

Environmental Effects on the Central Nervous System

by George W. Paulson*

The central nervous system (CNS) is designed to respond to the environment and is peculiarly vulnerable to many of the influences found in the environment. Utilizing an anatomical classification (cortex, cerebellum, peripheral nerves) major toxins and stresses are reviewed with selections from recent references. Selective vulnerability of certain areas to particular toxins is apparent at all levels of the CNS, although the amount of damage produced by any noxious agent depends on the age and genetic substrate of the subject. It is apparent that the effects of certain well known and long respected environmental toxins such as lead, mercury, etc., deserve continued surveillance. In addition, the overwhelming impact on the CNS of social damages such as trauma, alcohol, and tobacco cannot be ignored by environmentalists. The effect of the hospital and therapeutic environment has become apparent in view of increased awareness of iatrogenic disorders. The need for particular laboratory tests, for example, examination of CSF and nerve conduction toxicity studies, is suggested. Epidemics such as the recent solvent neuropathies suggest a need for continued animal studies that are chronic, as well as acute evaluations when predicting the potential toxic effects of industrial compounds.

Philosophers, historians, and scientists all respond to the effects of the environment, but each perceives it differently. An historical event is different to the man who reported it fresh than it appears to the historical researcher a century later. The facts of one generation become fancies or fables of the next. Each interpretation of the environment is unique for different individuals and in different cultures; and personal slant, bias, or pécadillo assures that each interpreter responds in his own fashion. Not only is the perception and reporting of responses complex and varied, but actual physical variability in responses to the environment is similarly complex. Even dizygotic twins exposed to the same toxin in the same uterus at the same time may vary in the amount of damage they display (1). Individuality and how it limits response, perception, or performance is not the subject of this monograph. Rather, this review reports what may happen to any vulnerable nervous system when it is exposed to a toxin or stress. The effect of environmental stress may well differ for each individual species, each personality, and each combination of genes, and this review can be concerned with only a small part of what has been reported to happen. Some effects of the environment are equivocal or

uncertain, some beneficial, and a few are clearly deleterious. It is the deleterious effects that are of interest in this review.

In addition to the anatomical classifications used here, there are many potential ways to classify the effects of the environment on the CNS. Logically, the environment itself (trauma, drugs, water, radiation, etc.) could be the basis for classification. Instead, much of this review is classified by particular sections of the CNS, (cortex, cord, etc.) and uses subcategories to include lists of toxins. Other organ systems (heart, lungs, kidney) are not specifically covered, reflecting the neurologists' bias that all other organs are in fact only supportive to the CNS and indeed have purpose only if the CNS functions. It is more convenient to ignore the multiple disasters to the CNS when supportive systems do fail than to pretend to discuss these supportive systems. Since the CNS is designed to respond to the environment, responses are to be expected and these responses in turn lead to secondary and tertiary effects of each upon the other. Secondary ripples and interrelationships are not emphasized, though many probably deserve particular study.

Classification of CNS responses, in addition to the basic anatomical orientation used here, could emphasize selective vulnerability, critical periods,

*Neurological Association, Inc., 931 Chatham Lane, Columbus, Ohio 43221.

behavioral responses, genetic predisposition, or neuropathologic responses to injury. Selective vulnerability is discussed as an example of the potential importance of just one of these subjects.

Selective Vulnerability

Selective vulnerability suggests a special responsibility of particular areas of the CNS to certain agents and numerous examples abound from all the neurosciences. The polio viruses (which also once selectively decimated particularly defenseless population groups) selectively damage anterior horn cells. Some polio patients present with a failure of respiratory neurons, a few with rare conditions such as cerebellitis; but the major brunt of the attack is on the motor cells of the anterior horn in the spinal cord, while sensory neurons are completely spared. The clinical weakness is often asymmetrical, suggesting that even the anterior horn cells of each side of the cord are not assaulted in an identical fashion. The localization to the anterior horn cells is so prominent that the clinical features of this viral disease were identified and prevention anticipated before other viral disorders of the CNS were recognized at all.

Herpes simplex is another strangely selective agent which in vulnerable individuals does not stay confined to a "cold sore" on the lips or to a smoldering venereal disease, but rather spreads to the medial temporal lobes and produces severe and permanent necrosis. Damage to the temporal or limbic areas by this virus can permanently alter memory or emotions. Such temporal localization by herpes could be due to a biochemical affinity between the virus and the temporal or limbic areas but the exact cause for such localization is unknown. Other viruses demonstrate other tastes. For example, the cerebellar lobes in cats can be devastated by a viral panencephalitis; and the common chickenpox virus of humans can also lead to major destruction of the cerebellum. Perhaps even more unique (because it depends on a certain species, plus immaturity, and damage to a particular region), is the destruction of the ependymal cells which can follow infection with mumps virus. A remarkable series of projects by Johnson and others revealed that this virus can lead to a later hydrocephalus following destruction of the ependymal linings in the ventricles of suckling animals (2).

Selective vulnerability is not limited to the effect of viruses on a single level or region of the CNS. Particular cells within a region may be responsive to certain drugs. Phenytoin can produce mild decrease in crispness of intellectual responses (3) in any patient, but occasional patients are so sedated

by this generally safe drug that it cannot be utilized in therapy. The individual variability in response to phenytoin can reflect abnormal parahydroxylation of the drug in the liver, constipation which changes absorption, pregnancy, or even results from major genetic differences in metabolism. When vulnerable individuals receive excess phenytoin (for them and their metabolic pathways) there can be a transient or a permanent cerebellar ataxia. Therapeutic and moderate amounts of phenytoin may stimulate the same Purkinje cells that are damaged by larger amounts of the drug, and there has been informal suggestion that stimulation of the cerebellum by phenytoin is part of the explanation for its anticonvulsant effect. The phenytoin story is even more complex than this brief summary, however. The same drug can lead to an increased incidence of cleft palates in human offspring of epileptic mothers as well as in mouse embryos after pregnant mice are fed phenytoin. In the toxic clefting phenomenon, once again, a vulnerable creature is injured at a certain time.

There are other drugs as relatively specific as phenytoin plus many drugs that are as nonspecific in their effect as alcohol. Alcohol, most particularly when linked with dietary insufficiencies, can effect the peripheral nerves, the periventricular region, mamillary bodies, or even the cortex. It is hard to separate the effects of alcoholism from the effects of poor nutrition, trauma, and associated drugs; but many believe that excess alcohol itself can produce significant cortical deterioration. Abuse of alcohol can certainly be linked with cerebellar deterioration. The mechanism is uncertain since the afflicted persons have often suffered from dietary irregularities as well as alcohol abuse, but the general linkage of alcoholism and cerebellar symptomatology is clear. The ataxia and slurred speech of acute drunkenness is similar in pattern to the permanent deficit seen in patients with alcoholic cerebellar degeneration. A temporary metabolic derangement, drunkenness, is eventually succeeded by a permanent anatomical lesion, cerebellar degeneration. Even within groups of alcoholics the vulnerability appears widely varied. Red wine drinkers may develop deterioration of the corpus callosum, another group of imbibers develops peripheral neuropathy, and some of the alcoholics seem to manifest intermittent alcoholic blackouts or withdrawal seizures. The exact cause for the particular vulnerability of a certain individual is often obscure.

As alluded to above, selective vulnerability can also relate to a particular period in the developing CNS. Too much, too little, or too rapidly changing; all varieties of homeostatic disturbances can damage the developing organism. The damage from a

protein-caloric deficiency, for example, is profound when it assaults the cerebrum of an infant, although a similar effect may be hard to detect in an adult. X-ray insult to the CNS varies not only between patients (3000 rads leading to damage of the CNS in one patient, another patient almost untouched by 5000 rads), but the severity depends on the age of the subject. In the fetus an entire organ system, the cerebellum for example, may be vulnerable during early development but immune a few weeks later. The cerebral areas with the most rapid metabolism, greatest local response to the toxin, most tenuous support systems, or with preexistent injury are most vulnerable. One general and repeated lesson from the CNS is that it is not only the character of the toxin but the overall state of the substrate that determines the response. Secondly, almost anything that produces a temporary effect can produce a similar permanent effect.

A related phenomena to selective vulnerability is the concept of critical periods. Critical periods implies staged development on a ribbon of time, and after passing a certain age marker the creature is no longer receptive or vulnerable. There may be only one precise period when development or learning can occur maximally. In birds, imprinting represents an obvious example. There is a short or finite time during which the baby duck can become attached either to its mother or, when mother is absent, to the keeper's foot. Imprinting, as Gottlieb (4) and others have shown, can be changed by prior conditioning to meaningful but unnatural sounds. No matter how imprinting is studied, there is a time during which changes must occur if they are to be effective, and after a critical period the animal may never assume the prior level of performance or may be fixated on an inappropriate object. Hubel and Weisel (5), in their now classic work on the visual cortex and lateral geniculate of kittens, demonstrated that if the animal is blindfolded early in life the lateral geniculate may never function adequately. The electrical field of the visual cortex also deteriorates to below the level present at the time light was excluded. Amblyopia exanopsia may be an example of a similar phenomena in humans. The retina may be normal, the cortex normal, but if one eye is deviated laterally long enough the image is permanently ignored and the function of that eye is irreversibly reduced.

Many psychologists, psychiatrists, and even moralists confirm that there are indeed critical periods of behavior in humans. Certain adjustments to the environment are appropriate at different ages and if not attended to properly and at the correct time, maximum ability may always be thwarted or lost. Any person has observed this in motor

skills—there is an optimal time to learn to ski, or skate, ride a bike, or hit a baseball. Failure to develop and utilize a system when it matures can thwart maximum performance in adulthood.

Some of these examples of selective vulnerability and critical periods are more speculative than scientific, others are patently self-evident. There exist extensive data, not reviewed here, that suggest neurophysiologic responses of the CNS can be enhanced by usage, often studied with electroretinogram, electromyograph, or nerve conduction. These neurophysiologic responses can be impeded by toxins and might be accelerated by early or enhanced demands.

This chapter organizes the effects of the environment on the CNS by an anatomical system and only secondarily by toxins or stresses.

Relevant Cranial Nerves

CN I (Olfactory)

The sense of smell is a major force in human behavior, to judge from the volume of advertising by the perfume and soap industry, though the power of olfactory stimulation is repressed or unrecognized by most adults. In other creatures, odors affect sexual arousal and hormonal function, as documented in an immense zoological literature. Olfactory phenomena may also affect feeding behavior and even in humans can certainly heighten enthusiasm for drink or solid foods. Olfaction may be useful in primitive societies to avoid dangerous toxins, and it is possible that evolutionary benefit or personal survival was once supplied by a desire for cleanliness. Olfactory sensitivity diminishes with age, but even when it is total, anosmia is rarely considered a major handicap. The armed services usually allows only a ten percent disability for a total loss of sense of smell.

The olfactory nerve is probably the cranial nerve most commonly destroyed in head injuries (6). Such rupture of olfactory nerve filaments at the cribriform plate is usually inconsequential for a well adjusted person. In addition to trauma and to congenital or to familial anosmia, acute viral illnesses can produce anosmia. It is possible that some metals (such as zinc) have a role in olfaction, but at present the relationship of olfaction to these agents is poorly defined. It is recognized that nasal, palatal, and other midline defects can result from teratogens, including particularly phenytoin and other anticonvulsants, but there are no data regarding an increased incidence of anosmia in children of epileptics who received anticonvulsants during pregnancy.

CN II (Eye)

The cornea can be scarred or damaged by infectious (viral, bacterial, or fungal) and by literally thousands of traumatic and environmental stresses (7). Certain traumatic agents such as pine or metallic dust can have special ophthalmologic significance. Trauma to the eye in sports and industry has been reduced by adequate helmets (football), waterproof glasses (prolonged swimming practice), and shielding glasses (industry). Metabolic insults to the eye include some of the aminoacidurias and galactosemia, neither a major public health problem but of medical importance since a few individuals with selected metabolic disorders can be helped by special diets.

It appears likely that anyone who lives long enough may develop a cataract of the lens and might also develop corneal opacities. There is no current metabolic explanation that explains the cause for the various familial types of cataracts, some of which have markedly different ages of onset, but environmental factors are not usually suggested as causal. The reduction in ability to tolerate glare (as on the highway) combined with a dislike for dim light is partly related to corneal and lens changes of aging and is so common that it deserves notice in lighting, highway, and vehicular designs whenever senior citizens are involved.

Cataracts related to diabetes, as well as other familial causes for cataracts, are of particular medical interest; but there is little firm evidence that modification of the environment accelerates or retards the development of such cataracts. Advice for a prudent diet, and in some families a trial of a low sugar or low fat diet, probably will not be completely preventive but is worth consideration. Food additives are reviewed in other chapters, there are no additives that are yet conclusively linked with significant ophthalmologic disease in man. Nevertheless, certain drugs, particularly phenothiazines in prolonged high dosage, can predispose to cataract (chlorpromazine) as well as to retinal changes (thioridazine) and other environmental factors may await discovery. Since the population group at greatest risk for iatrogenic (phenothiazines) cataracts is those patients in state institutions, and since medical care can be abominable in such institutions, routine ophthalmological monitoring can be considered for such populations (8). "Drug vacations" have also been suggested as a prophylactic measure, although such therapy interruptus is rarely employed, even though the psychiatric effect of the drugs is long lasting.

In addition to responding to drugs the retina is also affected by prenatal infections, including some

possibly preventable ones (toxoplasmosis, rubella) and others, some of which are theoretically preventable. A major epidemic of optic neuritis and myelopathy has been tentatively linked to cloquinal (9). Other retinal toxic states such as those resulting from alcohol and tobacco might, probably very theoretically, also be preventable. Though rare, the presence of visual and neurological symptoms in tobacco-alcohol amblyopia does occur and has been related by some to cyanide toxicity from cigars. Similar visual symptoms due to cyanide toxicity may occur in African patients with exclusive diets of cassava root (10). Ethambutol, methyl alcohol, and similar toxins are currently rare causes of blindness, and in most of these cases the source of exposure is usually clear. There are some familial groups for whom the optic nerve may be at particular risk, for example in individuals who have inherited a tendency to develop Leber's optic atrophy (11). Though partially sex-linked, the inheritance pattern in Leber's atrophy is variable and blindness may result from the effects of environmental factors on a vulnerable genetic substrate. In view of this example, plus the well accepted changes secondary to phenothiazines, it is impossible to discount the role of as yet undiscovered toxins in "idiopathic" retinal deterioration.

The importance of "minor" eye problems, such as amblyopia exanopsia, has become more apparent with each decade, as reflected by the steady lowering of the age at which surgery is attempted on the eyes of afflicted children. The magnitude of failure of vision in the unused eye reflects the length of time the image from the deviant eye has been suppressed. Less certain, but recently suggested in England (12) is the possibility that failure to develop strabismus and even overt dyslexia can originate from mild and undetected degrees of strabismus present very early in life.

Portions of the story of retrolental fibroplasia (RLF) can be used to illustrate the complex interaction of environment, predisposition, medical research, social, iatrogenic factors, and a resultant damage to vision. Over two decades ago it was apparent that RLF was a major cause of blindness in some areas (New York State) but almost nonexistent elsewhere (in Charity Hospital in New Orleans). RLF was clearly associated with prematurity; and attempts to expose the neonate to more or to less light, to vitamin A, and to more or to less antibiotics were all reported (13). None of these factors were relevant. RLF represented a new medical disorder and one that could be recognized even during the period of its development. Eventually the role of new technology as the basic cause of disease became apparent as the link of RLF with

incubators that could supply 100 percent oxygen was discovered. The relative lack of RLF in blacks and in other groups was thus explained, they were just not treated in incubators in the same fashion. A simple preventative measure also became available—just do not give too much oxygen. Even after the cause was clear, a federal cooperative study was undertaken and there was a delay of several years before this disease of technology became fully publicized. There still remains need for investigation into the optimal level of oxygen needed to avoid RLF and yet supply enough oxygen to avoid a significant cerebral defect, since a deficit in oxygen can create cerebral palsy.

Hearing and Vestibular (CN VIII)

The auditory and vestibular centers begin to develop in the fetus even before maturation of the visual system and perhaps the accelerated early development is partially due to environmental factors *in utero*. Sounds, including meaningful voices, are perceived early in life and are crucial for normal neural and emotional development. Clinicians often consider the psychological affect of profound deafness to be greater than that of profound blindness. Even for normals absence of sound contributes heavily to the effect of sensory deprivation. The role of excess sound in psychological development is more controversial, but there can be presumed to be an impact of background noise or music (or deliberate combinations of both) in our culture. There are suggestions that noise contamination affects behavior. Hearing, which can be permanently lost due to noisy occupations (14), may be transiently reduced by even one trip on a noisy rapid transit system (15). In certain occupations which are characterized by either very noisy or very quiet working conditions, deprivation of meaningful sound might lead to features reminiscent of a sensory deprivation experiment.

Drugs can be otologically selective in that for some individuals the major neurologic side effects of these medicines is damage to CN VIII, as with streptomycin, minocycline, garamycin, etc. (16). In the fetus, thalidomide produced gross anomalies of the ear, as well as the better known phocomelia (17). Even alcohol can produce a transient decrease in hearing function, as in one recent study on pilots (18). It is possible that major insults to hearing are additive and monitoring of auditory functions may be wise for some individuals receiving ototoxic drugs.

Cortex

Although recognized as a major problem in un-

derdeveloped countries and during wartime, protein-caloric deficiencies and vitamin deficiencies are rarely a clinical problem in the U. S. (19-21). Food faddism has become a major industry, however, and subgroups in our land not only avoid, but may favor unduly, certain food groups or substances: and in rare individuals eating becomes a religion that interferes with optimal health care. Even in normals, very poor nutrition can deleteriously affect cerebral function, as in the various avitaminosis that still occur occasionally. Chronic iron deficiency is a common affliction of rich and poor and continues to exist even in today's affluent society. Excess nutrition in vitamins is of as much lay concern as the more obvious excess caloric intake of most Americans. Strongly held opinions about self-administrations of various megavitamins or iron preparations is a common basis for discussion in the physician's office, but fortunately with the exception of vitamin A or D intoxication (22), most fad diets and most mild deficiencies or excesses are probably harmless unless they deflect from more rational efforts to secure health. Varied dietary patterns in pregnant women do continue to deserve study, however, though conclusive linkages with toxemia, fetal wastage, etc. is unclear. Hyponatremia and similar therapeutic misadventures are preventable errors in nutritional support (23).

Infection can affect not only the cortex but also any other portion of the nervous system. Susceptibility to infections depends on prior exposures plus general resistance, and certain groups at particular risk will continue to deserve surveillance. Diseases in young military recruits (meningoencephalitis) (24) warrants continued study, and there is much to be learned from many special and potentially epidemic situations encountered in residential schools or state hospitals. Animal reservoirs of infection in the environment deserving regular surveillance are pigeons (cryptococcus) (25), other birds (sparrows or starlings and St. Louis encephalitis), or domestic animals (porcine streptococcus or influenza) (26). Brucellosis (27), an abattoir-associated disease, is often associated with headache or visual symptoms. Public education may be needed regarding cherished pets, as in toxocara canis infestation or psiticoccus (28). The entire pattern of CNS infection may be changing; as is the medical awareness of certain infectious disorders. The prolonged effect of continued intracranial activity of the rubella virus is one example, as is the unusual manifestation of a measles-like virus seen in SSPE. A slow course following viral infection, or a "slow virus" disease, remains at least one conceivable potential effect of a program of inoculation with attenuated virus. The increased aware-

ness of "slow viruses" in the CNS demands continued caution in the planning for the release of such attenuated viruses for vaccinations. There have been reported cases of transfer of the viral degenerative state called Jakob's disease to individuals who received corneal transplants from persons who suffered from this virus (29).

Brain tumors can be produced experimentally by several organic compounds, particularly the nitrosoureas. In contrast to some types of bladder tumors, where over 50% seem to be a response to environmental toxins, there is little firm data regarding brain tumors in humans. Radiation therapy and chemotherapy, perhaps in a summative fashion, can lead to new neurologic syndromes (30, 31).

According to Caviness, accidental death and disability in our time has achieved a magnitude comparable to that of the plagues of the middle ages; with the cortex and brain as major recipients of the trauma (32). There were 8,111,000 head injuries in the U. S. in 1974, and over 1,900,000 of these were serious, with 6,600,000 days of hospitalization. Caviness estimates that 140,000 of these cases will develop seizures that will be persistent (7% of serious head injuries). At times new neurologic disorders (subdural, epidural, hygroma) other than seizures also occur months after injury (33). The incidence of post-traumatic seizures reflects constitutional and genetic factors, the extent of injury, and may be affected by prophylactic use of anticonvulsants (34) or anti-edema agents. The deficits are by no means limited to seizures, and many of the same patients have dementia or focal sensory and motor loss. The amount of intellectual function relates largely to the extent of trauma and to the quality of the brain before injury; but environmental and educational factors may also affect recovery. Relatively simple measures, perhaps some not yet considered, can reduce or prevent the extent of injury. As early as three decades ago, crash helmets were recommended for cyclists (35-37), but they are still not universal. Indeed, head injuries occur in as high as 30% of motorcycle accidents (38). Reduction in speed limit, improvement in driver skill, optimal design of vehicles, and protective devices are all relevant health concerns. Less clear is the long term effect of minor trauma such as repeated brief unconsciousness in teenage football players. Recognized and unsuspected birth trauma is generally accepted as a major cause of seizure disorders, but precise figures are hard to obtain. As the major environmental danger to life in the young, the potentially most economically shattering of illness, a cause of major and distressing morbidity, and one of the least studied of CNS disorders the incidence and type of major and minor trauma of the brain and

spinal cord deserves attention in any evaluation of the health of the environments available in this country.

Convulsions of other types than posttraumatic include febrile seizures, which may not be as innocuous as once was supposed. There is data from recent "kindling" studies that suggests that the threshold for future seizures can be lowered by repeated subclinical seizures (39). Complaints regarding the delay in release of anticonvulsants has been commented upon by both national neurological organizations (American Neurological Association and American Academy of Neurology) and intensive survey of potential benefits as well as the side effects of all anticonvulsants is highly desirable in view of their widespread need and use. The risk of death and injury in uncontrolled epileptics is significantly increased (40). Certain special phenomena, as convulsions after burns (41), or due to certain unusual toxins (such as Borax) (42), or from drug withdrawal may have significance for the environmentalist; both in research and in education. The complexities of "epilepsy" can be illustrated in many ways. One example is infantile spastic hemiplegia (43, 44). This condition may follow a high fever, particularly in a child who has developed marasmus or dehydration due to illness or neglect. Focal neurologic disease such as flaccid hemiparesis gradually evolves into spasticity with seizures and these in turn are affected by the availability of medical care. Each new case is unique and special, but attention to general health care, use of adequate anticonvulsants and an optimal educational environment may make the difference between a disgruntled crippled epileptic and a useful taxpayer.

Specific toxins that affect the cortex and CNS are almost innumerable, and their effects marvellously variable. Brief, selective, and very incomplete mention is offered as a reminder of the variety, and attention should be called to the extensive recent handbook for details (45). Lead causes encephalopathy in children and usually a neuropathy in adults, although encephalopathy can occur (46). Possible behavioral effects have been attributed to subclinical levels of lead in the environment. Mercury usually causes a neuropathy, but can produce both agitation and tremor. Mercury can be obtained through industrial exposure and as a pollutant in water. Mercury has been recently linked to disease in special population groups, including North American Indians. Arsenic is notorious for its presence in illicit alcohol and in concoctions from murderous relatives, but may also be increased in subclinical amounts in farmers who use insecticides. Thallium is a rare poison now, due to elimination

from over-the-counter solid rat poisons. Manganese deficiency has a controversial role in production of tremors or seizures in alcoholism and in other disorders, and toxicity from excess manganese can lead to cortical changes following prolonged exposure to manganese in animals and in humans. Monosodium glutamate is an almost ubiquitous agent that is rarely linked with disease in humans, but has been an experimental cortical toxin (47, 48). Glutethimide (49) and similar soporifics can represent very difficult problems when presenting as an overdose and any emergency room can testify that these and similar agents are very readily available in the community. Jimson weed contains organic toxins with marked anticholinergic affects and the plant is not controllable in the fields, although proper medical education may prevent death from the severe anticholinergic poisoning that results from ingestion of the plant. Hexachlorophene can cause damage to neuronal systems in experimented animals such as rats (50), swine (51), and possibly in humans (52-54). Marijuana has been linked to an "amotivational" syndrome (55). Hypoglycemia and hypernatremia are often both preventable causes of cerebral damage in infancy. Hypocalcemia in the fetus, particularly when associated with low calcium levels in the mother, may also be preventable (56). Carbon monoxide requires additional study regarding its effect through prolonged subclinical exposure (57, 58). There are reasonably good laboratory techniques available for study of this common environmental hazard. Vitamin A, as is well known, can produce severe cerebral edema when taken in excess.

Alcohol may well be the most all pervasive and widely used noxious drug in America. Even before birth, effects of alcohol abuse can be manifested in the "fetal alcohol syndrome" which includes malformations, small size, retardation, and other anomalous features in children born of alcoholic mothers (59-61). Alcohol predisposes to trauma of the brain (as contusion, subdural, epidural) and to peripheral nerve injury by entrapment or direct injury. Alcohol is a major cause of acute seizures in adults; in one study over 40% of acute admissions to hospital were abusers of alcohol (62). Combined with vitamin deficiency (Korsakoff-Wernicke Syndrome, cerebellar atrophy, etc.) or in withdrawal states (tremor, fits, delirium tremors) the secondary results of alcohol affect all regions of the CNS (63, 64). Furthermore, for many drugs metabolism is changed in acute alcoholic states (65). The alcoholic is at greater risk for infection, malnutrition, deprivation, and medical misadventure; but there well may be no truly useful environmental recommendations at this time (See recommendations below).

Additional research is indicated in the management of withdrawal states from alcohol and other drugs, as well as in study of other toxins associated with alcohol and in their combined neurochemical effects. Reasons for the high incidence of alcoholism in particular groups (Indians, Irish) or low incidence in other groups (Jews), continues to be worthy of study. Continued study of the direct effects of alcohol alone, as well as in clinical settings in which there is little malnutritional and vitamin deficiency, as in alcoholic dementia, seems indicated (66).

The largest single group of understudied neurologic disorders is the presenile dementias. Alzheimer's disease is a major public health problem, and up to 25% of state hospital patients over 60 suffer from this disease. Possible environmental causes (slow infection or aluminum intoxication) deserve increased study in the next decade.

Occipital Lobe

Among the special groups of patients who are at particular risk from the environment are residential students in institutions for the blind (some of which house both blind and deaf). Endemic infections, intoxications, and poor medical care can occur in these settings and in any similarly closed institution. In addition the eventual intermarriage of students is very common, and such marriages can lead to complex sortings of genetic disorders. Since many inherited forms of deafness or blindness are recessive, the offspring of these matings are often normal, and the severely handicapped and frequently devoted parents create a special environment for the child. There has been little involvement of organized medicine in such institutions even for the education of medical students. The results of efforts, at times almost punitive, of teachers or house mothers to eliminate unwanted features which are common in the behavior of the blind ("blindism," stereotypes such as rocking, awkward gait) has not usually been considered a social or pediatric problem. It is possible that this particular environment offers unique opportunities for behavioral and epidemiological studies.

The cortex and the white matter, can respond with demyelination to certain anesthetics, such as halothane (*in utero*) (67), as well as to recognized, overlooked, or inadvertent anoxia. Speculation regarding primary environmental factors in multiple sclerosis (MS) has abounded, partly because of the well known geographical distribution of the disease. Influenza or enteric viruses have been implicated, without certain proof. Immunologic features of the

patients with MS may well be contributors to the development of the disease. Much patient interest exists in special diets (gluten-free, lecithin, unsaturated fats, vitamin E), but there is no substantial evidence that special diets produce, predispose to, or ameliorate MS.

In the first task force report (68), there is an interesting allusion to vibrating tools producing damage of the CNS, and more recent references exist (69). Except in entrapment neuropathies, vibration in the environment is usually considered more nuisance than danger.

Some acknowledgement is necessary regarding the alarming increase in overdose problems of all kinds. Certain drugs, such as the atropine group (tricyclics, anti-Parkinsonian) may respond to particular antidotes such as physostigmine. These drugs when used even in small doses can affect memory, although deleterious long term effects are unclear. The development of drug treatment or information centers have been useful resources for the practitioner of medicine and new clinical problems or varieties of old ones will continue to deserve publication and study by directors of such drug treatment centers. There is no current convenient and rapid monitoring system to alert the medical community of a new form of drug intoxication or overdose.

Basal Ganglia

Barbeau has suggested that Parkinsonism represents an aging phenomena that can be accelerated by toxins, infections, or trauma (70). It is certainly true that the appearance in "normal" aging includes many extrapyramidal features, and it is probably not surprising that numerous toxins (particularly metallic ones) appear to cause accelerated dysfunction of the basal ganglia. Several of these toxins deserve special mention. Wilson's disease has a relationship to copper, can be diagnosed with relevant laboratory tests, and medical and dietary measures are often useful. For subjects at risk, (siblings in this recessive disorder), monitoring of copper metabolism in the preclinical state can be justified with enthusiasm. Less is known about several other rare diseases of the basal ganglia. Hallervorden-Spatz disease involves deposits of iron and can lead to a severe progressive dystonia. Fahr's disease includes calcification in the basal ganglia. Manganese miners can develop a dystonic form of Parkinsonism.

Phenothiazines produce complex neurologic disorders, often of great interest medically and legally. An acute dystonic state can be seen, and seems to

be more common in the young. Parkinsonism, or "pseudo-Parkinsonism" can develop after several weeks of therapy with phenothiazines and is reported to be more common in patients with a family history of Parkinsonism. Tardive dyskinesia is related to prolonged use of phenothiazines and is particularly likely to occur in patients who are old and in those patients who have organic brain disease (71, 72). Amphetamines, so commonly employed in the hyperactive child (73), can elicit not only anorexia but also choreiform movements (74). Tardive dyskinesia has been seen in children (75). This iatrogenic disorder, called tardive because of the long delay in developing symptoms after exposure, may be present in 15% of patients in state hospitals, but despite its frequency is often unknown to the practicing physician. A source of quiet and at times acrimonious controversy ten years ago, tardive dyskinesia is now well accepted and is an excellent example of some of the reasons for a delay in the discovery of any iatrogenic disease (76). ("It is the disease, not my medicine," or "the side effect is useful," or "the virtues of the medicine compensate for the side effect," or "don't discuss it, do you want a law suit or something?") Drug vacations and use of the minimal effective dosage may help prevent tardive dyskinesia.

Carbon monoxide can lead to a Parkinsonian state or even neuropathy (77, 78) in rare patients who are exposed to an overdose, but more usually produces transient coma or cortical damage. The effect of continued elevated levels of carbon monoxide in the environment is a matter of controversy, but it would be difficult to prove that such levels are completely innocuous.

There are environmental and genetic aspects of infectious, and of traumatic or postinfectious states in diseases that affect the basal ganglia (79), in addition to Sydenham's chorea (80). After the encephalitis lethargica epidemic in 1918, complex neurologic disorders were seen and have been considered likely to return with some future epidemic. Environmental contributors to basal ganglia diseases are not totally clear; each severe new epidemic of influenza will need study regarding long-term effects of infection on the CNS.

Brain Stem

Though the brain stem is of great interest to the neurologist, there are few environmentally induced disorders that affect this region primarily. Thiamine deficiency has been postulated to explain a rare inherited disorder of childhood (Leigh's disease), and extreme thiamine deficiency in the alcoholic can be associated with petechial hemorrhages in the

brain stem or with myelinolysis. Once a major cause of mental disease (pellagra), in this country avitaminosis is not considered a significant problem currently except for alcoholics. Multiple sclerosis can affect any portion of the CNS, including myelin in the brain stem; and a viral etiology, or an interaction of viral, immunological and environmental stresses is currently postulated as the major etiologic factor.

The persistent vitality of the brain stem and technological advances in medicine have lead to an interesting recent financial, medical (81), societal, and legal interface; the concept of brain death. Other than public education in the significance of trauma as a health hazard and of the need for renal transplants, there is no obvious responsibility for the environmentalist in the issue of brain death.

Cerebellum

There are numerous viral agents and chemical toxins that can lead to a temporary cerebellitis or to permanent cerebellar damage (82). In most, other than the epidemiology of infection or genetic predisposition, there is little of note for the environmentalist.

Panencephalitis can lead to cerebellar damage in cats and destroy or damage an entire colony. The mumps virus, particularly in the very young, can produce changes in hamster, rat, or man that damage subcerebellar regions, damage to the aqueduct causing hydrocephalus, or damage to the cerebellum itself. Some epidemics of chickenpox are strikingly associated with signs of cerebellar dysfunction, but what produces such variation during epidemics of viral disease is unclear.

The cerebellum, particularly the Purkinje layer of the cerebellum, is very vulnerable to anoxia as well as to hyperthermia. Educational efforts to encourage fluids and limit hot clothing in summer athletic training and for unseasoned military recruits has reduced the incidence of heat stroke (83). The familial disorder of malignant hyperthermia can produce a fatal result during anesthesia of at risk subjects (84). Though changes occur in muscles during and even between attacks in this entity, there is no completely reliable enzyme test for this uncommon and at times fatal entity of malignant hyperthermia. Elevations in temperature of any cause can lead to cerebellar damage that is irreversible. Cerebellar degeneration resulting from toxins other than alcohol does occur (85) but has been hard to investigate, partially because of the lack of definitive laboratory tests. Repeated and severe seizures, particularly in the setting of anoxia, will probably produce a loss of Purkinje cells, and cerebellar

degeneration can certainly result from therapy with phenytoin in both experimental and clinical situations. Since phenytoin and some antimetabolites such as fluorouracil can damage the cerebellum selectively, the possibility of unidentified cerebellar toxins in the environment cannot be dismissed.

Spinal Cord

The spinal cord can be damaged by any local infection, even unrecognized ones such as lues, and by other rare infectious agents such as toxoplasmosis (86). Specific occupational or avocational situations, such as "the bends" in aviators or scuba divers, may lead to injury of the cord (87). Environmental features are more obvious in some of the allergic responses of the cord, such as in the myelopathy that can result from vaccinations (rabies or smallpox) (88-91). Some venoms, including bee sting or spider venoms (92, 93), can produce severe allergic neurologic responses. Motor root, brachial plexus, peripheral nerve and even the cortex (94) may also be involved when the cord is affected by serum sickness and similar inflammatory reactions. Metabolic disorders such as pernicious anemia can selectively affect the cord, and some conditions such as amyotrophic lateral sclerosis (ALS) may have associated metabolic derangements in pancreatic or liver function in the late stages, although the basic cause of ALS still remains completely obscure. A more obvious factor is iatrogenic assault on the cord and its arachnoidal coverings, as in intrathecal injections of contrast material or medications (95), some of which (such as steroids for multiple sclerosis) are demonstrably worthless but can quite successfully produce arachnoiditis with secondary pain and motor or sensory deficits.

Odontoid fracture (96) and cervical compressive fracture is all too common as a diving or trampolene (97, 98) injury and every large community hospital is likely to see at least one each summer. Strenuous exercises of the neck and protective neck supports have probably greatly reduced the incidence of similar severe neck injury in football contact, but spinal cord injury can and does still occur in athletic events. Even minor trauma of the neck can lead to infarction of the cord in children (99) and unrecognized obstetrical trauma to the spinal cord or plexus (100) accounts for numerous cases of cerebral palsy each year.

Triothocresyl phosphate (TOCP) is one particular toxin that has been used extensively in study of pathologic responses of the cord and peripheral nerve (101-103). A major epidemic with this agent occurred during prohibition (104) (Jamaica Ginger

and "Jake paralysis"), but exposure is now uncommon in the U. S. though still reported overseas (Bombay, Morocco) from contaminated oils or foodstuffs. The clinical picture may represent a combined neuropathy and myelopathy with a spastic gait in the setting of a neuropathy.

In the past ten years there have been suggestions of a possible impact of the potato blight fungus in producing defects such as meningomyelocele and encephalocele. There is wide variation in the incidence of these defects in different parts of the world, but toxic environmental linkages (105, 106) remain obscure. Preliminary data (107) suggest that it is now possible to diagnose the defects antenatally from amniotic fluid and fetal research in the next decade may elucidate the cause of these disorders.

Radiation myelitis is an all-too-common complication of therapy with large doses administered to the spinal area (108). There are no careful studies at this time regarding the combined effect of chemotherapy and radiation.

Autonomic Disturbances

Certain people with autonomic dysfunction are particularly vulnerable to environmental stresses, for example children with the Riley-Day Syndrome may not tolerate anesthesia or underwater swimming. Except for postural hypotension, there are few other examples of autonomic disturbances in clinical medicine, but many drugs, including over-the-counter soporifics, contain agents that exert major effects on the autonomic system. Some of the more available herbal hallucinogens have marked autonomic effects (109, 110) and effects on memory plus a ready treatment (111).

Peripheral Nerves

Agents that produce a neuropathy may produce such an effect (1) indirectly or by damage to vascular or supportive tissue, (2) by damage to Schwann's cells and secondary segmental demyelination, or (3) by injury primarily to the neuron and then a "dying back" at the axon. The signs of a peripheral neuropathy are relatively stereotyped, with a decrease in motor power distally, decreased deep tendon reflexes, and decreased sensation (112). There is some suggestion of a difference in the clinical presentations after exposure to different poisonings, for example poisoning by arsenic is usually more painful than the neuropathy of porphyria, and the latter neuropathy may be more motor in pattern. Any neuropathic insult may be additive, and several toxins tend to summate in

their effect. In general, however, both the nerve pathology and the neurologic examination in cases with neuropathy fail to be completely specific and for this reason this section will be organized by noxious agents, not by region or by pathologic change. Allen's review (113) is a particularly good summary, organized by categories of toxins.

Metals

Lead: Lead as an industrial hazard (114) is less common now than in the last century, but environmental exposure has included foundries, mines, paint plants, and plastic industries which use lead stearate. Hobbies (115), foods, and homemade wines, even pet foods (116) can be contaminated. Residency near industries that use lead, old paint or house dust, colored inks, and illegal whisky are among the sources of exposure mentioned in recent literature (117-120). The habit of pica is important (121, 122), but only partially explains the high lead levels found in inner city children (123). There are new and useful diagnostic tests including measurement of aminolevulinic acid dehydratase activity in erythrocytes. The enzyme activity approaches zero with 100 $\mu\text{g}\%$ of lead in the blood. Blood levels (significance is 40 $\mu\text{g}\%$ or greater) of lead can also indicate undue subclinical exposure. Other useful tests include urine measures of coproporphyrin and the presence of basophilic stippling in the peripheral blood smear; and once lead intoxication is diagnosed there are treatments available (124). The clinical picture of lead intoxication includes encephalopathy ranging from impaired alertness to delirium and coma, and in adults a motor neuropathy can also occur. There is a predisposition of the child with sickle cell disease to develop neuropathy after lead intoxication (125). Alcoholics may also be more vulnerable than nonalcoholics to this toxin. Even the basic mortality rates are higher in lead workers than in the general population (126). Animal work has suggested that subclinical lead poisoning can impair brain function and there is a suggestion of increased incidence of hypertension in patients with high lead levels (127). Possible correlations between subclinical lead intoxication and impaired cerebrovascular, mental, or psychological performance remains controversial (128, 129).

Mercury: Mercury in the inorganic form can lead to mild neurologic disorder, but the clinical effect of organic mercury compounds can be devastatingly severe (130). The sources vary, and organic mercury has been found in some fungicides (see grain) (131), in fish, and in industrial plants (used as a catalyst for vinyl chloride) (132). There is even an increased hazard in dental offices (133). Other countries have reported the clinical features in se-

vere cases including weakness or spasticity in late stages (Minimata Disease in Japan), muscle atrophy, and even a pattern like ALS, plus sensorineural hearing loss, decreased vision, or a marked agitated delirium (134-137). Diagnostic tests for mercury include direct measurement of body products, plus electrical studies of nerve conduction (138) and when present in toxic levels, a high level of mercury can be found in samples of liver and kidney by biopsy as well as in the cerebellum and brain or by autopsy (139). Methylmercury can pass the fetal barrier, but in general young animals tolerate higher doses (140). The pathogenesis of mercury poisoning may include binding of sulfhydryl groups of proteins and the effect is very long lasting (141). Recent studies have indicated a high incidence of poisoning in those Indians in Northern Canada who eat large amounts of fish caught from contaminated waters (142).

Manganese: Manganese is only a sporadic cause of industrial poisoning, usually in the manganese or ferromanganese industries (143, 144). Large numbers of cases have been reported from Chile and India, but sporadic cases are reported from the U. S. (145). The major route of exposure for manganese is via inhalation of dust. The absolute levels in muscles, skin, blood, hair, and brain have been measured and of particular interest in the late development of a central disorder which is not just a peripheral neuropathy, but includes a fundamental disorder of the basal ganglia. The onset is 4-15 years after initial exposure and can include a severe mental disorder, a state similar to Parkinsonism, plus a severe dystonic syndrome. There is some suggestion of an increased absorption of manganese in association with anemia and nutritional deficiency. It is thought that manganese may produce some of its damage by a possible defect in neurotransmitter, since in the cases studied there is reduction in brain dopamine and homovanillic acid (HVA) as well as low levels of homovanillic acid in the cerebrospinal fluid. L-Dopa has been useful for symptomatic management.

Thallium: Thallium has become an uncommon poison now that rat poisons are more limited and since its depilatory qualities are not utilized cosmetically (146, 147), but it can still present as a puzzling case of neuropathy. Diagnosis can be suspected after the development of alopecia and confirmed by levels of the agent in urine or hair. Other metals such as tin, zinc, etc. may be crucially important in CNS functions, but are rarely indicted as cause of disease.

Solvents

***n*-Hexane:** *n*-Hexane poisoning has been found

in printing plants, paint factories, furniture repair shops, and in industrial plants that use glue (148, 149). Most cases have been associated with varnish or with a solvent used for rubber cements. Glue sniffers and "huffers" may also develop a neuropathy which could be due to hexane (150-152). Measurement requires samples of the atmosphere and levels above 500 ppm may be elevated sufficiently to produce damage. Serum pseudocholinesterase may be reduced in affected persons. The clinical findings included an insidious neuropathy, largely motor and largely distal. Some of the glue sniffers have developed more profound disturbances including mental changes; but most of these patients have been exposed to multiple toxins in addition to the *n*-hexane. There is no specific therapy. Samples of environmental air should be checked to diagnose this neuropathy and since the condition is usually mild, and recovery complete; ventilation, avoidance of overtime, and other simple measures may be all that is required prophylactically.

Methyl Butyl Ketone: Methyl *n*-butyl ketone (MBK) (153, 154) is usually obtained by inhalation in plants using the agent (often required for glued fabrics), and MBK may be found mixed with other agents. A recent outbreak resulted from substitution of MBK for other solvents after the oil crisis produced a change in availability (155-158). The clinical findings include an insidious neuropathy with paresthesias and distal weakness. Axoplasmic flow can be affected (159). There may be a common metabolite for *n*-hexane and MBK. The diagnosis is nonspecific but requires clinical suspicion plus a check in relevant plants for levels of MBK in the atmosphere as well as in agents used in manufacture (160, 161). Electromyography can be a useful screening procedure to detect subclinical cases of neuropathy.

Toluene: Toluene is usually considered non-toxic, but some changes in cerebral function have been suggested after chronic exposure to this agent (162). One of the major research areas that remains is to determine possible synergisms between toluene, *n*-hexane, and other solvents. Toluene is such a commonly used agent that interactions with other compounds and possible changes in the chemical structure during use or in the atmosphere deserve careful evaluation.

Trichloroethylene: Trichloroethylene, in addition to damage to other organs, can produce a cranial neuritis or more diffuse CNS disorder (163, 164).

Organic Chemicals

Cogeners of phthalate with higher alcohols are

used in the leather or fabric industry (165). The clinical features of toxicity include a mixed sensory and motor neuropathy, with occurrence only after several years of exposure.

Acrylamide is a much studied monomer (166-171) that is used in inks, and overdose can produce a rather mild neuropathy. There is considerable experimental data, and it has been found that a distal axonal neuropathy can be produced by acrylamide in most animals studied. The fundamental effect of the compound may be to produce a defect in protein synthesis.

Triorthoecryl phosphate (TOCP) and related compounds can produce a mixed neuropathy and myelopathy. It has been said that TOCP inhibits pseudocholinesterase.

Mipafox (172) and similar organic phosphorus pesticides can produce an acute and profound paralysis or death (173, 174). In some areas there seems no doubt but that the workers appear better informed about these agents than are the physicians.

Kepon can lead to severe tremors in individuals who receive toxic doses, and the variety of CNS effects is dwarfed only by the complex social and legal issues in the recent overdoses (175, 176).

The effect of herbicides in the CNS remains uncertain (177-179) and perhaps minimal, but since teratogenic effects are known, neuropathies may eventually be reported.

Gases

Carbon disulfide, now used in the manufacture of viscose rayon, in the past century produced hundreds of cases of intoxication with acute and chronic encephalopathy, neuropathy, etc (180). Modern ventilation systems and stringent regulations have largely eliminated this disorder.

Carbon monoxide is discussed above (cortex).

Methyl chloride is a foaming agent in the plastics industry that can produce transient ataxia, unsteady gait, and confusion (181).

Methyl bromide has been reported to produce persistent myoclonus (182) but also might be expected to produce a neuropathy.

Other Causes of Neuropathies

There are numerous other therapeutic substances that can produce a neuropathy (183), including dapsone (184), chloramphenicol, metromidazole (185), clioquinol, hydantoins, disulfiram, isoniazides, furans, thalidomide, vinca alkaloids, etc. Overdose with other agents, in addition to vitamins, can dam-

age the CNS (186, 187). Some of these various compounds may offer metabolic clues to other varieties of neuropathy and myopathy.

Any standard neurologic test lists dozens of metabolic causes for neuropathy, the most common one of which is diabetic neuropathy. Some have limited environmental or local interest, such as Tangiers' disease which was first reported from an island in the Chesapeake, but none are of primary environmental concern at this time.

Tick paralysis occurs in certain parts of the country but is rare indeed, as are the neuropathy and acute respiratory problems secondary to botulism. Both these forms of paralysis are probably preventable and both have educational significance for professional and laymen. The environmental importance of the viral neuropathies is harder to assess and many viral illnesses seem associated with muscle weakness and aches. Occasionally Guillain-Barré syndrome can seem to affect several persons in the same area, but probably secondary to viral illness rather than to hidden toxic exposures. Preexisting debility or other unknown factors may be additive in such cases. The recent postulated linkage between Guillain-Barré syndrome and the vaccine for swine flu may further accelerate investigation of the response of the CNS to allergic insults of all types.

The entrapment neuropathies include compressive neuropathies at any area where nerves can be pushed or pinched (188). "Bulb digger's" paralysis, a peroneal palsy, probably involves not only a squat occupation position but a familial predisposition. "Gunlinger's" or "postman's" palsy of the brachial plexus is also an occupational hazard for a few. A common tardy nerve palsy is that secondary to resting on an elbow (ulnar nerve) and is common in telephone operators, debilitated persons who rest on their elbows, and in habitués of saloons.

There are numerous basic elements which, when either in excess or deficient in the environment, can produce neurologic disease. Copper is an obvious example (189), but even silicon (190, 191) has been demonstrated to be necessary for the development of supportive tissue. These have been largely studied from the hematologic point of view and are not well understood as regards to significance or prevalence of neurological disease.

There are, in addition to viral neuropathies, many infectious agents that produce not only systemic symptoms but the clinical picture of an acute neuropathy. Diphtheria is now largely controlled by educational and epidemiological advances, but botulism still produces severe illness and fatalities in intermittent outbreaks (192-194).

Muscle Disease

The entire area of causal factors in muscle disease is almost as complex as that of the CNS. Walton's recent text is a good reference source (195).

Vascular Disorder

It is hard to overestimate the significance of cerebral arteriosclerosis in the CNS as a cause of disability and death. The major preventable contributors to this killer includes hypertension, diabetes, smoking, hypercholesterolemia, and possibly elevation of triglycerides. Recently the quantity of metals in water has been reported to correlate with vascular disease (196). The clinical features of arteriosclerosis of the cerebral vessels will not be reviewed here, but it is clear that diagnosis and treatment is inconsequential in importance when compared to the need for prevention. Nevertheless, other than control of blood pressure and a prudent diet, there is at this time unfortunately no prevention to offer most patients.

Bickerstaff (197) and others have reviewed the role of oral contraceptives in vascular disorders of the brain. In addition to an effect caused by a vasculitis or thrombosis, there is also a tendency for the production of hypertension after use of these agents.

Aneurysms and vasculitis can result from heroin addiction and particularly when impure compounds are injected intravenously (198).

Migraine attacks can be produced in vulnerable persons by diet, coffee, chocolate, tryamines, histamines in red wines, hypoglycemia, etc., but there is no general or universal toxin in the environment (except weather) which is currently indicted in attacks of this common malady. For some, specific environmental stresses can be very relevant, and even minor trauma (199) can be the major environmental cause of such headaches in susceptible individuals.

Patients who have had strokes are more vulnerable to thrombosis (200), but in addition, certain compounds, diazepam and phenytoin included (201), may predispose to thrombophlebitis during IV therapy; but other than alerting the physician there is no apparent responsibility for the environmentalist in this area.

Subject at Risk and Other Comments

There is a great deal that can be stated, much of which can be only philosophical, about the hazard

of becoming a patient. The fact that this report does not review such hazards does not indicate their nonexistence. It is instructive to be reminded however, as Crane has done, how extremely insidious iatrogenic disease can be. There are obvious as well as unconscious reasons why iatrogenic disorders are suppressed, missed, or ignored. There are many new therapeutic situations in which the beneficiary is at great risk. All the antimetabolites might produce reduced vigor and lead to secondary infection. Radiation is similar in overall effects to the antimetabolites, and if one deals with people more vulnerable in several different ways, the risks of radiation become even greater. The variety of responses obscures unpleasant facts of medical care, since every individual has critical or vulnerable periods, as in very early or very advanced age, and with any disease the resistance to environmental stress can be lessened. In any occupation the new worker may be exposed to unexpected hazards of toxins, most of which are fortunately mild. This review has suggested that there is selective vulnerability of the CNS to certain agents and toxic agents can affect quite specific regions of the CNS. These effects are not random and may indicate unexplained biochemical affinities between the toxin and the neuronal cells. Every new medicine is a potentially new CNS toxin. In the CNS two insults are often additive and produce a greater effect than the apparent sum of both. A partially damaged, depleted, or malnourished CNS can withstand far less anoxia or toxic damage than the normal. Nerve cells do not regenerate; once gone they do not return. Tumor, radiation, chemotherapy, and extreme age could be "additive" in their effect, and so monitoring for the effect of the toxin is very difficult. This is not to say that therapeutic toxins should be as severely monitored as optional or coincidental toxins. It is more acceptable to develop a side effect from life saving therapy than to develop a mild reaction caused by an unnecessary and undesired contaminant.

Certain population groups are at particular risk, including the very young, adolescents (trauma), recruits (new infection), alcoholics (almost any physical insult is additive in presence of alcoholism), and retarded or institutionalized persons. Noxious agents such as carbon monoxide may damage the fetus even if the mother is unharmed. Halothane or other anesthetics could also possibly do the same. Therefore, in any survey of vulnerable groups the fetal population deserves particular attention.

Behavior and Related Areas

Television has been postulated to cause an increase in violence, paranoia, and hyperactivity in

children (202, 203). Since there may be no educational source as all pervasive as TV, continued studies of its effect on behavior and physical health is mandatory. At present, common sense suggests that TV must be counteracted by other stimulation and that its use does not eliminate and may increase the need for other forms of cerebral activity than passive absorption of visual images.

The child with "hyperactivity" is a major pediatric problem, and this controversial and heterogeneous diagnosis includes many entities, some of which are not medical. As high as 1% of school children in some areas are on amphetamines for hyperactivity, and the long-term effects of these drugs is of major interest. For example, there are some data to suggest a syndrome akin to tardive dyskinesia in children on such medications, and a relative failure of growth has also been postulated in children who receive amphetamines for long periods of time.

Screening Tests

One major educational area for the public health service concerns study of the utilization of health services. It may become desirable, or necessary, to decrease not increase, the utilization of health professionals, and to encourage more use of medical judgment by home authorities. One sure protection from iatrogenic misadventure is to avoid the doctor when the problem is trivial. A more critical, even negative, view of screening programs of all kinds might result from intensive evaluation of the effectiveness of prior major screening efforts. There is strong feeling in some members of the medical community that routine or massive screening programs are likely to be inefficient, expensive, worthless, or all three. Alertness to toxins and other environmental stresses must include willingness to proceed with selective screening, but massive screening is not a substitute for intelligent search, an informed observer, and selective screening.

Tests and the Environment

No one test will give information on all neural processes in the human, but perhaps behavior and language come closest. In humans, language is a unique tool, both for history taking and to obtain insights into patient behavior from family members. The standard psychiatric tests of mental function are often less revealing than reports of behavior that are offered by social workers, family, or the patient himself. Language can also be a precise monitor as in new techniques such as the Porch Index of Communicative Ability. Since behavior is the feature that may be most affected when the cortex is

insulted, it is logical to turn to psychological measures for quantification. Although MMPI, trail making tests, Bender-Gestalt, flicker fusion, and similar tests can be helpful, all can be influenced by psychological factors, and none is without blemish. No test can substitute for thoughtful evaluation of the total problem. Similarly, though the neurologic exam may be the best measure to detect significant damage to the nervous system (particularly peripheral neuropathy) the neurologic examination only screens sensory, motor, cerebellar, and mental performance and is not a substitute for synthesis of the entire problem, nor is a neurological exam a replacement for a scholarly review of the clinical possibilities.

In some disorders, as in damage by drugs such as the phenothiazines which can affect either cornea or retina, a specially designed ophthalmological evaluation will be helpful to indicate the extent of tissue damage. Slit lamp or indirect ophthalmological techniques will often be required. In these techniques there is no substitute for a knowledgeable ophthalmologist. Similarly, as for example with some inhaled toxins, particular liver function tests or liver biopsy may document damage as well as does any single neurologic technique. Certain enzymes (CPK, aldolase) are of particular value in indicating muscle dysfunction, and others less commonly employed (cholinesterase) may be a clue to toxins such as TOPC or *n*-hexane.

Changes in cerebrospinal fluid can often suggest that the CNS has been damaged. Protein values are elevated in many, probably most, severe neuropathies, and yet toxicity studies in animals never sample CSF. In certain conditions one or another component can be studied, such as homovanillic acid levels in manganese intoxication, and when indicated these may be of particular interest. Dozens of enzymes can be detected in the CSF and yet there is little study of the effects of toxins on these CSF enzymes or of states in nature when these enzymes are deficient.

Neurophysiologic approaches, especially sophisticated electromyography, can be particularly useful in detecting peripheral nerve and muscle damage. Careful study of nerve conduction rates as well as evaluation of miniature endplate potentials (MEPP) is of value in some disorders. The routine electroencephalogram (EEG) is probably useful only in extreme toxic states, but with frequency analysis and evoked response techniques, additional insights can be expected from this readily available clinical tool. Other neurophysiologic techniques such as electronystagmography (ENG) or electroretinography (ERG) are of value when the optic nerves or retina is affected. These techniques

can be used in animal toxicity studies as well as in human research, but rarely are.

There is at least one incompletely tapped resource in neurologic research; natural animal models. Not only in man, but in animals (particularly mice), many genetic disorders have been identified and pure strains of these animals are available. Study of the influence of noxious substances on these creatures is not in vogue, but since difficulties in the CNS are often compound and may be more than additive, some animal models might be used to detect the presence of trace amounts of toxins.

One generality regarding tests is that no test substitutes for intelligent observation. Tests should be selected depending on suspicions, for example it is logical to suggest assessment of hearing in noisy environments. EMG may be a useful screening technique to detect the neuropathy caused by *n*-hexane, when a plant uses this compound. Since this neuropathy may occur without patient complaint, random screening in these plants could be justified. EMG will not, however, be a substitute for accurate atmospheric check. The purpose of the neurologic tests should thus be to confirm, and occasionally discover, the effect of a noxious situation. Thoughtful utilization of multiple tests, including biochemical ones, may then indicate precisely what the noxious material is, how to eliminate it, and perhaps even prevent future exposures.

Summary, Comments, and Recommendations

The central nervous system (CNS) is designed for appropriate response to the environment and is peculiarly vulnerable to many influences found in the environment. Selective damage to particular areas of the CNS is noted with numerous toxins, and certain individuals are considerably more vulnerable than others.

Unfortunately many of the influences on the CNS are hard to isolate, and sometimes the toxic agents produce changes in behavior or intellectual function that are difficult to study. The CNS responds differently than other areas: for example, the blood-brain barrier tends to protect the CNS from conventional carcinogens, although an increased overall mortality and incidence of brain tumors following exposure to vinyl chloride has been reported (204, 205). The production of tumors by certain carcinogens, as nitrosoureas, is under active investigation in experimental laboratories, but it seems probable that the incidence of clinical malignancy in the CNS is less influenced by environmental agents than is malignancy elsewhere in the body. On the other hand, production of malfor-

mations in the fetus can follow administration of many compounds, though systematic investigation of the mechanism of such effects has been limited. In the CNS the time of the administration of the toxin is as important as the nature of the toxin. For example, at certain stages of fetal development, radiation may damage the cerebellum; at another stage the same dose of radiation damages the neuronal cells in their migration from the ependyma to the cortex.

Even after the fetal period there is great variability of response, particularly between individuals. Phenytoin, and other hydantoins, may cause ataxia at one dose in one individual, while at a similar blood level not even clumsiness is evident in a second individual.

Other drugs, or toxins, or even pre-existing disease, may contribute to sensitivity, but individual and largely unknown metabolic differences are also crucial. The same infection may produce a fatal hydrocephalus in fetal animals of two species (hamster, rat) but will not always do so after the same exposure in apparently identical siblings of the same species. To detect the effect of toxins in any particular region of the CNS may require special techniques, but in many instances, as in the examples above, such definitive techniques are not available until after the final neuropathological assessment.

Peripheral neuropathy is perhaps the most obvious common result of environmental toxins in adults and can be detected clinically as well as neurophysiologically. Neuropathy in industries, or in avocational exposures, may be noted first in isolated patients and after such affected persons are identified then screening for neuropathy in population groups at risk (selective screening) should be encouraged. Screening may be required to locate subclinical and less severe cases. To this date, skilled neurologic examination and detailed electromyography remain the most useful screening tests for neuropathy.

Methyl *n*-butyl ketone (MBK) was discovered to be toxic after an outbreak of peripheral neuropathy was diagnosed by intensive combined efforts of scientists, union, and government agencies. This toxin had been used in a plant making coated fabrics, and the solvent had been required because of sudden changes in availability and costs of related chemicals. In such acute outbreaks, alert or suspicious workers, physicians, or management must first prove the presence of a problem and then at great expense of time and effort identify the specific culprit. MBK could have been identified as toxic in animals, before the human epidemic, if extended chronic studies had been done in animals. None had

been done.

At times an epidemic elsewhere, as in Minimata disease due to mercury in waters of Japan, or, closer at hand, as reported in 1976 in Indians in Northern Canada, will alert government agencies of a need to survey similar environments or groups in the U. S. Manganese intoxication, more common in Chile than in the U. S., is another example of a disorder that undoubtedly occurs in the U. S. but can be studied more thoroughly in another region.

Chronic lead poisoning has been associated not only with reduction in longevity, but with neuropathy and even psychologic disorders and hyperactivity in childhood. The toxins that can damage the nervous system number in the hundreds, as reviewed in excellent recent texts such as those by Dyck and Walton. Since so many chemical compounds can produce a peripheral neuropathy, this clinical phenomenon can be used to suggest the presence of a toxic effect in the environment or in the body. It is certain that as yet undiscovered toxic or metabolic causes of neuropathy await detection since a specific cause for at least 25% of cases with neuropathy remain unexplained even after very detailed evaluation. The very young, the old, the debilitated, and those with metabolic predisposition are particularly likely to be affected by smaller doses of noxious agents than the usual worker in the usual occupational setting.

RECOMMENDATION 1: ENVIRONMENTAL TOXINS AND DRUGS All evaluation of drugs or other potential toxins should include chronic as well as acute studies. MBK could have been detected as a toxic agent if chronic studies had been performed, although the acute experiments revealed no abnormalities.

Check of specific toxins in specific industries or environments should be encouraged. Lead is an obvious example. Mercury levels should be evaluated in groups of fishermen and in heavy consumers of fish. Discovery of any new toxin may automatically imply the need for a survey of relevant groups by government health agencies, as well as by the most proximate investigators.

Hobbyists at risk (furniture remodeling, lead soldiers, etc.) should be warned routinely, preferably in published journals of these groups as well as on labels of the relevant agents. The national trend toward more detailed labeling of all products including drugs should be encouraged and education in schools should include instruction in how to understand labels.

Research on carcinogens in experimental animals should be combined with a survey of the incidence of tumors of the CNS in groups that appear at risk. It is important to discover why the brain seems less

vulnerable to environmental carcinogens.

Iatrogenic disease and the difficulty in detecting it is of significance in the nation's health. For example, the phenothiazines produce at least three varieties of disorder in the basal ganglia. One of these, tardive dyskinesia, was particularly difficult to accept as genuine, at least partly because the dyskinesia was slow to develop and because of the iatrogenic aspect. Since these and other chemical agents can produce unpredicted long-term and even permanent effects on the CNS, prolonged exposure to other agents such as carbon monoxide must also remain suspect, even when exposure is at a low level.

Disease related to use of drugs is a major problem in diagnosis and treatment of new hospital admissions. A high proportion of new admissions are on unknown drugs. Automated measures of enzymes, blood counts, electrolytes, etc. have revolutionized medical care in the past two decades, but there is no similar routine check for serum levels of therapeutic and nontherapeutic drugs. Even cases of life-threatening coma due to overdose can at times be hard to identify because of a delay in laboratory reports.

RECOMMENDATION 2: DRUGS IN THE HOSPITAL AND NONHOSPITALIZED POPULATION Research in development of an automated and inexpensive drug monitor to be used for all hospitalized patients should be initiated.

Intensive research into the effect of ubiquitous or commonly used drugs, especially when used for children, such as amphetamines, aspirin, soporifics, and so forth, should be encouraged.

Specific drug labels should be made mandatory on all prescription drugs unless specifically ordered otherwise.

Package inserts of all drugs should be available to patients.

At times "epidemics" appear as sudden new diseases or as alarming new or previously unrecognized manifestations of old diseases. The recent concern with swine influenza is an example. Some neurologists have anticipated a possible return of post-viral Parkinsonism following this or similar infections. There is no obvious or generally recognized and easily mobilized mechanism for the study of unique or transient short-lived health phenomena. The most readily available research source is usually the local medical school or local investigative physicians. At times, Public Health Services can be the major resource and must be involved in the education efforts during such episodes. There might be an ongoing mechanism to rapidly initiate research efforts in strange, unique, or transient new health problems, but now there is none. By no means will all

these unexpected transient episodes be infectious or toxic, though acute infectious diseases and new toxins often have environmental and health significance of long lasting importance.

RECOMMENDATION 3: STUDY OF NEW PHENOMENA Current coordinative groups in the study of outbreaks of encephalitis should include military and public health groups. Utilizing the experience of such groups improves the rapidity of response in short-lived health phenomena.

There are individuals at particular risk in the environment. For example, adolescents sustain more trauma, smokers more lung infections, and aged or institutionalized patients may be more vulnerable to various social changes or medical fads. Furthermore, even for the most hardy of persons there are environmental situations in which there is unwanted risk. One such environment that is certain to receive increased research interest is the hospital. Steadily rising costs may lead to innovative new and safer approaches, but intensive physiologic monitoring and an exposure to drugs and chemicals can be anticipated by most who enter the hospital. The anxiety and medical efforts in intensive care units had been shown to produce extreme exhaustion in the patient and loss of REM sleep in regular wards and may be almost as severe a stress. The impact of any particular environment on health, particularly those environments not intensively studied, can be assumed to be underestimated unless disorders are obviously and overtly caused by the environment.

RECOMMENDATION 4: THERAPEUTIC ENVIRONMENT There should be encouragement in research on the influence of the hospital environment (state hospitals, intensive care units, differences in ward or private rooms, etc.). Such studies should include the interference of this environment with sleep and dignity, as well as an assessment of expense and overt environment hazards (such as electricity in coronary patients).

Hospitals should forbid smoking except in a few designated areas. The role of smoking is vascular and pulmonary diseases should be included in all health education.

The most hazardous feature in the U. S. environment is trauma. Trauma in the streets due to social disorder is inconsequential compared to that on the highways due to deliberate speed. Seizures, dementia, and focal neurologic deficit can all result from traumatic insults to the brain and literally tens of thousands of cases are produced annually. Less understood is the effect of lesser degrees of trauma on later intellectual performance. There is no question that athletic injuries of the knee can affect future function of the joint, but there is no certainty

regarding the equally common repeated minor cerebral traumata of athletic youth. Certain groups, the retarded for example (206), are at a particular risk. Future studies might properly be concerned with athletics as an environmental stress on brain and body.

RECOMMENDATION 5: TRAUMA When a "sport" is suspected to be particularly hazardous (hand gliders, skateboards, competition of children on motorcycles, etc.) there should be formal (legal or health) hearings to consider limitation of such activities, as was done for fireworks decades ago. Such reports are often performed at State or National Parks, and the Park Service may be a good reference source.

Research on the effects of trauma on the brain and spinal cord should continue to be encouraged, particularly research aimed at preventive measures. The interrelationship between acute trauma, occupation, therapeutic chemicals, and previous trauma continues to be worthy of investigation.

The fledgling specialty of "sports medicine" should be encouraged via special symposia, particularly in regard to changing patterns of athletics for women and in subjects at particular risk, as the retarded child (206).

An expert in sport medicine or orthopedics should be included on the board of trustees and professional advisors of all athletic organizations that are licensed or incorporated, as NCAA, Little League, etc.

Since the ototoxicity of noise is potentiated by certain drugs, such as diuretics or aminoglycosidic antibiotics, audiometric studies should be made of workers exposed to noise while taking medication that is potentially ototoxic.

Swimming lessons as a part of the public school curriculum should be encouraged, although it is unlikely this would reduce the incidence of drowning or diving injury.

It may be unnecessary to mention the insidious and devastating effect of alcohol on the nervous system. Alcoholics suffer more trauma and produce more trauma than other members of society. Alcoholics are particularly vulnerable to other toxins and detection of a second toxin may be difficult in this group of patients.

RECOMMENDATION 6: ALCOHOL there should be continued study of the effects of alcohol as a major toxin as well as studies of the effect of alcohol in the vulnerable or weakened person.

The mechanism of drug withdrawal is not well understood, and research in this area might lead to therapeutic advances. Withdrawal phenomena are similar for all major drugs that effect the CNS, but we fail to understand the process.

There should be studies of the effects of laws on

alcohol abuse. For example, what would happen if bartenders or hosts were held responsible for injuries to intoxicated persons served by them? What would happen to salesmen if they were held liable for injurious actions caused by minors who are sold the alcohol?

There are probably more varieties of chemical, neurophysiological, and clinical tests on the nervous system than on any other organ. Numerous unusual metabolic or genetic diseases can be confirmed only by special tests, many of which have helped elucidate our understanding of the nervous system. It is impossible to state with certainty that investigation using any one test will solve a neurologic puzzle. One reason the concept of screening or monitoring is raised so often is that many toxic or environmental phenomena first came to attention through an isolated or special case and only then numerous other cases were discovered. Since there are so many potential tests, however, surveys should be aimed for results, and good judgment in where and what to study remains as crucial as the test itself.

RECOMMENDATION 7: DETECTION OF NEW ENVIRONMENTAL PROBLEMS Continued support for the training of scientific physicians and academic specialists is mandatory. The push to train practitioners of medicine should not be allowed to suppress the creative or investigative spirit.

It might be possible, as hospitals become more innovative (207) as well as more closely monitored by federal agencies, to select a few representative institutions to maintain careful records on all admissions for: trauma, overdose, drug side effects, toxic states, industrial accidents, and alcoholism. No matter how well intentioned, however, collection of such data should not be initiated without clear purposes.

Use of electromyography, spinal fluid protein, and nerve biopsy should be encouraged in toxicologic research in animals, in an effort to detect latent neuropathy.

There should be encouragement of the development of newest physiological techniques (miniature endplate potentials, etc.) for detection of subclinical effects of noxious agents.

Major neurologic organizations should be encouraged to support symposia on the effect of the environment on the brain and behavior.

Several of the above recommendations have concerned education for scientists or public. Education is a proper role for almost any tax supported agency and is also part of every physician's responsibility. What education and what style of education for the public deserves additional formal consideration by environmental groups. Planning for such

education may reduce duplication and oversight.

The major preventable causes of vascular disease; namely hypertension and tobacco, deserve particularly thoughtful research and educational efforts. Actual mechanisms of injury by these agents remain incompletely understood, but some therapeutic changes in style of living in the U. S. can already be suggested. Sloth, overindulgence of food or alcohol, and tobacco are obvious old enemies. The continued search for hidden dangers must be combined with assault on known ones.

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