

DRUG RESIDUES STORE IN THE BODY FOLLOWING CESSATION OF USE: IMPACTS ON ENDOCRINE BALANCE AND BEHAVIOR – A METHOD FOR THEIR REMOVAL.

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Introduction

Retention of man-made chemicals in the body is a more widespread problem than previously thought. One study alone found 167 different contaminants in volunteers who do not work with chemicals or near industrial facilities.¹¹

Illicit drugs and medications are similar to pesticides and pollutants with respect to their potential for long term storage. Data exists demonstrating that drug residues persist in certain tissues, however, much more is unknown than is known. Compounds that tend to bioaccumulate do so because of their chemical nature. Most illicit drugs and medications are lipophilic, tending to deposit in areas rich in fat, especially adipose as well as other organs.

Tests to determine chemical safety and consequent health impacts do not take into account combinations of contaminants, thus effects are largely underestimated or unobserved. Retention in the body makes chemicals capable of negative health effects in a number of ways:

1. Many drugs and toxins mimic substances naturally found in the body and can directly enhance, reduce, or block normal chemical communication – often causing effects very dissimilar to those of the endogenous substance. Illicit drugs and medications may be stored in biologically active forms becoming available when later released back into circulation.
2. Retention of toxins in key organs can directly impair organ health and function.
3. Body tissues involved in eliminating toxins require certain nutrients. Nutrients

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used to detoxify are then not available for other processes creating local deficiencies. Chronic exposure may result in systemic deficiencies.

Adipose is not just a store of excess calories and other “unwanted” compounds. It is now known that hormones released by adipose regulate many bodily functions. Any disruption has potential for a multitude of adverse effects. The endocrine functions for the hormones of white fat are still being worked out and include roles in regulating emotion, energy level and basic body metabolism, hunger, and cravings. Another class of compounds released by white fat regulates inflammatory response. Emotional problems, fatigue, weight change, and inflammation are part of the cluster of symptoms characterizing toxic exposure. Research is just beginning to reveal how drugs disrupt the endocrine function of white fat, including ties to altered mood and cravings not fully explained by other psychoactive properties of the drug.

Preventing exposure is necessary and urgent. For those exposed, there is a regimen that holds promise. The Hubbard sauna method aids in broad elimination of chemical contaminants and includes components that restore health. Symptoms associated with exposures to drugs are alleviated using the Hubbard regimen, including improvements in mental health not seen using conventional drug rehabilitation methods.

Evidence for Drug Storage in Adipose

The focus in the 1960s and 1970s on whether or not various synthetic compounds could cause cancer completely obscured – for over two decades – the ability these synthetic chemicals have at very low levels to impact other aspects of health, including cognitive

behavior and reproductive function.¹⁹ Unfortunately for many species of birds and mammals – including mankind – these chemicals can now be detected in the fat of all of us.^{9,36} Data is emerging that demonstrates not only adverse health effects in our generation, but additional adverse effects for at least two subsequent generations.¹² While these findings are most commonly associated with pesticides, dioxins and dioxin-like PCBs, the relationship between fat solubility and biologic availability of many drugs indicates a need to better understand and address long term storage of the pharmaceutical category of foreign chemicals.

The fate and biological activity of a compound are largely determined by the chemical properties of that compound.⁶⁰ The distribution patterns and speed at which chemicals move into various tissues are largely driven by lipophilicity – the tendency of a compound to move into lipid-rich spaces. Drugs tend to be very lipophilic, to have a large distribution volume and to deposit in various tissues in the following order: lung, fat, heart, kidney, brain, gut, muscle and bone, preferentially accumulating in lysosomes.^{1,61}

Like environmental contaminants, drugs and/or their metabolites – both pharmaceutical and illicit – also have the potential to remain in the body for an extended time, contributing to the accumulation of complex mixtures of synthetic compounds.^{10,54,35} LSD was shown to have this property very early on.⁴ Cocaine has been demonstrated to rapidly move into the fat tissues following use.^{13,45,59} The even distribution patterns of cocaine and methamphetamine metabolites in adipose after drug-related deaths indicate these drugs had been stored for some time.³⁴ Phencyclidine (PCP) has been shown to persist in fat and brain tissues, an observation thought to account for some of the long-lasting

behavioral effects.⁴¹ PCP levels in fat decline for a few days following injection, but then remain relatively constant for up to three weeks, the longest time the levels were monitored. Further, stress can result in mobilization of PCP, amphetamine and their metabolites from fat into blood.^{14,53} The widely-prescribed benzodiazapene family of tranquilizers is also well-characterized with respect to its distribution and persistence in fat tissues.^{26,37,40} Even certain metabolites of alcohol – itself a water soluble substance – are found in liver and fat following use.⁴⁸

These storage patterns also apply to drugs with medical value. Studies show that the doses of various barbiturates and the tranquilizer diazepam when given to obese people must be substantially increased due to disposition into adipose resulting in reduced availability.^{5,6} Clearance is also affected, not because the kidneys are processing the drug differently, but because of a release from fat.^{1,2} Finally, a series of studies comparing the storage and clearance rates of drugs measured in fat people and then re-measured when these people lost their extra fat showed initial adipose distribution and retention that decreased after losing the fat.^{7,8} This research demonstrates a two-week retention in fat stores of several common medicines, longer times were not evaluated.

One of the most fat soluble substances of abuse is THC, a compound that is metabolized into over 60 different specific chemicals after ingestion/inhalation – a property that makes detection particularly difficult.³² For the first hour after administration, blood THC levels decline very rapidly. After the first hour, the THC decline is much slower – with a half-life of 50 to 60 hours.^{33,38} 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.⁴³ Accumulation in adipose of chronic users results in longer re-release and detection than that following single use.¹⁷ THC has been detected in adipose for up to 4 weeks after last use,²⁷ but sensitive assays can detect THC in blood and urine up to two months following discontinued use.^{16,23}

ⁱ Lysosomes are cell organelles responsible for breaking down foreign substances and waste products, especially common in certain white blood cells and liver and kidney cells.

Longer detection periods have not been evaluated.

Recent evidence shows that rapid sequestration of THC to fat leaves less than 1 percent of the consumed THC remaining in blood and available to reach the brain.

Interestingly, this low blood level actually correlates with the "pleasant sensory phenomenon" described by users.⁴³ A slow release of THC from stores into the blood, combined with very low blood concentrations required for a drug effect gives the possibility of flashbacks, a phenomenon that has been clinically documented coincident with a spike in blood THC measured two weeks after last use.⁴⁶

THC mimics endocannabinoids – cannabinoids made by the body. As predicted, release of the drug 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 involve very low levels of THC within the testicular compartment. These levels are of long duration due to re-release from fat stores.⁴⁴ Additionally, intra-uterine concentrations of endocannabinoids must be at a specific concentration for embryonal implantation. Increased levels of cannabinoids are linked with miscarriage.²⁰

Drugs Impact Adipose Functions: Influence on Addictive Behaviors

In addition to the possibility that low level, long term release of psychoactive chemicals from adipose may be directly responsible for adverse behavioral and physical health, the potential for adipose-stored chemicals to alter normal endocrine function of white fat is alarming. The old view of fat as a place for the body to store extra calories and possibly act as a "sink" where the drug is no longer in circulation changed dramatically in 1994 with the discovery of leptin,⁶² a hormone secreted by fat cells in white adipose tissue with regulatory roles in metabolism, food craving, endocrine function, behavior and mood.^{39,3} We now know that white fat secretes a number of

hormones revealing new interconnections between nutritional status, immune system and metabolic regulations²⁴ including metabolic syndrome – a cluster of symptoms that include insulin resistance, cholesterol imbalance, and weight gain.⁵⁸

Leptin functions as a key link between nutrition and the function of most, if not all other physiologic systems.²¹ Leptin levels communicate to the hypothalamus – a region of the brain that regulates many basic 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. Increased adipose volume will normally increase leptin levels, in turn signaling a decrease in hypothalamus endocannabinoids resulting in decreased appetite.^{18,22} The well-known "mad munchies" stimulation of appetite following ingestion/inhalation of THC from marijuana is an example of short-circuiting the white fat-hypothalamus feedback mechanism. An increasing amount of data highlights the broad reach of the leptin-hypothalamus relationship in endocrine regulation and energy balance.^{58,47}

Interestingly, leptin regulation appears to have a role in a number of addictive behaviors and craving. Use of cocaine and amphetamines depress leptin but decrease appetite.¹⁵ Leptin depletion results in increased cocaine and amphetamine regulated transcript (CART) in the hypothalamus³¹ – a region of the brain involved in sleep regulation, emotions, food and water intake, and other endocrine functions.^{56,42} Excess CART production has been associated with the anxiety that is part of the paranoia of drug addiction.²⁸ Food or alcohol consumption will turn off the anxiety by increasing leptin levels and subsequently turn off CART.

Plasma leptin and adipocytokine levels are increased by alcohol and heroin intake.^{25,51} Adipocytokines increase inflammation, a common secondary problem in these addictions. Increased plasma leptin is

associated with alcohol craving.²⁹ Inducing starvation and concurrent release of leptin caused animals to once again crave heroin after they had been through a prolonged drug free period.⁵¹

A possible vicious circle is suggested, including the components of drug intake, altered leptin secretion, unwanted behaviors, enhanced craving, and consecutively increased drug intake.

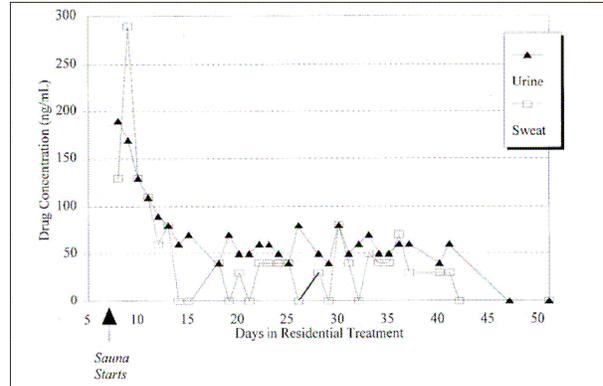
Use of Sauna Detoxification Treatment to Address Contamination from Drug Exposures

The Hubbard method of detoxification, a regimen including exercise, sauna bathing, and vitamin and mineral supplements, is a rehabilitative treatment intervention developed to aid in the broad elimination of chemicals and address adverse health affects resulting from chemical exposure.⁵⁰ Its safety and effectiveness treating a wide range of exposures have been established for more than two decades.

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

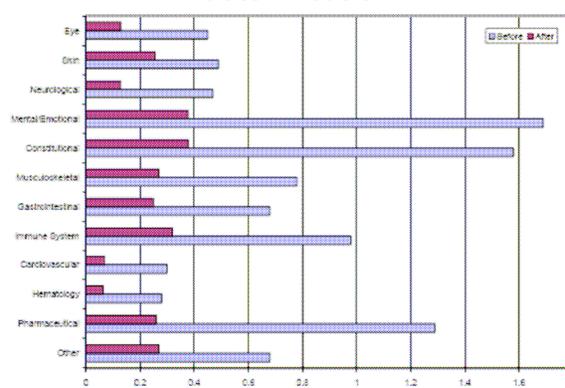
A preliminary study has demonstrated the ability of this method to eliminate cocaine and valium metabolites in sweat and urine of recovering addicts for up to five weeks following the start of sauna treatment.⁵² Figure 1 is a graph plotting levels of cocaine in sweat and urine of one of the six study subjects followed during the sauna regimen. The subject had completed several components of the Narconon program in the weeks prior to starting the sauna regimen, and had remained drug free after enrollment onto the Narconon program.

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



In the same study, 249 subjects were asked to self-report the severity of various physical symptoms before and after sauna detoxification. Figure 2 shows how the severity diminished on completion of the sauna regimen.

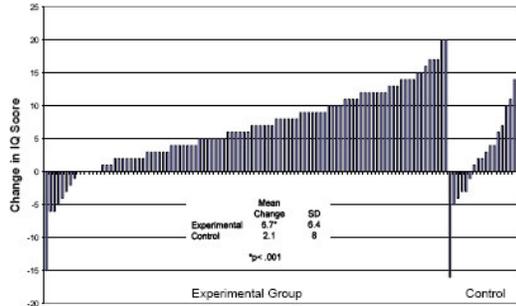
Figure 2: Symptom severity in 249 drug users before and after the Hubbard method of detoxification



An earlier study on 103 subjects, 41 of whom were substance abusers, demonstrated increases in Wechsler Adult Intelligence Scale IQ averaging 6.7 points.⁵⁰ 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 is an improvement that is particularly hopeful for sociopaths, a

Figure 3. Post Detoxification Change in Wechsler Adult Intelligence Scale



group with fourth scale scores not improved in other inpatient addiction programs. Removal of chemical residues combined with the restorative program components are addressing behavioral measures not thought to be attributed to physical parameters.

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	n
59 or less	+7.0	-0.7	+3.3	+3.3	n=15
60 - 69	-8.0	-3.0	-3.8*	4.2**	n=12
70 or more	---	-8.9**	-9.3*	9.0**	n=11

*p < .05 **p < .01

The Hubbard sauna regimen has been evaluated with respect to elimination of many different types of persistent toxins and ability to restore health. Polychlorinated biphenyls (PCB) – formerly used as an electrical insulator but discontinued for reasons of severe toxicity and environmental persistence –and polybrominated biphenyls (PBB) – a flame retardant still in broad use despite known toxicity – were reduced between 16% and 65.9% in study populations who had been exposed 5 and 10 years before detoxification.^{49,55} Studies of firefighters exposed to burning transformers filled with

PCBs showed impaired memory and cognitive functions and peripheral neuropathy 6 months following exposure. These symptoms

improved following detoxification treatment.³⁰ A study evaluating the Hubbard method as a treatment for residents of the area contaminated by the Chernobyl incident provides evidence that the program revitalizes the immune system and improves the general physical condition of the participant.⁵⁷

Conclusions

Several metabolic processes allow organisms to accommodate low doses of foreign compounds. While inherent detoxification pathways result in elimination via the liver and kidneys, and proteins that bind drugs effectively remove them from circulation, these systems do not eliminate certain types of compounds efficiently and their retention in fat is of utmost concern.

It is not currently known how long drugs and their metabolites remain stored in fat. However, current literature detected many different drugs and their metabolites for up to six weeks after cessation of drug use. Longer times have not been evaluated but the retention patterns indicate the possibility for even longer storage.

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 issues. Accumulation of drugs and their metabolites in adipose is likely to disrupt the endocrine functions of adipose or may be slowly released resulting in a myriad of adverse physical and psychological effects.

The weight of evidence regarding environmental toxins suggests that where exposure has occurred the Hubbard sauna regimen shows clear benefit to emotional and physical health. The regimen can be safely delivered as a component of drug rehabilitation and its apparent ability to remove drug metabolites from tissues may have use in other exposures including police

officer line-of-duty exposure and other second-hand exposure situations.

This data has important implications in health, drug education and prevention, drug

rehabilitation, forensic, and legal areas. The contribution of drugs and their metabolites to total toxic burden and resulting adverse health effects cannot be ignored.

REFERENCES:

1. D. R. Abernethy, D. J. Greenblatt, M. Divoll, and R. I. Shader, Prolongation of drug half-life due to obesity: studies of desmethyldiazepam (clorazepate). *J Pharm Sci* **71**, 942-4 (1982).
2. D. R. Abernethy, D. J. Greenblatt, M. Divoll, and R. I. Shader, Prolonged accumulation of diazepam in obesity. *J Clin Pharmacol* **23**, 369-76 (1983).
3. R. S. Ahima, Central actions of adipocyte hormones. *Trends Endocrinol Metab* **16**, 307-13 (2005).
4. J. Axelrod, R. O. Brady, B. Witkop, and E. V. Everts, The distribution and metabolism of lysergic acid diethylamide. *Ann N Y Acad Sci* **66**, 435-44 (1957).
5. R. A. Blouin, J. H. Kolpek, and H. J. Mann, Influence of obesity on drug disposition. *Clin Pharm* **6**, 706-14 (1987).
6. R. A. Blouin and G. W. Warren, Pharmacokinetic considerations in obesity. *J Pharm Sci* **88**, 1-7 (1999).
7. Y. Caraco, E. Zylber-Katz, E. M. Berry, and M. Levy, Significant weight reduction in obese subjects enhances carbamazepine elimination. *Clin Pharmacol Ther* **51**, 501-6 (1992).
8. Y. Caraco, E. Zylber-Katz, E. M. Berry, and M. Levy, Carbamazepine pharmacokinetics in obese and lean subjects. *Ann Pharmacother* **29**, 843-7 (1995).
9. Center for Disease Control (CDC), NHANES III Priority Toxicant Reference Range Study Data File Series 11, No. 4A. *Third National Health and Nutrition Examination Survey (NHANES III), 1988-94* (2000).
10. C. N. Chiang and R. L. Hawks, Implications of drug levels in body fluids: basic concepts. *NIDA Res Monogr* **73**, 62-83 (1986).
11. T. Colborn, Pesticides--how research has succeeded and failed to translate science into policy: endocrinological effects on wildlife. *Environ Health Perspect* **103 Suppl 6**, 81-5 (1995).
12. T. Colborn, Environmental estrogens: health implications for humans and wildlife. *Environ Health Perspect* **103 Suppl 7**, 135-6 (1995).
13. E. J. Cone and W. W. Weddington Jr, Prolonged occurrence of cocaine in human saliva and urine after chronic use. *J Anal Toxicol* **13**, 65-8 (1989).
14. J. R. Coveney and S. B. Sparber, Delayed effects of amphetamine or phencyclidine: interaction of food deprivation, stress and dose. *Pharmacol Biochem Behav* **36**, 443-9 (1990).
15. W. R. Crowley, G. Ramoz, K. A. Keefe, R. Torto, S. P. Kalra, and G. R. Hanson, Differential effects of methamphetamine on expression of neuropeptide Y mRNA in hypothalamus and on serum leptin and ghrelin concentrations in ad libitum-fed and schedule-fed rats. *Neuroscience* **132**, 167-73 (2005).
16. C. A. Dackis, A. L. Pottash, W. Annitto, and M. S. Gold, Persistence of urinary marijuana levels after supervised abstinence. *Am J Psychiatry* **139**, 1196-8 (1982).
17. M. J. DeLaurentis, K. McNeil, A. J. Mann, S. Clark, and H. M. Greenwood, An EMIT assay for cannabinoid metabolites in urine. *NIDA Res Monogr* **42**, 69-84 (1982).
18. V. Di Marzo, S. K. Goparaju, L. Wang, J. Liu, S. Batkai, Z. Jarai, F. Fezza, G. I. Miura, R. D. Palmiter, T. Sugiura, and G. Kunos, Leptin-regulated endocannabinoids are involved in maintaining food intake. *Nature* **410**, 822-5 (2001).
19. Environmental Working Group, *Body Burden - The Pollution in People*. 2003.
20. E. Fride, The endocannabinoid-CB(1) receptor system in pre- and postnatal life. *Eur J Pharmacol* **500**, 289-97 (2004).
21. J. M. Friedman, The function of leptin in nutrition, weight, and physiology. *Nutr Rev* **60**, S1-14; discussion S68-84, 85-7 (2002).
22. J. A. Harrold and G. Williams, The cannabinoid system: a role in both the homeostatic and hedonic control of eating? *Br J Nutr* **90**, 729-34 (2003).
23. D. J. Harvey, J. T. Leuschner, and W. D. Paton, Gas chromatographic and mass spectrometric studies on the metabolism and pharmacokinetics of delta 1-tetrahydrocannabinol in the rabbit. *J Chromatogr* **239**, 243-50 (1982).
24. P. J. Havel, Control of energy homeostasis and insulin action by adipocyte hormones: leptin, acylation stimulating protein, and adiponectin. *Curr Opin Lipidol* **13**, 51-9 (2002).
25. J. Housova, H. Wilczek, M. M. Haluzik, J. Kremen, J. Krizova, and M. Haluzik, Adipocyte-derived hormones in heroin addicts: the influence of methadone maintenance treatment. *Physiol Res* **54**, 73-8 (2005).
26. Y. Igari, Y. Sugiyama, Y. Sawada, T. Iga, and M. Hanano, Tissue distribution of ¹⁴C-diazepam and its metabolites in rats. *Drug Metab Dispos* **10**, 676-9 (1982).
27. E. Johansson, K. Noren, J. Sjovall, and M. M. Halldin, Determination of delta 1-tetrahydrocannabinol in human fat biopsies from marijuana users by gas chromatography-mass spectrometry. *Biomed Chromatogr* **3**, 35-8 (1989).
28. A. Kask, H. B. Schioth, F. Mutulis, J. E. Wikberg, and L. Rago, Anorexicogenic cocaine- and amphetamine-regulated transcript peptide intensifies fear reactions in rats. *Brain Res* **857**, 283-5 (2000).

29. F. Kiefer, H. Jahn, M. Schick, and K. Wiedemann, Alcohol self-administration, craving and HPA-axis activity: an intriguing relationship. *Psychopharmacology (Berl)* **164**, 239-40 (2002).
30. K. H. Kilburn, R. H. Warsaw, and M. G. Shields, Neurobehavioral dysfunction in firemen exposed to polychlorinated biphenyls (PCBs): possible improvement after detoxification. *Arch Environ Health* **44**, 345-50 (1989).
31. P. Kristensen, M. E. Judge, L. Thim, U. Ribel, K. N. Christjansen, B. S. Wulff, J. T. Clausen, P. B. Jensen, O. D. Madsen, N. Vrang, P. J. Larsen, and S. Hastrup, Hypothalamic CART is a new anorectic peptide regulated by leptin. *Nature* **393**, 72-6 (1998).
32. E. G. Leighty, A. F. Fentiman Jr, and R. L. Foltz, Long-retained metabolites of delta9- and delta8-tetrahydrocannabinols identified as novel fatty acid conjugates. *Res Commun Chem Pathol Pharmacol* **14**, 13-28 (1976).
33. L. Lemberger, S. D. Silberstein, J. Axelrod, and I. J. Kopin, Marijuana: studies on the disposition and metabolism of delta-9-tetrahydrocannabinol in man. *Science* **170**, 1320-2 (1970).
34. J. A. Levisky, D. L. Bowerman, W. W. Jenkins, D. G. Johnson, and S. B. Karch, Drugs in postmortem adipose tissues: evidence of antemortem deposition. *Forensic Sci Int* **121**, 157-60 (2001).
35. J. A. Levisky, D. L. Bowerman, W. W. Jenkins, and S. B. Karch, Drug deposition in adipose tissue and skin: evidence for an alternative source of positive sweat patch tests. *Forensic Sci Int* **110**, 35-46 (2000).
36. D. T. Mage, R. H. Allen, G. Gondy, W. Smith, D. B. Barr, and L. L. Needham, Estimating pesticide dose from urinary pesticide concentration data by creatinine correction in the Third National Health and Nutrition Examination Survey (NHANES-III). *J Expo Anal Environ Epidemiol* **14**, 457-65 (2004).
37. B. R. Martin, B. B. Bailey, H. Awaya, E. L. May, and N. Narasimhachari, In vitro metabolism of 1-phenyl-1-cyclohexene, a pyrolysis product of phencyclidine. *Drug Metab Dispos* **10**, 685-9 (1982).
38. A. P. Mason and A. J. McBay, Cannabis: pharmacology and interpretation of effects. *J Forensic Sci* **30**, 615-31 (1985).
39. J. A. Matochik, E. D. London, B. O. Yildiz, M. Ozata, S. Caglayan, A. M. DePaoli, M. L. Wong, and J. Licinio, Effect of leptin replacement on brain structure in genetically leptin-deficient adults. *J Clin Endocrinol Metab* **90**, 2851-4 (2005).
40. S. Minder, W. A. Daniel, J. Clausen, and M. H. Bickel, Adipose tissue storage of drugs as a function of binding competition. In-vitro studies with distribution dialysis. *J Pharm Pharmacol* **46**, 313-5 (1994).
41. A. L. Misra, R. B. Pontani, and J. Bartolomeo, Persistence of phencyclidine (PCP) and metabolites in brain and adipose tissue and implications for long-lasting behavioural effects. *Res Commun Chem Pathol Pharmacol* **24**, 431-45 (1979).
42. K. G. Murphy, Dissecting the role of cocaine- and amphetamine-regulated transcript (CART) in the control of appetite. *Brief Funct Genomic Proteomic* **4**, 95-111 (2005).
43. G. G. Nahas, The pharmacokinetics of THC in fat and brain: resulting functional responses to marijuana smoking. *Hum Psychopharmacol* **16**, 247-255 (2001).
44. G. G. Nahas, H. C. Frick, J. K. Lattimer, C. Latour, and D. Harvey, Pharmacokinetics of THC in brain and testis, male gametotoxicity and premature apoptosis of spermatozoa. *Hum Psychopharmacol* **17**, 103-13 (2002).
45. P. K. Nayak, A. L. Misra, and S. J. Mule, Physiological disposition and biotransformation of (3H) cocaine in acutely and chronically treated rats. *J Pharmacol Exp Ther* **196**, 556-69 (1976).
46. G. Niveau, [Cannabis-related flash-back, a medico-legal case]. *Encephale* **28**, 77-9 (2002).
47. U. Pagotto, G. Marsicano, D. Cota, B. Lutz, and R. Pasquali, The emerging role of the endocannabinoid system in endocrine regulation and energy balance. *Endocr Rev* (2005).
48. M. A. Refaai, P. N. Nguyen, T. S. Steffensen, R. J. Evans, Cluette-Brown J.E., and M. Laposata, Liver and Adipose Tissue Fatty Acid Ethyl Esters Obtained at Autopsy Are Postmortem Markers for Premortem Ethanol Intake -- Refaai et al. 48 (1): 77 -- Clinical Chemistry. 2002.
49. Schnare D.W. , Ben M., and Shields M.G., Body Burden Reduction of PCBs, PBBs and Chlorinated Pesticides in Human Subjects. *Ambio* **13**, 378-380 (1984).
50. D. W. Schnare, G. Denk, M. Shields, and S. Brunton, Evaluation of a detoxification regimen for fat stored xenobiotics. *Med Hypotheses* **9**, 265-82 (1982).
51. U. Shalev, J. Yap, and Y. Shaham, Leptin attenuates acute food deprivation-induced relapse to heroin seeking. *J Neurosci* **21**, RC129 (2001).
52. M. Shields, S. Beckmann, F. Tennant, and RM. Wisner, Reduction of Drug Residues: Applications in drug rehabilitation. Abstracts of the 123rd Annual Meeting of the American Public Health Association. 1995.
53. S. B. Sparber, S. Nagasawa, and K. E. Burkland, A mobilizable pool of d-amphetamine in adipose after daily administration to rats. *Res Commun Chem Pathol Pharmacol* **18**, 423-31 (1977).
54. A. Stoman, The absorption, distribution, and excretion of drugs and poisons and their metabolites. In *Progress in Chemical Toxicology*. pp 1-99. Academic Press, (1974).

55. Z. Tretjak, M. Shields, and S. L. Beckmann, PCB reduction and clinical improvement by detoxification: an unexploited approach? *Hum Exp Toxicol* **9**, 235-44 (1990).
56. Y. Tsuruta, H. Yoshimatsu, S. Hidaka, S. Kondou, K. Okamoto, and T. Sakata, Hyperleptinemia in A(y)/a mice upregulates arcuate cocaine- and amphetamine-regulated transcript expression. *Am J Physiol Endocrinol Metab* **282**, E967-73 (2002).
57. A. F. Tsyb, E. M. Parshkov, J. Barnes, N. V. Yarzutkin, N. V. Vorontsov, and V. I. Dedov, Rehabilitation of a Chernobyl Affected Population Using a Detoxification Method. *Proceedings of the 1998 International Radiological Post-Emergency Response Issues Conference* 160-165 (1998).
58. R. Vettor, G. Milan, M. Rossato, and G. Federspil, Review article: adipocytokines and insulin resistance. *Aliment Pharmacol Ther* **22 Suppl 2**, 3-10 (2005).
59. R. D. Weiss and F. H. Gawin, Protracted elimination of cocaine metabolites in long-term high-dose cocaine abusers. *Am J Med* **85**, 879-80 (1988).
60. R. F. Willes, E. R. Nestmann, P. A. Miller, J. C. Orr, and I. C. Munro, Scientific principles for evaluating the potential for adverse effects from chlorinated organic chemicals in the environment. *Regul Toxicol Pharmacol* **18**, 313-56 (1993).
61. K. Yokogawa, J. Ishizaki, S. Ohkuma, and K. Miyamoto, Influence of lipophilicity and lysosomal accumulation on tissue distribution kinetics of basic drugs: a physiologically based pharmacokinetic model. *Methods Find Exp Clin Pharmacol* **24**, 81-93 (2002).
62. Y. Zhang, R. Proenca, M. Maffei, M. Barone, L. Leopold, and J. M. Friedman, Positional cloning of the mouse obese gene and its human homologue. *Nature* **372**, 425-32 (1994).

