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Elimination of persistent toxicants from the human body

Stephen J Genuis

Abstract

There is compelling evidence that various chemical agents are important determinants of myriad health afflictions – several xenobiotics have the potential to disrupt reproductive, developmental, and neurological processes and some agents in common use have carcinogenic, epigenetic, endocrine-disrupting, and immune-altering action. Some toxicants appear to have biological effect at miniscule levels and certain chemical compounds are persistent and bioaccumulative within the human body. Despite escalating public health measures to preclude further exposures, many people throughout the world have already accrued a significant body burden of toxicants, placing them at potential health risk. As a result, increasing discussion is underway about possible interventions to facilitate elimination of persistent toxicants from the human organism in order to obviate health affliction and to potentially ameliorate chronic degenerative illness. An overview of the clinical aspects of detoxification is presented with discussion of established and emerging interventions for the elimination of persistent xenobiotics. Potential therapies to circumvent enterohepatic recirculation and a case report highlighting a clinical outcome associated with detoxification are also presented for consideration.

Keywords

bile acid sequestrants, chelation, cholestyramine, colon cleansing, detoxification, dialysis, enterohepatic circulation, environmental medicine, fasting, massage, plasmapheresis, phlebotomy, probiotics, saponin compounds, sauna therapy, toxicology, zeolites

Introduction

Since the Second World War, tens of thousands of synthetic compounds have been prepared and introduced into the environment to facilitate many industrial, domestic, and personal practices. With lack of forethought about potential risks of exposure, most of these manufactured compounds remain inadequately tested in relation to human safety. Through inhalation, ingestion, dermal application, injection or surgical implantation, vertical transmission, and via the olfactory conduit, many individuals throughout the world have been exposed to various toxic metals, petrochemical byproducts, and assorted synthetic compounds. Recent research confirms that some chemical agents are persistent both in the human body and in the environment and food chains. The scientific community has begun to witness the consequences of this unprecedented chemical revolution.

Emerging human and animal studies suggest significant potential toxicity associated with exposure to, and accrual of, some chemical compounds. As a result, numerous scientific journals are disseminating emerging information about the potentially adverse impact of bioaccumulative toxicant exposure. While public health measures have been implemented in some areas to protect individuals from further exposure, interventions to eliminate persistent toxicants from the human body ('detoxification') are also being investigated with the objective of preventing or ameliorating health problems in those who have accrued toxic materials.

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Methodology

In this paper, background knowledge with an overview of bioaccumulative toxicant exposure is initially presented to highlight the issue of persistent toxicants and to emphasize the ineluctable need for therapeutic interventions. This is followed by the specific objective of this work: to assess and present a review of the available research literature examining interventions that can be used within clinical settings to facilitate the removal of persistent bioaccumulative toxicants. Finally, a case history is offered to emphasize the potential clinical results achieved with detoxification of adverse chemicals.

This review was prepared by assessing available medical and scientific literature from Medline, as well as by reviewing numerous books, toxicology journals, conference proceedings, government publications, and environmental health periodicals. Searching techniques included key word searches with terms related to elimination of chemical toxicants. A primary observation, however, was that limited scientific literature is available on clinical techniques dealing with elimination of persistent toxicants or clinical outcomes associated with such interventions. Available publications were reviewed and incorporation of data was confined to information deemed to be of clinical significance. After the research and clinical data were compiled, information relevant for clinical practice was prepared in discussion format as well as in table form and is presented in this manuscript. The format of a traditional integrated review was chosen as such reviews play a pivotal role in scientific research and professional practice in medical issues with limited primary study and uncharted clinical territory.[1]

Overview of toxicant exposure and elimination

Emerging evidence from several scientific and governmental sources continue to suggest that we live in an era of unprecedented exposure of population groups to myriad chemical agents.[2,3] The Centers for Disease Control (CDC) recently published the findings of the 'Fourth National Report on Human Exposure to Environmental Chemicals' – the largest ever toxicant study on humans – and found that most Americans, young and old, have bioaccumulated numerous toxicants within their body.[2] An American Red Cross study on newborn blood also confirmed that unborn children are routinely exposed through vertical transmission.[4] Emerging data from various nations[5-11] verifies that routine exposure of population groups to and/or accrual of assorted xenobiotics (foreign chemicals) is not isolated to America but has become a prevalent problem in many jurisdictions. With myriad chemical compounds finding their way into the human body, evidence has recently emerged which suggests that exposure to, and bioaccumulation of, some toxicants are eroding human health.[12]

Although some toxic chemicals are being restricted and banned, many of today's populations have already been harmed by bioaccumulated toxicants. Numerous examples in the medical and environmental literature continue to demonstrate the problem. Elevated body burden of dioxins and related compounds, for example, have been associated with high blood pressure, elevated triglycerides, and glucose intolerance among the Japanese population[9]; the ongoing presence of lead in some paints and other materials have inflicted significant harm upon children in various jurisdictions including Africa and North and South America[8,13,14]; arsenic in the water supply has caused serious health issues for exposed groups in India and Bangladesh[5-7]; unfolding evidence suggests increased prevalence of altered hepatic, immune, and thyroid function in a large population of people exposed to drinking water contaminated with perfluorinated compounds in West Virginia[15]; and increasing evidence is emerging about the causal link between toxic exposure and illness in Gulf War veterans.[16] In response to emerging research linking toxicant exposure to health sequelae, important public health initiatives to preclude further exposure have been instituted in some areas.

Groups such as the World Health Organization, the United Nations, various non-governmental organizations, and several national governments have (i) sponsored epidemiological toxicant research, (ii) devised precautionary avoidance strategies, and (iii) instituted educational programs for health professionals about toxicant exposure.[17] Furthermore, various international groups, multinational organizations, and national governments are responding by declaring some chemicals to be toxic, by banning certain chemical agents and products containing them, and by entering into international treaties to reduce emission of some chemical agents, with legislation that least-toxic alternatives be used. While legislative and public health initiatives are crucial to prevent further exposure, additional measures are also required. For the generation of individuals already exposed, the proverbial fox has already entered the chicken coop and the

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pressing need for strategies to effectively eliminate bioaccumulated toxicants in order to address and preclude toxicant-related illness is evident.

In order to meaningfully discuss potential therapies to address the problem of toxicant bioaccumulation, an overview of some of the issues and challenges related to toxicant exposure and diagnosis will be initially presented. Toxicant chemical compounds generally fall into one of five broad categories (with some overlap): i) toxic elements; ii) petrochemicals; iii) synthetic chemicals; iv) chemical byproducts; and v) biological toxins. (Figure 1) It is important to note that human metabolites of some parent chemical compounds within these categories may also be active and inherently toxic to the human organism. Elements are chemicals often found in nature and are basic building blocks of matter. While some elements such as copper, iron, and zinc are essential for human health and only toxic in excess, there is no known biological role for lead, cadmium, aluminum, mercury, arsenic, and other exclusively toxic elements for which there may be no 'safe' level within the human body. Petrochemicals are compounds derived or extracted from raw materials of petroleum or other hydrocarbons – they include crude oil, diesel, and natural gas and may be components of products such as detergents, plastics and fertilizers. Synthetic chemicals are man-made creations, which are manufactured from basic laboratory compounds in order to yield novel chemical agents with properties that have potential industrial or domestic application. Chemical byproducts result from the decomposition, manufacturing, processing or combustion of various compounds. Examples of such byproducts include polycyclic aromatic hydrocarbons (PAHs) formed from burning wood, coal or tobacco; dioxins and furans produced in municipal waste incineration or paper pulp bleaching; and acrylamide formed in carbohydrate-rich foods such as potatoes that are fried, baked, or roasted at high temperatures. Biological toxins including bacterial endotoxins and fungal mycotoxins are byproducts or metabolites produced by living microbes such as bacteria or mold. While some mycotoxins such as ergot, for example, may have practical application, many mycotoxins are profoundly toxic to human health.[18] As mentioned, there is overlap in this categorization as some toxicant compounds, for example, may be active metabolites of chemical byproducts formed from the processing or combustion of synthetic compounds using agents originally derived from petrochemical sources.

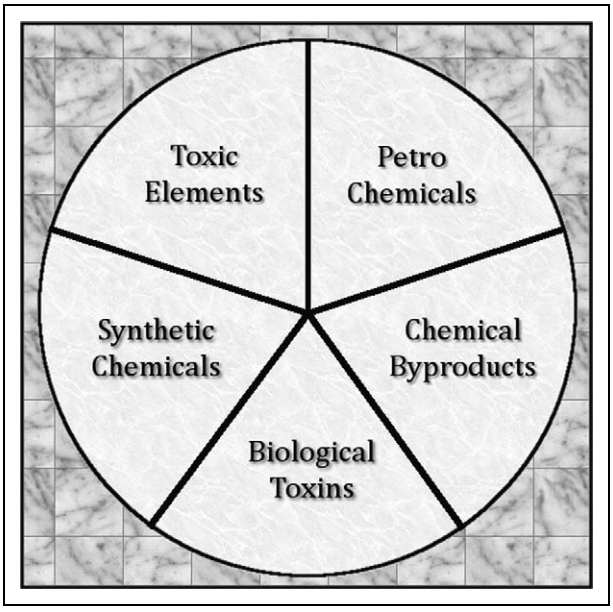

Figure 1. Categories of potentially toxic chemicals.

Recognized challenges associated with human toxicology research

With the recent claim by the CDC that 'virtually all human diseases result from the interaction of genetic susceptibility and modifiable environmental factors,'[19] increased attention in the medical community is being devoted to identifying modifiable environmental determinants such as chemical toxicants that may cause or trigger illness. Although widespread recognition of the toxicant problem and its association with human illness is increasing, precise understanding of the health impact posed by the spectrum of stockpiled xenobiotics is lacking. While extensive study is underway to definitively delineate health effects associated with specific toxicants, such research is fraught with challenges.

I) Incomplete understanding of toxicokinetics: There is limited available research in some aspects of clinical chemistry including (i) excretion pathways for many compounds, (ii) outcomes of interaction between many toxicants and inherent biochemistry, (iii) synergy and interaction between assorted xenobiotic compounds, and (iv) toxicokinetics for many of the chemical agents currently in our environment. As a result, a primary problem with human toxicant research is that bioactive mechanisms of impact for many contemporary chemical agents are not yet well understood.

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II) Ethical challenges: It is not possible to do prospective clinical trials on the human health effects of exposures as it is unethical to expose individuals or groups to potentially toxic compounds – accordingly animal studies as well as protracted and less reliable human observational studies are used instead. With diagnosed evidence of potentially dangerous toxicant bioaccumulation in individuals, however, there is also ethical imperative to intervene whenever possible, thus precluding long-term observation in some situations. Despite other types of research evidence, the lack of prospective randomized controlled trials has resulted in skepticism among some medical professionals about toxicants as a common determinant of illness.

III) Limitations of animal research: Although animal research has been the primary pathway for toxicant safety testing thus far, this type of research has limited usefulness. Animal detoxification mechanisms are often different than human systems,[20] and most animal testing explores short-term outcome rather than chronic effects. The lag from exposure to clinical outcome in people may be delayed for many years or decades – short-term animal safety research may have no validity when applied to delayed adverse outcomes in people.

IV) Chemical sequestration: Human chemical research and biomonitoring is difficult as standard testing to assess levels of some accrued toxicants is of limited value as many chemicals sequester in tissues and may not remain primarily in the bloodstream or may not be excreted in urine. Levels measured in peripheral blood or urine on a single occasion only represent a 'snapshot' that may not reflect the actual degree of contamination. Much research, however, has been based on serum or urinary levels of toxicants, a problem which limits the validity and usefulness of such study. Serum levels of xenobiotics tend to under-represent the total body burden of toxicants and serum values for some toxicants are unreliable as levels fluctuate due to movement in and out of cells depending on various factors including exercise and caloric intake.[21] Furthermore, tissue biopsies are not reliable as levels of toxicant accrual may vary from tissue to tissue and from one area of the body to another.

V) Genomic variability and chemical interaction: Many confounders also make it difficult to interpret the results of toxicant outcome studies. Each individual, for example, has a unique genome and may respond differently to toxic exposures. Synergy or interaction between various chemical compounds may also alter the impact of any individual agent. With the array of combinations and permutations of potential exposures continuing to unfold at an unprecedented rate, the reality is that there is a paucity of credible data on health sequelae of bioaccumulation for each individual compound or for collective chemical cocktails.

VI) Conflict of interest: Another concern is the influence of industry on chemical research. Many toxicology experts are employed or affiliated with companies that produce potentially toxic chemical products. It is repeatedly alleged that some industries hire scientists to further their message and to deflect attention away from the potential adverse impact of some toxicants.[22] Furthermore, some scientific publications assign industry-affiliated reviewers to assess emerging research on products produced by their companies, placing reviewers in a conflict-of-interest position with the power to influence decisions about publication of research exposing harm from such products.

VII) Inconsistent approach: There has been discussion in toxicological publications about the need to provide standardized objective approaches to toxicological analysis in order to optimally assist with decisions on harm causation and to improve subsequent decision making in risk management.[23] A move towards evidence-based toxicology (EBT) is underway, which aims to use objective approaches in a structured manner based on emerging scientific evidence, systematic methodological analysis, and transparent technique.[24] A criticism of EBT, however, is that this movement is heavily supported by certain industries who – rather than wishing to demonstrate definitive evidence of safety – wish to raise the bar of 'proof of harm' so high that it will be very hard to conclusively declare potentially dangerous compounds as being too risky or too toxic to release and disseminate.

In review, there are many challenges in interpreting exposure measures, biomarkers of body burden, and estimation of related toxic effects. Although challenges remain when attempting to conclusively

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quantify the impact of chemical exposures, long-term observational research has begun, nonetheless, to elucidate adverse clinical outcomes as a result of inadvertent human exposure to and bioaccumulation of toxicants. Public health and toxicology journals continue to divulge outcomes of such research with increasing frequency. Exposure to, and/or accrual of, selected chemical compounds appears to increase the risk for potentially serious clinical sequelae including cancer,[11] reproductive dysfunction,[25] endocrine dysregulation,[26] immune alteration,[27] congenital anomalies,[28] as well as neurological and psychiatric dysfunction.[29] In response to unfolding research demonstrating considerable harm, increasing exploration of interventions and strategies to facilitate elimination of bioaccumulative toxicants is underway.

Toxicant elimination

Study of the endogenous physiological excretion of toxic compounds has been the subject of many books and papers over the last few decades.[30] As the field of environmental health sciences in relation to multiple toxicant bioaccumulation is in its relative infancy, however, research into therapeutic interventions to eliminate the body burden of toxicants to prevent or overcome adverse health outcomes is, thus far, very limited.

It is important to clarify that there is a distinction between external exposure, internal dose, and accrued internal bioaccumulation. While individuals may be exposed to adverse chemical compounds, some agents are rapidly metabolized and excreted and do not remain in the human body. Other compounds may remain in the human body for a period of time depending on the efficiency of inherent detoxification mechanisms and the chemical properties of the agent. Finally, some compounds are poorly excreted and tend to bioaccumulate in tissues. Internal dosing of toxicant compounds cannot simply be determined by blood or urine testing as each distinctive compound behaves differently and some agents store in tissues with minimal or no evidence of the adverse compound in routine blood or urine testing.

Essentially, there are three routes to minimize accrual of xenobiotics: (i) precautionary avoidance of exposure; (ii) endogenous excretion; and (c) therapeutic interventions to enhance elimination. The main routes of elimination are through renal excretion, fecal elimination, and pulmonary exhalation. Other endogenous mechanisms of excretion, however, may include elimination through sweat, hair, nails, and secretions such as breast milk and tears.

Excretion pathways for different compounds vary depending on the chemical nature of the toxicant and the facility of the endogenous biochemistry to deal with it. In order for endogenous excretion physiology to operate effectively, proper nutrient status required for detoxification biochemistry is essential. Deficiency of nutrient compounds involved in conjugation and toxicant elimination, such as glutathione, glycine, and taurine, may impair normal elimination and result in toxicant bioaccumulation. Insoluble fiber, primarily found in nuts, seeds, greens, beans, rinds, and whole grains is also required for efficient fecal elimination of toxic waste through the gastrointestinal tract. In general, compounds that remain lipophilic and their lipophilic metabolites tend to be excreted primarily through fecal excretion, while hydrophilic compounds and their metabolites are generally eliminated in the urine. Some bile-excreted xenobiotics that are surface active, or which possess structural or behavioral properties similar to endogenous bile acids, however, may have slower elimination kinetics and remain persistent in the body due to enterohepatic recirculation (EHC).[31]

The EHC is a normal physiological re-absorption mechanism for recycling bile acids and acts as a means to conserve required biological compounds; this mechanism, however, can act as a hindrance to elimination of some toxicants. After hepatic processing, delivery of toxicant compounds into bile with subsequent excretion into the intestine accounts for much elimination. In addition, some compounds appear to be delivered directly to the lumen of the intestine by exfoliation of the epithelium or exudation across the mucosa.[30] Unconjugated compounds released into the gastrointestinal (GI) tract as well as conjugated toxicants freed by the action of enteric micro-organisms, however, become available to be re-absorbed and return to the liver through the EHC. Consequently, the cycle of excretion and re-absorption commences over and over again. The net result is that the process of recycling toxicants results in (i) repeated elimination by the liver thus consuming energy and nutrients, (ii) it severely prolongs the half-life of involved toxicant compounds, and (iii) it increases the potential health risk because of retained xenobiotics and persistent exposure.

Another impediment to elimination is a re-absorption mechanism in the kidneys. Some compounds may

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bioaccumulate due to renal tubular re-absorption mediated through organic anion transporters.[32,33] Although there has been discussion on the impact of pH changes on renal re-absorption of some toxicants, determinants of renal excretion are not completely understood.

Toxicant retention

Persistent compounds, depending on their chemical nature, tend to be stored in tissues or remain in serum, potentially affecting health outcomes. As an inherent defense mechanism to limit exposure of vulnerable organs to toxicants, lipophilic toxicants tend to be sequestered and stockpile within adipose tissue found in various organs including the brain. Some toxicant non-lipophilic compounds, however, may stay in blood with increased exposure to target organs and tissues. In the plasma, serum proteins may bind chemicals in order to limit their potential toxicity. Within the circulation, such toxicants are routinely shunted to the liver for elimination. While toxicant excretion can be impaired by factors such as liver disease, renal dysfunction, or deficiency of nutrients required for hepatic processes such as conjugation, some compounds remain persistent in the human body because of recycling within the EHC and/or renal tubular re-absorption.

Perfluorinated compounds (PFCs), for example, are a family of commonly used synthetic chemicals routinely found in furniture, clothing, carpets, and food packaging in order to repel oil and stains and are also used in the manufacturing of polytetrafluoroethylene (Teflon) – a non-stick surfacing often found in cookware. Exposure to PFCs is widespread and some subpopulations, living in proximity to, or working in fluorochemical manufacturing plants, are highly contaminated. Recent research has suggested that some common PFCs demonstrate reproductive toxicity,[34] hepatotoxicity,[35] neurotoxicity,[36] genotoxicity,[37] and are likely human carcinogens.[38] PFCs remain persistent within the environment due to their inherent chemical stability and are extraordinarily persistent within the human body due, in large part, to enterohepatic re-circulation. As a result, these agents have prolonged half-lives in the human body – thus increasing their potential adverse impact. Accordingly, there is increasing discussion about potential therapeutic interventions to intercept the EHC to facilitate more rapid elimination of such agents. There is no known clinical intervention at this juncture to preclude re-absorption of PFCs or other compounds within the kidney.

Interventions to facilitate excretion of xenobiotics

In order to diminish the risk associated with bioaccumulation of toxicant compounds in general, it is necessary to facilitate removal of such agents – this can be achieved by endogenous processing of the chemical into a non-toxic metabolite or by enhancing the rate of excretion from the body. Research is underway to find effective techniques to diminish the total body burden of toxicants, a process sometimes referred to as detoxification. With limited science reported in medical journals on methods to facilitate excretion of accumulative toxicants, the area of detoxification thus far has gathered attention primarily among practitioners of complementary and alternative medicine (CAM). 'Detoxification Centers' have become more prevalent, sometimes offering remedies with limited or no scientific validation including assorted 'cleanses' and 'detox' treatments to treat increasing numbers of patients who believe they have accumulated toxicants as a determinant of their affliction. Table 1 provides an overview of approaches purported to remove chemical toxicants from the body.

While some interventions that purport to facilitate toxicant excretion such as 'ionic foot baths' or 'ayurvedic leech therapy' lack vigorous scientific analysis and clinical trial evidence, there has been some research reported in the scientific literature about selected interventions to diminish the body burden of toxicants. For example, with the recognition that perspiration acts a means to excrete xenobiotics, some reports suggest that induced sweating may be useful in diminishing toxicant bioaccumulation. There is limited study thus far on which specific agents are excreted in sweat and at what rate, but research confirms toxic compounds such as methadone,[57,69] cocaine,[57] amphetamines,[56,70] crystal meth,[56,71] morphine,[71] and some heavy metals[72] appear in analytical studies on sweat. Although further study is required to determine the clinical usefulness of induced depuration through thermal techniques, several studies thus far have confirmed that induced perspiration through sauna therapy can diminish the body burden of assorted bioaccumulated toxicants including persistent polychlorinated biphenyls (PCBs), polybrominated biphenyls, chlorinated pesticides, hexachlorobenzene, and various other toxicants in exposed individuals.[73-80]

Another recognized intervention to diminish the body burden of some bioaccumulated toxicants is the

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Table 1. Selected interventions purported to facilitate detoxification of toxic materials

Type of intervention	Alleged mechanism of action	Effectiveness
Fasting	Lipolysis of fat cells releasing stored xenobiotics into circulation and available for excretion	Caloric restriction confirmed to significantly increased serum concentration of some toxicants[21,39]
Massage	Mobilization of toxins sequestered within muscle tissue into the circulation and available for excretion	Consistent confirmation of enhanced excretion of stored toxicants not found in the scientific literature
Chelation	Use of agents known to chemically bind specific toxins and to allow for excretion of chelate-toxin compounds	Recognized treatment for some types of heavy metal poisoning.[40,41] No evidence in the literature for removal of other types of toxicants
Plasmapheresis	Removal of a portion of the plasma compartment of blood – which contains protein-bound toxicants	Evidence in the scientific literature for excretion of some protein-bound toxicants[42,43]
Ionic Foot Baths	Sends a current into the body to generate positively charged ions that allegedly attach to negatively charged toxins and discards bound toxicants through foot pores	Consistent confirmation of enhanced excretion of stored toxicants not found in the scientific literature
Colonic Cleansing	Removes encrusted material from the colon thus diminishing absorption of toxicants and allowing for improved excretion of accumulated waste	Some discussion[44,45] but consistent confirmation of enhanced excretion of stored toxicants not found in the scientific literature
Exercise	Various mechanisms proposed including (i) lipolysis of stored toxins in fat cells with excretion through lungs and perspiration (ii) enhanced enzymes in detoxification pathways[46]	Preliminary research confirms enhanced excretion of some compounds with exercise[47,48]
Bile Acid Sequestrants	Medications which bind to specific compounds released into bile, preventing re-absorption within the enterohepatic recirculation (EHC)	Numerous studies confirm binding and release of specific compounds by some bile-acid sequestrants (BAS)[49,50]
Hemodialysis	Technique of circulating blood through filters outside the body to remove toxic materials	Effective with low molecular weight compounds. Limited ability to remove macromolecules such as protein-bound toxins.[51] Research to improve this technique is ongoing[52]
Prebiotics and Probiotics	Restoration of damaged germ environment in the intestinal flora facilitates GI removal of selected compounds	Emerging evidence of the role of prebiotics and probiotics in excretion of some toxicants[53-55]
Sauna therapy	Induced perspiration with excretion of toxicants into sweat	Numerous studies have confirmed release of selected toxicants[56,57]
Cleanses through various food and drink mixtures	Dietary interventions that allegedly stimulate endogenous release of stored toxicants	Consistent confirmation of enhanced excretion of stored toxicants not found in the scientific literature
Phlebotomy	Removal of toxicants retained in red cells and plasma compartments	Evidence for removal of excess compounds in specific conditions such as iron overload disorders[58]
Leeching	Leeches allegedly suck toxins from the blood	Confirmation of enhanced excretion of stored toxicants not found in the scientific literature
Herbal Supplements	Some supplements noted to facilitate excretion by enhancing intrinsic detoxification mechanisms	Evidence for detoxifying effectiveness of selected supplements,[59,60] but confirmation of enhanced excretion of the spectrum of stored toxicants by myriad supplements is not found in the scientific literature

(continued)

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Table 1 (continued)

Type of intervention	Alleged mechanism of action	Effectiveness
Medicated baths and hot springs	Immersion of body into medicated bath or hot springs facilitates absorption of compounds that enhance endogenous release; or alternatively, 'magnetic' effect to draw out toxins into the bath	Confirmation of enhanced excretion of stored toxicants not found in the scientific literature. Theoretical benefit of absorption of sulfur (involved in some detoxification biochemistry) in natural hot springs
Liver and gall bladder flush	Medicaments or foodstuffs inserted per rectum into the colon designed to stimulate liver dumping of toxicants into bile and gall bladder release into the intestine	Some discussion[44] in the scientific literature but consistent confirmation of enhanced excretion of stored toxicants not found
Zeolites (from naturally occurring volcanic sedimentary rock)	Through cation exchange, ingested zeolites release beneficial elements while capturing and binding toxicants. Heavy metals and other toxins are allegedly absorbed into the zeolite cage and then excreted	Animal research suggests safety[61,62] and potent effect with mycotoxins.[63,64] Binding of some toxicants[65] and heavy metals[66-68] in water, soil, and other mediums. Human research not found in scientific literature

use of medications that bind and remove certain heavy metals including lead and mercury.[40,41] Chemical therapies such as dimercaptosuccinic acid (DMSA) and dimercaptopropane sulfonate (DMPS), for example, have been found to be safe and effective chelators of some heavy metals.[81-84] Chelating agents work, in part, by interference with renal re-absorption of some heavy metal toxicants. The contention that chelation therapy has the ability to detoxify and cleanse the body via binding and removing all toxicants (including assorted synthetic chemical compounds) in the blood or tissues, however, is not supported by evidence in the literature.

In addition to single interventions, some methods of detoxification can be combined to facilitate xenobiotic removal. Hemodialysis in combination with use of chelating agents, for example, may be a safe and effective means to rapidly lower toxic metals – a potentially important strategy as high levels of mercury and lead can impair renal function, and concentrated exposure to cadmium can be toxic to the kidney.[85]

With the recognition that caloric restriction appears to greatly enhance lipolysis with release of assorted toxicants,[38] fasting techniques and restrictive dietary measures have also been explored as a means to diminish the body burden of toxic compounds.[39] Concern has been expressed about severe caloric restriction, however, as it may result in a surge of toxicants entering the blood stream and the cerebral circulation,[21,39] potentially precipitating health compromise in some patients. In addition, vigorous exercise also appears to induce lipolysis[86] and appears to enhance pulmonary excretion of various toxicants.[47,48]

Certain nutrient interventions are also being explored, which augment the removal of specific compounds[87] – malic acid, for example, appears to assist with the removal of retained aluminium,[59,88] while modified citrus pectin has been effective at facilitating elimination of lead.[60] Finally, a number of reports have emerged in recent literature which focus on interventions to facilitate elimination of persistent compounds such as PFCs by interrupting enterohepatic recycling.

Therapies to circumvent the enterohepatic circulation

Although most synthetic chemical compounds appear to be readily excreted in healthy individuals who are no longer exposed, some compounds persist as they are not easily metabolized or as a result of recycling within the EHC. Interventions to circumvent reabsorption within the EHC offer promise to diminish the body burden of persistent toxicants by facilitating excretion – with potential benefits for human health. With variations in chemical behavior and structure between different chemical agents, however, dissimilar interventions may be required to facilitate binding of dissimilar compounds in order to achieve EHC interruption – that is no one chemical therapeutic intervention is likely to circumvent enterohepatic recycling for all toxicant compounds.

Four types of pharmaco-therapeutic interventions have been discussed in the literature as potentially useful in circumventing the EHC. First, therapies that preclude fat absorption have been found to enhance the excretion of fecal fat and lipophilic toxicants – to this end, research is underway on non-absorbable

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fats that act as a lipophilic sink.[89] Preliminary results confirm that these types of compounds, such as Sucrose Polyester (Olestra), have been effective in enhancing fecal elimination of a variety of chemical agents including dioxins, furans, PCBs, and hexachlorobenzene.[89,90] Other compounds such as mineral oil[91] also appear to have some success in enhancing excretion by this mechanism.

Secondly, there has been preliminary work on interruption of fat absorption by interfering with pancreatic lipase. The drug Orlistat (Xenical) is a pancreatic lipase inhibitor that interferes with digestion of triglyceride and thereby reduces absorption of dietary fat.[92] Animal work suggests that enhanced excretion of some lipophilic compounds such as hexachlorobenzene may be facilitated by use of these types of agents.[31]

A third approach involves the use of adsorbent compounds that accumulate toxic agents from within the GI tract. For example, activated carbon such as charcoal and other compounds including bentonites, certain clays, and zeolites appear to have adsorbent action, which may decrease re-uptake of some compounds into the body. (Some zeolites appear to also work through cation exchange mechanisms.) Although animal studies have demonstrated promise, insufficient human research work has been done thus far to conclusively determine the clinical value of adsorbent compounds for toxicant removal. Some adsorbents, for example, appear to be effective in removing selected biological chemicals such as aflatoxins in animals.[93,94] Activated charcoal, however, has demonstrated inconsistent efficacy with elimination of stored compounds in human research.[91] Further study is required to assess the usefulness of these agents with the range of bioaccumulative compounds.

The fourth mechanism to circumvent enterohepatic recycling involves the binding of toxicants in the intestine via bile-acid sequestrants (BAS),[49,50,95-97] the most well known and studied of these is cholestyramine (CSM). CSM is a strongly basic non-absorbable resin that effectively binds various agents through anion exchange, interrupts enterohepatic recycling, and prevents intestinal re-absorption. As well as effectiveness at binding bile salts in the GI tract, CSM and other BAS have been shown to bind various bacterial endotoxins[98,99] mycotoxins,[95,100] enterotoxins,[101] PCBs,[102] some external biotoxins,[103] drugs such as methotrexate,[49] and they have also been used as agents to lower cholesterol levels. Cholesterol, for example, enters the intestine as a component of bile and is absorbed again and returned to the liver where the cycle of biliary excretion and re-absorption recur – CSM binds cholesterol, prevents enterohepatic recycling, and lowers serum cholesterol by facilitating excretion.

A paper published in the *New England Journal of Medicine* reported on a controlled clinical trial where CSM was successfully used to diminish serum levels of a toxic pesticide in exposed people[50] – a significant increase in the fecal elimination as well as decrease in body burden was observed in the CSM-treated group compared to the control group. Other non-absorbable resins such as colestimide have also been effective at eliminating certain toxicants, including PCBs.[49,104] In order to preclude potential adverse sequelae of these pharmaceutical compounds, particularly in developing children (such as induced deficiency of fat-soluble micronutrients by binding and eliminating these nutrients), research continues on the use of herbal agents such as saponins compounds (originating from soy or the yucca plant) which are alleged to have a similar BAS mechanism of action and which purport to be associated with less adverse effects.[105,106] The author was unable to find ample study in the scientific literature to determine the validity of this proposed hypothesis about saponins.

Therapeutic plasmapheresis

Plasmapheresis is a blood purification process that involves removal of whole blood from the body, separation of whole blood into the plasma component and red cellular elements, and reinfusion of the cells back into the body suspended in a plasma substitute such as saline, donor plasma, or donor albumin. The end result of therapeutic plasmapheresis, otherwise referred to in literature as therapeutic plasma exchange[107] or therapeutic apheresis,[108] is the removal of the body's own plasma without depleting red blood cells, and with the potential to remove protein-bound toxic substances contained within the plasma.

Although therapeutic plasmapheresis has been used in selected cases of autoimmune, infectious, rheumatic, and other types of disease states, this technique has recently been incorporated as a method of clinical detoxification. As well as successful outcomes in the treatment of potentially fatal mushroom poisoning,[109] plasmapheresis has been effectively employed to remove some pharmaceuticals, especially those with a high protein-binding capacity (thus not amenable to dialysis), from the circulation. For example, plasmapheresis has been useful in

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eliminating carbamazepine,[110] calcium channel blockers such as diltiazem[111] and verapamil,[112] hormonal agents including L-thyroxine,[113] phenprobamate,[42] and rituximab.[43] Removal of protein-bound heavy metals, such as mercury,[114,115] vanadium,[116] and chromium[117] and elimination of pesticides such as paraquat[118,119] and organophosphates[120] has also been accomplished through plasmapheresis. Increasing study is underway to determine the range of toxicants that can potentially be removed by therapeutic apheresis.

Although scientific study is underway to develop efficacious testing and treatment to eliminate the spectrum of adverse chemical agents, the prospect of widespread clinical application of such diagnostic and therapeutic measures remains low when considering the lethargic continuum of knowledge translation in medical practice.[121,122] With the ubiquitous problem of toxicant bioaccumulation and the link to illness, however, it is suggested that clinicians become increasingly apprised of the need for such testing and therapy. A case history is presented to illustrate the potential outcome with elimination of toxicants.

Case history as an example of chemical detoxification

In March of 1996, a generally healthy 33-year-old single woman in apparently excellent physical condition – non-smoker, non-alcoholic, never used illegal drugs, no prior history of mental or physical illness – suffered what was subsequently diagnosed as an acute, full-blown manic episode. Symptoms included visual hallucinations, insomnia, cognitive impairment, and delusional thoughts where the individual claimed to be receiving direct messages from the spirit world and from God. Her family brought her to the University Hospital of a major center as they were concerned with the sudden change in behavior.

As the patient had been employed in a printing company for 15 years and was exposed to numerous chemical toxins through direct skin contact and inhalation in poorly ventilated conditions, the family asked the treating physicians to assess for chemical poisoning. They claim the physicians appeared to ignore this information and immediately diagnosed her as having manic-depressive illness with psychotic features. She was promptly admitted to a psychiatric unit and antipsychotic medication was commenced.

For a period of more than 2 years, she remained very ill and was given various medications from which she suffered numerous harsh side effects including involuntary movements and a weight gain of 80 lbs. Despite pharmaceutical management, she continued to have manic episodes and required recurrent psychiatric hospitalization. She and her family were informed that her mental disability was an incurable chronic condition that she had to learn to live with. Upon considering her alleged prognosis, the patient became increasingly suicidal.

In 1998, the individual was seen by a physician trained in environmental health sciences and she underwent various investigations confirming she had bioaccumulated high levels of lead. As well as avoidance of further toxicant exposure, chemical detoxification of lead was undertaken with a heavy metal chelator and values of lead progressively diminished. Concomitant with the decline in accumulated lead, her psychiatric symptoms gradually subsided and all medication was discontinued. The individual has remained generally well for over 10 years, with no evidence of either bipolar disease or sustained recurrence of symptoms or signs of mental illness. The weight issue has persisted, however, as has intermittent difficulty with insomnia. After recovery, she was told by several doctors that detoxification treatment was nothing more than 'placebo.' Other accounts in the medical literature also document mental health affliction in association with toxicant exposure,[29,123-125] with recovery in some cases following measures to avoid or detoxify adverse chemical agents.[29,123,124]

Concluding thoughts

We live in the age of ubiquitous chemical toxicity. There is increasing global attention to the problem of persistent pollutants, both in the environment and within the human body. Compelling research suggests that accrued toxicants may lead to increased health risks in the long term. With the 21st century reality of escalating toxicant exposure and bioaccumulation among individuals and population groups, research is now underway to find potential interventions to facilitate excretion of persistent toxicants in order to diminish the body burden and to preclude or overcome related health problems.

Study of interventions to remove bioaccumulated toxicants, however, remains in its relative infancy and much scientific research needs to be done to identify credible modalities with potential to eliminate accrued xenobiotics. With the scientific knowledge

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currently available, how should clinicians and the public health community address the problem of toxicant bioaccumulation?

Thus far, three phases of intervention are required to address the problem of toxicant bioaccumulation. First, it is evident that precautionary avoidance to preclude further toxicant exposure is crucial.[126] This can be achieved by educational endeavors in schools and through media to promote awareness among individuals and population groups. This objective also requires regulation and public legislation to preclude the release of harmful chemicals into environments where individuals may be exposed. With considerable lag time between development of chemical compounds and the extended process required to confirm safety of each compound, it behooves the public health community and government officials to consider whether 'proof of safety' rather than 'proof of harm' should be required before potentially health-compromising compounds continue to be unleashed into the environment.[127]

Secondly, proper functioning of inherent toxicant elimination mechanisms need to be maintained in exposed individuals. Investigation and treatment for any physiological impairment of excretion should be undertaken to secure maximal liver, kidney, and pulmonary function. Adequate nutritional status for various biochemicals involved in excretion and detoxification physiology, such as reduced glutathione, need to be secured in order to maintain optimal and intact toxicant elimination physiology.

Finally, with much discussion in the popular media and alternative medicine circles about 'cleansing' and 'detoxing,' it is hard to winnow fact from fable in the area of detoxification therapies. In order to determine potential efficacy in the clinical care of exposed patients, therapeutic interventions to enhance elimination of persistent compounds require carefully designed clinical trials to determine evidence-based scientific validity for each modality. As the field of environmental health sciences is an emerging clinical area of medical practice with enormous public health significance,[128] it is imperative that the scientific and medical community stay apprised of the expanding problem of persistent toxicant bioaccumulation and become familiar with evidence-based clinical interventions that facilitate the removal of adverse chemical compounds.

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