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BEHAVIOR AS A SENTRY OF METAL TOXICITY

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ABSTRACT

any of the toxic properties of metals are expressed as behavioral aberrations. ome of these arise from direct actions on the central nervous system. Others rise from primary events elsewhere, but still influence behavior. Toxicity may e expressed either as objectively measurable phenomena, such as ataxia, or as ubjective complaints, such as depression. In neither instance is clinical edicine equipped to provide assessments of subtle, early indices of toxicity. eviewers of visual disturbances, paresthesia, and mental retardation exemplify he potential contribution of psychology to the toxicology of metals.

ehavior and nervous system function act as sensitive mirrors of metal toxicity. ensitivity is our prime aim in environmental health assessments. Early detect- on of adverse effects, before they progress to irreversibility, underlies the trategy for optimal health protection. Such an effort is hampered by the pectrum depicted in Fig. 1. Its range is extraordinary, but, even so, incom- plete. It is not any more lengthy because I excluded what struck me as too enuous, or not pertinent. Do not be misled, however. What I did include remains a puzzling assortment from an uncritical literature perched on the brink of unmitigated confusion. Most of the confusion, if I can blame a single cul- prit, stems from the vague, subjective nature of many of the items. They are complaints about internal states.

Some of the toxic actions in Fig 1 originate in direct nervous system dysfunction. Ataxia, for example, is most often of neurological origin. Other entries may reflect disturbances of systems less directly linked to behavior than the central nervous system. But behavior, because it expresses the integrated functioning of the organism, can indicate flaws in states and processes outside the nervous system. Simply consider how many different types of illness can induce "loss of appetite."

Whatever, the source, however, we are both troubled and challenged by the dif- ficulty of specifying the terms appearing in vague, impressionistic clinical reports or puzzling out the precursors of a terminal calamity. Some vagueness is inescapable when exposures have been limited to low levels or when symptoms represent only the early, incipient manifestations of a progressive intoxication.

DISCLAIMER

Also, metals do not act on a single substrate. They act on organisms. And organisms vary in behavioral history, genetic susceptibility, dietary status, and numerous other variables. Why expect a uniform response? The questions posed by Fig. 1 center on two issues: What represents a toxic dose as defined by behavior? How do we determine that quantity? The two issues are inseparable. Definitions of toxicity depend upon the criteria. Methylmercury is a useful example with which to frame this discussion, because there is no debate about its potency as a nervous system poison. Table 1 lists the signs and symptoms of methylmercury poisoning. They include sensory, motor, and non-specific categories. Sensory deficits are the most salient. Paresthesia (numbness and tingling) is considered to be the earliest detectable symtom, at least by clinical examination. U. S. standards for methylmercury in fish are based on that assumption and on coordinate extrapolations from epidemiological data. Paresthesia, however, is a subjective index. It waxes and wanes. Clinical and epidemiologic studies may compound these problems by asking subjects for retrospective reports. Despite these objections to paresthesias as a criterion, it provides crucial information. Where can we turn for alternatives?

Psychologists often refer to the twin concepts of reliability and validity. These describe characteristics of tests employed in psychological assessment: intelligence tests, personality tests, and achievement tests are examples. Reliability refers to the reproducibility of a test result. A reliable test yields comparable scores on different occasions. A valid test measures what it claims to measure. The criteria by which validity is determined comprise an extensive catalog of psychometric concepts and techniques. Both validity and reliability indices are missing from most clinical measures. In Iraq, paresthesia provided a crucial indication of methylmercury toxicity. But the presence of paresthesia could be determined only by questioning the victim. Would a respondent give the same answer to another questioner? On another occasion? To another form of the question? Such issues are pertinent to reliability. Do we have any idea of how these factors contribute to the high incidence of false positives observed in Iraq and elsewhere?

Validity poses a more complex issue. One way to verify paresthesia as an index of toxicity is to plot dose-response functions. Does the incidence of paresthesia rise with some index of exposure such as hair or blood concentration? Data from Iraq confirm that it does. But the ancillary questions remain unanswered. Does the magnitude of the effect show a proportionate rise? Could our precision be increased--can variability in response be reduced--with a different form of questioning? Can we devise a more objective form for the response? Since such questions pervade every aspect of metal toxicity, I should like to discuss them with specific examples taken from entries in Fig. 1. I will discuss certain aspects of length, then touch on the others in a more general way.

MENTAL RETARDATION

Many workers believe the developing brain to be exceedingly vulnerable to insult. Although the concept of neuronal plasticity, which emphasizes the flexibility of the developing nervous system, opposes this concept, authors such as Isaacson (1) and Goldman (2) have demonstrated and argued that, with appropriate tests and at appropriate times, the legacy of this damage emerges. Most cases of what we call "mental retardation" arise from developmental disorders of the nervous system in the fetus or neonate. The source of the disorder may be genetic, as in Down's syndrome, or may arise from trauma, or from infection, or from chemical imbalance in the nervous system, as in phenylketonuria. But mental retardation is a global term. It encompasses many different kinds of disabilities, all referred to a large discrepency between the performance of the target child and that of normal children. The question is considerably more subtle, however. Let me plagiarize

a question posed by David P. Rall, Director of the National Institute of Environmental Health Sciences. Suppose that thalidomide, instead of producing phocomelia, had instead reduced the victims' intellectual potential by the equivalent, say, of 10 IQ points. Would we even now be suspicious that thalidomide could induce developmental defects? The answer is frighteningly obvious. Let me use it as the context in which to ask questions about methylmercury and lead.

Methylmercury

Although a few cases of retardation were linked with methylmercury in Minamata (3), the recent experience in Iraq (4) confirmed that impression with more extensive data. Investigators from Iraq and and the University of Rochester have now documented the fact that mothers exposed to levels of methylmercury eliciting only minimal toxic symptoms, such as paresthesias, gave birth to children whose capacities are markedly diminished (5).

The full range of maternal exposure levels has not yet been surveyed. Observations of the offspring of women whose peak hair level exceeded 100 ppm indicate a markedly increased incidence of small heads, short stature, delayed speech, clumsiness, and other indices of central nervous system damage. All are gross enough to be detected without precise, psychological evaluation of the kind typically performed in diagnostic clinics. Minamata also implies that we are observing the expression of a legacy whose full consequences will remain unknown for decades (3), that defects may lie dormant or covert until other processes or events have intervened, such as aging, and will become visible once the reserve capacity of the brain has been consumed. In a landmark experiment in behavioral toxicology, Spyker (6) discovered that mice exposed prenatally to methylmercury might reveal no impediments in function until they reached old age. The more subtle deficits, furthermore, could be unmasked only by behavioral testing. Such defects may unfold for decades to come in Iraq. Many of these will remain undetected unless a major effort is launched to use the available tools of psychological testing in assessing the impact of this grim episode. It may not benefit the victims, but it surely will help us to determine the actual threat from mercury in the environment.

Lead

Because of its pervasiveness in our environment, no other metal has provoked as much concern about toxicity as lead. Its ubiquity means that we all are exposed. Our lead body burdens are remarkably high, in fact, given what is accepted as a toxic dose. And, as with methylmercury, it seems now that the chief victims, the most susceptible organisms, are children. It is on this point that the debate rages.

Substantial numbers of children in the cities of the United States, and elsewhere, carry body burdens that some investigators associate with deficits in academic performance, psychological test scores and behavior. Although lead, like mercury, is an ancient metal, it was not until the 1940's, when Byers and Lord (7) claimed that the aftermath of acute lead poisoning was a deficit in academic performance and behavior, that the public health community became aroused. Papers then began to appear to affirm or deny the conclusions reached by Byers and Lord, and gradually shifted emphasis from concern with the aftermath of gross lead intoxication to the consequences of elevated but asymptomatic body burdens. These questions also spurred studies of lead kinetics and reverberated into occupational exposures. None of these issues have yet been settled. But the background is worthwhile examining, because it clarifies some of the most profound issues in toxicology.

The proposition that asymptomatic lead exposure can produce behavioral deficits

carries epidemiology far beyond its conventional bounds. Rather than depending on mortality and morbidity, such questions are keyed to surveys with psychological tests of varying reliability and validity. To determine that a selected group of children differs in intellectual potential or achievement from another group requires us to make the following assumptions. First, that a test is available to measure intellectual potential. Many intelligence tests are marketed. Most are based on the assumption that, as a child grows, so does its intellectual ability. Test items, therefore, that discriminate between age groups are also assumed to reflect intelligence. Intelligence is an abstract concept, however, not a score. But even if we confine ourselves to test scores, other problems emerge. Those items that reliably discriminate between ages are retained, the others rejected. But the final standards do not apply to all cultures and ethnic groups. One of the most widely used of the tests, the Stanford-Binet, derives its norms from middle class white children (8). It certainly does not apply to the black population in American cities where we find the highest prevalence of elevated lead exposure. Another problem accompanying the choice of tests is that some tests can be broken down into subscores, others cannot. Since no single test encompasses all functions, most current studies now use several tests. Furthermore, the kinetics of lead make it doubtful that a single blood level determination reflects a child's total exposure. Peak blood leads are seen between the ages of one and three, when children are both mobile and explore the world with their mouths. Paint chips and dust then have a ready route of entry. Reliable intelligence testing, however, cannot take place until much later. Age five is probably the minimum. Some investigators overcome this flaw by employing tooth levels to evaluate the integrated exposure of the child. Needleman, from Children's Hospital in Boston, recently announced the results of a study of over a thousand children. With such a large population, and with tooth lead as the index of exposure, teacher behavioral ratings revealed significant differences between high lead and low lead groups, despite the fact that the high lead group remained clinically asymptomatic.

Some investigators assert that the disorder called hyperactivity or hyperkinesis is linked to elevated lead exposure (9). These studies report that children brought into the clinic with complaints diagnosed as hyperactivity show slightly elevated blood leads or body burdens compared to the controls. Such data, however, are only suggestive. Hyperactivity is a diagnosis that has to be made on the basis of multiple criteria. The defects implied by this claim are another example of how difficult it is to deal with adverse responses expressed in behavior. No single functional test is adequate; no single criterion is perfect.

An additional problem, but one that pervades all toxicology, also is exemplified by the debate about lead. The question of susceptible populations is especially relevant here, and it finds expression in many forms. Nutrition may play a key role. Laboratory evidence demonstrates that deficiencies in iron and calcium stores enhance lead toxicity (10). Iron deficiency seems to be the most pervasive nutritional problem in the United States, at least according to the recommended daily allowances postulated by the National Academy of Sciences. Inadequate calcium intake probably is common as well. Among black children, however, the problem expands because blacks are more likely to be intolerant to lactose. Since milk is a child's prime source of calcium, such children also may be more likely to suffer calcium deficiency than while middle class children. Dietary practices, some governed by genetics, can multiply the impact of a hazard.

Nutritional adequacy is linked to still another problem. The young organism is more susceptible to metal intoxication, in part, because the immature gut, in company with a predominatly milk diet, amplifies absorption of lead, mercury, and other heavy metals (11). Elevated uptake and retention, combined with the elevated vulnerability of the developing nervous system, all contribute to put

the young organism at much greater risk. Such mechanisms underlie the prevalent model of animal research on lead, based on the finding that neonatal lead toxicity can be induced by feeding a nursing rodent a high level of lead in the diet (12). It received a sharp impetus with the report that such treatment augmented locomotor activity in offspring (13). This phenomenon was adduced as a model for hyperkinesis, emphasizing the parallels with amphetamine, a prevalent mode of treatment for hyperkinesis, which also exerted an allegedly paradoxical effect in the treated mice. The source of those results has been questioned. The lead-treated animals also were undernourished, partly because the treated mothers, either because of illness or because of aversive tests, consumed less food (14). Simply reducing the mothers' food intake, and consequent undernutrition of the offspring, also leads to elevated motor activity, which, in turn, shows displaced amphetamine dose-effect functions (15).

Perhaps more significant than alterations in activity are reports that learned performances are altered by early exposure. Brown first reported that lead treatment, during the first ten days of life, a treatment that did not hamper physical development, impeded maze learning (16). These results have not been reproduced elsewhere. When the lactating female is fed less than 0.2% lead in her diet or drinking water, and offspring physical development is normal, performance deficiencies are difficult to document. We seem to be dealing with a threshold phenomenon, the same problem encountered in human studies. At those low levels we influence only organisms that are especially vulnerable. Our typical experimental designs and group statistics are insensitive to the low prevalence of these especially vulnerable organisms. A common finding in animal studies is that a minority of the animals, 10 to 30% perhaps, display aberrant responses. Their treated peers seem to perform no differently than controls. The statistical weight of these more resistant animals make it seem as though the only effect of the treatment is to enhance variability. More appropriate experimental designs and statistical analyses than those commonly used should be invoked for these questions. Following single animals for longer periods of time, studying them under a wider range of conditions, and calculating multiple indices may help resolve this enigma.

It also is important to recall that most human lead exposures peak after weaning. Is the weaning rat a more appropriate model? A recent experiment by Cory-Slechta is intriguing for its possibilities (17). Her lead exposures began when her rats were 22 days old. Lead acetate was dissolved in drinking water at concentrations of 50, 300, and 1000 ppm; these are for lower values than many previous investigators had used in the lactating mother model. She began training the animals at the age of 35 days, maintaining them at approximately 80% of the weight attained by freely-fed rats. They were trained to press a lever to obtain a 45 mg pellet of food. Not each response produced food. Only the first response at the end of a 30-second interval produced food delivery. The animals responded within the 30 seconds, however, although only the response at the end was necessary. This is typical of what is called fixed-interval performance, a behavior quite sensitive to many drugs (18). Both the 50 and 300 ppm animals developed elevated response rates. These gradually declined, a decline accelerated by ceasing treatment. This is the first demonstration that behavior is responsive to relatively low-level post-weaning exposures.

PARESTHESIA

I already have referred to this symptom as a prototype of the puzzles posed by subjective indices. Paresthesia, however, may reflect a process that can be defined more precisely. Clinical observations suggest that paresthesia may be correlated with, or serve as precursors of peripheral or central nervous system histopahtology as in methylmercury intoxication. Other reports suggest that

paresthesias may accompany signs such as attenuation of vibration sensitivity. Vibration sensitivity testing is a particularly apt illustration of the inadequacy of clinical examinations. Vibration sense typically is assessed with a tuning fork touched to the patient's skin. Amplitude is not controlled. Only one frequency is tested; 240 Hz is typical. Yet, receptors in the skin respond to frequencies ranging from a few Hertz to as high as 400 Hz or higher. Sensitivity also varies with frequency. Higher frequencies typically require lower amplitudes for detection. The receptors, moreover, appear to fall into two populations. One is optimally tuned to about 25 Hz, the other to about 300 Hz. To conclude anything about function on the basis of one frequency and one amplitude is equivalent to judging hearing acuity from a patient's response to a single tone.

Vibration testing is still a laboratory art, however, so I am not prepared to advocate screening programs based on vibrograms. The technology is instructive, however. Fig. 2 shows a system devised in our laboratories by Jacques Maurissen. The monkey's paw is restrained by a plastic mold that maintains its middle finger in contact with the tip of an electromagnetically-driven vibrator. Amplitude and frequency are specified by a computer program that controls the experiment. An accelerometer attached to the vibrating rod provides measures of frequency and amplitude accuracy. Fig. 3 is a typical plot of monkey performance under these conditions. Trained monkeys are as accurate as humans tested on a corresponding device in this laboratory. Although such an arrangement is a research tool, it should spur us to devise better methods for detecting somesthetic impairment. Correlations with nerve conduction measures would also help us specify a functional relationship important in screening programs.

VISUAL DISTURBANCES

Although paresthesias may be the earliest clinical accompaniment of methylmercury intoxication, the most enduring and well-defined locus of impairment is the visual system. Hunter, Bomford, and Russell conducted a pioneering study of four workers poisoned by a methylmercury fungicide in a seed dressing plant (19). Although the full spectrum of methylmercury intoxication was detectable in these patients, constriction of the visual field showed the most universally predictable progression and the least recovery. The Japanese experience at Minamata and Niigata provided a further depressing confirmation of these original observations (20). At Rochester, we undertook a series of experiments with primates in response to the episode of methylmercury intoxication in Iraq. Our aim was not intervention, of course. It was, instead, to develop a behavioral task able to follow the course of an intoxication. We believed that a technique capable of being reproduced from one setting to another would better serve the cause of environmental health than one that relied, say, on fine tuning of a clinical observation.

We already knew, from the Japanese experience, that the human visual cortex is a prime target of methylmercury intoxication. Calcarine cortex on the medial surface of the brain is the locus in visual cortex (the occipital lobe) within which the key damage occurs. How could this be translated into a valid and reliable experimental procedure? Only the primate could tell us. The visual systems of common laboratory species differ so from that of humans in both structure and function that it would have been futile to try to extrapolate to human conditions. Only non-human primates could serve in such a capacity, in particular, the Macaque monkey. A long history of research in experimental psychology had taught us that Macaque visual function, in every essential respect, was almost exactly like the human visual function and that the structure of the Macaque visual system virtually duplicates human visual organization (21). We also knew from this long history in experimental psychology that damage to the occipital lobe induces characteristic deficits. For example, destruction of the

visual cortex impairs the ability of monkeys to discriminate shapes or forms, even though, with subcortical structures intact, they retain the ability to distinguish brightness. Other key features of the visual system also guided our experimental strategy. The retinal elements called cones lie at the center of the visual field. They subsume color discrimination. They also enable discrimination of fine detail of the sort encountered in reading. But they require relatively high light levels for functioning. The periphery of the retina is dominated by the elements called rods. The rods respond to much lower levels of illumination than the cones. They are what we employ in night vision. They also are interconnected in such a way that they pool their sensitivities. Our reasoning then proceeded as follows. If peripheral vision is the earliest locus of destruction, even though its cortical representation is what is attached, an exposed animal's ability to distinguish dim targets will be the first indication of visual impairment. Moreover, since visual cortex seems essential for the discrimination of form, such an effect can be amplified by requiring animals to perform a visual discrimination of geometric shape. This rationale fulfilled our aims in a series of experiments conducted by Evans (22).

The monkeys, restrained in a primate chair, faced a panel to which were attached three plastic disks illuminated from behind. The plastic disks, when pushed by the monkey, triggered a switch closure sensed by the digital computer that controlled the experiment. The position of the three geometric forms (square, circle, and triangle) varied randomly from trial to trial. If the animal pushed the correct key, it received a small quantity of fruit juice through a spout near its mouth. Illumination of the target varied from rather dim to bright. By rather dim, I mean that brightness was so reduced that monkeys (and humans) require about 15 minutes in the dark before they are able to perceive its shape. Fig. 4 displays the results of the experiment in one monkey. Evans first administered a series of priming doses to bring its blood level to a desired target value. The blood value was maintained at the target value by weekly feeding of a biscuit that contained 0.5 mg/kg methylmercury. For the monkey whose performance is shown in Fig. 4, the first indication of methylmercury toxicity, a reduction in accuracy of performance at the lowest luminance, emerged about ten weeks after the start of treatment, becoming much more apparent at fourteen weeks. There was a partial recovery, probably because the animal learned other strategies for solving the problem. During this decline, performance at the higher light levels remained at 100% accuracy. It was only several weeks later that performance at brighter luminances began to slip, at a time when clinical symptoms also began to appear. Other exposed monkeys have shown a similar progression of impairment, its time course depending on treatment parameters. Swedish researchers, employing somewhat different techniques, but basing their approach on the same strategy, detected an analogous progression in Saimiri Sciurea (23).

I have stressed the strategy that prompted this experiment because I believe that behavioral and neurotoxicology need to exploit the resources afforded by psychology. The typical clinical neurological examination is both an unreliable and invalid tool for detecting incipient toxicity. Only the most thorough visual performance assessment, using tools developed by contemporary vision research is likely to meet the needs of environmental health science. Such an effort is underway in our own laboratories and derived from current models of visual function that conceptualize the visual system as an arrangement for analyzing both spatial and temporal frequency components of our visual world. This series of experiments also defined a number of issues critical to weighing the toxic potential of metals as well as other substances.

Species differences

Our original choice of the Macaque was guided by its history in neuropsychology,

and its documented relationships to the human. Structural and functional congruence are only two of the important principles governing extrapolation. The distribution of a toxic agent within the organism also determines its potency. Methylmercury is a central nervous system poison. Although brain damage underlies most of methylmercury's clinical effects, we still persist in trying to extrapolate from rodents to humans. Fig. 5 shows one reason for the futility of such an effort. The ratio of blood to brain level varies among species. In the primate, certain portions of the brain may contain as much as five times the blood concentration. In other species, the ratio might be unity. The rat's blood concentration is far higher than the brain concentration. Primates are expensive and rare. They should be used only when no other alternative is feasible. No other alternative is feasible if the visual system is our site of action, and our mission is to develop methods for the detection of incipient toxicity.

Pattern of damage

Fig. 6 displays topographical maps of damage to the primate brain. These are similar to the patterns mapped by the Japanese in the Minamata victims except for the lack of damage to the Macaque cerebellum. To a psychologist, this patterning provokes countless questions. Recall the list of signs and symptoms in Table 1. How are these related to the pattern of brain damage? We would expect impairment of somesthetic sensitivity given the pattern of destruction in parietal cortex. We might also expect impairment of hearing, because of damage to the temporal lobe. We also might expect more subtle functions to be impaired. It would not surprise many psychologists that clinical complaints of memory disturbances emerged. Lesions deep in temporal cortex can impair recognition and recall of visual stimuli in primates (24). This differential pattern of destruction in the monkey brain, which corresponds so closely to the pattern reported in humans, is one more reason why we would choose species to frame answers that are significant and relevant for the central issues.

Dose-duration relationships

In Minamata and Niigata, methylmercury toxicity arose from the consumption of fish eaten over a period of years. In Iraq, the episode was triggered by the consumption of grain consumed within a three-month period. Because the offending agent was recognized so early in Iraq, and because chemical methods for the measurement of body burden had been well perfected by then, it was possible to trace the clinical course in parallel with changes in body burden. Hair analyses also permitted a closer match of exposure history and toxic effects than was possible with the earlier chronic episodes (25). Do the Iraq data indicate a threshold or a no-effect level? Refer to Fig. 6. These data are based mainly on the Rochester experiment but supplemented by experiments elsewhere. They show most cogently that duration of exposure may be substituted for body burden in achieving the same toxic endpoints. If one's concern is a population that consumes methylmercury chronically, the data from Iraq and other sub-chronic episodes are not applicable. The chronic mechanism is probably a slow, insiduous destruction of brain tissue, finally achieving a wide enough lesion to overcome the inherent compensatory mechanism of the brain. At that point, the impairment becomes visible and overt. This slow insiduous process is more dangerous because it is less visible. Neuropsychology tells us that a series of small lesions of the same total size is less likely to induce behavioral disturbances than one produced all at once (26), but the end result is still the same. A large measure of the reserve capacity has been sheared off. It leaves the brain more vulnerable to other influences, including aging, that reduce its capacity.

SUBJECTIVE COMPLAINTS

Fig. 1 is a fairly accurate guide to the prominence with which subjective complaints appear in clinical toxicology. My list includes appetite loss, depression, dizziness, fatigue, headache, insomnia, jitteriness and irritability, somnolence. An intriguing galaxy, because such a constellation is roughly congruent with the syndrome of erethism, which is associated with mercury vapor intoxication. It also encompasses what an older generation of psychiatrists called neurasthenia; but that was merely a term that assuaged psychiatrists' anxiety about the absence of a specific clinical entity.

Many of these complaints herald the onset of more severe intoxications, so tools for a quantitative assay serve a preventive as well as research function. Our predecessors in psychopharmacology, because subjective actions are critical in evaluating CNS drugs, have either exploited available techniques or developed new ones for this explicit purpose. For example, the manual for Early Clinical Drug Evaluation (ECDEU) contains numerous scales and inventories applicable to environmental health problems. Assessments of mood states, subjective somatic symptoms, and other relevant indices can be performed with convenient relatively brief surveys. That such evaluations can contribute to the immediate task of hazard estimate is supported by evidence from Hanninen (28), who studied workers exposed to carbon disulfide, in Finland, and Valciukas et al (29), in the United States, who studied workers exposed to lead.

NEUROLOGICAL INDICES

Some of the entries in Fig. 1 refer to clinical neurological disturbances. Among these are convulsions, disorientation, dysarthria, incoordination and ataxia, polyneuritis, and tremor. It is an illuminating catalog of symptoms because all refer to rather advanced impairment, overtly detectable on conventional clinical examinations. We can assume that these overt manifestations of a toxic process are only the culmination of progressive destruction, and that more sensitive techniques could have detected the process at an earlier stage. Furthermore, clinical entities are not easily quantified and quantification is essential for plotting dose-effect and dose-response relationships.

Tremor exemplifies the problem arising from clinical criteria. Some clinicians believe they can detect and evaluate tremor visually. But physiological tremor is always present. Only gross amplitude changes can be detected clinically, often at a time when reversibility is questionable. Even more crucial, perhaps, pathological tremor may not be characterized simply by enhanced amplitude, but by a shift in its frequency spectrum. In tremor induced by industrial mercury vapor exposure, for example, we found not only an elevation in amplitude (power), but a more complex frequency spectrum chacterized by multiple peaks rather than by a single peak (30).

CONCLUSIONS

We know pathetically little about the behavioral toxicity of metals. This is equivalent to saying that we lack understanding of the processes that underlie metal toxicity, that we are unable to specify the early expression of toxicity, and that we even do not grasp the full spectrum of toxic manifestations. It is not a conclusion I can blame on a convenient target such as toxicology, or industrial hygiene, or clinical medicine. Our ignorance has been illuminated only during the past few years. It became visible after we came to understand that function, not tissue under a microscope, must serve as the main measure of incipient hazard. Now it is time to adopt the corresponding technology, and the obvious sources are psychology and behavioral science. They are eager for a collaboration.

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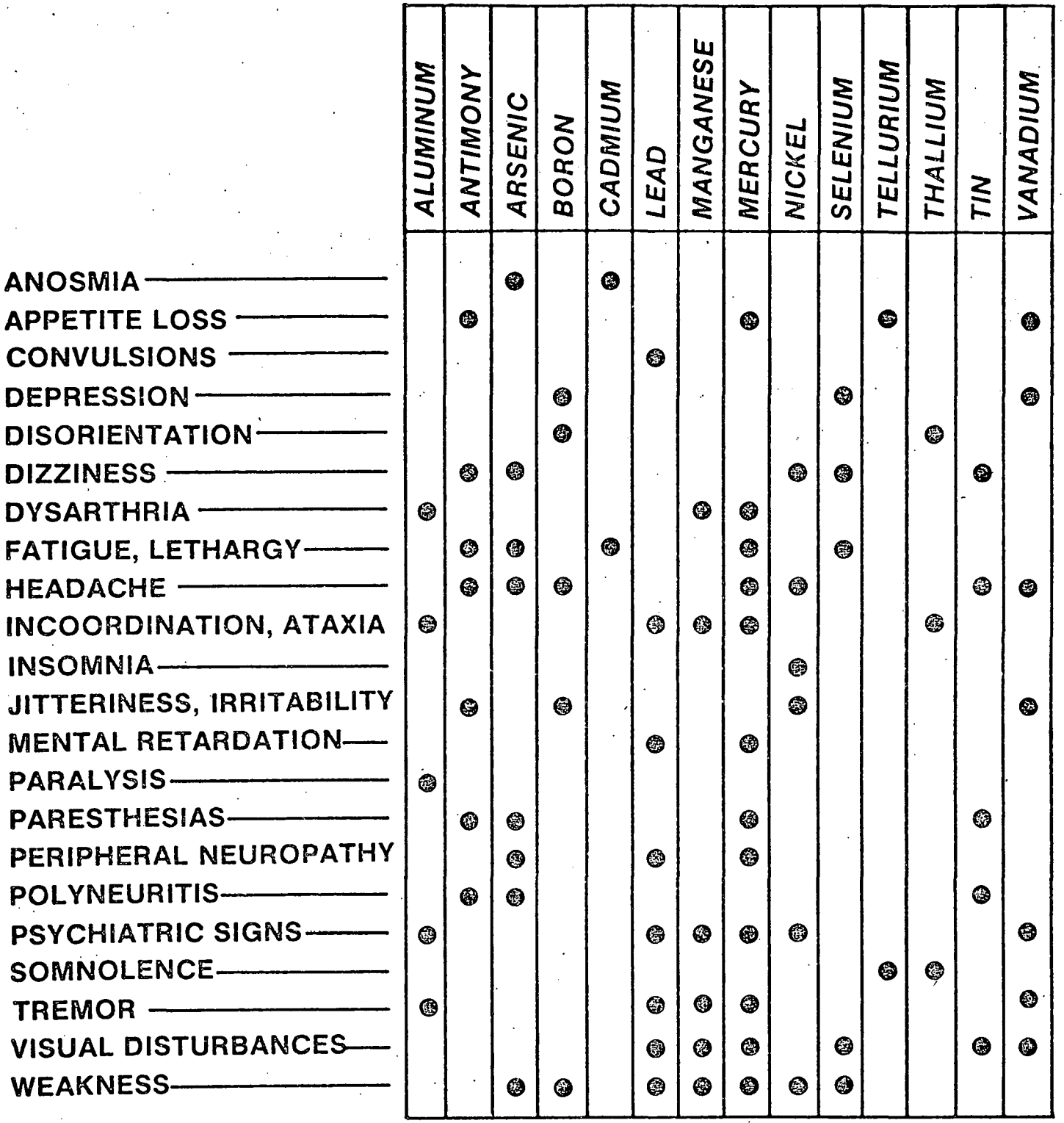
Fig 1



SYMPTOMS ASCRIBED TO METAL TOXICITY

Fig. 1 Matrix of toxic symptoms ascribed to metals.

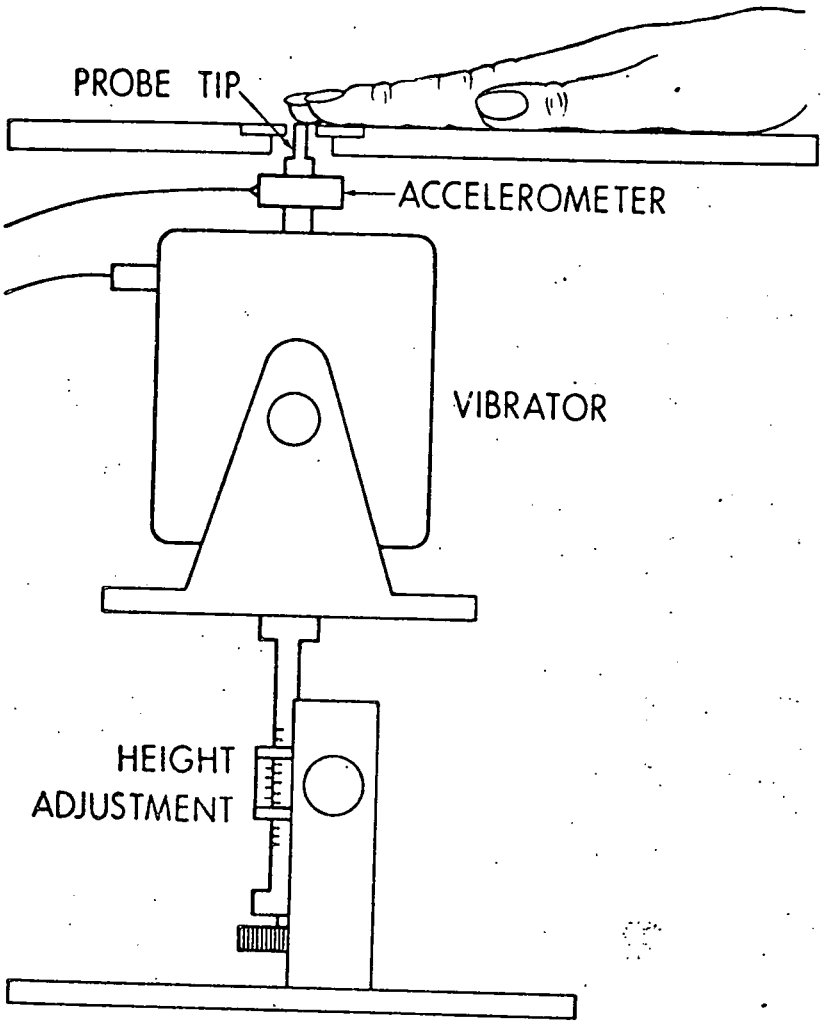


Fig. 2 System for delivering controlled vibration to the finger tip.

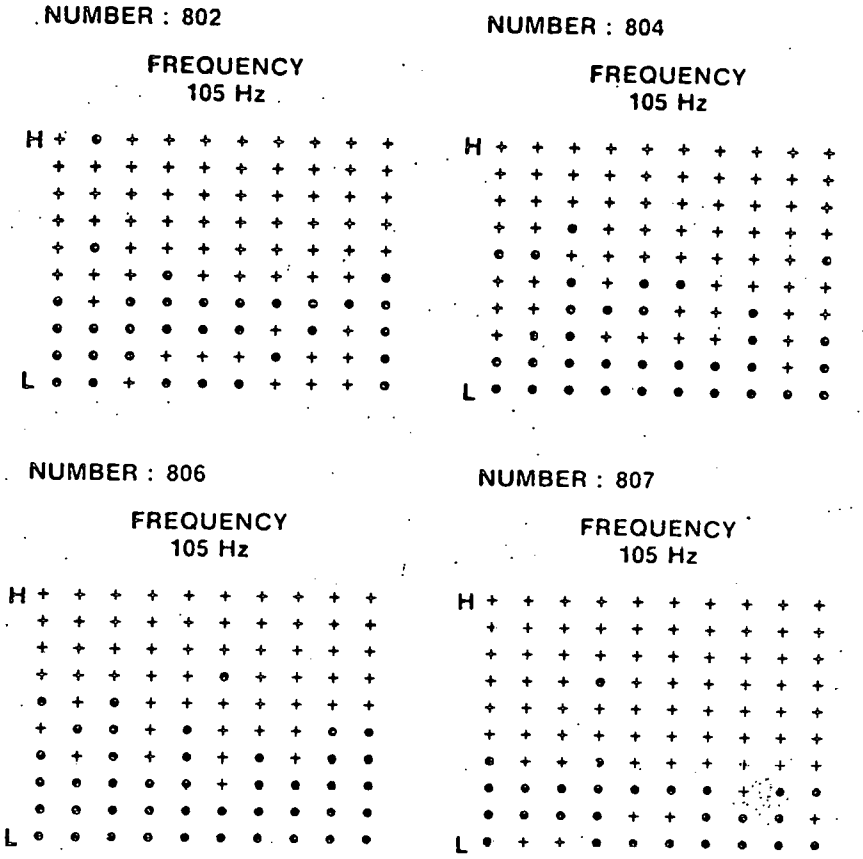


Fig. 3 Each matrix plot depicts the performance of one monkey. H is the highest and L the lowest amplitude in the series. Each amplitude was tested 10 times. Each correct detection is represented by +. Each failure to detect is represented by ∘. Very few mistakes are made at high amplitudes.

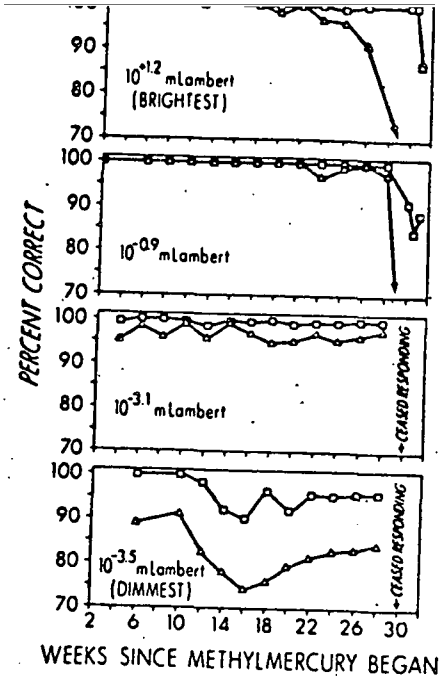


Fig. 4 Deterioration of visual performance in a monkey treated chronically with methylmercury.

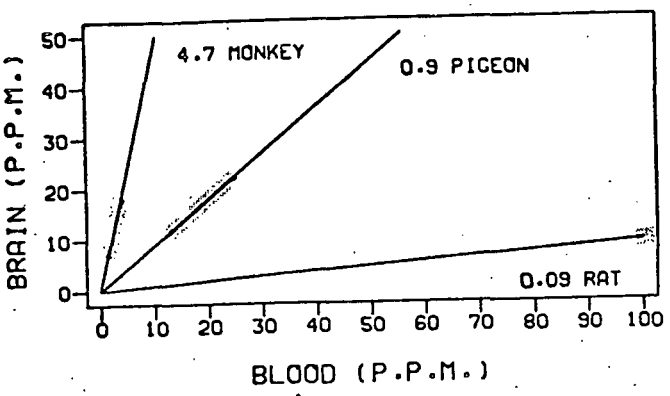


Fig. 5 Species differences in brain-blood ratios of methylmercury. Each line plots the relation between blood concentration and brain concentration; the numbers next to each line represent slope. Brain levels are based on the highest concentrations observed. Hatched areas depict concentrations correlated with the onset of overt signs. (Courtesy H. L. Evans.)

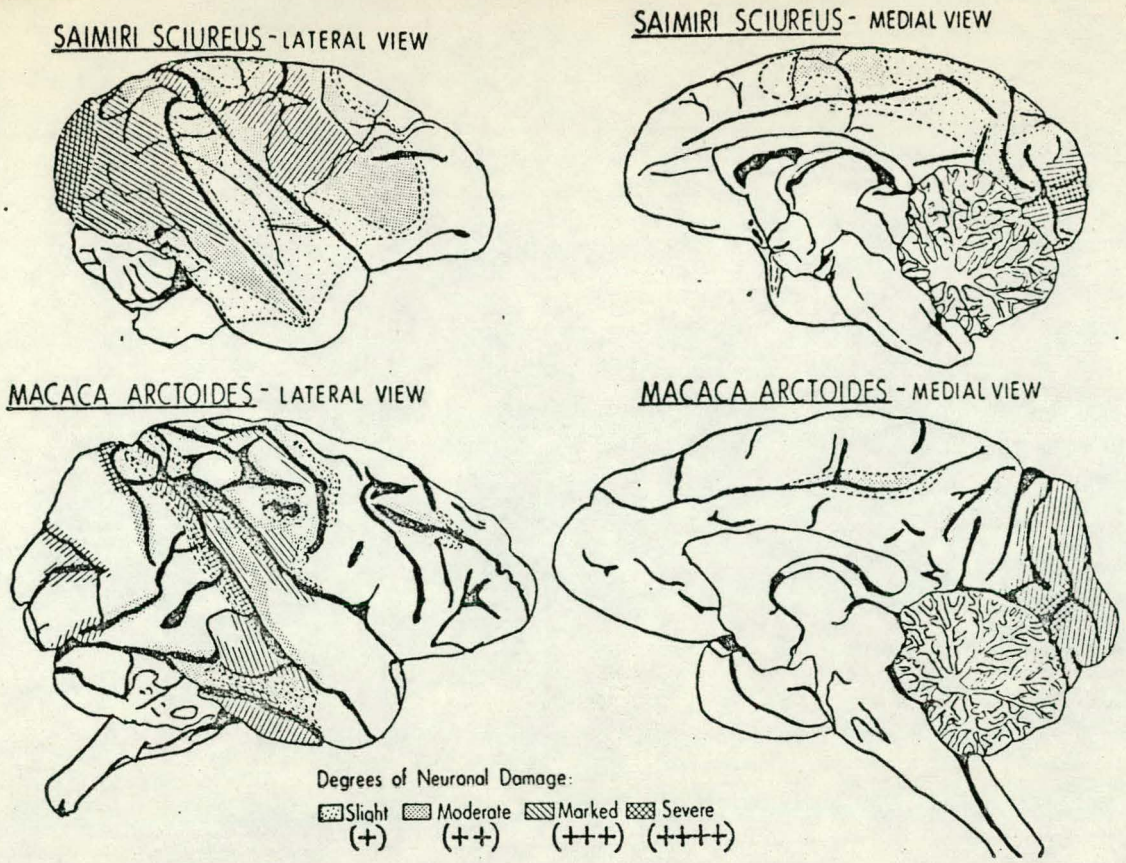


Fig. 6 Topographic portrayal of brain damage in monkeys exposed to methylmercury. Anatomic landmarks are indicated by heavy lines. Clear areas are free of histopathology. Striate cortex, as shown, was most severely affected area, particularly within calcarine fissure. Most severe damage in macaque brain appeared within sulci (from Garman, Weiss, and Evans. Copyright 1975 Springer-Verlag, Heidelberg).

INDICES OF METHYLMERCURY TOXICITY

- SENSORY
  - Paresthesia
  - Pain in limbs
  - Visual disturbances (Constriction)
  - Hearing disturbances
  - Astereognosis
- MOTOR
  - Disturbances of gait
  - Weakness, unsteadiness of legs; falling
  - Thick, slurred speech (Dysarthria)
  - Tremor
- OTHER
  - Headaches
  - Rashes
  - "Mental disturbance"

TABLE 1