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Diagnosis and Treatment of Patients Presenting Subclinical Signs and Symptoms of Exposure to Chemicals Which Bioaccumulate in Human Tissue

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ABSTRACT

This Conference is dedicated to examining all facets of "hazardous wastes and environmental emergencies." At the national, state and local levels, a tremendous nationwide effort is being exerted to clean up air, water and ground pollution. However, as the eminent environmental scientist Rene Dubos noted over 15 years ago, "The greatest danger of pollution may well be that we shall tolerate levels of it so low as to have no acute nuisance value, but sufficiently high, nevertheless, to cause delayed pathological effects and despoil the quality of life."

This paper examines some of the problems in attempting to diagnose and treat low-level body burdens of toxic chemicals and discusses a review of 120 patients who were prescribed detoxification treatment as developed by Hubbard to eliminate fat-stored foreign compounds.

INTRODUCTION

Four million distinct chemical compounds have been reported in the literature since 1965, with approximately 6000 new compounds being added to the list each week. Of these, as many as 70,000 chemicals are in current commercial production.' Human exposure to them is both direct and indirect: more than 3000 chemicals are deliberately added to food and over 700 have been identified in drinking water. Along with pharmaceuticals and recreational street drugs, the direct exposure to humans is considerable.'

A significant number of these toxic chemicals are lipid or fat soluble and tend to bioaccumulate, particularly in the fatty tissues throughout the body. Over 400 chemicals have been identified in human tissues, with 48 found in adipose tissue, at least 40 in milk, 73 in the liver and over 250 in blood plasma.' Examples of these types of lipid-soluble chemicals which tend to bioaccumulate are polychlorinated biphenyls, polybrominated biphenyls, PCP and THC. Evidence regarding the

persistence of these fat-soluble chemicals in humans has accumulated, especially with respect to the organohalides.

Several studies [4,5,6] have shown that fat biopsy samples taken as many as 18 months apart have shown no significant reduction in levels of PBBs and PCBs. This is a point of some significance; once these types of chemicals enter the body's fat stores, they are not easily removed from the body by natural mechanisms and, therefore, tend to bioaccumulate in the human body. By 1975, studies on adipose tissue levels of organohalides had shown that over 90% (and in some cases 100%) of the samples collected had detectable levels of DDT/DDE, Dieldrin, heptachlor, epoxide and PCB.[7,8]

There have been several large-scale human exposures to these lipophilic toxic chemicals; one example is the 1973 PBB exposure in Michigan. Most of you will recall the episode in which PBB, a fire retardant, was substituted for a cattle feed supplement, thereby contaminating a large portion of the meat and milk in the state of Michigan. By 1978, 97% of individuals tested in Michigan had detectable PBBs in their adipose tissue.' Several studies have estimated that these residents may bear this toxic burden throughout their lives. [10, 11, 12] Unfortunately, the effects of such long term burdens have yet to be determined.

DIAGNOSIS

Diagnosis of chemical intoxification has traditionally required a history of exposure to a known chemical and the finding of appropriate symptoms and clinical signs. Threshold limit values are based on the known effects of exposure to one chemical at a time over a known or limited time period. The "no-effect level", "safety factor" and "acceptable daily intake" have been considered sacrosanct for so long that the weakness of the rationale on which they are based may come as a shock." Most of these levels are based on pathological or tissue findings where possible."

However, we are concerned with the more subtle findings which may occur in neurological and other organ systems before permanent tissue damage has occurred. These more subtle changes take the form of symptoms common to all of us which can be related to other types of medical and emotional problems: increased fatigue, malaise, slowing of motor reactions, impaired regulation of appetite, reduced visual discrimination capacities under low levels of illumination, headache, irritability, tiredness, etc. These functional changes are seldom reflected in pathologic signs or findings. However, these behavioral changes may be more sensitive indicators of general organ system toxicity." Attempts at trying to recognize these "subclinical" or "subliminal" signs and symptoms of toxic exposure are not new: Goldberg in 1972 noted:

"Subliminal toxicology seeks to study levels of exposure that elicit no overt clinical effect on man or animal. The subliminal approach aims at discovering indicators of exposure and of effect that are so sensitive as to provide the required information at dose levels comparable with those to which the human population is actually being exposed.""

There are several problems which arise when attempting to provide health care to chemically exposed patients.

PROBLEMS IN DIAGNOSING LOW-LEVEL TOXIC EXPOSURE

Disease Progression

The chronic effects of low-level exposure to toxic chemicals have been studied in only a very few chemicals. Table 1 shows the progression of disease associated with bioaccumulation of PBBs and PCBS. Disease syndromes progress very slowly, and it may take many years of exposure before overt signs are present which provide pathologic diagnosis. Unfortunately, by this time many of the changes (carcinogenesis, peripheral nerve damage, central nervous system damage, etc.) are permanent and irreversible. It is essential, therefore, that early diagnosis of low-level bioaccumulations of toxic chemicals be made.

Table 1
The Progression of Disease Associated with Bioaccumulation of Polyhalogenated Biphenyls

EXPOSURE	BIOACCUMULATION (ppm) *				HEALTH INDICATORS	BIOLOGICAL RESPONSE	REF.
	PBB		PCB				
	Blood	Fat	Blood	Fat			
Ambient (less thar 35 years)	.00003	.004	.0023		None observed	Normal	(25) (26) (27)
Low-level or Ambient (greater than 35 years)	.011	.4	.005		Subtle symptoms	Many: e.g. fatigue, muscle weakness, nervousness, joint pain, headache (See Table of Symptoms)	(16) (28) (29) (30) (31
Occupational or Extended Low-level	.09	25	.044		Subclinical and clinical signs	Immune dysfunction. Elevated CEA titer. Elevated SGOT-SGPT	(32) (29) (16) (36)
Extended Occupational	.603	196	.356		Overt signs and symptoms	Dermal abnormalities. Abdominal pain. Eye irritation.	(16) (33) (27)
Massive				13	Premature death	Major systemic failures.	(34)
Lifelong Ambient Exposure				8.7	Premature death	Cancer	(35)

*Fat concentration measured on a per lipid weight basis

Nonspecificity of Symptoms

Many chemicals can cause identical symptoms. A review of the literature over the past 10 years for 46 selected chemicals shows many instances of wide overlap of symptomatology to exposure to these chemicals (Table 2). It is important to note that the symptoms related to lipophilic chemicals are not significantly different from those related to hydrophilic chemicals. Many of the symptoms may relate to psychiatric or psychological symptomatology. However, several studiesl6,17, 18 have shown that the existing differences between exposed groups and control groups could not be otherwise explained without considering an etiologic role for exposure to the toxic substances.

Chemical Cocktail Dilemma

Patients, and indeed all of us, are exposed to low levels of many different toxic compounds on a daily basis. Even with known drug interactions, the physician, nevertheless, has a difficult time keeping track of the interactions of the many different medications he may prescribe to a single individual. The literature of pharmacology and toxicology is replete with examples in which one

agent enhances the effects of others, either directly or indirectly." Reiter notes, "Although one might prefer to know more about the potential effects of toxicants when administered alone before we tackle the problem of mixtures, the 'real world' situation demands the development of a strategy for the evaluation of mixtures.""

Limited Data Base

With literally millions of compounds in existence and hundreds of thousands in production, only a very few chemicals have been researched in regard to their toxicology. As noted above, our data base represents a literature search covering the last 10 years and only 46 chemicals. Many papers are difficult to assess because titles do not reflect compounds actually studied.

Regarding chemicals which have been studied, it is very hazardous to extrapolate animal data to the human population." In regard to lipophilic substances, fat tissue levels of toxic chemicals may be as much as 500 times higher than blood levels; however, most papers in the past have referenced blood levels, which may have little or no relation to the chronic or subclinical symptoms."

"Self-Selected" Population Problem

Populations of chemically exposed and nonexposed individuals may sort themselves out in the case-finding process. Some individuals may be particularly stoic and not present themselves for evaluation until far into the course of a chemical toxicity syndrome, whereas others with few symptoms at all but fearful of exposure will be involved in the selection process. Occasionally, compensation factors will enter into motivation for individuals selecting themselves into or out of a study.

In summary, behavioral changes may well serve as the earliest indicator that some subtle, covert, toxic action is occurring in the body, hopefully at a time when the process can still be reversed."

PROBLEMS IN ATTEMPTING TREATMENT OF LOW-LEVEL TOXIC EXPOSURE

"Chemical Cocktail" Dilemma Revisited

As we noted above, many toxic lipophilic chemicals are stored at very low levels in the fat tissues. Therefore, a chemical-specific approach will not attack a problem which is not definable in terms of one chemical in the first place. It is also not generally possible to do tissue analyses for most toxic chemicals at these lower levels. Very few laboratories have tissue analysis capability at the parts per billion concentration level. Hopefully, this problem will change with improvements in analytical methodology.

Table 2
Symptoms Associated with Environmental Chemical Exposures

	SYMPTOM	BENZENE	CARBON	DISULFIDE	DIOXIN	LEAD	PBB	PCB
A.	IMPAIRED MEMORY			X		X		X
	CONFUSION			X				
	SLOWED ADOLESCENT DEVELOP.					X		
B.	HEADACHES			X		X	X	X
	SLEEPLESSNESS			X		X	X	X
	SLEEPINESS					X	X	X
E.	EYE IRRITATION						X	X
	DIMNESS OF SIGHT				X			
	BLURRED VISION						X	
	EYE OSCILLATION			X				
	PUPIL REACIONS					X		
G.	WEIGHT LOSS > 10 LBS.						X	X
	NAUSEA						X	X
	VOMITING					X		X
	ABDOMINAL PAIN							X
	ABDOMINAL CRAMPS						X	
	DIARRHEA						X	
K.	JOINT PAIN						X	X
	SWELLING OF JOINTS						X	
	MUSCULAR ACHES & PAINS						X	X
M	SPEECH IMPAIRMENT							X
	MUSCLE WEAKNESS			X		X	X	
	TREMORS					X		
	DIFFICULTY WALKING					X		
	SEIZURES					X		
	INCOORDINATION					X	X	
	DIZZINESS					X	X	X
	FATIGUE					X	X	X
N.	DEPRESSION			X		X	X	X
	NERVOUSNESS	X			X	X	X	X
	IRRITABILITY	X		X	X	X		
	EMOTIONAL INSTABILITY			X		X		
P.	VISION IMPAIRMENT					X	X	
	HEARING IMPAIRMENT					X		
	LOSS OF SMELL/HEARING						X	
	BURNING SENSATION						X	X
	PARESTHESIAS			X		X	X	X
	HALLUCINATIONS			X				
S.	RASH						X	X
	ACNE						X	X
	SUN SENSITIVITY						X	
	SKIN DARKENING/THINCKENING						X	X
	DISCOLOR/DEFORM. OF NAILS					X	X	X
	DRYNESS OF SKIN					X	X	
	INCREASED SWEATING					X	X	
	SLOW/POOR HEALING OF CUTS					X	X	

A. ASSOCIATIVE
B. PHYSIOLOGICAL RESPONSES
E. EYE
G. GASTROINTESTINAL
K. MUSCULOSKELETAL
M. MOTOR
N. NERVOUS SYSTEM
P. SENSORY
S. SKIN

Risk of Mobilization

There is strong indication that the so-called "flashback" phenomenon associated with the use of hallucinogenic substances may be related to the release of these stored substances when fat stores are mobilized by fasting, stress, etc. Some investigators conclude that mobilization of these and other lipophilic chemicals may not be desirable, while others feel strongly that the risk is small

and where a detoxification or excretion pathway exists, mobilization should be encouraged." Our experience strongly favors the latter position.

TREATMENT OF CHEMICALLY EXPOSED PATIENTS

When a diagnostic assessment suggests a potential chemical exposure basis for the symptomatology, especially when the symptoms are chronic in nature, a first-tier treatment can be used. This treatment, developed by Hubbard, has been shown to reduce chemical burdens in humans.23 24 We have examined the status of 120 individuals referred for treatment of health effects which diagnostic assessment suggests are likely to be due to low-level chemical exposure. Treatment consisted of seven components: *Physical exercise, preferably running aerobically for 20 to 30 minutes immediately prior to sauna exposure. *Forced sweating by sauna at 140-180'F for 21/2 to 5 hr daily, immediately following the physical exercise. The sauna was done in one period each day, with short breaks for cooling shower or additional exercise. Niacin (nicotinic acid) was used in gradually increasing doses on a daily basis throughout the program. These three components (exercise, forced sweating and niacin) all act as potent techniques for mobilizing fat, resulting in significant turnover of adipose tissue stores and consequent mobilization of the stored lipophilic toxic chemicals.

*Water, salt and potassium were taken as needed to avert dehydration or salt depletion, due to the concentrated sweating. *Polyunsaturated (Allblend) oil, from 2-8 tablespoons daily based on individual tolerance, was used to overcome enterohepatic recirculation because, as the fat-soluble toxic chemicals are released into the blood stream, many of them are carried to the gut where they are released intraluminally. There, they are reabsorbed into the lipophilic bile acids and recirculated back through the liver. The polyunsaturated oil tends to retard this recirculation effect and allow the toxic substances to be excreted through the colon. A considerable portion (10-15%) of the toxic materials excreted through the body will come out through the sebaceous sweat. *Calcium, magnesium and other minerals were added to replace those lost through the copious sweating from the sauna exposure. 9A regular daily schedule with balanced meals and adequate sleep was prescribed as a general health measure. No medications, drugs or alcohol were permitted during the period of the treatment program, unless prescribed by the supervising physician.

All patients for this program first had an extensive diagnostic evaluation, including a thorough medical history and physical examination by a physician, chemical evaluation of the blood and, in some cases, adipose tissue as well as sebaceous secretion evaluation. I

While we collected information on over 70 signs and symptoms, available literature provided control data for only 15 symptoms. These symptoms are associated with several types of chemical exposures, with fatigue, muscle pain and headaches predominant among them.

Our patient population, selected to replicate the age and sex distribution of populations reported in the literature, presented symptomatology similar, but not identical, to a chemically exposed population (Anderson). Table 3 indicates the percentage of the population with the various symptoms. Analysis of this chemically exposed reference population and our treatment population indicates that there was no statistically significant difference in the rate of symptom prevalence ($p @ 0.4$).

Post treatment of our patient population showed significant improvements in all but one symptom.

Table 3
Symptom Prevalence of Chemically Exposed and Unexposed Reference Populations and a Chemically Exposed Treatment Group

SYMPTOM	CHEMICALLY EXPOSED POPULATION[1]	HEALTHY POPULATION[1]	TREATMENT GROUP PRE-	TREATMENT GROUP POST-	
Rash	17%	9%	18%	4%	**[2]
Acne	12	5	16	4	*
Skin thickening	9	3	9	4	
Paresthesias (dermal sensations)	19	5	14	2	**
Weakness	13	3	16	4	*
Incoordination	21	5	7	0	*
Dizziness	20	3	18	2	**
Fatigue	52	15	79	5	**
Nervousness	22	2	14	4	*
Disorientation	6	0	11	0	**
Headaches	41	14	40	9	**
Joint pain	43	23	5	0	*
Muscle pain	23	8	42	5	**
Abdominal pain	13	7	33	11	**
Constipation	6	2	26	2	**

[1]These reference populations are discussed in Anderson, *et al*. (28) The chemically exposed population above is Group 3 and the healthy population is Group 4 in Anderson's report.

[2]The difference in symptom prevalence after treatment is significant at the following levels:
* = $p < 0.5$ ** = $p < 0.01$

Comparison of a healthy reference population and our post-treatment patient population indicated there was no statistically significant difference in their rates of symptom prevalence (p 0.3).

While we do not present these data as definitive evidence of a chemical basis for symptomatology observed, the treatment used was noninvasive, reduced chemical body burdens and reduced the severity and frequency of symptom prevalence.

CONCLUSIONS

In summary, we have discussed the problems relating to both diagnosis and treatment of patients presenting signs and symptoms of low-level toxic bioaccumulation. A treatment program was

discussed and preliminary data regarding 120 patients who completed the detoxification program was presented.

Large sums of money are being spent to clean up the external environment but, to date, only relatively paltry amounts have been spent investigating the cleanup of our internal milieu. Much effort lies ahead for all of us in addressing these related problems.

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