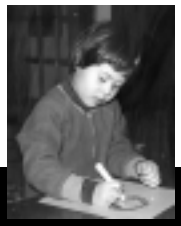
Chapter 1



Nature of the Problem

Children today face extraordinary challenges in the effort to succeed in an increasingly complex and demanding world. Parents, teachers, psychologists, and social workers know all too well that in the context of a high-tech, fast-paced world, many children are failing to meet fundamental challenges of daily life. In particular, the expectation to learn, exercise self-control, and participate respectfully in social groups has become for many a daunting challenge. These children are sometimes labeled as having learning disabilities, attention deficits, hyperactivity, autism spectrum disorders, or any one of a range of other developmental problems, depending on the mix and severity of their symptoms.

This report begins to examine the contribution of toxic chemicals to the origins of these disorders. We focus specifically on how neurotoxic chemicals contribute to developmental delays, hyperactivity, memory loss, attention deficit, learning disabilities, and aggressive behavior. Unlike an adult, the developing child exposed to neurotoxic chemicals during critical developmental windows of vulnerability may suffer from lifelong impacts on brain function.

Lead, mercury, alcohol, other solvents, some commonly used pesticides, dioxins, and PCBs interfere with normal brain development, with long term consequences for brain function. Some of these chemicals are used extensively in manufacturing and are emitted annually in the millions of pounds into the environment. Some bioaccumulate in the food chain and end up in our bones, blood, fat, urine, breast milk, ovaries, and sperm. They may then be passed to the developing child across the placenta, through breast milk, or in food. Many are so widely dispersed globally that Inuits in the Arctic, far from sources of industrial pollution, carry a large body burden of some of these chemicals. We believe that we can no longer ignore the mounting evidence that chemical exposures contribute to the epidemic of developmental disabilities.

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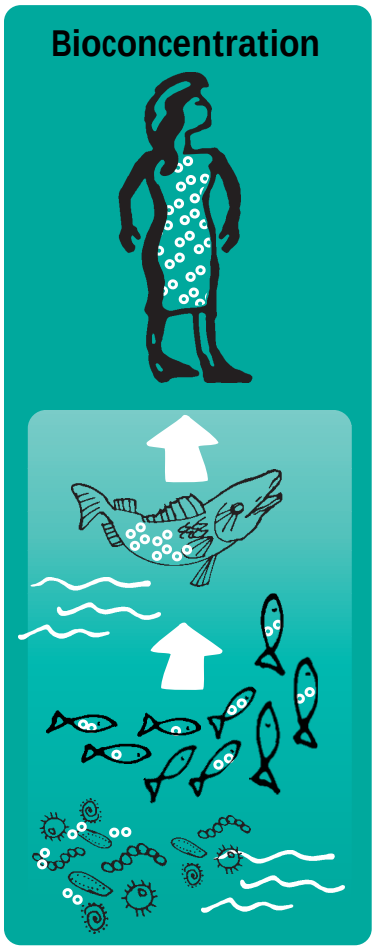
It is equally important that we understand why, with few exceptions, this connection has not been widely and openly discussed—a serious failure, since environmental exposures are eminently preventable. The reasons are complex,



At one point, it was thought that "the solution to pollution is dilution". But we have found that certain persistent toxins do not stay dispersed. Through the process of bioconcentration they are reconcentrated in the food chain. They are appearing in dangerous concentrations in food, especially in meat, fish, and dairy products.

varying from the differing historical interests of professional disciplines to the corporate influence on regulation of toxic materials. For decades various scientific disciplines have carved out their sovereign territories within which they work. Geneticists, toxicologists, sociologists, educators, and healthcare providers do not seem to communicate easily or frequently enough with one another. A broader perspective looks across professional boundaries and recognizes that interactions among genetic inheritance and social and physical environmental factors challenge a more simplistic understanding of each alone. Meanwhile, the chemical manufacturing industry continues to wield enormous influence in Congress and the regulatory system. Requests for neurodevelopmental toxicity testing of marketed pesticides are ignored and data are virtually absent for all but a few of the industrial chemicals in widespread use.

In this brief report, we review evidence for chemical contributions to some neurological developmental disabilities and explore reasons for the relative silence that surrounds this issue. Some readers may find the material too technical, others too simplistic. Our goal, however, is simply to help advance and inform the discussion so that we might begin to remove our children out of harm's way.

The Magnitude of the Problem

The impact of children's developmental disorders on children and families is immense. Parents, teachers, school administrators, and communities spend increasing amounts of time, money, and energy trying to help children acquire skills that once came more naturally. Afflicted children risk early school drop-out, teen parenting, drug abuse, crime, institutionalization and suicide. A constant, consuming struggle at the verge of failure is known all too well by the children, their families, and providers. The struggle to pull these kids out of the river, or keep them from falling in, is so consuming that we have little time to consider the disturbing question of what put them in this precarious state in the first place.

The number of children known to be affected by developmental disabilities is staggering and appears to be increasing.

- It is estimated that nearly 12 million children (17%) in the United States under age 18 suffer from one or more developmental disabilities, (defined as deafness, blindness, epilepsy, stuttering or other speech defects, cerebral palsy, delay in growth and development, emotional or behavioral problems, learning disabilities).[1] [2]
- Learning disabilities alone may affect approximately 5-10% of children in public schools.[3] [4]
- The number of children in special education programs classified with learning disabilities increased 191% from 1977-1994.[5]

- Attention deficit hyperactivity disorder (ADHD), according to conservative estimates, affects 3 to 6% of all school children, though recent evidence suggests the prevalence may be as high as 17%. [6] [7] The number of children taking the drug Ritalin for this disorder has roughly doubled every 4-7 years since 1971 to reach its current estimate of about 1.5 million.[8]
- The incidence of autism may be as high as 2 per 1000 children. [9] One study of autism prevalence between 1966 and 1977 showed a doubling of rates over that time frame.[10] Within the state of California, the number of children entered into the autism registry increased by 210% between 1987 and 1998.[11]
- Approximately one percent of all children are mentally retarded.[12]

These statistics suggest problems of epidemic proportions. The proliferation of agencies, organizations, networks, and special education programs dedicated to assisting children and families affected by developmental disabilities underscores the magnitude of concern. The cost of remedial programs, though not fully known, clearly places a heavy burden upon the limited resources of educational and social service organizations.

The Origin of the Problem

A variety of explanations have been offered in response to these trends. One line of thought holds that the epidemic is more apparent than real - a product of better detection and record keeping, increased reporting, or a result of rising demands of an increasingly technologic society that places a high premium on the ability to perform more complex tasks at younger ages. While these explanations may be partially correct, they are not convincing for teachers, providers, and parents of affected children. Many who are closest to these children doubt that disabilities of the observed magnitude and incidence can be fully explained by rising expectations, and they can not imagine that such disabilities escaped notice in the past.

Although there is little doubt that many aspects of learning and development are genetically influenced, for the vast majority of these disorders there is no evidence that genetic factors are the predominant cause. In fact, the few syndromes that appear to be exclusively genetic (i.e. Lesh Nyhan, Tay-Sachs, Fragile X etc.) are fleetingly rare. Studies of adopted children and twins shed light on the degree to which genetic and environmental factors contribute to neurodevelopmental outcomes. Although our understanding is incomplete, we are now certain that complex interactions among genetic and environmental factors play extremely important roles. It is no longer in keeping with the state of scientific understanding to attribute the bulk of these developmental disabilities to genetic inheritance. Rather, we now understand that the outcomes are the result of interacting factors, among which are exposures to environmental contaminants that are preventable.

Information about the potential neurotoxicity or developmental neurotoxicity of most of these chemicals is virtually absent.

In this report we review important findings from developmental neurotoxicology, a science dedicated to the study of the impact of chemicals on the developing human brain. It is well beyond the scope of this report to address this topic exhaustively. Rather, we provide a brief overview of the process of brain development, how it may be disrupted by chemical exposures during periods of vulnerability, and concentrate on several common exposures or contaminants. We emphasize that information about the neurotoxic potential of many other chemicals and pollutants is woefully inadequate. We embed this discussion in a larger framework that acknowledges the interactions among chemical, genetic, and socioeconomic factors in the origins of developmental disorders. While the disciplines of biology, environmental sciences, psychology, and sociology are typically separated by distinct methods, concepts, and traditions, an integrated perspective of child development is likely to be much more valid and informative. The child, at the center of this disciplinary fragmentation, will particularly benefit from an integrated perspective that takes advantage of advances in each field.

Chemical Proliferation, Exposures, and Inadequate Toxicity Testing

About 80,000 chemicals are in commercial use in the United States.[13] The great majority of these compounds have been synthesized since World War II and are, therefore, new to the human environment in the evolutionary time frame. Documented and potential exposures are substantial, as indicated by the presence of chemicals in humans (biomonitoring), environmental monitoring, and chemical use and release information. From the moment of conception until reaching adulthood, children are regularly exposed to large numbers of metals, solvents, pesticides and other industrial substances, alone and in complex mixtures.

The degree to which these exposures disrupt development of humans and wildlife is a question of considerable importance and concern. Yet, of the chemicals on the EPA's inventory, even basic toxicity information is missing from publicly available sources for nearly 75% of the top 3000 high production volume substances.[14] Information about the potential neurotoxicity or developmental neurotoxicity of most of these chemicals is virtually absent. For the relatively few chemicals that have undergone developmental neurotoxicity testing, animal tests are used to predict risks of human exposure. Yet, considered in the absence of human data, our experience with lead, mercury, and polychlorinated biphenyls (PCBs) shows that animal tests often grossly underestimate risks to human neurological development. For most chemicals, even animal data are totally missing, and no systematic effort is in place to examine the neurodevelopmental consequences of exposure to mixtures of compounds that characterize the real world.

In summary, large numbers of chemicals are widely used in consumer products and regularly discharged to the environment, resulting in widespread exposures. Our limited understanding of their full neurotoxic potential, has one particularly unsettling implication: What we already know about neurodevelopmental toxic threats to children is likely to be only the tip of an iceberg.

How This Report is Organized

In the following chapters we review the intersection of several disciplines. We discuss the tightly orchestrated, intricate cascade of processes that unfold during brain development, many of which are vulnerable to disruption by environmental factors. We discuss the spectrum of developmental disabilities, their public health impacts, and what is known about their multifactorial origins, including genetics and gene-environment interactions. We review documented links between exposure to a selection of neurotoxic chemicals and traits that appear during child development or in animal testing. In addition, we present evidence of widespread exposure to some neurotoxic chemicals and note the failure of the regulators to require adequate testing for health effects in order to protect vulnerable populations. We also present evidence that developmental neurotoxic effects are not merely a potential threat, but that, for some chemicals, they occur at commonly encountered exposure levels. Finally, an appendix provides a summary of the clinical syndromes addressed throughout the report.

Cautions

As is almost always the case when considering conditions with multiple, interacting causative factors, understanding the cause(s) of a particular child's neurological developmental disability is extraordinarily difficult. This is particularly true when much of the research that identifies risk factors like, for example, elevated lead levels, is based on epidemiological rather than individual studies. Although we can conclude with certainty that, across a population, elevated lead levels during child development will impair cognition and alter behavior, we can never say with any certainty the degree to which those functions are impaired in a particular child because of lead exposure. This is because cognition and behavior are the result of complex interactions among genetic, social, and physical environmental factors. Those interactions are virtually never understood in detail in a single individual, and although it is tempting to attribute a particular outcome in a particular person to one or another factor, such a conclusion is rarely possible. Rather, we must learn what we can from available population-based information, prevent potentially harmful exposures whenever possible, and accept the limits of our ability to assign causes in individuals.

Our understanding of the benefits of treatment after a disability is detected is limited. For example, even though we know that low-level lead exposures will impact brain development, it is difficult to predict the degree to which an individual child will benefit from lowering elevated

lead levels by chelation therapy. However, environmental remediation designed to eliminate ongoing exposures is obviously a sensible first step.

This report is intended to summarize and interpret important research, much of which is largely unknown to the public. The benefits of prudently avoiding exposure to known, suspected, or potential neurotoxicants are clearly implied. The implications of these findings for therapeutic medicine, however, are separate, complex issues that we do not address.

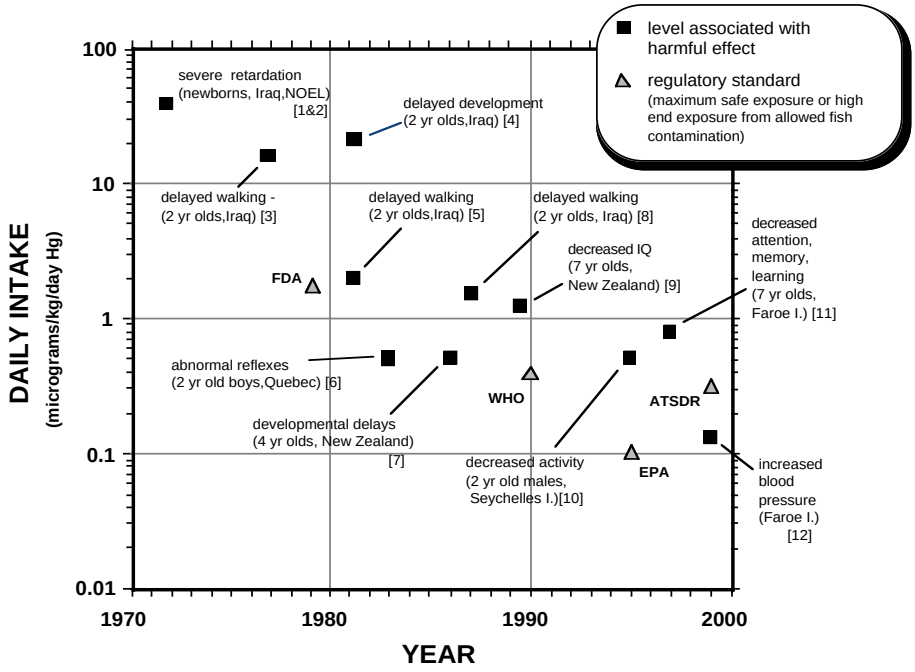
Historical Lessons

Placing our current understanding of these matters in an historical context is, as usual, a worthwhile exercise. The historical record clearly reveals that what are considered "safe thresholds" for known neurotoxicants have been continuously revised downward as scientific knowledge advances. For example, the initial "safe" level of blood lead levels was set at 60 microgm/dl in 1960. This was revised to 10 microgm/dl in 1990 when neurodevelopmental effects became clear at lower levels of exposure during critical windows of vulnerability. Now we know that neurodevelopmental effects occur at even lower levels of exposure, and many neurotoxicologists believe that there is no exposure, no matter how small, that is without impact on the developing brain. Updating the toxic threshold for lead with this new information would result in the addition of millions of children to the roles of those impacted by lead exposure – in addition to the one million currently recognized. Similarly, over the past 30 years, the recognized threshold for harm from mercury exposure has also relentlessly fallen. Recent studies suggest that, like lead, mercury may have no threshold below which adverse effects do not occur.

These observations raise serious questions about the adequacy of the current regulatory regime, which permits exposures up to "toxic thresholds" that eventually become obsolete only after more and more children are injured. What more do we really need to know before concluding that we must take the steps necessary to avoid contaminating food with mercury if we want to protect the developing brain?

It is also important to recognize that the implications of a small shift in some measure of neurological function differ for individuals and populations. For example, lead-related shifts in IQ or other neurobehavioral endpoints may be relatively small on an individual basis, but impacts at a population level are highly significant with broad ramifications. A 5- point decrease in the average IQ in a population of 260 million will increase the number of functionally disabled individuals by over 50 percent (those with IQ's of 70 or less), from 6 to 9.4 million, and simultaneously decrease the number of gifted individuals by over 50 percent (those with IQ's of 130 or greater), from 6 to 2.4 million. This shift translates into increased needs for special education and services as well as a significantly diminished intellectual capacity within the population as a whole.

Declining Threshold of Harm for Mercury



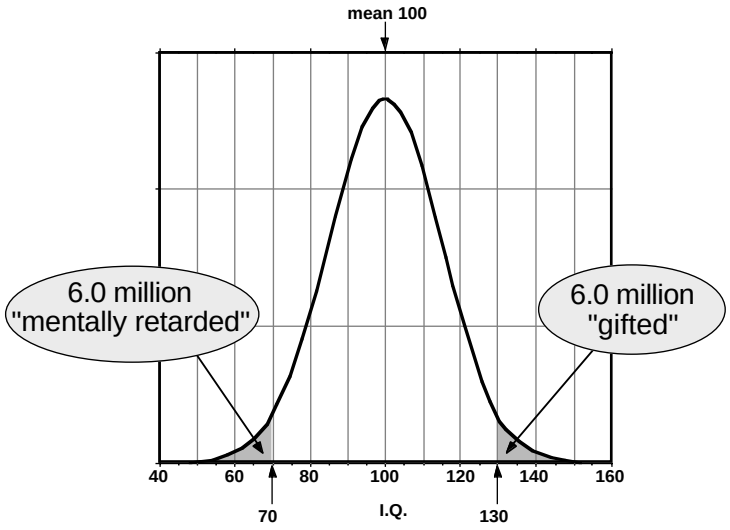
The proven threshold of harm tends to decrease as knowledge is accumulated. This figure shows the trend for one neurotoxicant: mercury. Scientific understanding of mercury's developmental neurotoxicity began with studies of the 1972 epidemic of mercury poisoning in Iraq. At that time case reports of infants severely retarded at birth identified an apparent toxic threshold for mercury exposure of greater than 34 ug/kg/d.[1] [2] (This appeared to be a "no effect level", or NOEL, for severe retardation at birth.) Within a few years, however, it became apparent that many children exposed prenatally to lower levels of mercury were delayed in learning to walk and talk, in spite of apparently "normal" development in infancy.[3] Subsequently, a variety of studies on diverse populations have established progressively lower thresholds for mercury effects by using increasingly sensitive measures of neurological function, and better statistical methods.[4] [5] [6] [7] [8] [9] [10] [11] [12]

A large, recent study has identified deficits in language, memory and attention that occur at prenatal mercury exposures under 0.85 ug/kg/d. This level is less than 3% of the toxic threshold identified in the initial observations from the Iraqi epidemic. The presence of a "discernible insidious effect" on language, memory and attention was noted, however, below even this low level[13] of 0.85 ug/kg/d, suggesting that the recognized threshold for neurological toxicity will continue declining as research methods improve.

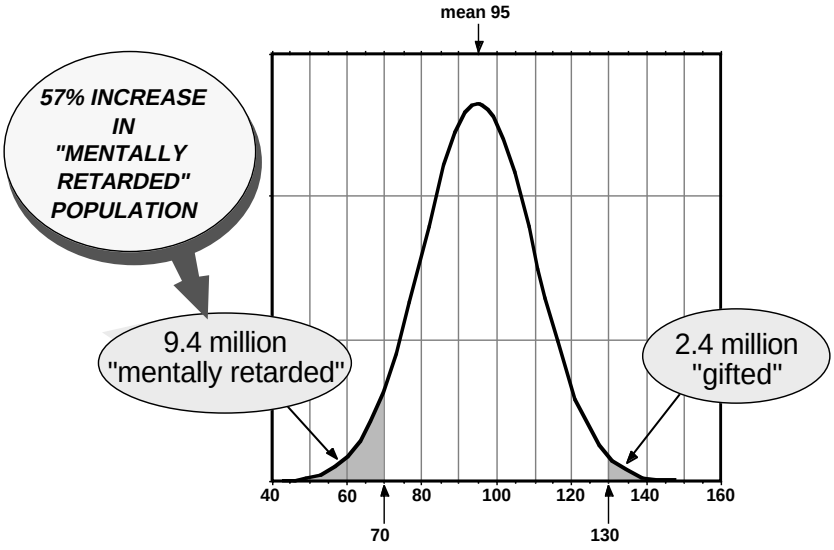
The black squares on the graph represent prenatal mercury exposures associated with adverse neurodevelopmental outcomes. The grey triangles represent World Health Organization (WHO), EPA, and Agency for Toxic Substances and Disease Registry (ATSDR) recommended limits for human mercury exposure. The standard issued by the FDA, it should be noted, regulates the level of mercury in fish, rather than in people. As a result, a wide variety of exposures may occur within the FDA regulatory limit, depending on how much and how often one eats fish, and the mercury level of the fish consumed. The indicated exposure is that of a 60 kg woman eating at the high end of fish consumption (100gm/d, the 95-97th percentile),[14] eating fish which are contaminated at the FDA permitted limit. In this worst case scenario, the woman is exposed to 1.65 ugm/kg/d, or about 16.5 times EPA's recommended safe limit.

Notes- 1.) Studies of the neurodevelopmental effects of mercury generally use hair or blood levels as markers of exposure, since these are more accurate indicators of exposure than dietary surveys. Health-based guidelines, however, are expressed as recommended limits of dietary exposure. For the purpose of comparing data between studies, and for comparing effects levels with regulatory guidelines, exposures as indicated by hair and blood levels of mercury have been converted to approximate equivalent dietary exposures. The quantitative relationships between food intake, hair and blood levels of mercury are described in the ATSDR Toxicological Profile for Mercury.[15] 2.) Study results that identified a range of exposures within which an effect was observed have been shown at the mid point of that range. Due to differences in study methodology, results are not strictly comparable between studies, and shown here mainly to indicate general trends over time.

Original IQ Distribution



Effect of a 5 Point Shift in Average IQ



POPULATION EFFECTS OF A SMALL SHIFT IN AVERAGE IQ

- The upper chart shows the distribution of IQ scores in a population where the average IQ is 100, and the standard deviation is 15. The grey area under the left "tail" of the curve represents the 2.3% of the population with an IQ <70, the score used to define mental retardation. In a population of 260 million, about 6 million people would fall below this line.
- The lower chart depicts an IQ distribution that results from lowering the average IQ by 5 points from 100 to 95. Now, 3.2% of the population, or 9.4 million people have an IQ below 70. This represents more than a 50% increase in the numbers of mentally retarded. The numbers of gifted, defined as those with IQ's greater than 130, have declined by more than 50% from 6 million to 2.4 million. Thus a small shift in average IQ results in greatly increased need for special education and services, as well as diminished intellectual capacity within the population as a whole.[16]

Spotlight

Missing: National Registry for Developmental Disabilities

Public health surveillance systems, such as birth defect registries and programs to monitor exposures to toxic substances, provide opportunities to follow trends, identify clusters, study causes, and plan preventive and service programs. Historically, federal and state government surveillance systems have focused on structural birth defects rather than developmental disabilities. As we have noted, however, some developmental disabilities may be thought of as functional birth defects, though they are often not accompanied by more easily detected structural abnormalities. Although this report is concerned with neurological developmental disabilities, the immune, endocrine, reproductive, and other systems may also function abnormally as a result of interactions of environmental and genetic factors during development.

Public health agencies often consider developmental disabilities quite separate from birth defects, though there is considerable overlap between the two. For example, the Centers for Disease Control and Prevention (CDC) assigns birth defect and developmental disability surveillance to two separate departments, which organize their programs in different ways. Yet, according to the CDC, nineteen percent of those with developmental disabilities also have birth defects, and 6.6 percent of those with birth defects have developmental deficits.

Definitions of developmental disabilities vary from federal to state and state to state agencies, particularly for cognitive disorders, and learning disabilities. This variability makes it difficult to monitor incidence, prevalence, and trends on a regional or national scale.

continued

DEVELOPMENTAL DISABILITY AS A FUNCTIONAL BIRTH DEFECT

Physical abnormalities evident at or soon after birth are readily recognized as birth defects, and chemical exposures are among several known causes of these abnormalities. Familiar examples include the severe arm and leg deformities resulting from prenatal exposure to the therapeutic drug, thalidomide.

Just as chemical exposures can cause defects in the physical structure of a limb or an organ system, early-life exposures can also impair function, often for a lifetime. Although structural birth defects resulting from maternal exposure to some teratogens have been recognized for centuries, functional defects have only relatively recently been recognized as part of a continuum of injuries that can result from prenatal toxic chemical exposures. For example, lifelong changes in endocrine, immune, or neurological function may result from chemical exposures before birth. Functional defects are often less immediately obvious than structural abnormalities, but are no less important since they constitute permanent impairments in the ability of an organ system to perform its function.

Public Interest Concerns

Public health and public interest groups have expressed three major concerns about ongoing surveillance activities:

1. Exposure data lacking

Environmental monitoring databases may be the only information available and are sometimes used, though those data are even less accurate surrogates of exposure levels.

Monitoring or estimating exposures to environmental contaminants, as well as health outcomes, is essential to identifying environmental factors that may be responsible for unexplained birth defects and developmental disabilities. Even a well-designed and implemented birth defect registry will have limited value if exposure data are lacking. Exposure monitoring may be accomplished by biological sampling (biomonitoring) or less accurately, by maternal questionnaires. Biomonitoring may include testing umbilical cord or infant blood, maternal blood, or maternal hair samples for metals, and other chemicals. DNA sampling can be used not only to examine for genetic causes of abnormalities but also, in some instances, to examine for exposures, since some toxicants leave a chemical specific "DNA fingerprint." Environmental monitoring databases may be the only information available and are sometimes used, though those data are even less accurate surrogates of exposure levels.

2. Developmental disabilities not included

Although major structural birth defects certainly deserve attention, many functional defects or developmental disabilities, including cognitive and behavioral abnormalites, remain uninvestigated. Surveillance for developmental disabilities, other than mental retardation, cerebral palsy, hearing and visual impairment, and epilepsy, is largely non-existent on a meaningful scale. In part this reflects the difficulty and expense encountered in establishing a large surveillance system for other disorders, but may also signal a reluctance to pursue incidence and trend data too aggressively because of the economic implications of diagnoses with attached mandated services.

3. Privacy concerns

Programs that include banking DNA or other biological specimens raise concerns about privacy and confidentiality. Some analytic data are predictive of future health or disease and have profound implications for insurability or employability. Because of concerns about unauthorized disclosure of information, individuals are often reluctant to participate in public health research projects that include the collection of personally identifiable data. Study participants usually lack ultimate ownership and control of data, and efforts to protect the privacy of individuals do not necessarily overcome underlying fears of inappropriate disclosure. The need for limited access to medical information by insurance companies, potential employers, health maintenance organizations, and others is recognized, but what the limits should be and how they are to be enforced is widely debated.

Mohawk Women's Breast Milk Study: Community Based Research Model

The Mohawk women's breast milk study was a research project designed to address concerns about privacy and data ownership. Investigators wanted to study the relationship between fish consumption and PCB breast milk contamination among nursing Mohawk women at Akwesasne, along the St. Lawrence River. Previously, PCBs from a nearby General Electric facility had been dumped or spilled onto Native American lands or into the river, contaminating soils, sediments, and the food chain. Mohawk women were reluctant to agree to participate in a study of their breast milk, without fundamentally restructuring their relationship with investigators from the New York State Department of Health. Rather than allowing outside experts to conduct a study in which community members would be passive participants, Mohawk women insisted on a more co-equal relationship in which they would assist in study design as well as own and control the analytic data. The study and results have been published in peer-reviewed journals.[1] Community members are among the authors. Breast milk PCB levels declined in the last three years of the six-year study, perhaps as a result of more consistent attention to advisories recommending against consumption of local fish by pregnant and nursing Mohawk women. This experience may serve as a useful starting point for dealing with concerns about privacy, confidentiality, and control of data in other circumstances.

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Citizen Database Fills Government Void

(With information taken from a piece written by Betty Mekdeci, Executive Director of the Association of Birth Defect Children, for *Birth Gazette*, Fall, 1997, with additional information added from a presentation by Ms. Mekdeci in October 1999)

The modern study of teratology (the study of birth defects) was born out of a world tragedy that occurred in 1962—over 10,000 babies born deformed as a consequence of their mothers taking the drug thalidomide. The National Birth Defects Registry (NBDR) was born out of the frustration of mothers, educators and other concerned citizens that critical information about birth defects and developmental disabilities was not being collected in the United States. It was created and is sponsored by the Association of Birth Defect Children with Betty Mekdeci at the helm. For twenty years Mekdeci has led a crusade to unravel the mysteries of why birth defects occur. Her efforts have brought her into the halls of Congress and into the lives of thousands of parents.

Like a sleuth collecting clues, the NBDR compiles information directly from the parents of infants and older children with birth defects, including functional defects that may go unrecognized at birth. Over 10,000 questionnaires have been distributed to try to piece together the puzzle of what has caused abnormalities ranging from limb deformities to learning disabilities.

The database has recently been utilized to analyze disabilities in the children of Vietnam veterans, with some disturbing results.

The database has recently been utilized to analyze disabilities in the children of Vietnam veterans, with some disturbing results. The registry has revealed a pattern of functional problems in Vietnam vets' children that includes significant increases in learning and attention problems, chronic skin disorders, benign tumors and cysts, allergic disorders, growth hormone deficiency, chronic infections, emotional/behavioral problems, prolapsed heart valves, and a range of conditions that may be consistent with a malfunctioning immune system. This pattern of disabilities is consistent with other research suggesting prenatal effects of dioxin on the developing immune system. The Vietnam veterans data has been presented to Congress, and cited in the report "Veterans and Agent Orange" (dioxin is a constituent of Agent Orange, the defoliant used in Vietnam).

This is no amateur operation. The questionnaire used to compile these findings has been evaluated and endorsed by a seven-member advisory board of national experts in reproductive biology, epidemiology, endocrinology, biochemistry and environmental biology. It is designed to act as an alert practitioner on a grand scale by searching for the "fingerprints" of teratogens. The reporting parent is also asked about the pre-conceptual exposures of the mother, and the father and mother's exposure history during pregnancy. Data from questionnaires are entered into a customized computer format, and automatically entered into more than 20 separate tables that can be connected in multiple ways for data analysis.

A recent report by the Pew Environmental Health Commission entitled "Healthy From the Start: Why America Needs a Better System to Track and Understand Birth Defects and the Environment," outlines the deficiencies of the state and national data collection systems for these disabilities. This is not news to Betty Mekdeci and her colleagues in Florida, who have been listening to the cries of the disabled children for decades.

The Association of Birth Defect Children, Betty Mekdeci, Executive Director, can be contacted at 930 Woodcock Road, Suite 225, Orlando, FL 32803. 407-245-7035. www.birthdefects.org

Footnotes to diagrams

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