues for smokers who use a nicotine vaccine to stop smoking.

Discrimination may arise if workplace based drug testing were to screen for cocaine antibodies before and during employment. A recovering cocaine dependent person would be at risk of losing an employment opportunity if cocaine antibodies were detected in a blood sample. If this

information were more widely disseminated to other workers, this could have a devastating effect on the employment prospects and recovery of the addict (*91*).

One way of avoiding these outcomes may be to accept Cohen's proposal that a society that wishes to have the benefits of a cocaine vaccine “must institute legal and behavioural changes that preserve privacy and confidentiality" (*91*). This requires a culture that encourages and supports the recovery of persons with drug dependence. Legislation that punishes discriminatory behaviour towards recovering persons with dependence has been adopted in the case of HIV infected persons; the adoption of a similar approach to persons who have been treated for cocaine dependence would be an important step towards reducing discrimination and protecting privacy.

The risks of loss of privacy and discrimination could also be minimised by using “passive” rather than “active” immunisation to prevent relapse (e.g. by administering antibodies to cocaine rather than a vaccine). This approach would not produce an enduring change in the person’s immune system and the antibodies would disappear over a period of weeks. These advantages would be purchased at the price of a shorter period of protection (without a booster injection) that may reduce treatment effectiveness. This may be a trade off that a patient concerned about privacy was prepared to make; it is a choice that they should be offered (*104*).

11.2 Access to Treatment

If pharmacological treatments derived from neuroscience research prove to be effective, the issue of ensuring equal access to treatment for all those who may need it is an ethical issue that needs to be addressed. If a substantial proportion of addicted persons are unable to access treatment because they are unable to pay for it, public funding may be needed to ensure that it is more widely accessible (*106*). Public provision of such treatment will require an economic justification, especially in the case of persons who are dependent on illicit drugs, many of whom will be indigent and unable to pay for their treatment. Advocates for publicly subsidised drug treatment will need to make clear the comparative economic and social costs of treating drug dependent people as against the current policy in many countries of dealing with addiction solely through the criminal justice system (*89,106*).

11.3 Legally Coerced Treatment

The potential use of a pharmacological treatment for drug dependence or a drug vaccine under legal coercion needs to be considered (*91*). It is often the first possible use raised when the concept of a drug vaccine is mentioned; community concern about this way of using drug vaccines may also adversely affect attitudes towards *any* therapeutic use. The issue accordingly needs to be discussed, even if it is a long way from being realised. There are good reasons for caution about any coerced use of a pharmacological treatment or a drug vaccine. The community does not have much sympathy for offenders who are drug dependent who engage in property and other crimes, so we may need to be more conscientious in protecting their legal and human rights.

11.3.1 The Rationale for Treatment under Legal Coercion

Legally coerced drug treatment is entered into by persons charged with or convicted of an offence to which their drug dependence has contributed. It is most often provided as an alternative to imprisonment, and usually under the threat of imprisonment if the person fails to comply with treatment (*116,117*).

One of the major justifications for treatment under coercion is that it is an effective way of treating offenders' drug dependence that will reduce the likelihood of their re-offending (*106,118*). This approach has historically been most often used in the treatment of offenders who are heroin dependent (*119*), although it has most recently been used with cocaine-dependent offenders in US Drug Courts (*89*).

The advent of HIV/AIDS has provided an additional argument for treating rather than imprisoning drug dependent offenders. Prisoners who inject drugs are at higher risk of having contracted HIV and hepatitis by needle-sharing prior to imprisonment (*120*). They are at risk of transmitting these infectious diseases to other inmates by needle sharing and penetrative sexual acts while they are in prison (*121*) and to their sexual partners after their release from prison. Providing drug treatment under coercion in the community is one way of reducing HIV transmission. The correctional and public health arguments for drug treatment under coercion are reinforced by the economic argument that it is less costly to treat offenders who are drug dependent in the community than it is to imprison them (*106*).

The impact of neuroscience theories of addiction may also increase societal preparedness to engage in the coerced treatment of addiction on paternalistic grounds. It may be argued, for example, that because addiction is a “brain disease”, addicts’ behaviour is not under their control and so legal coercion is needed to treat them against their will for their “own good”.

11.3.2 Forms of Legal Coercion

Offenders may be coerced into drug treatment in a variety of ways (*117,122*). After an offence has been detected, the police may decide not to charge the offender if he or she agrees to enter drug treatment. This form of coercion is not generally favoured because it is not under judicial oversight and so is open to abuse. Coercion into treatment may also occur after an offender has been charged and before being processed by the court. A court, for example, may postpone adjudication until treatment has been completed, as may happen in US "drug courts" (*123*).

An offender may be coerced into treatment after conviction. If this is done before sentencing, the Court may make completion of treatment a condition of a suspended sentence. Alternatively, an offender may be encouraged to enter drug treatment to help them remain abstinent while a sentence is suspended. Drug treatment may also be required after part of a sentence has been served: enrolment in drug treatment may be made a condition of release on parole. Alternatively, enrolment in drug treatment may be encouraged as a way of remaining free of illicit drugs while on parole.

The most coercive form of treatment for drug dependence is the "civil commitment" of addicts, which has been used in a number of US states over the past 60 years (e.g. the California Civil Addict Program). In civil commitment, an offender was sentenced to enforced treatment for drug dependence in a secure "hospital", often for an extended period. Compulsory hospital treatment was often followed by community based drug treatment under supervision. Failure to comply with treatment or supervision could result in a return to a secure hospital or transfer to a conventional prison (*122*).

11.3.3 Ethical Issues in Coerced Treatment

Coerced treatment involves the use of state power to force persons to receive treatment and so

unavoidably raises ethical and human rights issues (*55*). Some authors reject any form of treatment under coercion for cocaine or any other form of drug dependence. Szasz, for example, denies that drug dependence exists, arguing that all drug use is voluntary (*108*). According to him, the law should not prohibit adults from using any drug, and any drug user who commits a criminal offence should be punished, with no excuses by reason of drug dependence. The punitive consequences of this form of libertarianism have enjoyed more public and political support than the implications that it has for the legal status of currently illegal drugs.

Others, such as Newman, accept that dependence exists but oppose compulsory drug treatment on the grounds that it does not work (*124*). If treatment under coercion is ineffective (as Newman claims), then there would be no ethical justification for providing it. Of course, even if treatment under coercion is effective, it does not follow that it should be provided. The community may, for example, place a higher value on punishing than rehabilitating drug offenders or may reject any form of coerced treatment (*116*).

American evidence suggests that treatment for heroin dependence, such as, methadone maintenance, therapeutic communities and drug free counselling, is of benefit to those who receive it (*106*). But the benefits for any individual are still uncertain since treatment assists a bare majority of those who receive it (*106*), and relapse to heroin use after treatment is high. The treatment of cocaine dependence is much less effective than treatment for opioid dependence (125). This weakens the ethical justification for "civil commitment" for cocaine dependence but it may not rule out less coercive forms of treatment.

A consensus view on drug treatment under coercion prepared for the World Health Organization (*126*) concluded that such treatment was legally and ethically justified only if (1) the rights of the individuals were protected by "due process" (in accordance with human rights principles), and (2) if effective and humane treatment was provided. In the absence of due process, coerced treatment could become *de facto* imprisonment without judicial oversight. In the absence of humane and effective treatment, coerced drug treatment could become a cost-cutting exercise to reduce prison over-crowding.

The uncertain benefits of coerced treatment have led some proponents to argue that offenders should be allowed two "constrained choices" (*127*). The first constrained choice would be whether they participate in drug treatment or not. If they declined to be treated, they would be

dealt with by the criminal justice system in the same way as anyone charged with their offence. The second constrained choice would be given to those who agreed to participate in drug treatment: this would be a choice of the type of treatment that they received. There is some empirical support for these recommendations in that there is better evidence for the effectiveness of coerced treatment that requires some "voluntary interest" by the offender (*106*).

The most ethically defensible form of legally coerced treatment for drug dependent offenders is the use of imprisonment as an incentive for treatment entry, and fear of return to prison as a reason for complying with drug treatment. Offenders should have a constrained choice as to whether they take up treatment or not, and, if they choose to do so, they should be able to choose from a range of treatment options. And the process should be subject to judicial oversight and review.

If drug vaccines and pharmacological treatments are used under legal coercion, their safety, effectiveness and cost-effectiveness should be rigorously evaluated (*89*). We need to ensure that due process is observed and that effective and humane treatment is provided to drug dependent offenders. We also need to be realistic about what these programs can deliver. They are not a panacea for drug-related crime, or prison over-crowding but they may improve the poor record of incarceration (*106*). With these modest expectations and these safeguards, the use of pharmacological treatments and drug vaccines under legal coercion may have a *limited* role, as one of a range of treatment options offered to offenders. Any such use should be cautiously trialed and evaluated, and only after considerable experience has been acquired in their therapeutic use with voluntary patients.

12. Implications of Neuroscience for the Prevention of Addiction

12.1 Predictive Genetic Testing for Susceptibility to Drug Dependence

Technological optimists (e.g. *128*) have argued that the molecular mapping of the human genome will allow genetic screening of the population to identify persons at high risk of developing specific diseases, such as cancers and heart disease and presumably addiction. Identified high risk individuals can be given appropriate behavioural and pharmacological interventions to prevent these diseases from occurring. This approach has been described as "predictive genetic testing" (*129*). There are good reasons why it may be wise not to rush into screening for susceptibility to drug dependence in the general population.

First, predictive testing is most defensible when we screen for disorders in which a single gene confers a high risk of developing a serious life-threatening disease and when safe and effective interventions exist (*130*). When multiple genes predispose to common diseases, there are gene by environment interactions, with the result that these genes are “incompletely penetrant”, that is, a person with these genes has an *increased* risk of developing the disease, but the probability of their doing so is often still quite small (*129*). In general, the more genes that are involved in disease susceptibility, the less useful information about their genotype is to individuals. Some simple calculations show that there do not have to be many genes involved for this to be true.

Let us assume: (1) that there are three genes, each of which trebles the risk of some type of drug dependence (i.e. a relative risk of 3 which is higher than has typically been reported); (2) that each has a frequency of 10% in the population; (3) that the genes are inherited independently; and (4) that their risks are multiplicative. There would be 8 possible combinations of genotypes that vary in prevalence and relative risk. Most people (72.9% of the population) would not have any increased risk defined by these genes. Almost a quarter (24.3%) would have a modest 3-fold increase in risk. The group with a 9-fold increase in risk would comprise 2.7% of the population. Only 0.01% of the population would have the highest risk, a 27 fold increase in risk (*114*).

Second, given the low prevalence of high-risk combinations of susceptibility genes, a very large number of individuals would need to be screened to identify those with these genes. This is expensive and difficult to justify on public health grounds (*131*).

Third, screening is only justifiable if there is an effective intervention to prevent the disorder in those who possess susceptibility genes (*129*). No such interventions currently exist. The development of an effective drug vaccine would provide more incentive for screening, but it would also raise other ethical issues (e.g. about the right of parents to vaccinate their children). It would also raise serious questions of public policy, e.g. would it be more practicable to screen and vaccinate or simply to have universal drug vaccination? Who would pay the costs of either type of program? How likely is it that such a program would be publicly funded in the face of opposition from manufacturers of legal drugs like alcohol and tobacco?

Fourth, there is a possibility that predictive genetic testing may also have perverse and unintended effects (*115,130*). For example, what effects would testing adolescents for susceptibility to drug dependence have on their preparedness to try drugs? What effects would it have on health insurance and on the social stigmatisation of those who are at risk?

12.2 Implications for Drug Control Policies

Drug control policies aim to reduce the availability of drugs of addiction either by banning their use (in the case of controlled drugs like cannabis, heroin, and cocaine) or by reducing access to legal drugs such as alcohol and tobacco by imposing high taxes on them and restricting minors' access to them (*132*). These policies affect the whole community, not just those who are drug dependent, or at risk of drug dependence. One might argue that, on the grounds of efficiency and equity, drug control measures should be focused on those at highest risk of becoming drug dependent.

There are a number of problems with this superficially attractive argument. First, when multiple genes are implicated in most forms of drug dependence, it is impractical to identify the small number of individuals at highest risk, as argued above. Second, population screening for dependence susceptibility genes is a much more expensive exercise than simply taxing alcohol and tobacco, protecting minors and not allowing promotional activities. Third, one does not need to be drug dependent to experience adverse health effects from drug use, intoxication may be sufficient. Hence, the prevention of drug dependence would not prevent all drug-related public health problems.

One can also anticipate the argument that individuals should be given a choice as to whether they undergo genetic screening for susceptibility to drug dependence. If one accepts this argument, then the wealthy who can afford to pay may decide to be tested. There would be much less case, however, for government funding or private health insurance coverage for such screening.

13. Summary and Conclusions

There is strong research evidence that many addictive phenomena have a neurobiological basis. These include: the fact that psychoactive drugs act on brain neurotransmitters; evidence of a genetic contribution to vulnerability to addiction; the neural mechanisms of tolerance and withdrawal; and the discovery of the neural basis for the rewarding and dependence-producing effects of the major drugs of addiction.

The two major potential benefits to be gained from an improved understanding of the neuroscience bases of addiction are improved treatment and, possibly, the prevention of drug addiction. An improved understanding of the neuroscience basis of addiction requires animal studies of drug effects and drug dependence that cannot be done in humans; experimental studies in humans of drug effects and the neurobiological consequences of drug dependence; clinical trials of new pharmacotherapies for drug dependence; and, possibly, trials of pharmacological and immunological interventions that aim to prevent addiction.

After a century of debate about the ethics of biomedical animal experimentation, a legislative and regulatory compromise has been reached between two sets of competing views. On the one hand, there are those who would abolish all animal experimentation (e.g. proponents of animal liberation and animal rights). On the other, there are those who accept human dominion over animals, according to which animals either have no interests or human interests should always prevail over animals' when their interests conflict. This regulatory compromise has reduced the amount of animal experimentation that is done by restricting the species on which research can be done, using invertebrates where possible, and minimising animal pain and suffering. Under this compromise, animal research is publicly accepted and this includes extensive neurobiological addiction research on rats and mice. Proposals to develop primate models of addiction to provide a better model of human addiction may prove to be less acceptable to the public and may challenge the current consensus.

Human experimental studies of the neurobiological basis of addiction raise a number of ethical issues. One is the capacity of addicted persons to give their consent to participate in such studies. So long as participants are not intoxicated or suffering acute withdrawal symptoms at the time they give consent, there is no compelling reason for believing that persons who are drug dependent cannot give free and informed consent. The risks of drug administration, and the use

of neuroimaging methods in these experiments, generally do not pose as serious a risk to participants as provocation studies in disorders such as schizophrenia.

The ethical issues raised by clinical trials of new pharmacotherapies have been extensively debated, and a consensus has evolved on the conditions that must be met. These include: free and informed consent; an acceptable risk-benefit ratio; and protection of participant privacy and confidentiality. Trials with drug dependent persons require special attention to informed consent to ensure that persons are not intoxicated or experiencing withdrawal symptoms when deciding to participate in trials. Placebo comparisons may be ethically acceptable in such trials *if* there is no effective pharmacotherapy and *if* participants are also offered good quality psychosocial care.

Preventive pharmacological interventions for addiction do not yet exist and are likely to be highly controversial if they are developed. It is a possibility that may loom larger in the future with the development of interventions that have a potential preventive use, foremost among which are drug vaccines. The ethical issues raised by these approaches need to be debated now. The risks of stigmatisation and discrimination that are raised by any preventive intervention that identifies high risk subjects will need to be dealt with. So too will issues of consent in minors and the potential risks to participants of immunological interventions.

Neuroscience research on addiction will affect the long running debate between moral and medical models of addiction by promising to provide a causal explanation of addiction in terms of brain processes. According to one influential version of this approach, addiction is a "brain disease" that results from the flick of a metaphorical switch in the brain that occurs as a result of chronic drug abuse (*107*). This perspective undermines the moral view that addiction is wholly a matter of individual choice and hence that drug users are best dealt with by punishment and imprisonment.

Medical models of addiction may not be a wholly positive development if they lead to simple-minded policies. It may, for example, lead to seductive simplification that if we identify the minority that is genetically and biologically vulnerable to alcohol dependence, then the rest of the population can use alcohol with impunity (*109*). It can also lead to an abdication of responsibility for one's behaviour (*110*) and to a preoccupation with individual explanation of behaviour to the neglect of social policy options for reducing addiction, including drug control policies. The challenge for the addiction neuroscience community will be to develop an understanding of

addiction that gives biology its due without depicting addicts as automatons under the control of receptors in their brains.

The use of pharmacotherapies and drug vaccines under legal coercion is likely to be contentious. It is an arguably ethical policy if the process is under judicial oversight and if offenders are offered constrained choices of (a) whether or not to accept treatment, and (b) the type of treatment that they accept. Any coerced use of a cocaine vaccine should be done cautiously and only after considerable clinical experience with its use with voluntary patients. It should be trialed and its safety, effectiveness and cost-effectiveness rigorously evaluated. Such an evaluation also needs to examine any adverse social or ethical consequences.

The most immediate benefit of work on the neuroscience and genetics of addiction may be more effective drugs to assist addicts to stop using their drugs of choice. It may also allow better matching of addicts to treatments. Population screening for genes that confer susceptibility to drug dependence are unlikely to be practical.

Neuroscience research on addiction is not likely to reduce the role of public health drug control policies. It is much simpler, cheaper and more efficient to discourage the whole population from smoking tobacco, for example, than it is to attempt to make smoking safer by identifying those at highest risk of nicotine addiction or smoking-related disease. The same is arguably true for alcohol and illicit drugs.

The preventive use of a drug vaccine is speculative and ethically contentious. Any trials of their preventive use should be preceded by extensive clinical experience with a vaccine in voluntary patients who are cocaine dependent. A higher standard of safety would be required if it was used preventively, and important ethical issues would be raised, such as, consent to its use by minors, the protection of privacy, and the prevention of discrimination.

References

1. **Mora F**. The brain and the mind. In Gelder MG, Lopez-Ibor JJ, eds. *The New Oxford Textbook of Psychiatry*. Oxford, Oxford University Press, 2000: 153-157.
2. **Stahl SM**. *Essential psychopharmacology: Neuroscientific basis and practical applications.* Cambridge, Cambridge University Press, 1996.
3. **Anthony JC, Helzer J**. Syndromes of drug abuse and dependence. In Robins LN, Regier DA, eds. *Psychiatric disorders in America.* New York, Academic Press, 1991: 116-154.
4. **Helzer JE et al.** Alcohol abuse and dependence. In Robins LN, Regier DA, eds. *Psychiatric disorders in America: The epidemiologic catchment area study.* New York, The Free Press, 1991: 81-115.
5. **Kessler RC et al.** Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the national comorbidity survey. *Archives of General Psychiatry,* 1994, **51**: 8-19.
6. **Andrews G et al.** Prevalence, comorbidity, disability and service utilisation. Overview of the Australian national mental health survey. *British Journal of Psychiatry*, 2001, **178**: 145-53.
7. **United Nations International Drug Control Program**. *World drug report.* Oxford, Oxford University Press, 1997.
8. **Murray CJ, Lopez AD**. Evidence-based health policy--lessons from the global burden of disease study. *Science*, 1996, **274**: 740-3.
9. **Mathers C et al.** *The burden of disease and injury in Australia.* Canberra, Australian Institute of Health and Welfare, 1999.
10. **National Academy of Science**. *Pathways of addiction: Opportunities in drug abuse research.* Washington DC, National Academy Press, 1996.
11. **Adler MW**. Human subject issues in drug abuse research. College on problems of drug dependence. *Drug and Alcohol Dependence*, 1995, **37**: 167-75.
12. **Bierut LJ et al.** Familial transmission of substance dependence: Alcohol, marijuana, cocaine, and habitual smoking: A report from the collaborative study on the genetics of alcoholism. *Archives of General Psychiatry*, 1998, **55**: 982-8.
13. **Kendler KS**. Preparing for gene discovery: A further agenda for psychiatry. *Archives of General Psychiatry*, 1999, **56**: 554-5.
14. **Merikangas KR**. The genetic epidemiology of alcoholism. *Psychoanalytic Quarterly,* 1990, **20**: 11-22.

15. **Merikangas KR et al.** Co-morbidity and familial aggregation of alcoholism and anxiety disorders. *Psychological Medicine*, 1998, **28**: 773-88.
16. **Goodwin DW et al.** Alcohol problems in adoptees raised apart from alcoholic biological parents. *Archives of General Psychiatry*, 1973, **28**: 238-43.
17. **Heath AC**. Genetic influences on alcoholism risk: A review of adoption and twin studies. *Alcohol Health and Research World*, 1995, **19**: 166-171.
18. **True WR et al.** Common genetic vulnerability for nicotine and alcohol dependence in men. *Archives of General Psychiatry*, 1999, **56**: 655-61.
19. **Prescott CA, Kendler KS**. Genetic and environmental contributions to alcohol abuse and dependence in a population-based sample of male twins. *American Journal of Psychiatry*, 1999, **156**: 34-40.
20. **Tsuang MT et al.** Genetic influences on DSM-III-R drug abuse and dependence: A study of 3,372 twin pairs. *American Journal of Medical Genetics*, 1996, **67**: 473-7.
21. **Schuckit MA**. New findings in the genetics of alcoholism. *JAMA*, 1999, **281**: 1875-6.
22. **Altman J et al.** The biological, social and clinical bases of drug addiction: Commentary and debate. *Psychopharmacology (Berl)*, 1996, **125**: 285-345.
23. **Markou A et al.** Neurobiological similarities in depression and drug dependence: A self-medication hypothesis. *Neuropsychopharmacology*, 1998, **18**: 135-74.
24. **Benowitz NL**. Nicotine pharmacology and addiction. In Benowitz NL, ed. *Nicotine safety and toxicity*. Oxford; New York, Oxford University Press, 1998: 3-18.
25. **Iversen LL**. *The science of marijuana.* Oxford, Oxford University Press, 2000.
26. **Di Chiara G, North RA**. Neurobiology of opiate abuse. *Trends in Pharmacological Sciences*, 1992, **13**: 185-93.
27. **Romach MK et al.** Attenuation of the euphoric effects of cocaine by the dopamine D1/D5 antagonist ecopipam (SCH 39166). *Archives of General Psychiatry*, 1999, **56**: 1101-6.
28. **Koob GF et al.** Opponent process model and psychostimulant addiction. *Pharmacology, Biochemistry and Behavior*, 1997, **57**: 513-21.
29. **Nutt D**. The neurochemistry of addiction. *Human Psychopharmacology*, 1997, **12**: S53-S58.
30. **Mattick RP, Hall W**. Are detoxification programmes effective? *Lancet*, 1996, **347**: 97-100.
31. *Methadone maintenance treatment and other opioid replacement therapies.* Ward J et al., eds. Amsterdam, Harwood Academic Press, 1999.

32. **Streeton C, Whelan G**. Naltrexone, a relapse prevention maintenance treatment of alcohol dependence: A meta-analysis of randomized controlled trials. *Alcohol and Alcoholism,* 2001, **36**: 544-52.

33. **Volpicelli JR**. Alcohol abuse and alcoholism: An overview. *Journal of Clinical Psychiatry*, 2001, **62**: 4-10.

34. **McCance EF**. Overview of potential treatment medications for cocaine dependence. In Ching N, Bridge P, eds. *Medication development for the treatment of cocaine dependence: Issues in clinical efficacy trials*. Rockville, M.D., National Institute of Drug and Alcohol, 1997: 36-72.

35. **Fox BS**. Development of a therapeutic vaccine for the treatment of cocaine addiction. *Drug and Alcohol Dependence*, 1997, **48**: 153-8.

36. **Bachman JG et al.** *Smoking, drinking and drug use in young adulthood: The impacts of new freedoms and responsibilities.* Mahwah NJ, Lawrence Erlbaum, 1997.

37. **Kandel DB, Chen K**. Types of marijuana users by longitudinal course. *Journal of Studies on Alcohol,* 2000, **61**: 367-78.

38. **Hser YI et al.** A 33-year follow up of narcotic addicts. *Archives of General Psychiatry*, 2001, **58**: 503-508.

39. **Fu CH, McGuire PK**. Functional neuroimaging in psychiatry. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, 1999, **354**: 1359-70.

40. **Gilman S**. Imaging the brain. First of two parts. *New England Journal of Medicine*, 1998, **338**: 812-20.

41. **Kling MA et al.** Opioid receptor imaging with positron emission tomography and [(18)F]cyclofoxy in long-term, methadone-treated former heroin addicts. *Journal of Pharmacology and Experimental Therapeutics*, 2000, **295**: 1070-6.

42. **Martin-Soelch C et al.** Reward mechanisms in the brain and their role in dependence: Evidence from neurophysiological and neuroimaging studies. *Brain Research Brain Research Reviews,* 2001, **36**: 139-49.

43. **Sell LA et al.** Activation of reward circuitry in human opiate addicts. *European Journal of Neuroscience*, 1999, **11**: 1042-8.

44. **Brody BA**. *The ethics of biomedical research: An international perspective.* Oxford; New York, Oxford University Press, 1998.

45. **Gorelick D et al.** Clinical research in substance abuse: Human subjects issues. In Pincus HA et al., eds. *Ethics in psychiatric research: A resource manual for human subjects protection.* Washington, American Psychiatric Association, 1999: 177-218.

46. **Beauchamp TL, Childress JF**. *Principles of biomedical ethics.* Oxford, Oxford University Press, 2001.
47. **Rachels J**. *The elements of moral philosophy.* New York, McGraw-Hill, 1993.
48. **Singer P**. *Practical ethics: Second edition.* Cambridge, Cambridge University Press, 1993.
49. **Rawls J**. *A theory of justice.* Oxford, Oxford University Press, 1971.
50. **Dworkin R**. *Taking rights seriously.* Cambridge MA, Harvard University Press, 1977.
51. **Nelson JL**. *The rights and responsibilities of potential organ donors: A communitarian approach.* Washington D. C., The Communitarian Network, 1992.
52. **Jonsen AR**. *The birth of bioethics.* Oxford, Oxford University Press, 1998.
53. **International Federation of Red Cross and Red Crescent Societies and Francois-Xavier Bagnoud Center for Health and Human Rights**. Human rights: An introduction. In Mann JM et al., eds. *Health and human rights: A reader*. London, Routledge, 1999: 21-28.
54. **Mann JM et al.** Health and human rights. In Mann JM et al., eds. *Health and human rights: A reader*. London, Routledge, 1999: 7-20.
55. **Mann JM**. Medicine and public health, ethics and human rights. In Mann JM et al., eds. *Health and human rights: A reader*. London, Routledge, 1999: 439-452.
56. **Gostin L, Mann JM**. Toward the development of a human rights impact assessment for the formulation and evaluation of public health policies. In Mann JM et al., eds. *Health and human rights: A reader*. London, Routledge, 1999: 54-71.
57. **Resnik DB**. *The ethics of science: An introduction.* London; New York, Routledge, 1998.
58. **Rachels J**. *Created from animals: The moral implications of Darwinism.* Oxford; New York, Oxford University Press, 1991.
59. **Matfield M**. Animal experimentation: The continuing debate. *Nature Reviews Drug Discovery*, 2002, **1**: 149-152.
60. **Naquet R**. Ethical and moral considerations in the design of experiments. *Neuroscience*, 1993, **57**: 183-189.
61. **American Psychological Association Science Directorate**. *Research with animals in psychology*. Washington DC, 2001 (American Psychological Association).
62. **Preuss TM**. Taking the measure of diversity: Comparative alternatives to the model-animal paradigm in cortical neuroscience. *Brain Behavior and Evolution*, 2000, **55**: 287-99.
63. **Nestler EJ**. Genes and addiction. *Nature Genetics*, 2000, **26**: 277-81.
64. **Singer P**. All animals are equal. In Kuhse H, Singer P, eds. *Bioethics: An anthology*. Oxford, Blackwell Publishers, 1999: 461-470.

65. **Regan T**. Do animals have a right to life? In Regan T, Singer P, eds. *Animal rights and human obligations.* London, Prentice-Hall Inc, 1976: 197-204.

66. **Regan T**. *The case for animal rights.* Berkeley, University of California Press, 1983.

67. **Varner GE**. The prospects for consensus and convergence in the animal rights debate. *Hastings Center Report,* 1994, **24**: 24-28.

68. **Petrinovich L**. *Darwinian dominion: Animal welfare and human interests.* Cambridge MA; London, MIT Press, 1999.

69. **Monamy V**. *Animal experimentation: A guide to the issues.* Cambridge, Cambridge University Press, 2000.

70. **Ashcroft R**. Selection of human research subjects. In Chadwick R, eds. *The concise encyclopedia of the ethics of new technologies.* New York, Academic Press, 2001: 255-266.

71. *Research involving persons with mental disorders that may affect decisionmaking capacity*. Rockville MD, 1999 (National Bioethics Advisory Commission Report).

72. **Roberts LW, Roberts B**. Psychiatric research ethics: An overview of evolving guidelines and current ethical dilemmas in the study of mental illness. *Biological Psychiatry*, 1999, **46**: 1025-38.

73. **Shamoo AE**. *Ethics in neurobiological research with human subjects: The Baltimore conference on ethics*. Amsterdam, Gordon and Breach, 1998.

74. **Hall LL**. Medication discontinuation and symptom provocation in research: A consumer and family perspective. *Biological Psychiatry*, 1999, **46**: 1017-20.

75. **Carpenter WT, Jr. et al.** The rationale and ethics of medication-free research in schizophrenia. *Archives of General Psychiatry*, 1997, **54**: 401-7.

76. **Alves WA, Macciocchi SN**. Ethical considerations in clinical neuroscience. Current concepts in neuroclinical trials. *Stroke*, 1996, **27**: 1903-9.

77. **D'Souza DC et al.** Symptom provocation studies in psychiatric disorders: Scientific value, risks, and future. *Biological Psychiatry*, 1999, **46**: 1060-80.

78. **Carpenter WT, Jr.** The schizophrenia ketamine challenge study debate. *Biological Psychiatry,* 1999, **46**: 1081-91.

79. **Avila MT et al.** A comparison of symptom provocation procedures in psychiatry and other areas of medicine: Implications for their ethical use in research. *Biological Psychiatry*, 2001, **50**: 479-86.

80. **Miller FG, Rosenstein DL.** Psychiatric symptom-provoking studies: An ethical appraisal. *Biological Psychiatry*, 1997, **42**: 403-9.

81. **Fergusson DM, Horwood LJ**. Cannabis use and dependence in a New Zealand birth cohort. *New Zealand Medical Journal*, 2000, **113**: 156-8.
82. **Cochrane AL**. *Effectiveness and efficiency: Random reflections on health services.* Abingdon, Berkshire, Nuffield Provincial Hospitals Trust, 1972.
83. **DeAngelis CD et al.** Reporting financial conflicts of interest and relationships between investigators and research sponsors. *JAMA*, 2001, **286**: 89-91.
84. **Davidoff F et al.** Sponsorship, authorship, and accountability. *New England Journal of Medicine,* 2001, **345**: 825-6; discussion 826-7.
85. The tightening grip of big pharma. *Lancet,* 2001, **357**: 1141.
86. **Horton R**. Medical editors trial amnesty. *Lancet*, 1997, **350**: 756.
87. **Reidenberg MM**. Releasing the grip of big pharma. *Lancet*, 2001, **358**: 664.
88. **Spooner C, Hall W**. Preventing substance misuse among young people: We need to do more than "just say no". *Addiction* (in press), 2002.
89. **National Research Council**. *Informing America's policy on illegal drugs: What we don't know keeps hurting us.* Washington DC, National Academy Press, 2001.
90. **McGorry PD et al.** Ethics and early intervention in psychosis: Keeping up the pace and staying in step. *Schizophrenia Research*, 2001, **51**: 17-29.
91. **Cohen PJ**. Immunization for prevention and treatment of cocaine abuse: Legal and ethical implications. *Drug and Alcohol Dependence*, 1997, **48**: 167-74.
92. **McGlashan TH**. Psychosis treatment prior to psychosis onset: Ethical issues. *Schizophrenia Research*, 2001, **51**: 47-54.
93. **Cornblatt BA et al.** Treatment of the schizophrenia prodrome: Is it presently ethical? *Schizophrenia Research*, 2001, **51**: 31-8.
94. **DeGrazia D**. Ethical issues in early-intervention clinical trials involving minors at risk for schizophrenia. *Schizophrenia Research,* 2001, **51**: 77-86.
95. **Levy F**. Attention deficit hyperactivity disorder. *British Medical Journal,* 1997, **315**: 894-5.
96. **Lynskey MT, Hall W**. Attention deficit hyperactivity disorder and substance use disorders: Is there a causal link? *Addiction,* 2001, **96**: 815-22.
97. **Swanson JM et al.** Attention-deficit hyperactivity disorder and hyperkinetic disorder. *Lancet*, 1998, **351**: 429-33.
98. **Carrera MR et al.** Cocaine vaccines: Antibody protection against relapse in a rat model. *Proceedings of the National Academy of Sciences of the United States of America*, 2000, **97**: 6202-6.
99. **Fox BS et al.** Efficacy of a therapeutic cocaine vaccine in rodent models. *Nature Medicine,* 1996, **2**: 1129-32.

100. **Carrera MR et al.** Suppression of psychoactive effects of cocaine by active immunization. *Nature,* 1995, **378**: 727-30.

101. **Johnson MW, Ettinger RH**. Active cocaine immunization attenuates the discriminative properties of cocaine. *Experimental and Clinical Psychopharmacology*, 2000, **8**: 163-7.

102. **Kosten TR et al.** Longitudinal safety and immunogenicity of a therapeutic cocaine vaccine. *Drug and Alcohol Dependence*, 2000, **60**: S250.

103. **Cohen PJ**. No more kicks. *New Scientist,* 2000, **166**: 23-36.

104. **Hall W, Carter L**. Ethical and policy issues in trialing and using a cocaine vaccine to treat and prevent cocaine dependence. National Drug and Alcohol Research centre Technical Report, 2002 (in press).

105. **Kaebnick GE**. Vaccinations against bad habits. *Hastings Center Report,* 2000, **30**: 48.

106. **Gerstein DR, Harwood HJ**. *Treating drug problems volume 1: A study of effectiveness and financing of public and private drug treatment systems.* Washington DC, Institute of Medicine, National Academy Press, 1990.

107. **Leshner AI**. Addiction is a brain disease, and it matters. *Science*, 1997, **278**: 45-7.

108. **Szasz TS**. *Ceremonial chemistry.* Holmes, Learning Publications, 1985.

109. **Hall W, Sannibale C**. Are there two types of alcoholism? *Lancet*, 1996, **348**: 1258.

110. **Nelkin D, Lindee MS**. "Genes made me do it": The appeal of biological explanations. *Politics and Life Sciences*, 1996, **15**: 95-7.

111. **Valenstein ES**. *Blaming the brain: The truth about drugs and mental health.* New York, The Free Press, 1998.

112. **Walton R et al.** Genetic clues to the molecular basis of tobacco addiction and progress towards personalized therapy. *Trends in Molecular Medicine*, 2001, **7**: 70-6.

113. **Munafo M et al.** New directions in the genetic mechanisms underlying nicotine addiction. *Addiction and Biology*, 2001, **6**: 109-117.

114. **Hall W, Lynskey, M. and Madden, P.** The genetics of tobacco use: Methods, findings an policy implications. *Tobacco Control*, 2002, 11, 119-124.

115. **Marteau TM, Croyle RT**. The new genetics. Psychological responses to genetic testing. *BMJ*, 1998, **316**: 693-6.

116. **Hall W**. The role of legal coercion in the treatment of offenders with alcohol and heroin problems. *Australian and New Zealand Journal of Criminology*, 1997, **30**: 103-120.

117. **Spooner C et al.** An overview of diversion strategies for drug-related offenders. *Drug and Alcohol Review,* 2001, **20**: 281-294.

118. **Inciardi JA, McBride DC**. *Treatment alternatives to street crime: History, experiences and issues.* Rockville MD, National Institute of Drug Abuse, 1991.

119. **Leukefeld CG, Tims FM**. Compulsory treatment: A review of the findings. In Leukefeld CG, Tims FM, eds. *Compulsory treatment of drug abuse*. Rockville MD, National Institute of Drug Abuse, 1988: 236-251.

120. **Dolan K et al.** HIV risk behaviour of IDUs before, during and after imprisonment in New South Wales. *Addiction Research*, 1996, **4**: 151-160.

121. **Vlahov D, Polk BF**. Intravenous drug use and human immunodeficiency virus (HIV) infection in prison. *AIDS Public Policy Journal*, 1988, **3**: 42-46.

122. **Gostin LO**. Compulsory treatment for drug-dependent persons: Justifications for a public health approach to drug dependency. *Milbank Quarterly*, 1991, **69**: 561-93.

123. **General Accounting Office**. *Drug courts: Information on a new approach to address drug-related crime.* Washington DC, United States General Accounting Office, 1995.

124. **Newman RG**. Involuntary treatment of drug addiction. In Bourne PG, eds. *Addiction.* New York, Academic Press, 1974: 113-126.

125. **Platt JJ**. *Cocaine addiction: Theory, research, and treatment.* Cambridge MA, Harvard University Press, 1997.

126. **Porter L et al.** *The law and the treatment of drug and alcohol dependent persons - a comparative study of existing legislation.* Geneva, Switzerland, World Health Organization, 1986.

127. **Fox RG**. The compulsion of voluntary treatment in sentencing. *Criminal Law Journal*, 1992, **16**: 37-54.

128. **Collins FS**. Shattuck lecture--medical and societal consequences of the human genome project. *New England Journal of Medicine,* 1999, **341**: 28-37.

129. **Evans JP et al.** The complexities of predictive genetic testing. *BMJ*, 2001, **322**: 1052-6.

130. **Holtzman NA, Marteau TM**. Will genetics revolutionize medicine? *New England Journal of Medicine,* 2000, **343**: 141-4.

131. **Vineis P et al.** Misconceptions about the use of genetic tests in populations. *Lancet,* 2001, **357**: 709-12.

132. **World Health Organization**. *Guidelines for controlling and monitoring the tobacco epidemic.* Geneva, World Health Organization, 1998.