

“CUTTING THE GORDIAN KNOT OF DRUG ADDICTION CONFUSION”

Strategy of Seduction vs. Seduction of Strategy

We know that methadone is the best drug used in addiction treatment. Therefore our only problem in addiction medicine is that we do not have a methadone for all the other drugs of addiction.

Leading Science Administrators in Australia and USA.

“I didn’t inhale”

Bill Clinton quoted in an addiction medicine textbook commissioned by the Academic Deans of Australian Medical Schools ¹

It’s not about drugs

Present work

Conceptual Understanding of addiction

On 1776 Thomas Jefferson penned the immortal words that

“men ... were endowed ... with ... inalienable rights... among these are life, liberty and the pursuit of happiness” ²

not only into the founding document of the United States, but in time, into the very basic fabric of the cultures of the Western world. The pursuit of happiness has come to be accepted as the fundamental right of every breathing and living human on the planet in the free nations of the world.

At the conceptual level Jefferson’s famous phrase also, albeit to be sure unwittingly, boldly underscores the apparent contradiction at the heart of the drug debate. An enormous body of evidence now exists from the modern neurosciences demonstrating that addiction unequivocally stimulates the pleasure system of the brain in the limbic structures, the extended amygdala and the pre-frontal cortex ^{3,4}. This leads to an immediate conclusion, supported by many and funded by the mighty, that since drugs make you happy, the chief end of government is to supply as many drugs as often as possible and in any imaginable amount to all who may wish to partake of their all too obvious pleasures; or at the very least not to interfere with those who might wish to do so. If the fast way to achieve the idyllic state referred to by Jefferson is simply to “get stoned”, “get wasted” or “get high” then why not go right ahead? In particular since this is an inalienable right of every man, then surely our personal *liberties* demand just this, particularly if it can be done in a manner which does not interfere with the pleasure seeking endeavours of others? Or could there be more to things than the simplistic libertarian argument so many want to hear?

Surely the siren voices of the maidens of pleasure cannot always lure life’s unwary travellers onto the rocks of destruction and drug induced destitution?

Surely to believe the line that unbridled hedonism is the ultimate social virtue one must accept the premise that the seduction of our desire for pleasure and relaxation is the ultimate social good. It would follow that a society totally consumed with pleasure seeking is the chief end of human existence and the very pinnacle of social organization. Indeed historians who have reviewed this subject repeatedly find that societies caving into the seduction of unbridled pleasure and sensuality are on a usually rapid social decline, punctuated by all forms of social decadence and depravity. The strong and indeed almost invariable link between decadence and social decay has been documented by, amongst others, the Father of American Sociology, Pitirim Sorokin⁵. The same is obviously true today, in every area where addiction is commonplace, in every large city centre troubled by addiction, ghettos and gangs, in every remote mountain village from Morocco to Cuba to Afghanistan to Colombia to Amsterdam where drugs run riot so too does a myriad of commonly associated social, medical and criminal pathologies.

Patients readily acknowledge their love – hate relationship with their drug of choice. The clinical course of the addiction seems to be a dynamic cost – benefit equation. In other words when the trouble caused by the addiction is too severe patients cry out for help – often not for the addiction itself, but for its effects. Those around them hope that this will lead to a definitive address of the underlying issue, but this is often only temporary. Memories of bad experiences mellow and fade with the passage of time. As the patient moves into sobriety and life improves, the delusions that “I am stronger now”, “I am over it now”, “It won’t happen again”, “I can control this now”, and especially “One taste won’t matter” start to grow.

Why is addiction defined in countless textbooks as a “chronic relapsing disease”? Why do our patients always return to their substances despite numerous detox episodes? What is it about the addicted personality which is so different? Why can one person have a social drink, but another’s life is totally consumed by the “demon drink”? Given that trouble is common to all humanity, why do some apparently choose to drown their sorrows in the bottle or the needle? Given that hospitals normally use narcotic painkillers for post-operative analgesia, why are some people’s lives consumed by that sensation, whereas the great majority of patients leave hospital and re-commence their lives?

A dramatic way in which we can help patients understand this dichotomy is to ask them if they have children, or if they hope to have them. Generally the response is affirmative. Then one asks them how they would feel if we were to seek to administer their drug of choice to their child. Of course they object strenuously. One patient calmly told me that he would have to kill me. We then have a scenario where for the adult the drug of choice is the most wonderful thing in the world and the thing to which their whole existence has been devoted, whilst for the child this drug represents the very quintessence of evil, absolute impurity, destruction, non-life and often a horrible lonely awful death. I point out that this represents two very different and in fact opposite views of the same drug. Then I ask them which view is more likely to be correct, their own view or their view for their children? They will generally agree that it is the view for their children.

In other words they themselves have been seduced by the lie of pleasure and personal seduction. Their life does not work, and there is endless trouble and tragedy in and around them because their life has been devoted to serve the lie that their life is about themselves, their pleasures and their feelings – all of course via their drugs. Hence the real issue is their *perspective* of the drugs – it is their *seduction*. That is to say...

It is not about drugs. It is about addiction. When addiction is understood as a certain way of viewing drugs – as the mainspring of life – then addiction becomes a very sinister and powerful – not to mention destructive - delusion.

To which the radical cure is clearly the truth: the truth as relates to themselves and also to life. Which is likely why many of the most successful programs in the long term take a spiritual perspective on these problems. They boil down fundamentally to a statement of belief. Understood in this dimension, the statements “life is drugs” or “life is pleasure” are at once profoundly spiritual; and profoundly false.

Use of the naltrexone implants dramatically divorces the drug use from the empty and chaotic life, underscoring this point⁶⁻¹². Whilst naltrexone implants allow opiate use in opiate addicts to be arrested immediately, it does not necessarily restore virtue, value, direction, a healthy identity or normal emotional state.

The reality of the drug debate is that a few well financed and tightly organized groups have launched a largely highly successful strategic assaults on the global traditions of drug prohibition which were introduced in the twentieth century in a pan-global response to the menace and predations of drug addiction on the peoples of diverse lands, particularly Egypt.

Hence one observes a potent confluence between the siren voices of the seduction of pleasure – AKA “pragmatism” - (“everybody’s doing it”, “you will not surely die”, “just one taste won’t hurt”, “it's only recreational use” “it's not so bad if you snort it up or smoke it”, “its better if the government supplies it in pure form”, “provide clean free needles to reduce HIV spread”, “a clean fit for every hit”, “medical cannabis”, “heroin trials”, “shooting galleries”) and the strategic interests of the drug and addiction multinational criminal and associated corporations with a vested commercial or academic interest in the expansion of the drug trade. Just as we saw the “long march through the institutions” which followed on as a sequel to the post – war alternative lifestyle era and the direct and deliberate enactment of a defined social agenda, so too have we seen a less well heralded, but even more obvious takeover in the West of the culture of pleasure. One observes a confluence of a strategy of siren-like seduction of individuals and of peoples, and the quintessential seduction of the strategy of unbridled power. This is particularly well displayed in the addiction arena with modern university based academic meetings in favour of drug liberalization with leaders in the profession from several nations commonly among the invitees. The implications of this professional takeover are far reaching indeed. It implies that irrespective of the result of major political events such as national elections, whichever government is voted into power is advised by the same academic elites apparently largely consumed with their own internal agenda. In

other words government is at grave risk of being perennially mis-advised, with few administrations with the moral fortitude of the recent British government decision to reschedule cannabis from Class C to B in the face of oppositional expert advice.

At the risk of stating the obvious addictive drugs after all, are addictive. This well known neuropsychological fact implies at the economic level that the demand for them is potentially infinite. In other words, in contradistinction to most other goods and services there is a potentially limitless market for these agents. This translates to virtually unlimited financial gain for those who can gain control of this unbelievably lucrative bazaar. This creates for many in key positions an irresistible allure of almost unlimited global economic ascendancy, including cultural and ideological domination.

Hence in this area one sees an organized global confluence of two powerful streams, the seduction of strategy and the strategy of seduction (particularly by the widespread use of misnomers and the dissemination of misinformation, disinformation and half-truths). Nevertheless as my patients have noted many times, to be overcome by seduction one must release one's personal sovereignty to the object of one's desire; and in so doing one is weakened. Thus fundamentally at the spiritual level and subsequently at the medical, social, relational, organizational, employment and structural level, the addicted and the society which hosts them is progressively, inexorably and inevitably weakened.

It would appear that conceptualization of what might be broadly terms the "libertarian argument" for drug liberalization omits four key factors from its theoretical constructs. As such it would appear to flounder irreparably on a real world "reality check", and be irreconcilably out of touch both with common observed experience and modern scientific research alike, despite the obvious limitation of the largely inadequate research base on these subjects. The areas of oversight of the libertarian view are:

- 1) Addiction is by definition chemical slavery, and weakens the individual;
- 2) Addiction is demonstrably toxic;
- 3) Addiction is highly contagious;
- 4) Addiction's effects are Transgenerational;
- 5) Addiction's many costs are born in substantial measure by others.

It is appropriate to consider these in further detail. Since the definition of drug addiction invariably includes persistent use despite adverse medical social and / or criminal consequences, the addicted may be rightly said to be in a formal sense "enslaved". Since slavery is the opposite of liberty, libertarian arguments may be formally said to be misplaced. The fact that not all recreational users become enslaved by habitual use is irrelevant for virtually all habitual users were at one time small time users. Recreational use is perhaps one of the highest risk categories for the enslavement of habitual use. Without the recreational pool, there would be no filling up of the heavily addicted pool with its high attendant death rate.

Secondly addiction is toxic. Modern science is beginning to describe some of these toxicities of extended exposure to drugs of abuse, and the extension of the concept of liberty to self-poisoning is at best controversial, particularly if it predictably results in *unhappiness*. In particular the toxicities of addiction can be chronic or long term. They may be in part reversible with cessation of use, although this area is not well studied. It is also likely to exacerbate pre-existing pathologies including medical, social, psychological, criminal and employment / employability factors. This theme will be expanded below.

Thirdly addiction is socially contagious as the drugs are usually shared and bought and sold with friends. This is especially true amongst sexual intimates who frequently cannot resist the allure to share the altered sensorium their partner is experiencing. In this sense addiction is socially and sexually contagious. That it is also associated with the transmission of sexually transmissible diseases including genital ulcerative disease and HIV compounds these associations. In view of the extreme social infectivity of addiction, one might ask “What are the libertarian rights of the untreated plague victim?”

Fourthly there is a literature demonstrating that many of the effects of addiction are passed on to offspring of exposed mothers, and sometimes fathers. Again this theme is described in more detail in the following section. Surely the libertarian philosophy extends to newborns the right to a normal birth, start in life and developmental stages uncomplicated by known exogenous neuro- and somato-toxins? The pattern one observes repeatedly is that the most disadvantaged parents who are least able to cope with unruly, hyperactive, difficult or chronically unwell children, are the very parents who produce just such children, who themselves become enormously disadvantaged by both in utero and post-natal exposures including a frequently deprived and neglected upbringing.

And finally, since mental and physical illness has been demonstrated to be part of virtually every established chemical addictive syndrome, this combination of long term poor physical health, frequently with long term mental health issues, reduces or completely abolishes the capacity of the addicted to care for themselves and their loved ones. They therefore become a burden on the welfare system, the health system, the child welfare systems, the mental health care system as well as the criminal justice system. Indeed one recent and very thoughtful study demonstrated that long term opiate dependent patients are likely to require geriatric medical and general gerontological care prematurely¹³. Hence far from being an individual libertarian issue, the addiction of the individual becomes a major cost to the other members of society which is borne in many dimensions.

It is this inadequate understanding of addiction both conceptually and at the toxicological level which underlies not only the making and the publication of the opening quotes such as that from leading Science administrators in the USA in relation to methadone, and a remark usually attributed to Bill Clinton (“*I didn’t inhale*”), but of even more concern, its being quoted in a textbook designed for Australian health professionals studying in the area and commissioned by the

Committee of Academic Deans of Australian Medical Schools, arguably the highest medical authority in the land, and quoting this grossly trivializing comment in its opening introduction to the chapter on cannabis¹.

The Australian Paradox.

Australia is frequently said to have done exceptionally well amongst the global family of nations in the effort to reduced its cigarette smoking rates. Based on our national drug strategy household surveys, rates of daily cigarette smoking fell from 33% to 21% 1985-2004 in males and from 30% to 18% 1988-2004 in females¹⁴. Advertisements describing the effects of smoking have appeared on prime time television, are seen on highway billboards, and are plastered obviously on the front of cigarette packets themselves where they take up more than 25% of the front of the packet. Depicted scenes include black gangrenous toes, lung tumours, atheromatous arteries with thick pasty pultaceous material exuding from one end of a frankly diseased aorta, patients on oxygen gasping for breath, and pregnant abdomens with remarks about baby being too young to smoke. Medical treatments for nicotine dependence are available over the counter in pharmacies and at Federally subsidized rates on prescription through any family doctor. All this has been achieved in only a few short years particularly following the major tobacco company settlement. In the field of tobacco primary and secondary prevention then Australia showed that it can be done. ... After all, “everybody knows.”

It is therefore a matter of great curiosity and perplexity that this same nation is also amongst the worst in the developed world for the use of the illicit drugs heroin, cannabis and amphetamines^{15,16}. Cocaine use here is lower than elsewhere, probably owing largely to our geographic distance from the major cocaine source nations and supply routes, and the diminutive size of our domestic market. Recent trends however show very strong and rapid growth in this drug also, albeit starting from a smaller base in the alternate community.

This stark and remarkable paradox sets up an extraordinary conundrum. How can one of the best nations on the planet for tobacco be at the same time one of the worst nations for illicit drugs of addiction with probably the fastest growing cocaine market?

The answer it would seem is that when it comes to illicit addictive drugs in this country “Nobody knows.”

And therein lays perhaps the greatest pearl of drug policy for the rest of the world. For any nation to ride high and free from the global scourge of drug addiction, strong and forthright educational efforts must be paramount. “Everybody must know.”

Here we do not. The truth is hard to find and the general public is kept in the dark. The dominant ideology governing drug policy is harm minimization which openly condones both increased drug use¹⁷ and full drug decriminalization¹⁸; indeed

debate is often led by a well known group quite overtly entitled “Australian Drug Law Reform Foundation”¹⁹.

Our domestic situation contrasts with that in Sweden, where drug education in schools is widespread, is interwoven into many school curricula, and is widespread in society. As a result Sweden has one of the lowest drug use rates of any of the developed nations.

Implications of key findings of addiction toxicology literature

A brief consideration of some of the most important findings from the addiction toxicology literature is useful and instructive at this point. The issues to be discussed will be addressed under the following headings, albeit there is significant overlap between the categories as will readily become apparent.

- 1) Sperm abnormalities
- 2) Chromosomal toxicity – Telomere dysfunction
- 3) Cancerogenicity
- 4) Transgenerational Effects
- 5) Atherosclerosis
- 6) Hair graying
- 7) Bones / Osteoporosis
- 8) Teeth
- 9) Psychiatric disabilities
- 10) Stem cell depletion
- 11) Immunosuppression
- 12) Acceleration of the Ageing / Degenerative Process
- 13) Methadone

Sperm Damage

It would seem paradoxical and somewhat abstruse that in an era when there is so much discussion about stem cells and in particular embryonic stem cells, that there would appear to be so little interest in the toxicology of the fundamental ingredients of the ultimate human embryonic stem cell, the human zygote, namely, the gametes, the egg and sperm which are well known to form that zygote. There is a literature, albeit largely some decades old now, relating almost every conceivable abnormality of sperm from human males exposed to cannabis including chromosomal aberrations, abnormal distribution within the nucleus of chromatids, nuclear vacuolation, headless sperm, tails with angulations in them, small shrunken heads, grossly abnormal forms, heads with abnormal mitochondrial “power segments”, multiple loose tails, abnormal motility patterns, azoospermia and hypospermia (absent and low sperm counts) and absolute teratozoospermia (all abnormal forms). The implications for any zygote which manages to survive and develop what are obviously highly lethal and severe mutations, would appear to be likely potentially extreme²⁰⁻³⁴. Broadly similar defects are believed to follow alcohol exposure,

opiates and other drugs of abuse^{21, 35}. Opiate exposure is typically associated with reduced sperm number, motility and viability³⁵⁻⁴³. Cocaine has been shown to interfere with DNA methyltransferases 1 and 3a with defects of epigenetic imprinting and short term memory and learning ability in offspring of exposed fathers⁴⁴⁻⁴⁶.

Chromosomal and Telomeric Dysfunction

In particular Nahas has shown in a heavily intoxicated rat model that all three major cannabinoids found in cannabis tetrahydrocannabinol, cannabidiol, and cannabidiol are severely toxic to chromosomes and cause multiple end to end joinings including the formation of ring chromosomes⁴⁷. Nahas's group also confirmed the finding of grossly abnormal human sperm including decapitated forms following exposure to smoked cannabis⁴⁸. Findings such as this strongly suggest that the cannabis exposure is associated with a functional defect at the end of the chromosomes, known as the "telomere". This is a key finding, for the telomere is a key functional component of the chromosome. The ends of chromosomes are specially protected by a special multiprotein complex collectively called "shelterin". This protein cap, together with a T-loop formed in the overhanging single strand is designed to prevent activation of the nuclear DNA repair machinery which would normally splice and repair the DNA break. This telomeric end zone of the chromosome has been implicated in several major diseases including the ageing process, cancer induction, mental retardation and foetal malformations. For this reason telomeric molecular physiology is an area of intense scientific interest and current enquiry, with major papers appearing frequently in the world's leading scientific journals⁴⁹⁻⁶⁵. Nahas's finding implies severe derangement at this locus. An alternative explanation for the finding of apparently "sticky chromosomal ends" is that diverse cannabinoids might be associated with double stranded DNA and chromosomal breaks. However the toxicological impact of this if true is even worse than that described for telomeric dysfunction. Of concern, similar findings have been reported for methadone³⁵.

Evidence is presented (see below) that several addictions are associated with a cluster of disorders which together represent accelerated phenotype of advanced ageing, as documented above for methadone in humans¹³. The "Barker hypothesis"⁶⁶⁻⁷² suggests that many disease of old age commence in utero during gestation. Since the great majority of studies to examine the sperm, the acknowledged precursor of the zygote, demonstrate deleterious changes which might loosely be described as a form of "ageing", it might be that not only are these embryo's aged from conception, but in fact are likely aged prior to conception even occurring!!

Association with Cancer

Given the robust and frequently demonstrated association of lung, head and neck and bladder cancers with tobacco and or alcohol abuse it should come as little surprise to note that cannabis has been associated with cancers of the lung⁷³, head and neck⁷⁴, congenital leukaemia⁷⁵ and with cervical neoplasia⁷⁶⁻⁷⁸. Indeed cannabis is well known to stimulate the MAP (mitogen activated protein) kinase pathway¹ which is a well known pathway involved in cell growth in both

developmental and malignant conditions . MAP kinase pathway stimulation has been especially associated with non-Hodgkin's leukaemia formation particularly in such syndromes as von Recklinghausen's disease. Cannabis smoking is also associated with large number of free radicals, which has been estimated by one author as high as 10^{18} oxy-radicals per puff by virtue of the large number of partially oxidized products present in the smoke! Oxy-radicals have been documented to be released both on receptor binding and events related to subsequent downstream intracellular signalling events following binding to the $G_{i/o}$ G-protein receptors ⁷⁹⁻⁸², and also by mitochondrial uncoupling by stimulating mitochondrial uncoupling protein 2 ^{83, 84}. Indeed in one experimental system it has been suggested that cannabinoids *normally* signal by inducing oxy-radical attack on the key DNA base guanine, with subsequent DNA repair by nucleotide excision and base excision repair ⁸⁵. Oxygen radicals have themselves been extensively implicated in major diseases such as congenital malformations, atherosclerosis, cancer and ageing.

Transgenerational Defects

Some of the most worrying effects of addiction relate to their effects on the following generation/s. There are many reports of post-natal and developmental deficits induced by opiates ⁸⁶⁻⁸⁹, methadone ⁹⁰⁻¹⁰⁶, cocaine ^{91, 107-114}, amphetamine ¹¹⁵⁻¹²¹ and cannabis ¹²²⁻¹²⁶. The most careful studies invariably report significant neurological learning emotional and behavioural deficits continuing into the neonatal, childhood and adolescent periods reflected in conduct, behaviour and learning skills, and at times in the rate at which they subsequently proceed to drug use themselves.

Reduced fertility has already been mentioned. This is not only a quantitative effect but also likely a qualitative effect, with reduced numbers of children being born, and an increased incidence of various defects in those offspring.

The ageing of the gametes at a stage even prior to fertilization has been discussed above.

A very high incidence of leukaemia in offspring has also been discussed ⁷⁵, and is consistent with the genotoxic and chromosomal toxicity studies mentioned above.

Atherosclerosis

Some drugs of abuse notably methadone and to a lesser extent cannabis, are associated with known cardiovascular risk factors such as cigarette smoking ¹²⁷⁻¹³⁰, significant weight gain ¹³¹⁻¹³⁴, glucose intolerance / diabetes ¹³⁵⁻¹³⁷, hypertension, appetite stimulation, inactivity ¹³⁸, immune suppression ^{136, 139-143} and others. It is not surprising therefore that occasional careful studies detect signs of greatly accelerated atherosclerosis in this group with 4% with a mean age of 30 years rising to 17% with a mean age of 50 years with evidence of >75% coronary artery

narrowing¹⁴⁴. Similar findings have been reported with amphetamine¹⁴⁵ and cocaine¹⁴⁶ abuse. However it is equally clear that much more work needs to be done in this area.

It should also be noted that atherosclerosis is increasingly being understood as a chronic immunoinflammatory disease¹⁴⁷⁻¹⁵⁷. Given the increasing understanding of the immunosuppressive activities and secondary immunostimulation profile found in addiction^{158,159} one might imagine that more work would be merited in this area, particularly given the known interaction between addictive agents and endothelial function in the lining layer of the major blood vessels^{79-81, 160}.

In this context it is worth remembering the aphorism from vascular surgery that “one is as old as one’s arteries.” In that around 50% of the deaths in western nations are related to cardiovascular mortality, this is clearly a truism. Furthermore it suggests that were some technique of determining vascular age developed, it would serve as a surrogate marker for biological age. Such a methodology does exist known as radial applanation tonometry. It has been applied for some years in my clinic and does confirm that for most addictions there is dramatic acceleration of the vascular ageing process in chronically addicted persons. One report of this work in the scientific literature has already been made¹⁶¹. Since all the addictive drugs have been implicated in the addiction related immunosuppression^{142, 162-164} it would seem eminently possible given what we now know about the pathogenesis of atherosclerotic disease, that they will largely be associated with clinical manifestations of vascular dysfunction.

It is fascinating that five large genome wide screens on two continents found that the gene products of cyclin dependent kinases 2A and 2B (CDKN2A and CDKN2B; namely P16INK4A and P15INK4B), two well established markers of senescent cells¹⁶⁵⁻¹⁸³ located on chromosome 9p21 proved to be the major genes associated with atherosclerosis^{184, 185}. Clearly, in the light of the above findings, there is a need to study the expression of these gene products in arterial and other tissues in addicted patients.

Hair Graying

Results from this clinic reported for the first time a highly statistically significant finding that drug addicts were two- to three- fold greyer in the hair as measured at the temple and vertex respectively¹⁸⁶. This is a very important finding because temporal graying has long been seen as the clinical sign *par excellence* of human ageing. It strongly suggests moreover that the evidence which is seen of damage to diffuse organ systems is associated with ageing of the organism. That it was seen at both temple and vertex suggests that this is not just a localized change occurring in the temporal area, but generalized across the whole of the scalp. This finding fits with the suggestion above of increased oxygen radical flux associated with smoking cigarettes and cannabis. It is important because it ties together at the conceptual level the diffuse multisystem diseases and dysfunctions which have been documented¹⁴⁴ with carefully collated evidence of premature gerontological biomarkers^{158, 187} and geriatric disease states¹³. This state of accelerated ageing is

known as a “progeroid disorder”^{127, 158, 159, 188-195}, from which it appears that addicts likely suffer, in most body systems.

Osteoporosis

A very important study from Boston university has shown an association between opiate use including a mean of three years on methadone, and osteoporosis, with 83% of a sample of *males*, with a mean age of 42 years being in the osteoporotic range¹⁹⁶. Whilst the study noted a number of significant covariates, it seems clear that the opiate addiction and treatment itself is nevertheless strongly implicated in this devastating finding. It should be noted that similar findings have been demonstrated in experimental models with both cannabinoids¹⁹⁷ and stimulants which bind to adrenergic receptors¹⁹⁸. It is worth reflecting on the implications of this important result.

Most obviously the bone is a very hard tissue. Clearly one must wonder what the implications for more delicate soft tissues might be, if bony structures are so ravaged by addiction. What is the damage incurred by more delicate tissues such as the brain, or gonads?

Secondly an extensive literature (actually PubMed documents 40,000 references)¹⁹⁹⁻²⁰² documents the large impact which immune and cytokine activation have on bony physiology. It is likely therefore that long term immune activation plays a key role in the massive degree of bony erosion which is observed.

Thirdly the ready availability of the bone mineral densitometry test allows us to study at a single point in time, the cumulative effect of organ dysfunction over a protracted period of time. The skeleton is somewhat unique in this respect. This test then effectively allows us by taking a spot measurement to integrate over time the effect of cumulative damage sustained by this organ system. This affords then an invaluable opportunity to interrogate the so-called homeostatic hypothesis which has been argued at length in various contexts in relation particularly opiate substitution therapy²⁰³⁻²⁰⁸. The argument goes that whilst methadone (or other addictive drugs) may induce a perturbation in various physiological parameters in the short term, with time, *homeostatic* adjustment occurs and the system returns towards the normal set point. The basis for this assertion is that various hormonal or immune parameters of interest return towards the normal range and are said to be no longer different from the pre-treatment levels as usually judged with Student's t-tests.

But such an analysis begs a key question. And that is “*Do various parameters actually return completely to normal, or do they just return towards normal?*” Because if they only return towards normal, this implies that there remains a residual functional deficit. Over time such a deficit may become physiologically relevant. This concept is referred to as *allostasis*²⁰⁹⁻²¹³. As the implications of such thinking are important, it is worth a little formal consideration. Consider the following table relating to compound interest calculations. Note that many of our patients have been using drugs for 10-20 years, the average in many reported series

being about 9-10 years of drug use. One should also note that most clinics have some patients who have been involved in this lifestyle for 30-40 years.

Compound Interest Table

Principal	Interest	Term	Maturity	Net Gain
Positive Interest				
100%	1.0%	30	1.35	34.8%
100%	1.0%	40	1.49	48.9%
100%	2.0%	20	1.49	48.6%
100%	2.0%	30	1.81	81.1%
100%	2.0%	40	2.21	121.0%
100%	2.5%	10	1.28	28.0%
100%	3.0%	10	1.34	34.4%
Negative Interest				
100%	-1.0%	30	0.74	-26.0%
100%	-1.0%	40	0.67	-33.1%
100%	-2.0%	20	0.67	-33.2%
100%	-2.0%	30	0.55	-45.5%
100%	-2.0%	40	0.45	-55.0%
100%	-2.5%	10	0.78	-22.4%
100%	-3.0%	10	0.74	-26.3%

This table indicates that if of 100% is invested at 2% annually over 20 years, one has the significant quantity of 148.6% after an investment term of 20 years. Similarly for the other rate and term parameters. One notes that as low a rate of interest as 1% annually over 30-40 years compounds to 35-50% gain. In other words a low rate of interest over a long term can become highly important when the initial sum matures.

Conversely a *low* rate of *negative* interest can similarly become significant over a period of time. In particular it is easy to foresee a 2-3% annual rate of bone loss in our addicted patients, which over 1-2 decades becomes highly significant and may account for 20-30% loss of bone mass. If the rate of disequilibrium in the normal rate of bone turnover is as little as 1%, over three to four decades this compounds to a net loss of 26-33%. A 2% rate of bone loss for 40 years yields a massive 55% net loss.

If similar changes are occurring in other body systems, as is implied by some of the most careful autopsy studies¹⁴⁴, then the overall toll on the whole organism would be significant indeed.

The simple reality is that the “homeostatic” hypothesis has not been tested to this

degree of accuracy. In my view findings such as these in the bone argue strongly for an *allostatic* situation where normal physiological homeostatic mechanisms return the status quo *towards* normal, but the set point is altered somewhat. These calculations demonstrate that the alteration in the set point does not need to be great, for it to make substantial differences in outcome over the long term.

Teeth

The association of poor dental health with tobacco and alcohol use is legendary amongst the dental profession²¹⁴⁻²¹⁶. Similarly many studies document the association between poor dentition and illicit drug use^{129, 217-221}. This has at least two further ramifications.

The poor dental health has been linked with systemic atherosclerotic disease^{156, 222-229}. Clearly the inflamed oral tissues (gums, jaw bones and teeth / tooth stumps) become a focus of inflammatory activity and stimulate the immune system at a low level for an extended period of time. This “inflammatory engine” can then act on diverse tissues throughout the body with known deleterious effects on bone, brain and arterial tissues.

Secondly at least one careful study has also demonstrated a statistical association between dental health and a simple index of psychological health both in addicted and non-addicted patients²²¹. Although one might at first find such a link puzzling, a link between dental and mental disease has been shown for schizophrenia^{230, 231}, and it may be that rather than a direct causal link, dental and mental pathologies share a significant underlying disease process, via impairment of stem cell and immunostimulatory pathways. It is well known that if one is buying a horse it is routine to check the teeth. The same might apply to humans, albeit perhaps by different pathways.

Psychiatric disabilities

Psychiatric disabilities are legendary amongst chronically addicted patients^{7, 138, 232-241}. A modern understanding of the way the brain is wired, and the dynamic function of synapse formation and maintenance demonstrate that to a large extent brain function determines brain structure. Activity is a key determinant of brain function and thereby brain structure. Memories are formed as synapses are strengthened by several mechanisms, as a result of the traffic occurring through them. Since addictive drugs are either depressants or stimulants they change patterns of brain activity. The depressants (alcohol, cannabinoids, opiates) reduce the overall level of brain activity which given this understanding is toxic in itself. Stimulants (cocaine, amphetamine and nicotine) increase brain activity but in abnormal patterns which itself may be unhelpful. All these agents, and especially stimulants, are directly neurotoxic to a lesser or greater extent, and particularly when combined in the common combinations in which they are encountered clinically. It is little wonder then psychiatric complications are commonplace in the clinical management of our patients. There has been much discussion recently about “dual

diagnosis” of psychiatric and addictive disorders. Far from being a rarity, current clinical experience that this may actually be the *usual* situation in patients presenting for assistance with their addictive disorders. In other words the factor missing from the current activism is the *commonality* of neuropsychiatric presentation in addicted patients, rather than their supposed rarity.

Since the brain structure and function is susceptible to environmental influences therefore, including by gene – environment interactions, it follows that it is particularly vulnerable in utero. This explains the plethora of positive studies documenting neuropsychiatric and educational deficits after *in utero* exposure noted above.

It is worth considering the likely mechanisms responsible for this inordinate rate of psychopathology in addicted patients. Obviously the high density opiate, cannabinoid and adrenergic receptors on neurons, glia, endothelial cells and all inflammatory cells (including platelets) may be expected to have a major effect. Interactions between immune cells, brain neuronal stem cells, an unfavourable alteration of the glial / neuronal differentiation ratio in lineage fate determination for CNS progenitor differentiation, and the potent interaction between immunostimulatory and stem cell susceptibility to cytokine and immunological activity, will likely play a major role in the CNS as elsewhere throughout the body.

A vast body of modern neurophysiological literature attributes the molecular substrate of major neurocognitive processes to events such as:

- 1) Calcium fluxes and cycling,
- 2) Subcellular compartmentation of calcium and other molecules,
- 3) Receptor trafficking to and from the membrane and synaptic cleft, particularly relating to glutamate receptor subtypes, AMPA, NMDA and metabotropic receptors, and their respective receptor subtypes,
- 4) Membrane affinity,
- 5) Glial – neuronal interaction,
- 6) Activity of resident and immigrating inflammatory cells,
- 7) Complex molecular mechanisms of synaptic vesicle release,
- 8) Mechanisms of post-synaptic density formation assembly and recycling, particularly relating to PSD-95,
- 9) Generative processes of synaptogenesis, dendritogenesis, neuronogenesis, axoplasmic transport and axonal guidance,
- 10) Neurotransmitter uptake and recycling within the synapse, and between neurones and glia,
- 11) Synaptic vesicle release,
- 12) Protein and insoluble protein disposal – amyloid, A β , tau, proteosomal degradation,
- 13) Neurovascular interactions – especially with the capillaries and the blood brain barrier.

As addictive drugs have been shown to derange virtually all of these various steps, severe degrees of psychocognitive impairment are to be expected in the setting of

short and long term exposure to drugs of addiction. Whilst references are not provided for this section they are more than well attested in the contemporary neuroscience literature and the interested reader is referred to leading neuroscience journals such as Neuroscience, Journal of Neuroscience, Neuron, Nature Neuroscience, Nature, Cell and Science for more detailed discussions. A fascinating summary of some of these changes in the context of neuro-aging is also provided in the “Frontiers in Neuroscience” monograph “Brain Aging” by David Riddle ²⁴².

Stem Cell Depletion

A significant literature describes the capacity of all addictive drugs to slow cell growth ²⁴³⁻²⁴⁵ on the one hand and to potentiate apoptosis or programmed cell death ²⁴⁶⁻²⁵⁰ on the other. The stem cell hypothesis of ageing suggests that ageing at the organismal level is reflected by impaired cell health at the cellular level including reduced function, reduced growth, increased senescence, and cell loss by apoptosis, necrosis and other pathways ^{251, 252}.

This is critical. We know that the stem cell pool in most tissues declines dramatically with ageing ^{53, 55, 56}, and that this pool is key to tissue growth and renewal. Any exacerbation of this relative shortfall with age would clearly further imperil tissue viability and ultimately the fitness of the organism.

In a pilot study my clinic has documented an apparent shortfall of stem cells in humans in two major lines ²⁵³. As further funding and research opportunities allow this work can be extended to larger sample sizes, more stem and progenitor cell lines, detailed molecular profiling of these cells, studies of replicative limits of the progenitor cells obtained, studies of their DNA repair and integrity maintenance systems and their telomeric physiology.

It should also be noted that the obstetric evidence cited above of so many studies showing an inordinate number of babies born to addicted mothers which have small brains, small heads, small bodies, and an increased rate of prematurity is itself strong evidence of interference with stem cell activity and growth during in utero development. The premature births also likely indicates immune stimulation of the uterus, so that this pattern of growth and brain growth retardation and premature birth is consistent with the overall mechanistic paradigm presented of stem cell inhibition – cell death potentiation and immunosuppression - immunostimulation.

Moreover there is a very important interaction with the next area of interest.

Immunomodulation

The immunosuppressive effects of addictive drugs have been mentioned at several points, and the interested reader is referred for further detail to discursive treatments of this subject ^{142, 162-164, 254, 255}. One of the very common and dramatic ways this presents clinically is that patients frequently have appalling dental health and incipient dental abscesses. However because they are so immunosuppressed the

body does not fight back against a cavernous hole in the jaw. When the immune system is restored by treatment with an opiate antagonist which has been shown to largely restore the immunosuppression¹⁴² the patient then complains of mouth pain and swelling due to the formation of a dental abscess, because the innate bactericidal ability of his immune system has been restored.

Four main factors are pertinent to the present discussion. Firstly careful study of these patients^{158, 159, 187} demonstrates that addicted patients bear evidence of both immunosuppression, and immunostimulation. An appropriate analogy would be with an old car which is failing relatively rapidly. As the engine dies, it needs to work harder to keep up with the speed limit. In other words the engine is working harder not because it is stronger, but because it is weaker. A similar situation seems to apply to these patients. The drug induced immunosuppression results in a chronically activated immune system, which is exacerbated by chronic infections such as mucus in the airways of the lungs, abscesses beneath the skin due to missed injections, often appalling dental health, frequently chronic viral or other hepatitis, fatty liver, injected particulate matter, particulate matter in the lungs from smoking of various substances, and intravenous drug using amongst others. This immunosuppressed but simultaneously immunostimulated state is referred to as “immunomodulation”.

Secondly major degenerative diseases are recognized as having an important chronic inflammatory component. This is true for atherosclerosis^{148, 152, 154, 155, 157, 223, 256-258}, osteoporosis^{259, 260}, and neuropsychiatric disorders²⁴² including multiple sclerosis and Alzheimer’s disease.

Thirdly this pattern of non-specific immune activation has been identified in elderly people who are not ageing in a healthy manner. Indeed various European researchers have been able to identify an unhealthy immunophenotype which dramatically prospectively predicts mortality in a group of elderly patients²⁶¹⁻²⁶⁹. Particularly relevant then in this discussion is the demonstration of a direct link between one of the main nuclear transcription factors responsible for immune stimulation nuclear factor kappa B (NF-κB), DNA damage and a progeroid clinical syndrome¹⁹⁰.

Fourthly stem cells themselves are known to be acutely sensitive to immune factors particularly cytokines which exercise a strong negative effect on their proliferative activity²⁷⁰⁻²⁷⁴. Importantly this implies that addicted persons will incur damage in the long term not only by virtue of their stem cell depression, and their immunomodulation, but the combined effect of both may in fact be of particular importance.

Acceleration of the Ageing / Degenerative Process

Clearly all of the above processes add up to a significant acceleration of the ageing process. It should be mentioned that most of a list of the diseases of old age²⁷⁵ have been described amongst drug addicts^{13, 144, 276}. Evidence has been presented that

addicted patients have progeroid signs of ageing in the following systems:

- 1) Brain
- 2) Immune
- 3) Hair
- 4) Reproductive
- 5) Hormonal
- 6) Teeth
- 7) Bones
- 8) Stem cell
- 9) Cancer
- 10) Mortality ^{78, 240, 277-286}

In this connection it should be noted that cancer is overwhelmingly a disease associated with ageing.

Formal demonstration and exhaustive proof of this finding has not as yet been performed, but nevertheless it does seem to be well worth pursuing as funding and research opportunities become available.

In this connection, and as mentioned, this clinic has been studying the biological or vascular age of patients for some years. Evidence has been assembled that further confirms this hypothesis for the illicit drugs most commonly used in this country, amphetamines, opiates and cannabis, and this data is presently being prepared for publication.

Methadone

In this country, and it would appear also in many others, methadone has achieved iconic status amongst treatment professionals even beyond what it may merit as for a long time the “gold standard” of treatment for opiate addiction. This is reflected in the opening quotation from one of the world’s foremost and well resourced Science administrators. Indeed this remark has been heard on both sides of the Pacific Ocean.

Does the thinking behind this remark reflect a full understanding of the toxicological issues raised above, particularly the discussion about the difference between homeostasis and allostasis, and the elegant demonstration by ourselves ^{76, 127-129, 159, 186, 221, 253, 287} and others ^{13, 73, 74, 196, 288-290} of the evidence for acceleration of the ageing process by the ravages of long term addiction?

Whilst the many benefits of methadone treatment to save lives and reduced HIV transmission are well documented and frequently cited, increasing questions have been raised in recent scientific papers appearing in the published literature establishing links between methadone and dental disorders ^{129, 217, 218, 220}, significant weight gain ¹³¹⁻¹³⁴, hormonal suppression ^{139, 291-294}, immune suppression ^{136, 139-143}, osteoporosis ¹⁹⁶ and glucose intolerance / diabetes ¹³⁵⁻¹³⁷ amongst many others.

Indeed I recently met a young couple who had both gained 35kg in their four years of methadone treatment.

It is also worth mentioning that agonist maintenance treatment aim to *reduce* the amount of heroin used. For example the NEPOD trials conducted in 14 centres around Australia found that heroin addicts treated with agonists reduced their using from about 26 days per month to about five days per month. Such programs accept therefore continued drug use. They acknowledge that many patients sustain both a heroin habit and a methadone habit. It is said that for some, methadone simply makes it more convenient to use heroin, as one is not sick in the morning on waking up. In this sense they are truly “maintenance programs”. Another leading authority recently noted that it is typical and expected for half the stabilized methadone patients to continue using heroin, one third to use occasionally, and for one sixth to use with an unchanged frequency ²⁹⁵. Such “treatment results” are considered unremarkable with this modality.

Another corollary of this is that the impact of drug supply droughts is minimized. Australia recently had a heroin drought for many years, but the ability of the government to “maintain” patients on sponsored programs throughout this lengthy period, (in addition to other factors such as the prescribed opiate epidemic), meant that its effect was minimized in terms of reducing opiate addiction within the country.

The central concern here is that a young patient may present to an addiction clinic at some time in the future, who had say a puff of cannabis at a party some years prior. He might be distressed, and the commonest reason for personal distress is a dispute in his close personal relationships. Addiction professionals, being in general a compassionate, understanding and very caring group decide to place him on indefinite cannabinoid maintenance treatment. The reader should not think that this is unlikely for in fact hundreds of suitable compounds have been synthesized to perform this task, many of them far more potent stimulators of the CB1 receptor than tetrahydrocannabinol (THC). Cannabis of course has been shown several times to be a gateway drug for both social ²⁹⁶⁻³⁰¹ and molecular reasons, so his drug using career is effectively both launched and underwritten – by the Government!

In other words, since most young people will take a drug at some point in their youth, virtually the whole of our younger population becomes at risk of being placed on an indefinite maintenance program which for practical purposes is permanent, and perhaps, again like methadone, can only be withdrawn from with the greatest of difficulty.

In this sense the ideology behind methadone, that of permanent government maintenance programs for everybody, threatens the well being and indeed viability of advanced civilizations. In making these remarks one does not seek to dispute the benefits which have been extensively attributed to methadone in terms of lives saved by treatment with the drug. However it is equally important that given that this drug has now unequivocally achieved iconic status, notwithstanding its demonstrated immunosuppressive effects including enhancing experimental HIV infection ^{140, 141}, it is important to carefully review the ramifications of the

conceptual portrayal of the agent within addiction medicine as very much “larger than life”, and its role now in setting a paradigm of treatment development for the whole drug discovery and addictions treatment industries.

A Plan to Advance – Research and Education

Given the demonstrated success of a broad information campaigns widely disseminating information to the populace the centrality of the major databank in relation to addiction is clear. In comparison with the excellent public education which is readily and generally available in relation to tobacco, that relating to illicit drugs of addiction is, at least in this nation, abysmal. However the state of relative ignorance in the general populace directly reflects that within the professional and scientific community. Despite the all too obvious evidence of rampant devastation in virtually every area of life in long term addicted patients, Science in general has lagged way behind the obvious clinical evidence at the coal face in describing and characterizing the evident damage. It is true of course that the effects of some neurotoxicities related to various drugs particularly cocaine are being worked out seriously and with a thorough going and determined investigational strategy by very fine schools³⁰²⁻³⁰⁶. Such can in general not be said for other addictive drugs particularly outside the central nervous system where it is likely that some of the most telling addiction related toxicology occurs. A very dramatic example of this occurred this year in the USA, where despite cannabis decriminalization being widely discussed in many state legislatures, the voice of Science (at least to this interested if distant observer) was conspicuous by its absence in the thunderous and cacophonous scientific silence. Considering that the NIH alone invests around \$USD 1billion annually in addiction research, that is outside of the very considerable and well known American philanthropic bequests directed to research, one can only be staggered that so much investigative effort would apparently seem to be unrelated to the burning issues confronting that nation, and in reality many others.

Hence a rational plan for a way forward would be to use proven public health preventative techniques particularly related to widespread generalized popular education in this fight. We have shown that we can it can be done, in relation to even more prevalent substances such as tobacco. Modern educational techniques can of course be quite sophisticated and include web based and interactive digital methods, as well as traditional classroom based and popular methods described above for nicotine. The issue comes with the relatively deficient content presently available for publication.

Whilst the neuroscience is progressing reasonably well under its own steam by the usual methods of Science, this does not seem in general to be true for addiction toxicological research related to other body systems. Most experts trying to work in this area are quite agreed that many of the issues raised above are clearly not

receiving nearly enough research attention. In my view it would appear that the most urgent issues facing a community genuinely concerned about the ravages of addiction on their young outside but not excluding the neuraxis would include:

- 1) Stem cell and tissue regenerative defects,
- 2) The implications of the described progeroid immunomodulated profile, cytokines and CD56^{bright} Natural Killer cells,
- 3) Particularly on stem cell populations and key organ systems,
- 4) Free radical fluxes – direct and indirect induction,
- 5) Genetic including chromosomal damage,
- 6) Telomere (end chromosomal) damage,
- 7) Sperm and germ cell toxicology,
- 8) Mitochondrial pathologies.
- 9) Arterial structure and function,
- 10) Bony structure and function,
- 11) Dental disease particularly immunology and gingival stem cell activity,
- 12) The ability of addictive drugs to induce premature ageing syndromes in model organisms such as mice,
- 13) Studies of micro-RNA,
- 14) Investigations of major age related pathways including Sirtuins^{275, 307, 308}, circadian genes^{304, 309, 310}, AMP kinase³¹¹, sympathoadrenal stimulation, gonadal signals, P16, P19, P21, P53, Dec1, Mcl1 and DcR2⁵⁶, NF- κ B¹⁹⁰
- 15) Neuronal – glial interactions in the context of addiction.

The pattern is that with the on-going rapid advances in biology important new biological systems are discovered every few months. The obvious issue if the toxicology of addiction is ever to be understood in detail is for these various systems to be studied in the context of the various addictive drugs.

It would therefore seem that educational methods exist and are tried and well proven to have the ability to influence a population for good in relation to drugs of addiction. The problem relates mainly to areas upstream of education, namely a block within the research community, to studying in a deliberate and determined manner, key areas of interest. This block is related to the fallout of a long term academic strategy.

To my mind at least the matter turns on our response to seduction, to strategy, and to the potent mix of the interaction of the two, in our general and scientific communities. The present paper outlines a way forward for the international research community, should we possess the courage and will to pursue the course which is clearly required. If we continue to take the “soft option”, we will inevitably be forced to pay a stiff price, potentially for generations to come. We absent the outcomes of formal rigorous and thorough going scientific investigation from the popular debate at our grave peril.
