Behavior as a Common Focus

of Toxicology and Nutrition

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Almost no one lacks an opinion about the current safety of our food supply, and almost never are the opinions vented without keen emotion. The public sways in rhythm to the debate, simultaneously poised to believe the worst and to ignore it. Toxicology and nutrition have become inseparable companions. Toxicology and nutrition, however, are coupled not only as adjoining facets of persistent conflict, but as sciences. Diet provides the path of entry for many potentially harmful substances. Nutritional status underlies and reflects many toxic disorders. And nutrient intake may enhance or diminish the impact of many toxic agents.

Toxicology and nutrition also share common themes. Both matured, from disciplines focused on blunt, direct measures of survival, to sciences concurrently peering into the molecular machinery of the cell and groping at elusive disorders of behavior. Nutritional science arrived at this perspective about behavior somewhat earlier, but the fledgling science of Behavioral Toxicology now is speedily closing in on its disciplinary counterpart -- what Josef Brozek once termed Psychodietetics.

Trying to portray the relationships among toxicology, nutrition, and behavior in a short paper is equivalent to depicting the round solidity of an apple on a flat canvas. You may admire its evocative qualities, but you can't get your teeth into it. But since my duty here is to evoke rather than to nourish, I will try to frame these relationships by discussing a selection of cogent examples. I will organize the discussion by category of toxicant.

Essential Nutrients

Toxicity is not confined to dietary intruders. Even essential components of the diet, in excess, can produce toxicity. Much of the public seems to

regard vitamins with the same linear optimism with which truck drivers perceive amphetamines; if one is good, ten are ten times as good. An overabundance of vitamin A, for instance, produces a characteristic toxic syndrome. Vitamin A can also exert toxic consequences in the fetus, some of which are not obvious without behavioral testing. Hutchings and Gaston (1974) administered 90,000 units of vitamin A to pregnant rats on days 17 and 18 of gestation. The offspring showed no retardation of growth or development; but, when tested later with various measures of operant performance, they responded at lower rates than controls. Subsequently, Vacca and Hutchings (1977) noted that cell proliferation in the developing cerebellum had been altered by vitamin A treatment.

Essential metals are also toxic when ingested in excess. Indeed, the margin between the critical minimum and incipient toxicity is remarkably small (Weiss, 1977). Manganese is an intriguing example because a deficiency of manganese is especially telling for the developing organism and its absence induces abnormalities in the vestibular system. Occupational exposure is our main source of information about the toxicity of excess manganese. In the manganese mining communities of South America, the early signs of toxicity are labelled locura manganica or manganese madness, because affected miners often show pathological laughter (Rawal, 1960). This phase of toxicity is succeeded by one whose salient features mimic those of Parkinsonism. Cotzias (1971) discovered that this syndrome could be treated by L-Dopa, now a prevalent therapy for idiopathic Parkinsonism. Neurochemical investigations have found manganese to induce depletion of dopamine in brain areas, like caudate, where it is a major neurohumor (Neff, et al., 1969). Despite its link to an active research area in neurochemistry, manganese has not been scrutinized more than superficially for behavioral toxicity.

Toxins

Biological poisons, those produced by plants and animals, abound in food (National Academy of Sciences, 1973). One well known to pharmacologists is ergot, the fungus claviceps purpurea, which may infect other cereal grains but is especially potent in rye. It ravaged medieval Europe, where it acquired the name Saint Anthony's Fire because of its vascular symptoms. Ergot is chemically related to LSD and is employed therapeutically to treat migraine. The early symptoms of poisoning are coldness and numbness of the extremities, and psychological complaints, indices that are not strikingly specific (Devitt, et al., 1970).

Tremorgenic mycotoxins are produced by many fungal species, some of which are common food contaminants. Steyn (1977) distinguishes two major classes of agents that act upon the CNS. One class is represented by citreoviridin, and produces ascending paralysis in experimental animals. The second class induces sustained trembling, and contains some members derived from tryptophan. Norris et al (1980) have demonstrated that two such tremorgenic mycotoxins, verruculogen and Penitrem A, isolated from Penicillium, act on central synapses responsive to amino acid transmitters. Behavioral studies performed by Sobotka et al (1978) indicate that these actions are reflected in functional disturbances.

Neurotoxic fungal products are not a problem disposed of in remote history. Wilson et al (1977) emphasize their relevance to health and nutrition, and urge a program to define the extent of contamination, the toxic

mechanisms, and their relationship to structure. Behavioral Toxicology can be a valuable contribution to such an effort, primarily because it offers a continuum of endpoints without which the relevant issues can be addressed only crudely. For example, minor changes in fine motor control by trained animals may be the best criteria for determining the most relevant neurochemical events that presage more gross neurologic and chemical phenomena. Gross toxicity, expressed either as death or as clear pathology, represents a stage of toxicity at which so many systems may be overwhelmed that any pursuit of specificity is fruitless.

Marine biotoxins pose a parallel set of questions (McFarren, 1971). Ciguatera poisoning (icthyosarcotoxin) is endemic in the central Pacific and Caribbean. It can be carried by hundreds of fish species and is undetectable without a bioassay. The source of Ciguatera toxin has been narrowed to dinoflagellates inhabiting coral reefs. Investigators in Hawaii discovered that the mongoose is sensitive to ciguatoxin, but it does represent a somewhat limited assay system. Ciguatera is economically important because it hampers the commercial exploitation of productive fishing areas. Since it produces symptoms of sensory neuropathy in humans, animal behavior tests would provide an appropriate measure of toxicity. Such a measure could help define rational action levels based upon a chemical assay, because such assays are developed more easily with a specific endpoint for guidance.

Cycads represent one of the most instructive and fascinating plant toxins because they originally were proposed as a potential explanation of why the indigenous population of Guam displays such a remarkable incidence of amyotropic lateral sclerosis (Kurland, 1972). Although a relationship was not

established, attempts to find one uncovered a potent neurologcal poison. Several groups of investigators have documented its capacity to impair nervous system development and to produce associated behavioral changes. Cycasin (methylazoxymethanol glucoside) and the acetate produce microencephaly in many species (Haddad et al, 1979), effects rather similar to those produced by ionizing radiation (Hicks and D'Amato, 1976).

Toxic Metals

Evolutionary processes incorporated some of the metals into living functions. The other metals play antagonists' roles. Except for circumscribed occupational exposures, much of their toxic threat is posed by their incorporation into food. Methylmercury is the most completely documented example.

During the early 1950s, the inhabitants of Minamata, a village on the Japanese island of Kyushu, suffered an outbreak of a mysterious neurological illness. The source of the illness finally was traced to the consumption of fish and shellfish from Minamata Bay that had been contaminated by methylmercury. The methylmercury had been discharged by a chemical plant that employed mercury as a catalyst in the production of acetaldehyde and vinyl (Tsubaki and Irukayama, 1977). Before that discovery, hundreds of people had been victimized. Some died. Others were maimed permanently. The reverberations of Minamata still linger (Smith and Smith, 1975). Almost 10 years later, a similar episode tormented Niigata, a city on Honshu, and from a similar source.

Methylmercury took on the status of a broad ecological threat with two scientific discoveries. First, the finding that inorganic mercury, like that

dumped into waterways by chlor-alkali plants, could be converted into the highly toxic methyl form by organisms in bottom sediment, and then ascend the food chain from plants and plankton to fish consumed by humans. Second, the reports that marine fish, especially predators such as tuna and swordfish, bore substantial body burdens of methylmercury even though there were no industrial sources in the ocean. These findings prompted many surveys of methylmercury contamination and questions about its toxic parameters.

Methylmercury is a potent CNS poison. It destroys brain tissue and leaves an array of neurobehavioral impairment (Figure 1). Among its most salient signs is concentric constriction of the visual field, sometimes progressing to the point of blindness. The distinctive topography of the human visual system makes nonhuman primates such as macaques, whose visual system structure and function is nearly identical to that of humans, the only feasible laboratory model. They show almost the same pattern of neuropathology, with cortical damage dominant and most prevalent in deep sulci such as the calcarine fisure. They exhibit peripheral constriction of the visual field, and impairment of form discrimination at scotopic luminance levels (Evans et al., 1975).

Our studies of visual impairment were aimed at the detection of incipient functional toxicity in adult organisms, a strategy that called upon joint assessments of behavior, pharmacokinetics, and histopathology. But the feature of methylmercury toxicity that commands the most current concern is perinatal susceptibility, and its consequences for the organism long beyond the period of exposure. Although the Japanese investigators of what came to be known as Minamata Disease postulated enhanced sensitivity by the fetus and

neonate, their data were slim, and derived from only a handful of cases. Dramatic confirmation came from an epidemic of methylmercury poisoning that struck Iraq in the winter of 1971-72.

The Iraqi government had ordered 80,000 tons of seed grain, consisting of wheat, rye, and barley, for the 1971 planting season. They specified that it be treated before shipment with methylmercury fungicides, which are quite effective. Much of the grain, largely from Mexico, arrived after the planting season, but was distributed to the Iraqi farmers with the injunction that it was not to be baked into bread. The warnings were not effective. Perhaps 5,000 Iraquis died, with ten times that many suffering severe poisoning. University of Rochester scientists, led by Thomas W. Clarkson, were asked to help, and began to document the extent of the tragedy (Clarkson, 1977).

Now, eight years later, the aftermath of that episode becomes increasingly clearer. The offspring of mothers who experienced only mild or moderate symptoms during pregnancy are developmentally retarded. Figure 2 compares the children of two groups of mothers differentiated on the basis of hair concentrations. Since hair serves as one of the excretory routes for methylmercury, and maintains a rather constant relationship to blood concentration, an analysis of hair segments reflects the recent history of methylmercury exposure. Further analysis of the Iraqi data, confirming the Japanese hypothesis, demonstrated that the exposed fetus is about four times as sensitive as its mother. Methylmercury is also transferred through maternal milk, so that breast feeding enhances the risk. The sensitivity of the developing brain, combined with the inability of the fetus and neonate to excrete methylmercury effectively (Doherty, et al., 1977), probably account for enhanced perinatal vulnerability.

Enhanced sensitivity to toxic processes by the developing organism is also the theme that dominates questions about the safety of current lead exposure levels. Lead has been a ubiquitous environmental contaminant since antiquity. It even has been blamed for the erosion of Roman hegemony, because the Romans fabricated plumbing (etymology!) from lead and stored their wine in lead casks. Lead became a political as well as toxicological issue in our own society because of childhood poisoning from leaded paint, particularly from interior surfaces. Although prohibited now, lead-based paint from old and decayed housing has left an enduring legacy whose significance is debated. The arguments center on the criteria of adverse effects. Blatant lead encephalopathy is now rare, a consequence of screening programs and much more alert public health agencies. But what of subtle toxicity in the absence of clinical signs? Is the capacity for academic achievement limited by elevated but asymptomatic lead body burdens? Are conduct disorders promoted?

Although such a debate may appear somewhat remote from nutritional science, it is, in fact, clearly joined with it. Foodstuffs provide additional sources of lead besides those ingested (or breathed) directly. Drinking water (from lead pipes) may be contaminated. Susceptibility to lead toxicity depends on diet; high intakes of calcium, iron, and other diet constituents exert protective actions (Levander, 1977). And the predominant animal model is the neonatal rodent, whose lead source is maternal milk. As with methylmercury, the developing organism is at double jeopardy. The immature nervous system is coupled with immature metabolic and kinetic mechanisms and a diet that enhances retention (Kostial and Kello, 1979). Yet, most investigations in humans have examined school-age children, have employed

the rather labile, short-term blood lead as an index of exposure, and almost universally have treated diet as an inconsequential variable.

Metal neurotoxicity does not end with mercury and lead. I compiled the matrix in Figure 3 to indicate the breadth of functional deficits that have been ascribed to metal toxicity. Although some of the entries come from clinical reports and weak epidemiology, it does illustrate that many metals have been linked to psychological and behavioral disturbances and to neurological impairment. Since so much of metal toxicity arises from one metal displacing the function of another, we ought to consider how diet might help optimize resistance to toxicity, especially in the very young organism.

If these issues seem remote, I urge you to acquaint hourself with recent surveys of the impact of acid rain. The unrestricted burning of fossil fuels, especially unscrubbed high-sulfur coal, is accelerating the deposition of toxic metals into soil, waterways, and fish at an alarming rate. Vitriolic opposition to environmental controls by electric utilities and local politicians in the midwest will provide temporary financial relief for them, surging prosperity for toxicology, and permanent destruction of the Adirondacks.

Manufactured Contaminants

Although the risks posed by metals arise primarily from industrial and commercial production, metals are part of the natural environment. The remarkable ingenuity of modern chemistry, however, has spawned an immense catalog of novel structures never before encountered by biological entities. The adaptive mechanisms of living systems seem to insulate us from

catastrophe, but the often tragic limitations of adaptation have taught us to be wary. Legislation such as the Toxic Substances Control Act of 1976 (TSCA), which mandates premarket assessment of toxicity will help. But it will not obliterate the consequences of our previous apathy and ignorance. It will not restore the Love Canal to a pristine waterway nor cleanse the thousands of recognized and concealed chemical dumps exuding their contents into the environment.

Foodstuffs and drinking water represent the main sources of human exposure, and also one reason why toxicity may remain camouflaged for a long time. Diverse consumption patterns multiplied by highly variable individual susceptibilities would blur the relationship even if the endpoints were consistent. But they are not. Often they emerge only when severe, irreversible consequences have supervened. Incipient toxicity often is marked by a collection of vague, subjective, nonspecific psychological and somatic complaints resembling what psychiatrists, desperate for a label, used to term neurasthenia. They resist quantification. Yet, quantification of these amorphous symptoms may yield the only basis for an evaluation of adverse effects.

Consider the PBB episode in Michigan. Dairy farmers were shipped, labelled as feed supplement for their cattle (Nutrimaster), polybrominated biphenyls (PBBs), widely employed as fire retardants (Firemaster). Milk production from prize herds began to fall, cows developed skin lesions and began wasting away, and deformed calves began to appear. The victimized farmers were accused of poor management and nutritional practices. Until the source of the epidemic was identified, however, many Michigan farm families

and consumers ingested meat and dairy products contaminated with a potent poison. The apathy and resistance of Michigan's public officials impeded the detection and control of contamination for such a long time that the exposed population expanded far beyond the original limits.

The health hazards of PBBs are poorly defined for exposures below lethality. The predominant complaints are psychological: tiredness, headaches, somnolence, nervousness, depression, and dizziness are the most frquent, and significantly differentiate the exposed population from a matched group of Wisconsin farm families (Valciukas, et al., 1978). Retrospective assessments, however, are a tenuous basis for conclusions when they are confounded by bitter debates and accusations such as those stirred by the PBB episode. It is the same reason that Agent Orange, the dioxin-contaminated herbicide dispersed over Vietnam, continues to provoke arguments between veterans groups and the government.

The immense number of chemical dumps in this country, many of them illicit, means that such arguments will not fade. Food and drinking water will be contaminated. A focal concern, because they are a focal target, will be children. Teratology will become an even more visible issue than it is now, because the more we learn about the consequences of perinatal exposure, the more alert we become to the possibility of behavioral rather than structural teratology (Spyker, 1975; Bowman, et al., 1978). We also are certain to become more aware of possible adverse consequences to breast feeding, given its ability to transfer toxic substances from mother to child (Yaffe and Stern, 1976).

Self-Contamination

The substances discussed so far are distributed through the environment, and enter food and water without our individual control. Other agents are consumed voluntarily, by individual choice, are not components of required nutrients, and pose both recognized and potential hazards. Alcohol and caffeine are the prototypes.

Both substances are consumed by most people in modest quantities; that is, in quantities that produce no detectable adverse effects. Under these conditions, they are viewed almost as foodstuffs. They still may contribute problems. Almost every other substance toxic to adults is more toxic to the developing organism, sometimes by a remarkable ratio. Moderate alcohol consumption by pregnant humans seems to carry a risk for the fetus. The Fetal Alcohol Syndrome, although recognized even by Hellenic physicians, was not fully documented until the 1960s. Its distinctive physical features, however, may represent only the more blatant cases. Some investigators suspect that even quite restrained alcohol consumption may produce adverse behavioral sequelae in the offspring (Abel, 1980). Few investigators are willing to postulate a safe or threshold level.

Caffeine has parallels mainly in logic. It is an effective CNS agent, and can provoke toxic manifestations at high intake levels. No "Fetal Caffeine Syndrome," however, has yet been described (Gilbert, 1976). But caffeine still manages to evoke some unsettling questions. Most of them stem from our ignorance of the hazards of perinatal exposure. Although not a conventional teratogen, caffeine, like other CNS drugs, may be a behavioral teratogen (Sobotka, et al., 1979), its effects largely inaccessible without sound

behavioral testing. If it were, it simply would confirm what has become clear with other CNS drugs, which interfere with brain chemistry and neuropharmacologic development, but fail to produce morphologic abnormalities.

Caffeine and alcohol not only pass unimpeded through the placenta, but appear in breast milk. Since the plasma half-life of caffeine in neonates is almost 100 hours compared to the adult value of 4-5 hours, it can accumulate to higher levels in the infant. We know little about the consequences of perinatal caffeine even though the neonatal brain is more immature neuropharmacologically than it is morphologically, and even though the safety of coffee and cola drinks has been assumed by the public.

Food Additives

An avalanche of technology in food processing and packaging has spawned countervailing resentment and controversry. "Organic" and "natural" denote not only a felicitous marketing stratagem but a movement. Although the emotionally charged issue of cancer still dominates debate, another argument recently emerged with the assertion that certain food additives (and some natural substances) can provoke behavioral disorders in susceptible children (Feingold, 1975).

Most observers familiar with recent research now acknowledge that some children with behavior problems improve on a diet that eliminates synthetic colors and flavors, and that some children respond adversely to challenges with synthetic food colors (Lipton, et al., 1959). Furthermore, both neurochemical (Mailman, et al., 1980) and animal behavior experiments (Shaywitz, et al., 1979) confirm that at least some synthetic colors are pharmacologically active.

These findings have spurred discussions both about the policy issues they impinge on and about the responsible mechanisms. The dominant policy issue is the role of behavioral testing in hazard evaluation. A two-year feeding study with 100 rats costs close to one-quarter million dollars. Although some of the same animals could be assigned to behavioral and neurochemical studies, such a new requirement would add substantially to the investment required to market a new additive. Many observers question whether an investment of that size is likely to yield commensurate returns. A second, related issue, is the quantity of resources devoted to toxicity testing when we may be dealing only with a susceptible subgroup of individuals. The issue was resolved for cancer by accepting either a zero or infinitesimally small risk. I doubt that the FDA or any other agency could afford politically to impose equally stringent limits based on behavior, or indeed, any functional criterion. Furthermore, none of us are yet secure enough in our grasp of mechanisms to recommend standardized procedures or endpoints that would serve as indices of risk.

We do not understand, for example, why the Feingold diet helps a certain subset of children. Nor do we understand the processes by which synthetic colors act on behavior. Are we dealing with pharmacologic phenomena or with hypersensitivity reactions? Partly because Feingold's original observations were made in the course of treatment for allergy, subsequent observers tended to frame their experiments and interpretations in that same context. The allergy literature also supported such a view. Reports of associations between the ingestion of food colors and flavors and hypersensitivity reactions have appeared regularly in that literature (Amos and Drake, 1976; Neuman, et al., 1978). That literature also is the source of the hypothesized

connection between salicylate hypersensitivity and reactions to food additives. Figure 4, for example, shows the results of a challenge study with tartrazine (FD&C No. 5) in aspirin-sensitive patients (Juhlin, et al., 1972). Similar reactions can be evoked in many such patients by salicylate esters and benzoic acid derivatives from plant sources (Noid, et al., 1974). I consider the salicylate connection a metaphorical term, because such patients also are sensitive to substances with no structural similarity to salicylates. Indomethacin is a striking example. Neither for food additives nor for salicylates, however, have any immunological correlates been demonstrated. Substances such as synthetic colors could only act as haptens, attaching to macromolecule carriers to provoke an antigen-antibody reaction.

We are unlikely to see a quick demise to such hypotheses, however, because of the predominantly nonspecific nature of the behavioral complaints attributed to allergies. Figure 5 is a list that I compiled from the extant literature, which is based on clinical impressions. The absence of adequate experimental data has helped establish the specialty known as Clinical Ecology (Dickey, 1976). It is based on the unassailable premise that some diseases, ills, and complaints arise from agents in the environment, including foodstuffs, that provoke sensitivity reactions. Even if the premise is softened to replace "sensitivity" with "intolerance", it still mandates vague and lengthy clinical maneuvering. Given the absence of any suitable techniques to predict allergenicity or intolerance from animal and laboratory screening procedures (FASEB, 1977), we will have to evaluate such claims by a methodical program of human studies.

The behavioral phenomena reported by Feingold, however, are much more likely to be pharmacologic in character. That is, the offending substances

act like drugs. There are two bases for that assertion. The first is the acute nature of the behavioral response (Weiss, et al., 1980; Swanson and Kinsbourne, 1980). The second is the evidence favoring a dose-effect relationship (Shaywitz, et al., 1979; Swanson and Kinsbourne, 1980). A dose-related action places these issues in a different regulatory contest. If only a small, circumscribed, susceptible subgroup of children respond to a particular additive, it can be marketed with appropriate warnings. But if the intensity of response, and the incidence of responders depends on dose, how can hazard be estimated without an assessment of dose dependencies?

These issues remind me of the controversy surrounding monosodium glutamate (MSG). Even before the discovery of its neurotoxic properties (Kizer, et al., 1977) in the immature rodent brain, it was shown to be the source of the Chinese Restaurant Syndrome (Reif-Lehrer, 1976). At first, it was thought that only a few miserable, idiosyncratically sensitive individuals could be victimized by overenthusiastic Chinese chefs. Later, Schaumberg et al. (1969) demonstrated that everyone was sensitive. It was simply a function of dose. MSG exemplifies another regulatory issue similar to the one posed by colors. How should we treat food additives that fill a cosmetic rather than a safety or economic role? Do such agents require us to insert behavior into the equation of risks and benefits? Perhaps we should weigh the comments of the celebrated Chinese gourmet, Irene Kuo (1977):

> "What we knew as 'taste-essence' in China was a seasoning agent made at home primarily from dried fermented wheat gluten and/or soybean protein, often further enriched with powdered dry shrimp or seaweeds. It was used to enhance weak flavors, such as watered-down broths, poorly seasoned

foods from unskilled hands, or meager meat dishes, intensifying primarily the natural flavors of meat and poultry. While 'taste-essence' is of Chinese heritage, it was never accepted by the elite society of gastronomy where cooking skill and lavish use of natural ingredients are the essence. Today's version is a chemical compound known as monosodium glutamate or MSG and to me it does nothing to enhance flavor. Rather it gives food a peculiar sweetened taste that I find absolutely distasteful, and for some people it has unpleasant side effects."

Summary

Behavior as an index of toxicity parallels its role as an index of nutritional impairment, just as toxicology and nutrition share other common themes. Intersections among the three disciplines arise because foodstuffs serve as one of the major routes of toxic exposure and also because food elements modify toxicity. With this perspective, the safety of our food supply is examined in the contexts of essential nutrients, toxins, toxic metals, manufactured contaminants, self-administered toxicants, and food additives.

Figure Legends

Figure 1. Symptoms and signs of methylmercury toxicity

Figure 2. Relationship between mothers' methylmercury hair levels and neurological signs in the offspring

Figure 3. Neurobehavioral symptoms and signs associated with metal poisoning

Figure 4. Sensitivity to tartrazine in aspirin-sensitive patients

Figure 5. Psychological and behavioral complaints attributed to food allergies

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