Health and ill health are dependent on the conditions under which we live and the ways in which we behave. Appropriate education can make a dramatic difference in long-term wellbeing, whereas educational deprivation can have dire consequences for human welfare [1]. Many contemporary structural and behavioural factors, including nutrition, poverty and drug abuse, contribute to the burden of human disease [2, 3]. This review overviews some emerging biomedical findings of potential concern — the suspected association between chemically induced euphoria and elevated risk of depression in those with no particular genetic risk factors.

A biological perspective of pleasure and depression
The impact of mental illness is becoming a serious public health issue. A number of studies suggest an overall increase in depressive disorders is occurring, especially among the most recent birth cohorts [4]. Epidemiological studies present some alarming statistics on rising rates of depression in the 20th century — the chance of an individual suffering severe depression is 10 times more likely if they were born in the second half of the last century compared to the first half [5]. Not only is severe depression now much more common, it also occurs in much younger individuals and, since major depression recurs in about half of those who have had it once, the extra 10 years of vulnerability to depression means more suffering [6].

Depression (co-existing as it does with anxiety) is linked to a range of risk behaviours such as smoking, alcohol consumption, eating disorders and illicit drug use [7]. The reverse situation — the genesis of depression in drug-abuse — is much less clear. Whether artificially altering the brain’s neurotransmitter ratios (vital for stable moods) impairs the system, so as to increase the risk of clinical depression in formerly healthy individuals, is yet to be proven. Such a hypothesis may, at least in part, explain the recent observed increase in depressive disorders.

When recreational drug-use increases the risk of psychiatric illness in formerly healthy individuals, this raises other issues such as ensuring that appropriate information is made available and that educational support, aimed at raising user awareness, is provided. Up to 25 per cent of drug and alcohol abusers commit suicide, and the suicide rate is 35 times greater in those who suffer from mood disorders relative to the general population [15, 16]. However, this does not explain whether depression causes substance abuse and eventual despair or vice versa, since the two clearly interact.

Recreational drugs — alcohol, cannabis, amphetamines, MDMA (ecstasy)

Early evidence suggests that some of the harmful effects from casual consumption of mood-altering recreational drugs are invisible and cumulative, risking depression in formerly healthy individuals. If such an association can be identified then this raises questions of whether doggedly pursuing the elusive state of ‘happiness’ represents a little suspected form of illness, and whether society provides adequate support for making appropriate informed choices.

Irina Pollard
and cocaine — powerfully alter mood [4], but whether real and cumulative harm can be sustained from casual consumption of these recreational drugs is not easy to evaluate.

Frequent use of the synthetic drug MDMA, a potent hybrid compound of the hallucinogen mescaline and the stimulant methamphetamine, has neurotoxic effects on specific nerves in the brain that regulate serotonin — the neurotransmitter linked to memory, cognition, mood regulation, sleep, pain and a host of other functions [8-13]. Long-term use of MDMA may also cause behavioural disorders such as anxiety and psychotic depression [14].

**The emotional brain**

Mood is the consistent extension of emotion in time, while emotion is typically transient and responsive to an individual's thoughts, activities, and social situations. Mood, or the state of emotional balance, influences the way an individual interacts with and perceives the world. Mania and clinical depression (bipolar illness) are disturbed emotional states that distort and magnify what is considered 'normal' emotional experience. For example the experience of happiness, or love, is intensified to the delusional in mania, and sadness or grief becomes despair in depression.

Moment-to-moment adaptive regulation is important for physical and mental balance. In changing environments, where emotional stability is threatened, compensating homeostatic mechanisms are activated in order to adapt to changing conditions. This is known as 'reactive homeostasis' or the General Adaptation Syndrome (GAS) [17, 18]. When the GAS is activated the cerebral cortex (the analytical or conscious brain), the limbic system (the emotional brain) and the hypothalamic-pituitary-adrenal, or stress axis, are mobilised. A hyperactive GAS is a characteristic feature of depression — these homeostatic mechanisms are activated regardless of whether the stimulus is real and life-threatening or chemically-induced [19].

The emotional, or limbic, brain is central to working memory, depression and also serves as the prime target for consciousness-changing/mood altering substances. The functional compartments of the limbic brain include the thalamus, hippocampus, amygdala, hypothalamus and pituitary gland (Figure 1).

The thalamus processes incoming information from the senses (eyes, ears, nose, touch, etc.), and outgoing information from the brain, acting as a relay station where information is appraised and decisions are made. The hippocampus, central to the operations of memory consolidation and learning, is where the thalamus's information is sorted and significant emotional memories are adapted for long-term storage in the frontal region of the limbic system. Situated in the front portion of the hippocampus and intimately connected to the hypothalamus, is the amygdala, which is involved with emotional experience and reactions. The amygdala, originally thought to play a central role in the acquisition and processing of fear, anger, flight and defence (all GAS-mediated), is now known to be crucial in processing emotions indispensable for social communication [2]. The hypothalamus, together with other brain circuits, is involved with motivation and reward mechanisms. Through the endocrine system it controls most of the body's housekeeping needs such as brain clocks, temperature regulation, appetites for food, sex, aggression and pleasure. Attached to the hypothalamus is the pituitary gland, which orchestrates the messenger hormones influencing the homeostatic stability of every organ in the body including the brain itself.

The brain circuitry which synchronises the differing levels of the fight/flight and reward systems are highly complicated and beyond the scope of this review. Suffice it to say, the emotional brain is richly connected to a plethora of other brain centres/circuits, particularly the cerebral cortex, or higher brain centres, of the mind. These communication systems linking the limbic brain and other brain regions help to generate a holistic and adaptive response to changing environmental conditions.

**Disordered communication**

Given that depression involves mental processes that extend beyond the range of what is considered 'normal', it is easy to see how the brain's disturbed homeostatic stability affects the normal housekeeping functions of the body, such as sleep/wake cycles, appropriate behaviour, physical well-being and emotional stability. As a consequence, normal adaptive mental processes such as emotional awareness, sustained concentration and decision-making can be distorted. It follows that the hormones circulating in the bloodstream, by which the brain orchestrates the body's homeostasis, lose their daily rhythms as the upheaval of brain regulation and physical deterioration progresses.

From the neurobiologist's perspective, depression is understood as a disordered flow of brain neurotransmitters controlling information perception, and a loss of behavioural resilience secondary to changes in neuronal regulation and disturbed brain chemistry. Alcohol, amphetamines, cocaine and cannabis can add to disordered communication among the brain's neurons [20]. Major effects contributing to disordered communication — apart from a generalised neurotoxicity — include impaired neurogenesis, atrophy of dendritic processes and a resultant reduction in networking, and decreases in neurotransmitter receptor numbers [21-23]. Toxicologists, such as David Smith (director, Free Clinic in the Haight Ashbury area of San Francisco) maintain that those who abuse, or smoke potent forms of marijuana, risk anxiety and depression which contribute to the development of full-scale cannabis psychosis [24]. Recent studies support the suspected association between regular cannabis use and mental illness such as depression and schizophrenia [25].

The active ingredient of marijuana, Δ-9 tetrahydrocannabinol, may induce psychotic depression but such information has not been adequately publicised in ways which enable the public to make informed decisions concerning abstinence or moderation [26].
Stressful challenges in the body or environment can profoundly impact on brain regulation. Communication between brain cells is accomplished by means of neurotransmitters, neuromodulators and neurohormones, which operate through a network of synapses. The relative activity of these communicating systems is believed to play a large role in determining moods of variable excitement or withdrawal. Chronic stress, and consequent withdrawal from social engagement, can damage neurons in key brain regions, such as the hippocampus and its memory storage mechanisms [22]. Stress hormones have particularly adverse morphological effects in the hippocampus because this structure is a primary glucocorticoid target site [22].

Dopamine: the courier of addiction
Neurotransmitters such as dopamine, norepinephrine, serotonin and acetylcholine are the key brain messengers maintaining the flow of information across the synaptic junctions of the limbic brain. When the balance of these neurotransmitters is disturbed, emotional regulation becomes unstable and the syndromes of depression and mania may develop. Dopamine, for example, is the messenger of the brain’s reward system, that is, it generates the subjective feeling of pleasure or happiness and for this reason has been dubbed the ‘courier of addiction’. Dopamine is also the messenger that appears to operate in excess in severe mania or acute schizophrenia, dominating the pathways of limbic communication and fermenting these psychoses [27].

When this syndrome is exogenously induced, the condition is sometimes referred to as chemically-induced manic-depressive psychosis. Heroin, cocaine, amphetamine, MDMA, alcohol, nicotine and marijuana all work by raising dopamine levels to unnatural highs at unnatural speeds — although the relative toxicities, risks and pleasures vary according to each drug’s characteristics [20]. Cocaine blocks the protein that removes dopamine from the synaptic cleft; amphetamine stimulates dopamine release; heroin and nicotine activate dopamine neurons by binding to non-dopamine receptors, although how these receptors interact with the dopamine ones remains to be elucidated.

Dopamine, as well as being a neurotransmitter, is also a major neurohormone mediating neural interactions between the brain and the pituitary gland. Dopamine drives the reward systems of the brain and is often aided and abetted by noradrenaline. Noradrenaline, like dopamine, acts as a neurotransmitter and neurohormone driving sympathetic pathways mediating the emergency (GAS) response, and providing adrenergic stimulation to the adrenal medulla activating the secretion of, among other substances, adrenaline. Another major neurotransmitter found in the brain, acetylcholine, is not believed to be directly involved in emotionality.

Stress and neurotransmitter systems
Serotonergic neurons serve as chemical moderators in the limbic system, balancing the dopamine and noradrenaline systems in their actions. Serotonin plays a key role in the regulation of arousal and has a significant influence on the release of pituitary hormones regulating the levels of cortisol and related stress hormones. In the absence of serotonin’s calming effect sleep becomes fragmented, fear and agitation increases and, as a result, any tendency toward mania or depression is easily triggered [28]. Lowered serotonin concentration also leads to impaired impulse control and heightened aggression [29].

Stresses such as grief, loss of love, bereavement, physical illness, chronic drug consumption can all disturb the neurotransmitter systems that sustain communication among the neuronal centres of the limbic brain. When these stresses are chronic the brain may become sensitised to recurring episodes of mania and depression. Overall brain neuronal organisation and behaviour becomes more rigid and inflexible in manic-depressives compared with normal healthy individuals. This is adaptive because illness equates with vulnerability and just as sick animals withdraw in self-preservation, so human withdrawal is preferable to dynamic flexibility. Thus, neurologically, the emotional brain’s homeostatic system adopts a new steady state, one less responsive to the environment and less adaptive.

The biology of addiction
Scientists are beginning to appreciate the common neurobiological mechanisms of addiction, and how it drives compulsive behaviour. Drug abuse is a complex phenomenon and its etiology reflects a multiplicity of environmental and genetic factors. Whatever its etiology, the drug of choice effectively ‘fixes’ an acquired or deeply embedded need for an emotional transformation. Addiction used to be defined in physical terms such as the severity of the withdrawal. However, many drugs of addiction, such as marijuana, do not produce severe withdrawal symptoms yet are addictive. Accordingly, a streetwise concept has developed nicknamed the three Cs: Compulsion, loss of Control, and Continued use despite adverse consequences, as being a more realistic definition of addiction [24].

The generation of addiction has clear-cut commonalities in addition to each drug’s specific mechanism(s) of action that produces the distinctive drug experience. The subjective ‘high’ that these drugs promote corresponds to the sudden increase of brain dopamine activity alone, or in combination with other neurochemicals. In cocaine use, for example, both dopamine and noradrenaline are artificially enhanced creating heightened alertness and levels of energy [4].

Owing to dopamine’s potency and biological significance, the body protectively reacts to fake stimulation by fading its response to repeated fake stimuli. Prolonged cocaine or heroin use, for example, lowers the brain’s homeostatic set points and the manner in which dopamine is effectively used. This down-regulated function can persist for up to two years after an addict has stopped taking the drug [20].

Thus, repeated drug-intake, while initially stimulating the desired rush, provokes the brain to accommodate (reactive homeostasis) to the prevailing conditions by decreasing its previous baseline level which, in turn, forces the addict to increase the drug intake in an effort to bring back previously normal working dopamine levels within the brain [30]. The brain’s reduced dopamine synthesis continues the craving long after drug use ceases.

Numerous epidemiological studies indicate that drug-dependence can be overcome without difficulty, suggesting that physiological dependence is not an essential part of addiction. According to one study, of 10,000 burns patients who received pain-relieving morphine injections for weeks or months, 22 patients abused the drug after discharge all of whom had a
The pursuit of happiness

According to the Oxford-based neurologist Susan Greenfield [20], pleasure is the most basic of all our emotions, characteristic of the infant state of consciousness. Here, feeling is not greatly tempered by personalised values, history and a unique view of life. Pure emotion is devoid of the mind’s significant connections, as it deals with the immediate inner world populated by the abstractions of touch, taste, texture and colours. Healthy adult brains are not configured to tolerate ‘an out of mind’ state for more than a few minutes so the feeling of pleasure inevitably fades into thinking. It is adaptive for moods of extreme pleasure to give way to moods generating fearfulness which signal caution.

Given this, is it accurate to equate pleasure with happiness? Is there something we can learn by swapping the descriptive terms ‘pleasure’ and ‘happiness’ with the biological ‘emotion’ and ‘mood’? From the brain’s perspective the two are not equivalent since pleasure (neurotransmitter-generated emotion) is transient and happiness (stable homeostatic state) is emotion extended or mood. From a biological perspective, mood is the consistent extension of emotion in time, while emotion is typically transient and responsive to the thoughts, activities, and social/chemical situations of the moment. Further, it is mood — the state of emotional balance — that powerfully influences the way the world is felt, interacted with and perceived.

Happiness, from a biological point of view, demands both the mind’s powers of reasoning and emotional intelligence — the understanding and use of emotional information to enhance, not exclude, thinking. Since the desired happy state of mind cannot be felt to order, the major divide between our contemporary consumer-orientated culture and its happiness-promoting advertising, is further highlighted.

It appears that physicians, researchers and bioethicists have paid little attention to the history of happiness-seeking behaviour when evaluating individuals with depression. If, indeed, the use of drugs for pleasure can be shown to deregulate the brain’s neurochemical pathways sufficiently enough to generate severe depression in those with no inherent genetic risk factors, then it needs to be asked whether society provides adequate support for making informed choices in the evaluation of risks and benefits. Of particular concern is that addiction and depression may well impair a person’s competence to make an informed choice; that is, consent to make a rational choice of whether to partake or not of certain recreational drugs.

Adults have the right to make decisions, even if they may seem unsound to others, but whatever the decision it needs to be a truly informed one. Decisions made on medical and scientific matters, especially as they relate to health, are of major bioscience and bioethical concern. The present review aims to provide sufficient background information to raise the level of discrimination in evaluating risks and benefits when making personal life-style decisions, such as those involving recreational drugs.

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Assoc Prof Irina Pollard is a biologist, based in the Department of Biology at Macquarie University, NSW, with expertise in stress physiology, reproduction and teratology. She is a co-founder of the new ethical discourse 'bioscience ethics'. Her major research/teaching impacts are in lifestyle stresses (particularly drug consumption) and their effects on fertility, development and subsequent health of the offspring. These studies have generated a deep concern for social justice and, as a result, she's also active in community education corresponding regularly on scientific matters through television, radio and the print media. She’s been guest speaker at many international meetings in the former USSR, Europe, Japan, India and the US, and has enjoyed sabbatical/visiting scientist phases at overseas Universities including Oxford, Cambridge, London, Montpellier, Paris, Madras, Kanazawa and Tsukuba. These experiences, as well as those at Macquarie University, have lead to the publication of two comprehensive, interdisciplinary texts in area of human reproduction and bioscience ethics. Pollard is also a co-author of the forthcoming ‘UNESCO/IUBS Bioethics Dictionary’ now freely accessible for general feedback at www.biol.tsukuba.ac.jp/~macer/biodict.htm

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