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Drug residues store in the body following cessation of use: Impacts on neuroendocrine balance and behavior — Use of the Hubbard sauna regimen to remove toxins and restore health $\stackrel{\mbox{\tiny\scale}}{\sim}$

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Summary For decades, scientists have investigated the environmental and human health effects of synthetic chemicals. A growing body of research has illuminated the spectrum of consequences deriving from our reliance these substances and their proliferation in air, water, soil and the food chain. Of particular concern is the fact that residues of many man-made chemicals are now detectible in virtually every person. A key to a chemical's tendency to persist in tissues once it has entered the body is its lipophilicity. Substances that are poorly soluble in water and quite soluble in fat have relatively free access, via lipid-rich cellular membranes, to the cells of all organs including the ability to cross the blood-brain and placental barriers. Substantial data exist demonstrating that in addition to pollutants, drugs and their metabolites dispose to tissues high in fat content, including brain and adipose. While their characteristic lipophilicity permits drugs and medications to reach target tissues, thereby producing therapeutic effects in the present, current perceptions of risk may be ignoring the possibility that adipose accumulations of illicit drugs and pharmaceuticals may lead to future patterns of ill health similar to those associated with exposure to other categories of xenobiotic chemicals. Empirical data are beginning to characterize the myriad regulatory functions of adipose hormones, including roles in cravings, cognitive function, energy level, and inflammation as well as changes in adipose hormone levels associated with drug use. Included in this data are the observation that a rehabilitative treatment intervention introduced by L. Ron Hubbard in 1978 to aid in the broad elimination of chemicals from body stores improves symptoms common to both chemical exposure and drug addiction. The regimen, which includes exercise, sauna bathing, and vitamin and mineral supplementation, is utilized by nearly 70 drug rehabilitation and medical practices in over 20 countries. At present, much more is unknown than is known regarding long-term drug retention and effects. This subject deserves careful evaluation given its potential implications for health and chronic illnesses of poorly defined etiology (such as chronic fatigue syndrome), as well as drug abuse prevention, drug rehabilitation, forensic and legal areas. © 2006 Elsevier Ltd. All rights reserved.

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Introduction

Research now reveals detectible levels of humanmanufactured toxins in all individuals. One study alone found 167 different contaminants in volunteers who did not work with chemicals or near industrial facilities [1].

Accumulations of chemicals in body tissues are increasingly associated with patterns of adverse health including suppressed or inappropriate/ hyperreactive immune function (autoimmunity, asthma, allergies), cancers, cognitive deficits, mood changes, neurological illnesses, changes in libido, reproductive dysfunction, and glucose dysregulation [2,3]. There is even concern that pregnant women exposed to toxins can pass disorders on to their children — even for several succeeding generations [4].

While policy initiatives such as the European REACH (the name REACH refers to its three key steps: Registration, Evaluation and Authorization of Chemicals) appropriately trigger an authorization process to regulate environmental chemicals exhibiting certain hazardous characteristics considered of "very high concern" - such as persistent bioaccumulative toxics and endocrine-disrupting chemicals - it is noteworthy that chemicals classified as "pharmaceuticals" have many similar characteristics but are not addressed with the same caution as environmental chemicals. Environmental chemicals with bioaccumaltive tendencies are avoided for their potential to cause adverse health, while the use of nonbiological drugs that may have comparable persistence is generally encouraged.

Although these categories of compounds are given different names and are differentially regulated by law, are they really so different? Perhaps, emerging research argues, addictive and avoidant individual behaviors are simply different responses to the same underlying mechanism [5].

Within the spectrum of these chemicals, the key to their similarity is lipophilicity — the tendency of a compound to diffuse into lipid-rich spaces. Many of these substances are poorly soluble in water and quite soluble in fat, including the white adipose tissue and all cellular membranes — thereby giving them relatively free access to the cells of all organs, body wide. Hence, long-term storage, both within adipose and elsewhere, and the possibility that these chemicals may contribute to a cumulative toxic burden, are important issues.

Tests to determine chemical safety and consequent health impacts do not take into account combinations of contaminants; thus, effects are largely underestimated or potentially unobserved. A single perturbation may not *appear* to shift the dynamic system, but with each additional perturbation an instability is added, capable at some point of tipping the balance between states described as ''health'' and ''illness.''

There are many mechanisms by which retention in the body can negatively impact health.

Chemical-communication mimetics

Many drugs and toxins mimic substances naturally found in the body and may directly affect normal *trans*-cellular chemical communication by hormones and cytokines¹ – such structural mimetics often causing effects quite dissimilar or even opposite to those of the endogenous substance (for example blockage of a receptor normally accessible to a hormone). This may occur locally within a tissue (paracrinely), or endocrinely as drugs/toxins are released from body tissues back into circulation. Further, circulating drugs and toxins may occupy sites on plasma transport proteins thereby subtly interfering with the equilibria kinetics that govern plasma transport of nutrients and hormones, for example.

Genetic/metabolic disruption

Retention of toxins in key organs may directly impair organ health and function by a number of intracellular mechanisms, including disruption of the sophisticated networks that regulate situational gene expression or the delicate feedbacks by which the intermediates and products of constitutive metabolic chains regulate the activity of key metabolic enzymes.

Nutrient deficiency

Eliminating toxins requires certain endogenous substances; for example, catabolism of retinol is accelerated during drug metabolization by the microsomal pathway, thereby contributing to hepatic vitamin A depletion [6]. Nutrients used during metabolic processes of detoxification are concomitantly or subsequently not available for other metabolic processes, thus creating local deficiencies. Chronic exposure may result in systemic deficiencies.

¹ Cytokines are local (autocrine/paracrine) mediators and hormones involved in cellular communication, particularly prevalent in the immune response and associated tissue-regulatory processes.

Adipose tissue is a very intricate organ and not merely involved in storing excess calories and ''unwanted'' compounds. Recent research reveals that hormones released by adipose tissue regulate many bodily functions including emotional state, energy level and body metabolism, hunger and cravings, inflammatory response, and also modulate immune function. Not surprisingly, symptoms associated with disruption of these systems are common in those exposed to environmental chemicals and also in substance abusers [5].

Hypothesis

The 1960s and 1970s were largely focused on the question of whether a diverse collection of synthetic compounds could act as carcinogens, hence, largely ignoring the potential impact of these substances, acting at low levels, to impact other aspects of health, including cognitive behavior and reproductive function [1].

Coincident with new research that reveals accumulations of chemicals in the fat of a very high percentage of human populations [7], the range of adverse effects has expanded considerably. Recently, emotional problems, fatigue, weight change, and inflammation have been recognized as symptoms of exposure to diverse lipophilic toxins and drugs [2]. Data are emerging that demonstrates not only adverse health effects in the present generation, but the potential for additional adverse effects for at least two subsequent generations [8].

While these findings are most commonly associated with pesticides, dioxins, and dioxin-like PCBs, the fat solubility and biological availability of many drugs implies the necessity to better understand and subsequently address long-term storage of pharmaceuticals and illicit drugs. In other words, to segregate these chemicals from the barrage of other foreign nonbiologicals to which we expose ourselves, based largely on sociological distinctions, may well be meaningless.

Both the biological activity of a compound and its physiologic disposition (ultimate fate) are largely determined by its chemical properties in relation to extant biological structures and processes [9]. Barring specific transport mechanisms, the distribution patterns and speed with which chemicals diffuse into various tissues are largely driven by lipophilicity – the thermodynamic tendency of a compound to dissolve into lipid-rich spaces. With certain exceptions (e.g., insulin), drugs tend to be very lipophilic and to have a large distribution volume. They tend to deposit in various tissues in the following order: lung, fat, heart, kidney, brain, gut, muscle and bone, preferentially accumulating in lysosomes² [10], directed to these organelles by evolutionarily established cellular processing pathways.

While not as well characterized as environmental contaminants, illicit drugs and other pharmaceuticals share a number of chemical characteristics with environmental toxins. Evidence of their persistence in body tissues is sufficient to postulate that they disrupt the endocrine function of white fat, including ties to altered mood and cravings not fully explained by other psychoactive properties of the drug.

Research is mounting that the long-term effects of drug consumption are greater than has been assumed [11–13]. It is not simply the case that these effects occur during active drug use, but rather that these effects continue after discontinuation of drug use. It may require a much longer period for drugs or their metabolites to be fully cleared from the body than previously supposed, with consequent residual physical and psychological effects. Dose—response curves fail to assess such longer-term system dynamics despite evidence of effects far below typical use levels in certain cases.

Evidence for drug storage in adipose

As is the case with environmental contaminants, drugs and/or their metabolites - both pharmaceutical and illicit - have the potential to remain in the body for an extended time, contributing to the ongoing accrual of complex mixtures of synthetic compounds [14–16]. The case of LSD is illustrative in this respect, its long-term adipose accumulation were demonstrated in very early investigations [17]. Research has also shown that cocaine rapidly distributes into the fat tissues following ingestion [18]; and a symmetric, equalized-concentration distribution [19,20] of cocaine and methamphetamine metabolites in postmortem adipose suggests long-term storage of these drugs [21]. Phencyclidine (PCP) has been shown to persist in fat and brain tissues, an observation postulated to account for some of its long-lasting behavioral effects [22]. Although PCP levels in fat initially decline over the few days following ingestion, measured levels then remain relatively constant for up to 3 weeks (the longest time the levels were monitored).

² Lysosomes are ubiquitous cellular organelles responsible for breaking down foreign substances and waste products; they are especially common in certain white blood cells (leukocytes) and liver and kidney cells.

Furthermore, stress (with its beta-adrenergic³ lipolysis) can result in mobilization of PCP, amphetamine and their metabolites from fat into blood as a consequence of concomitant fatty acid release [23,24]. Even certain metabolites of ethyl alcohol – itself a water-soluble (but amphiphilic) substance – persist in liver, adipose and in very high concentrations in brain where they mediate cellular damage [25,26].

Pharmaceuticals

Not surprisingly, given the lipophilic criterion. these storage patterns also apply to therapeutic prescription and OTC drugs. Fluoxetine (Prozac[®]) can be detected for six weeks in urine following cessation of use [27], likely a release from tissue accumulation through phospholipid binding and lysosomal trapping [28]. The widely prescribed benzodiazapene family of tranguilizers is also well-characterized with respect to its distribution and persistence in fat tissues [29-31]. Studies show that the doses of various barbiturates and the tranquilizer diazepam (Valium®) must be substantially increased when administered to obese people due to disposition into adipose that results in reduced availability [32,33]. Clearance by urinarv excretion is also affected, not because the obese individual's kidneys are processing the drug differently, but because the release from fat into blood with shifting chemical equilibria increases blood concentration and therefore renal load the renal glomeruli simply filtering a greater concentration of drug [34,35]. Finally, a series of studies comparing the storage and clearance rates of drugs measured in obese individuals and then remeasured after these individuals had shed their extra fat clearly showed that the initial adipose distribution and retention had decreased after fat loss [36,37]. This research demonstrated a 2-week retention in fat stores of several common medications; longer times were not evaluated, but the connection between fat storage and lipophilicity regardless of the sociological/therapeutic status of a compound - appears clear. The question of how long pharmaceuticals and their metabolites persist remains open. Significant reassessment of side-effect profiles may be called for, which take into consideration long time frames and combinatorial accumulation.

"Street" drugs

Among abused substances classed as "recreational" or "street" drugs. THC (the main psychoactive component of marijuana and hashish) is one of the most fat-soluble substances of abuse. THC is metabolized into over 60 different specific chemicals after ingestion/inhalation - a property that makes detection particularly difficult [38]. During the first hour after administration, blood THC levels decline very rapidly. Subsequently, the THC decline is much slower – with a half-life of 50-60 h [39,40]. This biphasic elimination curve and long apparent half-life of detectable blood THC levels is actually due to rapid disposition into lipid-rich tissues and subsequent re-release [41]. Accumulation in adipose of chronic users results in more-extended re-release kinetics by comparison with that following single use [42]. THC has been detected in adipose for up to 4 weeks after last use [43], but sensitive assays can detect THC in blood and urine up to two months following discontinued use [44,45]. Longer detection periods have, unfortunately, not been evaluated.

Recent evidence shows that rapid sequestration of THC into fat leaves less than 1% of the consumed THC remaining in blood and available to reach the brain. Somewhat paradoxically, in contradiction to conventional wisdom about drug dosage, this low blood level actually correlates with the ''pleasant sensory phenomenon'' described by users [41]. A slow release of THC from stores into the blood, combined with very low blood concentrations required for a drug effect, makes possible the phenomenon of flashbacks, which have been clinically documented coincident with a spike in blood THC measured 2 weeks after last use [46].

THC mimics endocannabinoids — cannabinoids made by the body. As predicted, release of THC from stores will alter normal levels of THC and adversely affect those functions under endocannabinoid control. For example, a biologic explanation for the long-observed decrease in male sperm count in otherwise healthy marijuana users appears to require the action of only very low levels of THC within the testicular compartment. These levels are available and of long duration due to re-release from fat stores [47]. Additionally, intra-uterine endocannabinoids must be at a specific concentration for embryonal implantation. Increased levels of cannabinoids are linked with miscarriage [48]

The lesson of THC appears to be both its longevity of effect and its activity on endocrine physiology at low blood concentrations; it may thus provide a model for long-term effects of

³ Stress-related high catecholamine levels in blood can be induced from psychological reaction or environmental stressors and cause general physiological changes in preparation for physical activity (fight-or-flight response) including increases in heart rate, blood pressure, and blood glucose levels.

adipose-stored drugs. Should this ''low-dose'' clinical-effect on re-release phenomenon be applicable to other lipid-stored nonbiologicals – drugs and toxics alike, alone or in combinations – it is conceivable that this could occasionally explain other clinically diagnosed but mechanistically unexplained syndromes.

Drugs impact adipose functions: influence on addictive behaviors

In addition to the possibility that re-release of psychoactive chemicals from adipose may be directly responsible for adverse behavioral and physical health, the potential for adipose-stored chemicals to alter the normal endocrine function of white fat is cause for significant concern. The view of fat as a ''storage depot'' for the body's disposition of extra calories - and a "sink" where drugs no longer in circulation are sequestered - changed dramatically in 1994 with the discovery that adipocytes in white adipose tissue secrete leptin [49], a hormone with regulatory roles in metabolism, food craving, endocrine function, behavior and mood [50,51]. We now know that white fat cells, like all adult cells, have a differentiated metabolism with concomitant differentiated gene expression. White fat secretes a number of hormones that reveal new interconnections between nutritional status, immune system, and metabolic regulations [52] as well as metabolic syndrome - a cluster of symptoms including insulin resistance, cholesterol imbalance, and weight gain [53].

Leptin

With direct neuroendocrine effects, leptin levels form a key link between dietary status and the function of most, if not all other physiologic systems [54]. Leptin levels communicate to the hypothalamus — a brain region that regulates many fundamental survival processes including food intake, thermoregulation and control of anterior pituitary secretion which, in turn, regulates other components of the endocrine system including thyroid, adrenal, ovarian and testicular function.

Low leptin levels act as a trigger of the complex neuroendocrine adaptive response to fasting. This response includes the drop of energy expenditure, amenorrhea in females, decreased sexual function in males and delayed onset of puberty in prepubertal children.

Increased adipose volume will normally increase leptin levels, in turn, signaling a decrease in hypo-

thalamic endocannabinoids, thus resulting in decreased appetite (except in certain individuals with inherited dysfunctions of this control system) [55,56]. The well-known ''compulsive munchies'' stimulation of appetite following ingestion/inhalation of THC is an example of short-circuiting the white fat-hypothalamus feedback mechanism. An increasing amount of data highlights the broad reach of the leptin-endocannabinoid systems on metabolic functions [57].

Consistent with its fundamental role in ingestive behavior, leptin regulation appears to have a role in a number of addictive behaviors and cravings. Alcohol and heroin intake decrease plasma leptin and other adipocytokine⁴ levels in a manner not linked with body mass index [58]. Leptin and other neuroendocrine peptides that indirectly regulate the hypothalamus—pituitary—adrenal axis may modulate the intensity of craving or the intensity of the alcohol withdrawal syndrome [59]. Increasing plasma leptin during the first few weeks of alcohol withdrawal is associated with craving [60]. In animal models, starvation-induced release of leptin was concurrent with heroin cravings after a prolonged drug-free period [58].

Leptin increases result in increasing cocaine and amphetamine regulated transcript (CART) in the hypothalamus [61] — normally followed by decreased appetite. CART is also operant in sleep regulation, and emotions [62,63] and has been associated with the anxiety that is part of the paranoia of drug addiction [64]. Food or alcohol consumption will quench the anxiety by leptin's regulation of CART. Use of cocaine and amphetamines depress leptin, decrease appetite and increase anxiety using the CART pathway [65].

In addition to regulating activity of the hypothalamus-pituitary-adrenal axis, leptin receptors (a member of the class I cytokine family [66]) have been found on many peripheral cell types including all cell types of innate (nonspecific) and adaptive immunity. Emerging details regarding leptin's immunomodulatory roles are suggestive of a range outside of which either elevated or reduced leptin levels result in inflammation or immunosuppression [67,68]. Leptin is involved in the differentiation and activation of white blood cells. Leptin up-regulates the phagocytic and oxidative burst functions of macrophages and monocytes [69,70], upregulates expression of HLA-DR antigens (when T-lymphocytes recognize specific human leukocyte antigens - HLA presented on the surface of tissues as foreign, they

⁴ Adipocytokines are cytokines secreted (released) by adipose tissue.

produce a cell-mediated immune response. Elevated HLA-DR is often associated with low SF-36 scores, fatigue, and body pain [71]), and shifts the immune state toward the T lymphocyte Th1 cyto-kine-production profile with increased production of pro-inflammatory cytokines including IFN- γ and TNF- α , in turn increasing the efficacy of cytotoxic macrophages and the proliferation of CD8+ T lymphocytes [72]. In contrast, the low leptin levels associated with acute starvation are associated with a decreased CD4+/CD8+ T lymphocyte ratio resulting in immunosuppression with a predisposition to opportunistic infection [73].

Studies of heroin and alcohol addictions have measured similarly low levels of circulating leptin to those reported in starvation [67,74]. While leptin will normally decrease endocannabinoid levels [75], THC from marijuana has been shown to skew the balance of T lymphocytes toward the antiinflammatory Th2 cytokine response [76,77]. Interestingly, certain of the benzodiazepine family of drugs, such as diazepam, inhibit immune functions, while others, e.g., alprazolam, enhance immune responses [78]. Leptin levels in response to toxic exposures tend to vary among reports, however, additional data are emerging in that area as well: The leptin receptor involved in hematopoietin/ interferon-class cytokine receptor activity is among those genes with transcription levels affected by mercury exposure [79].

This web of psycho-neuro-immunologic endocrine interactions has behavioral implications that are perhaps most well described in chronic fatigue syndrome (CFS). This literature describes increases in CD4+ T lymphocyte counts and upregulated proinflammatory T lymphocytes [80,81]. Activated immune surveillance cells release cytokines and neuropeptides that cross the blood-brain barrier and inform the central nervous system of damage. In turn, this signals a neuroendocrine response that involves thermoregulation, sleep, and appetite. Studies comparing immune system function in individuals with CFS triggered by known chemical exposures [82], viral infection, or Gulf War syndrome [83] show these groups as all having similarly altered T lymphocyte ratios and function along with disturbed hypothalamic function; a disturbance similar to that seen with depression. One difference is that the elevated leptin levels measured in depression are not seen in CFS [78].

Adiponectin

Exclusively secreted from adipose tissue into the bloodstream, adiponectin modulates a number of

metabolic processes, including glucose regulation, insulin sensitivity and fatty acid catabolism. Inversely correlated with body mass index in healthy people, the hormone plays a role in metabolic disorders such as type-2 diabetes, obesity and atherosclerosis. Recent characterization of this hormone suggests it has anti-inflammatory effects that are protective against fatty liver disease in alcoholics [84]. Heroin abusers and those who enroll in methadone maintenance treatment, have decreased

Resistin

adiponectin levels [67].

So named because of observed insulin resistance in mice injected with this adipose-secreted hormone, elevated levels of resistin have been documented in chronic heroin abusers and methadone maintenance clients [67].

Tumor necrosis factor α (TNF- α)

An immunoregulatory cytokine secreted by many tissues including adipose and macrophages in the course of damage and acute-phase responses, TNF- α further modulates many aspects of immune function and inflammation, a common secondary problem in addictions; a symptom often addressed through use of more drugs. MDMA (ecstasy), alcohol consumption, heroin use, etc., alter production of TNF- α and disrupt immune function indirectly through release of endogenous immunomodulatory substances [85].

These findings suggest a possible vicious circle, including the components of drug intake, altered leptin secretion, unwanted behaviors, enhanced craving, altered immunological status, and consecutively increasing cycles of drug intake. Little is known regarding how long these patterns exist after cessation of all drug use.

Given the known endocrine (e.g., glucocorticoid) impacts on other systems, expectations are that further research will illuminate additional aspects of immunological and inflammatory regulation. These regulations may be directly changed by the presence of chemical residues.

It should be noted that symptoms similar to those described above have been observed following the uncharacterized exposures of Persian Gulf War veterans, WTC rescue workers, and other victims of large-scale exposure incidents are not abating with time, perhaps due to accumulated toxic residues that alter the normal functions of adipose. The suggestion that ''time will heal'' has proved to be hopeful rather than factual.

Use of sauna detoxification treatment to address contamination from drug exposures

The existence of evidence that elimination of drug and chemical residues, combined with physically restorative measures, can resolve long-lasting symptoms adds support to the hypothesis that their impact on the body is similar.

The Hubbard method of detoxification, a regimen including exercise, sauna bathing, and vitamin and mineral supplementation, is a rehabilitative treatment intervention developed to aid in the broad elimination of chemicals and thereby address adverse health affects resulting from chemical exposure and tissue accretion [86]. Its safety and effectiveness in treating a wide range of exposures have been established for more than two decades.

This regimen has been implemented as one component of the NarcononTM Drug Rehabilitation Program, since 1979 (the Narconon program is a completely drug free, social-educational program with a series of standardized components). The Hubbard sauna detoxification method has been delivered to over 21,000 individuals to address cravings and other protracted withdrawal symptoms stemming from the physical aspects of addiction.

Preliminary data indicate the ability of this method to eliminate cocaine and valium metabolites in sweat and urine of recovering addicts for up to 5 weeks following the start of sauna treatment [87]. Fig. 1 illustrates levels of cocaine in sweat and urine of one of the six study subjects followed during the sauna regimen. All study subjects had discontinued drug use and were tested drug free while completing several components of the Narconon program in the weeks prior to starting the sauna regimen.

In the same study, 249 subjects were asked to self-report the severity of various physical symptoms before and after sauna detoxification. Fig. 2 shows diminishment in reported severity upon completion of the sauna regimen.

Evidence of drug metabolite elimination also sheds light on data published in Medical Hypotheses in 1982: An earlier study on 103 subjects, 41 of whom were substance abusers, demonstrated increases in Wechsler adult intelligence scale IQ averaging 6.7 points [86], data shown in Fig. 3. This same study showed a decrease on several scales of the Minnesota Multiphasic Personality Inventory profile. Table 1 shows the change in fourth-scale scores — a decrease in this category representing an improvement particularly hopeful for sociopaths, a group whose fourth-scale scores had not improved in other inpatient addiction programs. Such behaviors may well have a significant physical (i.e., neuro-pharmacological) component.

The Hubbard sauna regimen has been evaluated with respect to elimination of many different types of persistent toxins and the relationship of such toxin-removal to subjective reduction in adverse symptoms. Polychlorinated biphenyls (PCB) — formerly used in electrical insulation but discontinued for reasons of severe toxicity and environmental persistence — and polybrominated biphenyls (PBB), flame retardants still in broad use despite known toxicity,



Figure 1 Cocaine metabolites in sweat and urine during sauna detoxification.



Figure 2 Symptom severity in 249 drug users before and after the Hubbard method of detoxification.



Figure 3 Post-detoxification change in Wechsler adult intelligence scale.

Table 1 MMPI asocial/amoral personality (fourth scale) decreases in drug abusers after detoxification					
Initial PD score	Opiates only	Hallucinogens only	Opiates and hallucinogens	Total	
59 or less 60–69 70 or more	+7.0 8.0 	-0.7 -3.0 -8.9**	+3.3 -3.8 [*] -9.3 [*]	+3.3 -4.2 ^{**} -9.0 ^{**}	n = 15 n = 12 n = 11
*p < .05; **p < .01.					

were reduced between 16% and 65.9% in study populations who had been exposed 5 and 10 years before detoxification [88,89]. Firefighters exposed to burning PCB-filled transformers showed impaired memory and cognitive functions as well as peripheral neuropathy at six months following exposure. These symptoms improved following detoxification treatment [90]. Although a very different contamination, use of the Hubbard regimen to address adverse health effects following the Chernobyl incident provides evidence that the program revitalizes the immune system and improves the general physical condition of participants [91] observed symptoms that have marked similarities to chronic fatigue syndrome [92].

Discussion

Various metabolic processes allow organisms to accommodate low doses of foreign compounds. While inherent detoxification pathways result in elimination via the liver and kidneys, and binding proteins effectively remove drugs and toxics from the circulation, these systems do not efficiently eliminate certain compounds and their retention in fat, possibly long-term, is of utmost concern.

There is not a great deal of research that clearly indicates how long drugs and their metabolites remain stored in fat. However, current literature points to studies that detected many different drugs and their metabolites for up to 6 weeks after cessation of drug use. And although longer residence times have not been evaluated, retention patterns indicate the possibility of even longer storage. For lipophilic chemical structures for which no convenient biochemical transformation/elimination pathway exists, it seems reasonable to postulate potentially very long residence durations in adipose.

Disposition and probable long-term storage of drugs and other toxins has a high potential for long-lasting metabolic alterations with a likely role in drug reversion. Accumulation of drugs and their metabolites in adipose is likely to disrupt the endocrine functions of adipose. This may contribute to other effects on health including increased frequency of infections resulting from altered immune function starting a CNS feedback mechanism of neuroendocrine-modulated changes in metabolic function, depression, anxiety and fatigue. Accumulations of drugs and metabolites may also, during a pattern of slow, low-concentration release, result in a myriad of subtle but adverse physical and psychological effects.

Increasing numbers of studies on the short- and long-term effects of various illicit drugs on humans

are being published and more are needed. Because of limitations on research using human subjects, the studies have not always be as rigorous as desired and can be cited by drug users to discredit findings of harm, including the emergence of web sites that may or may not provide accurate data.

The likelihood that these effects exist is supported by the fact that where exposure has occurred, a regimen aimed at reducing accumulated toxins has consistently relieved symptoms associated with substance abuse and chemical exposures. Experimental questions regarding the utility of this sauna regimen in drug treatment regimens should include assaving for mobilization and elimination of various drugs and their metabolites from body stores as well as determining their reductions in adipose tissue. Longitudinal measures of leptin, ACTH, TSH, and cortisol, T lymphocyte profiles, and other parameters of immune function should be explored to help explain mechanisms of actions of sauna detoxification as well as drug action and safety. Neuropsychological function, health and quality of life questionnaires and self-reported changes in craving scales will become important to understanding long-term effects of drugs.

In addition to its application in drug rehabilitation, this regimen may have uses in other exposures including police officer line-of-duty exposure and other second-hand exposure situations. Forensics laboratories have noted positive drug screen results months after illicit hazardous materials exposure by police officers, positive test results coincident with symptoms of adverse health the officers self-report as ''drug-related.''

Conclusions

The contribution of drugs and their metabolites to total toxic burden and resulting adverse health effects cannot be ignored. Simply assessing direct impacts of a drug on a specific unwanted symptom, may overestimate the compound's real therapeutic index because indirect side-effects, including effects of longer-term adipose-tissue storage are rarely, if ever, assessed. This is akin to the broader economic assessment of environmental impacts of substances such as high-nitrogen fertilizers, which, although they may boost immediate crop yields, can in the longer term, lead to eutrophication of aquatic ecosystems as they leach from soils into groundwater. Although the subject of this paper focuses on single-organism ecology - that of the human body - the principles of longer-term and more globally inclusive assessment are quite similar.

Preventing exposure is necessary and urgent. For those already exposed, there exists a clinical detoxification regimen that holds promise. These data have important implications in health, drug education and prevention, drug rehabilitation, forensic, and legal areas, and perhaps most importantly, in the ever-burgeoning societal tendency to treat symptoms of toxic exposure by increasing rather than alleviating toxic burden.

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