ABSTRACT: Behavioral toxicology is now established as a component of the environmental health sciences. Its rise paralleled recognition that the adverse health impact of environmental chemicals should be gauged by how people feel and function, not solely by death or overt damage. Its compass extends across the total spectrum of environmental chemicals, including heavy metals, solvents, fuels, pesticides, air pollutants, and even food additives. Psychology can help resolve many critical issues in environmental health science.

Odious waterways and corrosive smog are such tangible evidence of pollution that they evoke tangible remedies. But eliminating blatant pollution is no more than a first step in managing the environment and protecting human health. Some of the most toxic contaminants are also the most elusive. How can we assess the impact of chemicals that, in passing through the environment, may be transformed into other substances, may be dispersed by atmospheric processes, may enter the food chain in unpredictable guises, or may trigger biological reactions whose consequences remain dormant for decades? To multiply this ambiguity, how do we evaluate toxic processes expressed other than as overt disease or death? Especially, how do we detect an insidious degradation of function, especially if it unfolds gradually over years of toxic exposure or after a latency of half a lifetime?

The nascent discipline of behavioral toxicology arose as one response to such questions. Behavioral measures were seen to fulfill unique roles. One derives from the realization that many substances act primarily on the nervous system. They include heavy metals such as mercury, lead, and manganese; organic solvents such as carbon disulfide and toluene; pesticides such as the organophosphates; air pollutants such as carbon monoxide. A second reason is more subtle; it derives from the observation that many poisonings, before they bloom into overt clinical signs, may be heralded by vague, subjective, nonspecific psychological complaints. Finally, there are substances whose actions, although not mediated directly through nervous system mechanisms, produce distinct behavioral reactions. For example, the main oxidant in photochemical smog, ozone, is a deep lung irritant eliciting subjective discomfort.

This unique role for psychology grows out of a new perspective by the environmental health sciences, particularly environmental toxicology, and by public health leaders. Toxicology, the science of poisons, used to be a discipline ruled by the clear criteria of death and tissue pathology. The new issues that emerged from our delayed recognition of environmental hazards, however, stimulated new questions about adverse effects on health. Were death or tissue lesions the only feasible end points? What about disturbances of function? Isn't it important to discover how people feel and perform or to intervene when "behavioral changes dangerous to a patient and others can occur before the individual realizes that he or she is poisoned" (Michael, 1982)? Once we were alerted to these questions about function, it was a natural step to turn to the discipline whose business it had been for over a century to provide scientific answers to questions of this type.

Behavioral toxicology is so young that its formal debut in the United States did not occur until June 1972, shortly after the winter snows had melted in Rochester (Weiss & Laties, 1975). Like many new disciplines, it coalesced from fragments of old ones: toxicology and its emphasis on pathology, behavioral pharmacology and its parallel inquiries about drug effects, industrial hygiene and its recognition of functional indexes as the basis for many standards of allowable exposure to workplace chemicals. It is also indebted to I. P. Pavlov, because his stature in Soviet science helped to elevate CNS function to a sovereign place in USSR hazard assessment (Glass, 1975).

Behavior also was seen to have special virtues as a criterion of adverse effects. First, it is a nondestructive assay: Its subjects' livers need not be fed into a blender to quantify damage. Also, it is an assay system (Weiss, 1978b) reflecting an Organism's total functional capacity, not simply one component of it. Such attractive attributes come at a price, however.
Behavior's global nature also may allow compensatory mechanisms to thwart the early detection of an irreversible pathological process. Behavioral assays are expensive, especially when compared, for example, to in vitro tests of mutagenesis. Behavioral methods also offer a bewildering spectrum of choice, which is an advantage in pursuing a science of behavior, but an aggravating source of indecision for a chemical manufacturer or regulatory agency forced to define hazard. Perhaps most troublesome of all, how are functional measures to be evaluated? What actions are implied by a finding that the current workplace exposure standard for a volatile organic solvent lengthens reaction time by 10%? Or by a report that prenatal treatment with high doses of a common pesticide elevates locomotor activity in two-month-old rats? These are not idle questions or academic exercises; standards and regulations may be built on them. The Toxic Substances Control Act (TSCA) of 1976 specifies behavior as one of the criteria for judging the safety of new chemicals. Unease about the impairment of psychological development by lead helped to diminish its role as a fuel additive. The carbon monoxide standard prescribed by the Environmental Protection Agency (EPA) is based partly on behavioral data. These issues and questions become clearer in the context of specific substances. I've chosen, from many possibilities, a set of agents meant to illustrate the diversity of settings, issues, and contaminants that entail psychological questions.

I will begin by discussing metals, because they are the most ancient pollutants released by human activities. Metallic mercury demonstrates the importance of quantitative measures of motor function in assessing subclinical impairment, as well as the lack of sound psychophysiological data about the total syndrome of mercury poisoning. Methylmercury, a highly toxic organic compound of mercury, illustrates the discipline and problems of behavioral teratology, that is, the consequences of prenatal toxic exposures. Another metal, lead, shows how difficult it still is, even after an immense outpouring of research, to disentangle toxic behavioral consequences from other environmental variables and to relate them to appropriate biological measures of exposure. Organic solvents illustrate even more graphically the issue of quantifying nonspecific neuropsychological features of toxicity, especially early in the course of poisoning when many of them are likely to be subjective. They also demonstrate how psychological approaches such as psychophysics could help detect and trace subtle sensory impairment. A discussion of pesticides shows how monitoring adverse effects by psychological measures may yield more information than monitoring them by blood chemistry. Air pollutants are used to exemplify a class of contaminants whose effects may not lie directly within the nervous system; in some instances, these effects are best revealed by behavioral methods. Finally, in a discussion of food additives, I try to show how the neglect of behavior in safety testing has provided misleading estimates of safety margins.

Metals

Metals are so ubiquitous that many of them came to play essential roles in the evolution of living systems (Weiss, 1978a). Other metals, perhaps because of their geological distribution, remained outside the orbit of living processes. But all metals, even the essential ones, can be toxic, and the margin between essential and hazardous levels may be surprisingly narrow. Manganese and vanadium are both essential elements, yet they have been implicated in syndromes ranging from movement disorders resembling parkinsonism to manic-depressive psychosis. Excessive exposure to metals can damage many different organ systems and biological processes and has been implicated in a remarkable range of adverse signs and symptoms involving the central nervous system (CNS) and behavior (Figure 1).

Mercury

Among the best documented entries in Figure 1 are those associated with mercury. This slippery, silvery metal, liquid at room temperature, is one of the metals exploited by humans since antiquity. Its toxicity has been recognized almost as long (Maurissen, 1981). The cardinal sign of mercury-vapor poisoning is tremor, which begins to develop around the eyelids and eventually invades the limbs, especially the hands. Inorganic mercury compounds at one time were used to prepare animal hairs for felt hats. These processes released mercury vapor into the factory atmosphere, exposing workers to concentrations above the safety limits prevailing at the time. Since Danbury, Connecticut, was the center of the industry, the mercury-induced tremors came to be known as "hatter's shakes" or "Danbury shakes."

Mercury has many other applications: as electrodes in the chlor-alkali process for producing chlorine and caustic soda from brine, in electrical equipment, in dental amalgams, in chemistry laboratories. In 1970, we encountered an instance of mercury poi-
One of the women, who had worked at the job for 15 years, was almost disabled by the severity of her tremor, and could hardly hold a glass of water without spilling. Because we already had embarked on a study of mercury-induced tremor in monkeys, and had a method available for measuring it, we were asked to help quantify the tremor to better monitor the course of treatment and recovery. The patient placed her finger in a lucite trough attached to a strain gauge and tried to apply a force between upper and lower bounds (10 and 40 grams) designated by lights on a signal box (Wood, Weiss, & Weiss, 1973). At first, tremor amplitude was remarkably high. The output of the gauge was amplified, traced on a polygraph, and transmitted to the analog-to-digital converter of a computer for quantitative processing. After nine months without further exposure, both the mercury levels in her blood and the tremor fell to normal levels. There was a marked change in other characteristics of the tremor as well. Early in treatment, the spectrum of tremor frequencies showed multiple modes. Nine months later, it was marked by a single dominant frequency.

Psychologists would hardly find it surprising that we felt it necessary to record, quantify, and analyze the extent of this motor deficit. Psychologists have quantified motor function in contexts ranging from infant development to human engineering to the effects of brain lesions in monkeys. Clinical medicine, in contrast, typically evaluates tremor by visual inspection and interprets it according to the physician’s experience. The unsuitability of clinical criteria led Langolf, Chaffin, Henderson, and Whittle (1978) to adapt our technique for monitoring chlor-alkali workers exposed to mercury. Now that exposures in dental offices and laboratories are coming under increased scrutiny, psychologists might be asked what other measures of psychophysiological function might help detect subclinical toxicity. This is an important question not only in itself, but because such measures could help to identify some sources of the psychological complaints accompanying mercury intoxication. These complaints are an intriguing feature of mercury poisoning and form a distinct enough cluster to have been given a label, erethism, a word from a Greek root meaning “to irritate.” The characteristic features of erethism resemble what psychiatrists used to call neurasthenia. Hatter’s shakes were typically accompanied by erethism. Wright’s (1922) survey of 108 hatters turned up 53 with symptoms such as irritability, timidity, apprehension, restlessness, vasomotor disturbances, easy blushing, exaggerated reflexes, and slight speech abnormalities. Improvisational questionnaires and clinical medical surveys cannot substitute for careful psychometric and psychophysiological measures of symptoms, but current workplace standards are based on the former kinds of clinical data.

Another aspect of mercury poisoning provokes even more serious questions. Methylmercury, an organic compound of mercury, was first synthesized during the 19th century. It proved to be a potent nervous system poison but also an extraordinarily effective fungicide, especially in protecting seed grains, and it dissipates into the soil once the seeds are planted. Great Britain encouraged its use during World War II to ensure abundant grain crops. No
one conceived of it as an ecological hazard until the 1950s.

Minamata is a small fishing village on Kyushu, the southernmost of the major islands of the Japanese chain. Beginning about 1953, inhabitants of the area were attacked by a central nervous system affliction that came to be known as “Minamata disease.” The villagers called it Kibyo, or mystery illness, because no etiologic agent could be found. They did discover, however, that neurological abnormalities were induced in cats fed fish and shellfish from Minamata Bay. Minamata disease finally was traced to methylmercury contamination of seafood from the bay (Tsubaki & Irukayama, 1977). A search for the source of the organic mercury led Japanese scientists to a factory that used inorganic mercury as a catalyst. The factory dumped its effluent into the bay, but only after adventitiously converting the mercury into the potent organic form, which then was incorporated into the food chain and finally consumed by humans (Smith & Smith, 1975). A decade after Minamata, a similar epidemic erupted in the city of Niigata.

Until 1970, North America perceived such episodes as remote aberrations. Then a graduate student at the University of Western Ontario discovered that fish in the Great Lakes bore unexpectedly high levels of methylmercury. His disclosure instigated a survey of contamination in the United States, which found that fish and wildlife in half the states carried excessive levels of methylmercury. Even oceanic fish like tuna and swordfish, once thought to be free of contamination, revealed puzzlingly high concentrations of methylmercury, and swordfish were barred from interstate commerce. As governmental agencies sought to assess the extent of hazard, we became aware of how little was known about this substance. Our information came from a handful of rather crude laboratory animal studies, a few industrial accidents, and scattered disasters like Minamata. It was not a satisfactory basis for erecting safety standards.

When exposure standards are proposed for environmental toxicants, they incorporate a safety margin broad enough to reduce the community’s risk to acceptable levels. Methylmercury cannot simply be banned; the methylmercury in fish, particularly marine species, is partly the contribution of geologic sources. Some of the methylmercury in freshwater species may be the contribution of acid rain, which promotes the uptake of the poison by lowering the pH of the aquatic environment. Calculations of safety margins determine which species from which areas can be marketed. But safety margins set on the basis of function are difficult to calculate, and the chief expressions of methylmercury poisoning arise because it destroys brain tissue, leading to sensory, motor, and nonspecific functional deficits.

Paresthesias (numbness and tingling) in the extremities and around the mouth seem to be the earliest symptoms of intoxication in adults. They are difficult to quantify, however, and their baseline prevalence varies markedly among populations. Visual deficits also are early features of intoxication, and they arise from cell death in the occipital cortex. Victims experience constriction of the visual field (tunnel vision) and allied deficits such as loss of night vision. Such deficits have been reproduced in monkeys trained on various visual discrimination tasks (Berlin, Grant, Heilberg, Hellstrom, & Schultz, 1975; Evans, Laties, & Weiss, 1975; Merigan, 1980; Rice & Gilbert, 1982). Psychophysical experiments with primate species were adopted as a strategy for correlating exposure variables, brain damage, and performance because the literature of neuropsychology provided a firm guide for asking such questions. It told us what visual dysfunctions arose from occipital lesions and convinced us that only primates could provide adequate animal models to the symptoms that arise in humans.

Minamata also suggested that methylmercury damaged the fetus far more severely than the adult, a suggestion consistent with other findings about the enhanced susceptibility of the developing brain to toxic challenges such as alcohol. Teratology is the discipline that studies what in lay terms are called birth defects. Like toxicology, it had emphasized morphology. With the realization that postnatal consequences might be expressed as functional rather than structural aberrations, a new discipline began to emerge: behavioral teratology. Its role is exemplified by a question once put by David P. Rall, director of the National Institute of Environmental Health Sciences and of the National Toxicology Program. Suppose, he asked, that the drug thalidomide, instead of inducing missing limbs and other deformities, had simply lowered intellectual potential by the equivalent of 10 IQ points. Would we ever have become aware of any adverse consequences? Given the difficulty of connecting even gross morphological consequences with thalidomide, the answer is disquieting enough to have provoked several countries into requiring behavioral teratology data for new drugs.

A later methylmercury episode provided the most cogent confirmation of what had been suggested by Minamata. In the winter of 1971–1972, the government of Iraq ordered 80,000 tons of seed grain (wheat, barley, and rye) from Mexico and the United States, specifying that it be treated with a methylmercury fungicide. Much of the grain was distributed to Iraqi peasants after the planting season, however. Although the farmers were told that the grain had been treated with a poison, many were skeptical of the government’s warnings. The bags were marked as poisonous, but in Spanish and English. Some of the farmers washed off the pink dye that identified the treated grain, a maneuver that did not remove
the fungicide. Other farmers conducted some primitive toxicology, feeding the grain to farm animals, or in one case, to the farmer's mother-in-law, without observing toxic signs. They were misled by the latency of several weeks before overt signs of poisoning would manifest. The aftermath was a probable loss of about 5,000 lives, with perhaps 10 times that many persons seriously poisoned.

Thomas W. Clarkson, a widely recognized expert on mercury toxicology, and other members of the University of Rochester faculty were called on to assess the episode in collaboration with Iraqi physicians. The scope of the poisoning permitted them for the first time to construct dose-response functions based on population samples of reasonable size (Clarkson & Marsh, 1976). These largely confirmed the profile of adult disabilities traced at Minimata and Niigata. Their assessments of fetal exposure, however, greatly magnified the concerns engendered by Minamata.

Minamata mothers who had experienced only minimal symptoms, such as paresthesia, delivered infants who later exhibited appreciable developmental retardation. There, however, the number was so small that a definitive assessment was impossible. Iraq provided more compelling evidence. A sensitive analytical method for measuring organic mercury in tissue permitted the Rochester scientists to trace the course of exposure in pregnant and nursing women. Hair grows at a rather constant rate, about one centimeter per month. Hair also serves as one of the elimination pathways of methylmercury, maintaining a fairly stable ratio of about 250:1 (hair:blood). By chopping the hair into centimeter sections, it was possible to determine when the mother began eating the tainted bread, when she reached her peak body burden, when ingestion stopped, and the subsequent decline of body burden. Since maternal milk also contained methylmercury (in a concentration about 3% of the blood level) infants could consume considerable quantities. And in the Iraqi countryside, children are often fed at the breast until two years of age.

Once appropriate mother–infant pairs were identified and documented, Rochester and Iraqi observers began periodic visits to the countryside to record the development of the children. Although the kind of rigorous evaluation that might be performed in the United States was not feasible, the 93 children under surveillance already have answered the most pressing question. Even at relatively modest maternal blood levels, the offspring may be significantly retarded, showing delays in speech, motor function, and other indexes of development (Clarkson, Cox, Marsh, Myers, Al-Tikriti, Amin-Zaki, & Dabbagh, 1981). Whether because of special vulnerabilities intrinsic to the developing brain or the metabolic defenseslessness, so to speak, of the fetus and neonate, the ecological hazard of methylmercury is amplified in the young organism. Moreover, if Minamata and several laboratory animal studies (e.g., Bornhausen, Musch, & Greim, 1980; Eccles & Annau, 1982; Spyker, 1975) are reliable guides to the future, the disabilities may become even more pronounced as the children age. Now that these Iraqi children are being increasingly challenged in school, it is more critical that they be evaluated by the best contemporary techniques because there are many areas of the world whose inhabitants consume large quantities of fish containing substantial concentrations of methylmercury. To set standards requires us to determine exposures producing subtle, not overt, impairment. What techniques might be suitable for assessing rural children in an Arab country or in comparable non-Western settings? The ingenuity of current developmental psychology is sorely needed for these important issues—issues about safety margins that continue to arouse concern by the U.S. Food and Drug Administration, the World Health Organization, and many governments. This concern stretches across almost the entire spectrum of environmental contaminants, including the polychlorinated biphenyls (PCBs) and the currently notorious dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin, or TCDD).

**Lead**

Mercury may be the most dramatic neurotoxic heavy metal, but lead is just as ancient, equally subtle, and more dispersed in the environment. Its reproductive toxicity has been held responsible for the decline of Roman hegemony, since the Roman nobility stored wine and preserves in leaden casks and even added lead compounds as sweetening agents (Gilfillan, 1965). Lead was first exploited so long ago that occasional skeletons from the oldest civilizations may reveal signs of excessive concentrations of lead. It is now distributed so pervasively through the environment (and living tissue) that we can only guess at what the early evolutionary load might have been.

Overt lead toxicity in adults takes a multifaceted form. Stomatitis and colic are prominent in acute or subchronic poisoning. Neurological and psychological features prevail in low-level, chronic intoxication. Wrist-drop and foot-drop, once frequent among painters and other exposed workers, now are rare because of improved industrial practices and increased alertness to toxicity. But more subtle indexes of impairment are still detectable with precise psychological and neurological testing, even in workers displaying no clinical dysfunction and carrying body burdens well below the values previously associated with toxicity (Hanninen, Mantere, Hernberg, Seppalainen, & Kock, 1979; Valciukas, Lilis, Eisinger, Blumberg, Fischbein, & Selikoff, 1978).

Our concerns about lead, however, stem mainly from the amplified connection between exposure and
consequence in the developing human. Even in the superficially clean setting of the suburbs, children exhibit body burdens of lead many times higher than those revealed by human skeletons in eras before the development of mining and smelting. Public health concerns are aroused even more in the aging cores of central cities, where the interiors of many buildings were once covered with lead-based paints, where street dust contains the combustion products of leaded gasoline, and where many children manifest lead body burdens uncomfortably close to overtly toxic levels. Most communities and their health agencies are now alert to the hazard of lead poisoning. Peeling, flaking surfaces are repainted, blood lead determinations are routine, and pediatricians are more prone to intervene with drugs that accelerate lead excretion. But the dispute about what constitutes a hazardous body burden has only become more intense because the focal question is now more subtle: Do asymptomatic but elevated body burdens of lead express themselves as psychological or behavioral impairment? Is there a threshold for toxic effects? The economic implications of what is defined as a “safe” level impinge not only on gasoline refiners, owners of urban real estate, and lead battery manufacturers, but on public agencies, because too high a level and its psychological aftermath also is costly to society (Provenzano, 1980).

Despite a plethora of studies dating from the provocative paper of Byers and Lord (1943), who reported persisting behavioral deficits after recovery from lead poisoning, the issue has been drifting toward resolution with frustrating slowness (Bornschein, Pearson, & Reiter, 1980a). Many studies have been flawed by inadequate control groups, by inappropriate tests, by mistaken assumptions in their statistical analyses. Many also were hampered by two fundamental biological problems. One is the lability of blood lead concentration, which reflects only recent exposure but which typically has served as the biological index of lead exposure. If peak intake occurs between the ages of 12 and 36 months, when children explore the world with their mouths and their nervous systems are still immature, how useful is it to correlate test performance with blood lead at age six or older? The second problem arises from the distribution of susceptibility. Especially when the questions center on threshold, is it not reasonable to expect only a modest proportion of children to demonstrate adverse effects?

Yet, despite these obstacles, objections, and flaws, a consensus is developing that current lead exposure indicators disclose a problem at even relatively modest values. One recent contribution was particularly provocative. Needleman, Gunnoe, Leviton, Reed, Persie, Maker, and Barrett (1979), recognizing the inherent defects of many earlier studies, turned to teeth as a biological indicator. Deciduous teeth, like bone, serve as lead repositories because dentine incorporates lead as it grows. An analysis of baby teeth, then, provides an integrated index of exposure during the early years. Needleman and his group collected teeth from over 3,000 children in the Boston area. They then selected children from the lowest and highest deciles and subjected them to a broad psychological evaluation. The high-lead children had lower scores on many dimensions: intelligence test scales, psychomotor performance, and conduct. All of the children who contributed teeth also were rated by their teachers according to a standard inventory. Perhaps the most intriguing section of the entire study is the striking relationship between scores on individual inventory items and tooth lead concentrations. Systematic observation in the classroom, using the techniques developed by applied behavior analysis, is also a fruitful approach (Needleman, Note 1), yielding even more convincing relationships. Even so, some observers are unhappy about the possible influence of family social and economic status and parental intelligence on the observed differences, contending that treating these as covariates and compensating for them statistically is not sufficient. For example, although Winnieke et al. (1983) essentially verified Needleman et al., they found that social class played a statistically significant role in performance differences. Winnieke (Note 2) also has found, however, that lower social class enhanced the risk of adverse effects from lead exposure, a finding parallel to those from the malnutrition literature. Such interactions are a crucial argument for behavioral assessments. Recent advances in psychometric techniques, such as structural equation methodology, have not been enlisted in pursuing these questions. Since both causes and consequences are surely multivariate in character, such techniques could give a unique perspective on the issue.

The difficulties posed by studies of human populations make well-designed animal experiments that much more crucial. Although many earlier animal experiments suffered from major problems such as reduced food intake in exposed animals, most current researchers now carefully limit lead intake so as to eliminate undernutrition and, incidentally, to produce more realistic body burdens of lead. Even with these precautions, it is clear that a legacy of elevated lead during development portends significant behavioral disruption. Rice, Gilbert, and Willes (1979) detected several subtle signs of deviant performance in rhesus monkeys treated from birth to achieve blood levels within the range of values displayed by a significant proportion of urban children. For example, performance on fixed-interval schedules of reinforcement was marked by high rates of responding, interrupted by long pauses, in the treated monkeys. Cory-Slechta and Thompson (1979) reported that low concentrations of lead in drinking water consumed by young,
weanling rats produced aberrant fixed-interval performance. Serial measures of blood lead, in a systematic replication of this study (Cory-Slechta & Weiss, 1982), indicate that such aberrant performance occurs at concentrations approaching those of even many suburban children. Only a handful of properly conducted studies now exist in the published literature (Bornschein, Pearson, & Reiter, 1980b), representing a tiny fragment of behavioral techniques with obvious potential in this research. Schedule-controlled performance, for example, has been exploited only minimally (Bornschein, Pearson, & Reiter, 1980b).

Solvents and Fuels

Volatile organic solvents and fuels are traditional occupational hazards because exposure mostly occurs through inhalation, an exposure medium difficult to control. The American Conference of Governmental Industrial Hygienists (ACGIH, 1978), which publishes assessments of and recommendations for exposure standards in the workplace (threshold limit values), defines the "short-term exposure limit" as: "the maximal concentration to which workers can be exposed for a period up to 15 minutes continuously without suffering from 1) irritation, 2) chronic or irreversible tissue change, or 3) narcosis of sufficient degree to increase accident proneness, impair self-rescue, or materially reduce work efficiency . . ." (p. 2).

The number and variety of volatile agents able to exert potent central nervous system and behavioral effects is staggering. Most dissolve easily in fat, a property that enhances their penetration of the blood-brain barrier. These agents are used in extraction processes, degreasing formulations, refrigerants, paint and lacquer thinners, glues, printing, electrical insulators, fumigants and pesticides, synthetic fiber production, and other industrial applications. Many appear in consumer products. Synthetic fuel technologies are certain to multiply both applications and exposures. Yet, even with their venerable history and broad industrial penetration, the exposure standards for these salient neurobehavioral poisons spring mainly from clinical observations and inchoate epidemiology. A few examples illustrate the breadth of psychological questions and issues that they have prompted.

Carbon Disulfide

During the cold curing of rubber, especially useful in the manufacture of surgical appliances, thin strips of rubber were dipped into a special solution containing the solvent carbon disulfide (Hunter, 1969). Prevalent in France in the middle of the 19th century as a cottage industry, this process subjected thousands of workers to consequences as diverse as mania, headache, irritability, and polyneuritis. Delpech's precise depiction in 1856 of carbon disulfide poisoning as a toxic neuropathy was challenged in 1889 by Charcot, one of Freud's most influential mentors, who ascribed most of these signs and symptoms to his specialty, hysteria. Toward the end of the century, carbon disulfide assumed an even more important industrial role with the introduction of the viscose process for manufacturing rayon, which liberates carbon disulfide vapor into the workroom atmosphere. About 350 million kilograms of carbon disulfide were produced in the United States in 1974, but its role in commerce is not reflected by the volume of laboratory research devoted to it (Levine, 1976; Weiss, Wood, & Macys, 1979; Wood, 1981).

Severe neurological impairment, however, is no longer an issue because regulations in the United States and other nations limit exposure. Questions about hazards now center on the potential for subtle psychological and neurological impairment. Even the issue of elevated suicide rates in viscose workers has been raised (Mancuso & Locke, 1972). One of the pioneering applications of psychological testing to questions stemming from industrial exposure was undertaken in Finnish viscose workers by Hanninen (1971). She appraised three groups of workers, 150 in total. One third had manifested overt features of carbon disulfide toxicity, one third had been exposed without clinically detectable toxicity, and one third had been exposed occasionally or not at all. Hanninen subjected each worker to a psychological test battery comprising the Wechsler Adult Intelligence Scale, several psychomotor tests, and even the Rorschach. To evaluate the pattern of differences, she performed a multivariate analysis that helped define three clusters. Adding indexes of disturbed ocular microcirculation and coronary heart disease to the neuropsychological findings further enhanced the separation of exposed and control workers (Raitta & Tolonen, 1980). Workers with clinical deficits were clearly different from the others, but even the workers without clinical manifestations showed some evidence of impairment and could be distinguished from the unexposed workers. Research groups in the United States, Italy, Scandinavia, and elsewhere have since adopted similar approaches to assessing the long-term consequences of occupational exposure to solvents. Scandinavian investigators, in fact, now accept the validity of an "organic solvent syndrome" that embodies features such as depression, retardation of movement, and electrophysiological abnormalities. The issues involved here are not just current standards of exposure, but, for example, the validity of a claim that 20 years of employment in a certain industry has led a worker to exhibit destructive personality changes. Such claims are now being presented to the courts where, I am certain, clinical psychologists will be called as expert witnesses.
Toluene Solvents and Axonopathies

Toluene (methyl benzene) also is produced by the millions of kilograms, finding its way into many products and processes. Unlike some other solvents closely related to it chemically, it seems not to present major threats to any organ system (such as the liver) or to be linked to cancer. Like other volatile solvents, however, its CNS properties can be abused. It is the main solvent in the model glues inhaled by U.S. teenagers for their intoxicating properties, and upon which even very young children in some countries have become dependent (Sharp & Carroll, 1978). Glue-sniffing is not exclusively a teenage practice, however. It also has exacted victims in the workplace. Vinyl chloride is a major industrial chemical, serving as an intermediate in the production of the ubiquitous polyvinyl chloride. It had been assumed to be relatively safe until incriminated in a series of worker deaths from a rare fatal liver tumor and then, later, in other forms of cancer (Selikoff & Hammond, 1975). Since occupational epidemiology proceeds by trying to quantify exposure, investigators requested estimates of exposure from industrial hygiene and safety personnel in 33 plants, grading the exposures as low, medium, or high. Adding to the intrinsic variability of such estimates were a few unique practices, however, as described in a pioneering source of pharmacologic information:

Inevitably, some of the guys came to enjoy getting high on vinyl chloride. They would lean over into the vats and breathe deeply . . . and then do it again. “Some would become like alcoholics,” says one longtime Goodrich worker. “They would breathe it again and again until they passed out.” (Klein, 1976, p. 44)

Substance abuse, particularly of drugs, has enlisted the efforts of many psychologists, especially those specializing in behavioral pharmacology. Their research has demonstrated that drugs of abuse are self-administered for their reinforcing properties, not simply, say, to attenuate aversive withdrawal symptoms. These demonstrations have been so cogent, in fact, that self-administration data are required by regulatory agencies such as the Food and Drug Administration for evaluations of new drugs, such as analgesics, that pose the threat of abuse liability. The widespread availability of intoxicating solvents is a cogent reason for investigating their abuse potential as well, and for taking measures, equivalent to denaturing alcohol, to reduce this potential. Since primates self-administer inhalants such as nitrous oxide (“laughing gas”; Wood, Grubman, & Weiss, 1977) and toluene (Wood, 1979), we have available a model system, based on a behavioral assay, for testing both abuse liability and possible countermeasures. Biochemical assays cannot answer such a question.

Solvents and Axonopathies

The ultimate dangers of solvent abuse were highlighted by chronic solvent sniffers in Europe and Japan who developed severe neuropathies from their habit. Most of their problems arose from the solvent n-hexane, found in glues and petroleum ether. It is not an extremely toxic material, but the high concentrations to which the sniffers repeatedly exposed themselves exacted a price. These events triggered investigations into the underlying mechanisms, and the discovery that the neurotoxicity of n-hexane is actually a property of a metabolite, 2,5-hexanedione.

U.S. interest in this property quickened after an episode in Columbus, Ohio (Allen, Mendell, Billmaier, Fontaine, & O’Neill, 1975). In June 1973, a 43-year-old man was admitted to the neurosurgery service of Ohio State University Hospital. He worked in the printing department of a coated fabrics plant. About four months after becoming a printer operator he began to suffer symptoms such as weakness, stiffness, and difficulty in walking. On examination, he was thought to have either a motor neuropathy or motor neuron disease. Two months later, during a second visit, he produced a list of five fellow workers with similar complaints. Suspecting a toxic etiology, the alert physician contacted the Ohio Department of Health, which confirmed the five additional cases. All six patients worked in the same plant and in the same area. The plant manufactured vinyl-coated fabrics and vinyl sheets used for wall coverings or automobile interiors. Men in the printing department were exposed to inks and solvents containing methyl ethyl ketone (MEK) and methyl n-butyl ketone (MBK). Not only did they breathe the fumes evaporating from the printed fabrics and from the machines, but washed their hands or shoes in the solvents, and even ate in the work area.

As intoxication progressed, both sensory and motor deficits appeared. The sensory symptoms typically began with paresthesias in the hands and feet. Motor deficits usually began later, and were marked by weakness of the intrinsic muscles of the hands and feet. With some skillful chemical analyses, sensitive epidemiology, and luck, MBK was incriminated as the source of the outbreak and 2,5-hexanedione isolated as one of its metabolites. At the time, the threshold limit value for MBK was 100 parts per million (ppm). It is now 25 ppm. The National Institute for Occupational Safety and Health has recommended a reduction of the 10-hour, time-weighted concentration to 1.0 ppm.

This history is not meant as a discourse on epidemiology. I recited it because it is a cogent example of the way in which early toxic manifestations tend not to arouse suspicions because of their subtle and nonspecific nature. Psychology, however, has tools that
could enable it to specify the nonspecific (Weiss, 1983). MBK, n-hexane, and many other agents display a commonality of effects on peripheral nerves often labeled as a “dying-back” neuropathy or as a central–peripheral distal axonopathy (Schaumburg & Spencer, 1979), because CNS tissue also is damaged. Retrograde axonal degeneration, beginning at the distal end of the nerve, gradually advances centrally, with the longer, larger, myelinated fibers degenerating before the shorter, smaller diameter fibers. The experimental data have been accumulated mainly to verify the neuropathologic mechanisms, and few behavioral data have been published that could yield clues about the correspondence between the early sensory changes and their neuropathologic and histochemical accompaniments. Moreover, the sites of central damage, including the hypothalamus, suggest that even more subtle, psychophysiological aspects of toxicity would emerge with appropriate experiments (Schaumburg & Spencer, 1978).

One reason that specific functional deficits may remain undetected is the typical neurological or medical examination, which is directed not toward the detection of subtle impairments but toward the diagnosis of frank disease. An example of how easily incipient sensory impairment could escape clinical scrutiny comes from an experiment on acrylamide, a chemical adopted for applications ranging from grouting in mine and tunnel construction to strengthening cardboard to helping to separate solids from aqueous solutions. Because it creates distal axonopathies and is easily administered in food or drinking water, it often serves as a prototypical neurotoxicant (Tilson, 1981). Maurissen and Weiss (1982) trained monkeys to discriminate vibratory stimuli applied to a finger. The monkeys, seated in a special Plexiglas enclosure during testing, released a lever when they detected vibration applied to a finger by an electromagnetically driven rod. The sense of touch is so sensitive that the amplitude of vibration had to be controlled to tenths of a micron. Chronic acrylamide treatment gradually raised the threshold for vibration for both low- and high-frequency stimuli, a shift that did not dissipate for many months after treatment ended. Consider how a neurological examination might assess decreased somatosensory sensitivity. The patient would be asked to report a pin or cotton wick lightly contacting the skin, or a tuning fork pressed against it. Even with a tuning fork, the most quantitative of the methods, only one frequency would be explored and its amplitude would be controlled only in the grossest sense. A recent publication (Merigan, Barkdoll, & Maurissen, 1982) suggests another easily ignored effect of acrylamide. These experimenters trained monkeys to discriminate gratings on the face of an oscilloscope to assess the intactness of spatial frequency mechanisms. Such fundamental mechanisms are believed by many visual scientists to underlie the discrimination of complex visual stimuli. Averaged visual-evoked potentials, generated by similar stimuli, also were examined. The monkeys received acrylamide until they began to show clear signs of toxicity. Once dosing ceased, the animals recovered in all functions but one—visual acuity. Their ability to resolve high-frequency gratings (narrow, closely spaced bars) remained impaired, probably because of irreversible damage in the optic tract. This is just the kind of effect that a worker would not notice and that a clinician would be unlikely to detect. Animal psychophysics has now alerted us to this possibility. These two examples indicate to me that psychophysical methods, reflecting the elegance and precision developed by several generations of psychologists, should be the ultimate arbiters of incipient sensory system toxicity, especially if toxicity, should it occur, is to be arrested during its early, reversible phases. Some industrial organizations agree and are adopting vibration sensitivity as a guide to excessive acrylamide exposure. But two studies hardly comprise a literature.

Pesticides

Almost every major pesticide acts by inducing neurotoxicity. It is not surprising, then, that pesticides offer similar hazards to humans. The literature accumulated around this problem embraces nearly every technique found in psychology. As with many of the substances already discussed, the core argument is not about hazard, but about the extent of risk. It is a debate about dose—about how much exposure is a threat to health. It is a debate locked into ambiguity, as with lead, because the end points are so intangible. Consider how difficult it is to gauge whether farm workers exposed to low levels of pesticides suffer from subtle behavioral or neurological deficits. It is not just defining what constitutes a deficit or applying appropriate methods that present the challenge, but also detecting a progression so subtle and vague that it is ignored.

An instructive episode occurred in the 1970s. The pesticide and pesticide precursor Kepone (chlordecone) had been manufactured until 1973 by Allied Chemical Corporation. Production was then transferred, at the same site, to a newly established firm largely operated by former Allied employees. In 1975, an alert internist in Hopewell, Virginia, the site of the plant, examined a patient with severe tremors. He requested that the Center for Disease Control, the federal government’s main agency for epidemiology, analyze a serum sample for Kepone. It proved to be markedly elevated (Cannon, Veazey, Jackson, Burse, Hayes, Straub, Landrigan, & Liddle, 1978), a result that stimulated investigations by both state and federal agencies. Inspectors found massive contamination at
the site and indications of widespread toxicity. The major expressions consisted of nervousness, tremor, incoordination, weight loss, skin rash, sterility, abnormal liver function parameters, ocular flutter, and joint and pleuritic pain. Personality changes also occurred, marked by irritability, problems with recent memory, and depression, but not every worker showed the same collection of signs and symptoms. The Hopewell situation is uncommon because the exposure was so severe. Until the internist forwarded the blood sample for analysis, however, neither management nor the workers raised the issue of toxicity in public. There was convincing evidence, too, that exposure to lower levels of Kepone could induce toxic responses. Two wives of workers reported histories of tremor, presumably arising from dust carried home on their husbands’ clothing. The neurotoxic manifestations of Kepone stimulated a literature on the mechanisms of toxicity that is still expanding vigorously (Tilson & Mactutus, 1982).

Other pesticide classes (Kepone is an organochlorine and a distant relative of DDT) present different profiles of toxicity. The organophosphate insecticides, chemically related to the most potent war gases, act by inhibiting the enzyme acetylcholinesterase, which inactivates the neurotransmitter acetylcholine after its release into synapses. Nervous tissue levels of acetylcholinesterase are so redundant that, in many circumstances, they can be reduced by two thirds without notably impairing function. Also, tolerance quickly develops in rats to the acute behavioral effects of organophosphates (Bignami, Rosic, Michalek, Milosevic, & Gatti, 1975). But is this true of the skills required by crop-duster pilots whose blood levels of cholinesterase may have been reduced to one fourth of normal? Duffy and Burchfiel (1980) reported enduring EEG abnormalities in workers exposed during manufacture to the organophosphate war gas sarin. Some organophosphates also induce structural damage, a property responsible for several tragic outbreaks of neurotoxic poisoning (Morgan, 1982).

The organophosphate pesticide leptophos (Phosvel) was implicated in a revealing outbreak. Exposed workers in a Texas manufacturing plant (Xintaras & Burg, 1980), experiencing toxic reactions, consulted private physicians, who were puzzled by the peculiar constellation of signs and symptoms. These included anxiety, hallucinations, impaired memory, disorientation, drowsiness, headache, tremulousness, dizziness, paresthesias, diminished muscle tone, and ataxia. Although organophosphate intoxication seemed a possible cause, cholinesterase activity in the blood remained within normal bounds, leading the neurologists to suspect encephalitis or a demyelinating disease such as multiple sclerosis. This is a good illustration of how total reliance on an indirect chemical or biological measure can lead an inquiry astray. Only after they had weighed the delayed neurotoxicity characteristic of some organophosphates did the correct diagnosis emerge. In reviewing this episode, Xintaras and Burg (1980) note that, “The onset of some effects, in fact probably most of the effects, is so insidious that the worker may not realize that any change is taking place. The insidious nature of the effects makes base-line data, taken at the beginning of employment and/or exposure to a suspected neurotoxic chemical, imperative to assess exposure effects” (p. 673). Given the leptophos and Kepone experiences, should not a large component of these data be psychological? Of course, but how many of our personality inventories, say, are suitable for the repeated screening of large populations? How often, in fact, do we ask such longitudinal questions, and what might we learn about the stability of psychological assessments over long time periods were we to do so? Such questions offer opportunities for advances in psychology independent of a contribution to toxicology.

Air Pollutants

The Clean Air Act evolved from public resentment of the esthetic unpleasantness and obvious health menace of polluted air. Some of the health implications are not so obvious, however, and constitute questions for behavioral toxicology. An agent need not act directly on the CNS to evoke behavioral effects. It could act as a distracting irritant, for example, or produce a nonspecific depression of function reflected in a diminished capacity to perform certain tasks.

Some examples of what could be such indirect effects can be drawn from claims in the Soviet literature. In studies performed by Bustueva and her co-workers (National Air Pollution Control Administration, 1970), humans exposed to sulfur dioxide, sulfuric acid mist, and other atmospheric pollutants were alleged to show altered sensitivity to light. For example, during the course of dark adaptation, elevated sensitivity (lowered threshold) was claimed to follow exposure to low concentrations of sulfur dioxide, sulfuric acid mist, and combinations of the two. More recent work by Bokina, Eksler, Semenenko, and Merkur’ yeva (1976) claims alterations in the EEG and visual evoked potentials from exposure to minimal concentrations of ozone. Like other Soviet claims, these are not accompanied by convincing technical details.

Carbon monoxide is one of the agents singled out for control by the Clean Air Act. It exerts its toxicity through its affinity for hemoglobin, which transports oxygen in the blood. Carbon monoxide displaces oxygen, combining with hemoglobin to form carboxyhemoglobin and to deprive tissues of oxygen. The blood of heavy smokers may contain carboxy-
hemoglobin levels of 5% to 7% or greater. A detailed review of the carbon monoxide literature by Laties and Merigan (1979) concluded that this level is close to the threshold for observing impaired vigilance performance. Areas of dense automobile traffic can produce high enough concentrations of carbon monoxide so that prolonged exposure (rush hour on the San Diego freeway, say) might push some drivers into that range. Many questions remain, however, about the adequacy of the data. Their resolution embodies decisions with considerable economic significance.

A neglected aspect of the response to air pollutants is what might be called subjective state, which is measured by psychologists to assess everything from the impact of psychotherapy to the effectiveness of advertising. Data from Great Britain, gathered before the radical cleansing of London air, indicated that chronic bronchitis patients experienced a heightened response to heavy smog. The response was reflected not so much by measures of pulmonary function as by subjective indexes of discomfort. Direct sensory irritation is yet another property of air pollutants mostly unexplored by precise behavioral measures, especially in the laboratory. Eye irritation, for example, may be the earliest sign of excessive concentrations of organic pollutants in smog. Alarie (1981) noted that 30% to 40% of all Threshold Limit Values and Federal Ambient Air Quality Standards are based on subjective reports of irritation. Regulatory decisions may be based on such data because complaints can serve as warnings of impending damage.

Behavioral measures assess a different facet of the adverse effects of airborne irritants than measures of lung function. Ozone is an intensely irritating gas and the principal oxidant in photochemical smog. At high concentrations, it severely damages lung tissue. At moderate levels, it may produce biochemical changes and reversible pathology in the lung. At lower levels, it may elicit complaints of discomfort ranging from chest pains to lethargy to confusion, as reported by air crews and passengers subjected to raised ozone concentrations during high-altitude jet flight. Since such subjective reactions may herald impending damage and are undesirable in themselves, we undertook to more carefully define the behavioral consequences of ozone exposure.

After first examining lever-pressing (relatively sedentary) performance in rats during ozone exposure (Weiss, Ferin, Merigan, Stern, & Cox, 1981), we turned to a venerable psychological tool, the running wheel (Tepper, Weiss, & Wood, 1983), because exercise enhances the toxicity of ozone. Rats were adapted to living in small enclosures attached to running wheels. For 12 hours every night, we recorded activity by attaching switches to the wheels and transmitting switch closures to an online computer. The rats were exposed to ozone during the middle six hours of this period. We confirmed the contribution of exercise to ozone toxicity. The rats reduced their activity significantly at concentrations of 0.12 parts per million, the EPA upper limit for human exposure, which is regularly exceeded in Los Angeles and elsewhere. They did so mostly by extending the pauses between successive bouts of running. In further experiments at this concentration, they reduced lever-pressing responses that released a brake from the wheel and fixed-interval-schedule running for food delivery (Tepper, Weiss, & Wood, 1983). We believe that these reductions reflect the aversive consequences of exercise during ozone exposure, not physiological impairment—in other words, avoidance behavior. Wayne, Wehrle, and Carroll (1967) posted a similar interpretation in a study of high school cross-country runners. They found high inverse concentrations between performance and oxidant concentration measured one hour before meets, and attributed their findings to what might be called diminished motivation rather than to diminished physiological capacity. Other inhalation toxicologists and respiratory physiologists have offered similar explanations for corresponding experimental data in humans (e.g., Folinsbee, Silverman, & Shephard, 1977). There are no human "motivational" data as we understand them, however, only the results of symptom questionnaires accompanied by measures by pulmonary function. In contrast, consider the volume of psychological research devoted to questions that logically are congruent with this one.

Direct sensory irritation can also be measured by behavioral methods, which provide different information than that provided, say, by reflex responses of the respiratory system. Regulatory actions depend on many sources of information about adverse effects. In its recommendations for future research, a report on air pollution states: "Photochemical reactions of vapor-phase organic pollutants produce irritating effects, but indices of such effects have received little attention. Experimental tests in animals and systematic studies of human reactions in normal and occupationally polluted atmospheres should be carried out" (National Research Council, 1976, p. 282). Psychologists are accustomed to measuring aversiveness. Wood (1979) adopted the tactic of training mice to terminate the flow of ammonia into a chamber by inserting their snouts into a metal cone equipped with photocells. Latency to respond was inversely related to concentration. The power of such techniques has led us to question the meaning of more traditional definitions of irritation based solely on pulmonary measures such as disruption of respiratory pattern. Humans will not tolerate such concentrations, and no review board would allow tests in humans of a newly synthesized agent anyway. Humans avoid or escape noxious airborne substances, and animal test-
Food additives may not superficially seem to have much in common with air pollutants and organic solvents, but they too have been alleged to elicit many psychological and neurological complaints. People do not complain, after all, of enzyme inhibition or receptor blockade; they complain of headaches, lack of energy, depression, and other symptoms with psychological content.

The possibility that food additives might prompt behavioral complaints and disturbances achieved almost no recognition in the biomedical community until Ben F. Feingold (1975) proposed that some of the children diagnosed as hyperactive or hyperkinetic actually suffered from idiosyncratic responses to such ingredients. Although the validity of Feingold’s claims is disputed, he introduced an issue whose connotations transcend the limited question of the etiology of hyperactivity (Weiss, 1982). Food additives are probably the most ubiquitous products of modern chemistry. Since 1958, they have had to undergo toxicity testing before market introduction. The test protocols emphasize pathology, especially cancer. They do not include testing for behavioral toxicity. A distinguished panel of toxicologists, reviewing current protocols for food additive toxicity testing, recommended, however, that “psychotoxicity” be considered for inclusion in such protocols (FASEB, 1977). This recommendation gains even more cogency from some of the findings that emerged from trials of the Feingold hypothesis and from experiments with animals demonstrating that young rats given food colors at levels prevailing in the human diet (see Table 1) display behavioral abnormalities (Goldenring, Wool, Shaywitz, Batter, Cohen, Young, & Teicher, 1980; Shaywitz, Goldenring, & Wool, 1979). The Food and Drug Administration, however, still does not require behavioral testing, in contrast with its reaction to the Canadian protocols for food additive toxicity testing, recommended, however, for them to be dismissed by special interests. A proposed rise in the allowable lead content of gasoline was stemmed by objections from scientists and physicians concerned about the behavioral consequences for children. Acid precipitation enhances the uptake of methylmercury by fish, posing the question of whether pregnant women should consume fish from Adirondack lakes. More and more data are now confirming the suspicion that even low levels of PCBs and other chemicals of that general class can produce subtle behavioral deficits, especially in the developing organism, and that breast milk, because of the lipid solubility of such substances, is the primary vehicle for neonatal exposure (Barlow & Sullivan, 1982). Government agencies have to determine how to quantify such issues, how to predict hazard to humans from animal testing, how to calculate risk on the basis of functional measures. Almost the total range of psychological techniques, specialties, and skills bears on these efforts.

Psychology is positioned to deal with many of the most troubling issues of environmental toxicology. Note the statements from a recent unpublished gov-

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government report on the potential health effects of toxic chemical dumps:

We do not have tests to recognize effects on the nervous system.

Another issue of concern in conducting epidemiological studies is to design survey instruments (questionnaires) which are resistant to the emotional issues involved.

There are virtually no useful tests for preclinical stages . . . and diseases of specific organ systems such as the central nervous system.

A few years ago at a regional meeting of psychologists, I delivered an address titled, "Help Wanted: 25,000 Behavioral Toxicologists." The title was not supposed to be wholly serious, but perhaps it was not such a gross exaggeration after all.

REFERENCE NOTES

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