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TO: DR. D.A. BROMLEY

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August 20, 1991

D. Allan Bromley, Ph.D.
Director
Executive Office of the President
Office of Science and Technology Policy
Washington, D.C. 20506

Dear Dr. Bromley:

Thank you for your recent letter. Apparently the wrong article was enclosed in my last letter to you. I wanted to send to you my recent review "Genetic Neurological Diseases" which was published in my recent book "Comprehensive Neurology" Raven Press Ltd., New York 1991. I enclose with this letter the correct article and hope that you find it interesting.

With my best wishes, I remain

Sincerely yours,

Roger Rosenberg

Roger N. Rosenberg, M.D.

RNR:ns

Enclosure

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Comprehensive Neurology,
edited by Roger N. Rosenberg,
Raven Press, Ltd., New York © 1991.

CHAPTER 2

Genetic Neurological Diseases

Roger N. Rosenberg and Jay W. Pettegrew

The classic eponymic neurologic diseases discussed in this chapter produce characteristic pathologic changes in specific nuclei and fiber tracts in brain, spinal cord, and peripheral nerve. The disorders are usually progressive and symmetrical in their pathologic and clinical expression, and they often have a clear genetic basis of inheritance or have a suggestion of familial involvement. The disorders involve specific regions or systems of the nervous system such as cerebellar nuclei and also involve fiber tracts of the corticospinal or extrapyramidal motor system, resulting in specific neurologic symptoms and signs referred to as *system degenerations.*

In 1902 Gowers referred to these inherited degenerative diseases as *abiotrophies*—that is, inborn errors of metabolism. This term implies the occurrence of neurologic disease as a result of an impairment in the metabolic state of the brain, spinal cord, or peripheral nerve. Recently (as will be discussed), enzyme deficiencies (i.e., chromosomal breaks), specific immunologic defects, abnormalities in nerve growth factor, and slow, latent, viral-like infections of the brain have been identified as specific etiologic bases for some of these abiotrophies.

It is of great interest and importance that in most of the inherited degenerative disorders to be discussed, the primary emphasis of disease involves the neuron, with changes produced in astrocytes and oligodendrocytes being presumably of a reactive and secondary nature. Intensive research regarding most of the disorders mentioned here is currently under way in many laboratories, and it is anticipated that with a better understanding of the program of genetic molecular differentiation involving the neuron (i.e., by utilizing recombinant DNA techniques, by studying the altered gene products present, or by studying defects in the regulation of their synthesis in these various disorders), the mechanisms for the pathogenesis of these diseases will become clearer and specific therapy will become available.

We have witnessed in the past decade an exponential increase in our knowledge concerning the basic enzyme defects and metabolic consequences of many autosomal recessive disorders in the categories of the gangliosidoses, leukodystrophies, mucopolysaccharidoses, glycogenoses, and heavy metal storage disorders. When these autosomal recessive diseases are used as models, it is hoped that the basic molecular defect in several autosomal dominant system degenerations discussed here, such as Huntington's disease, Joseph's disease, olivopontocerebellar atrophy, Alzheimer's disease, myotonic muscular dystrophy, tuberous sclerosis, and neurofibromatosis, will become clarified (1).

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PROGRESSIVE DEMENTIA

Alzheimer's Disease

Alzheimer's disease was originally described in 1910 by Alois Alzheimer (2), and it refers to the occurrence of a presenile dementia with an associated diffuse atrophy and resultant reduction in mass and weight of the brain. The occurrence of the presenile dementia is insidious and progressive over many years, and it is usually not associated with other significant neurologic abnormalities. It is important to distinguish this disorder from a senile dementia that similarly produces an insidious and progressive impairment in intellectual functioning, but in an older population. A convenient arbitrary division between a senile and presenile dementia might be age 60 years, when the first symptom of impairment occurs. Both senile dementia and Alzheimer-type presenile dementia represent similar disorders both neuropathologically and clinically, with the Alzheimer form merely occurring earlier in age and sometimes progressing more rapidly.

Alzheimer's disease may be familial. There is an increased risk of occurrence if a patient's parent or sibling was affected. Down's syndrome occurs more frequently in families with Alzheimer's disease than in the general population. An autosomal dominant form of inheritance is present in about 10% of affected families, and there is a wide range of age of onset within a family (as reviewed in ref. 3). In one series, reported by Breitner et al. (4), female relatives ap-

peared to develop the disease earlier than males. An interesting report by Bird et al. (5) described five families with autopsy-proven disease with autosomal dominant inheritance. All five families are descendants of a group of immigrants known as the Volga Germans, who came to the United States between 1870 and 1920. The concordance rate in one study by Nee et al. (6) for monozygotic twins was 41% and 40% for dizygotic twins. Their study supported the view that Alzheimer's disease cannot be entirely accounted for by a single autosomal dominant gene, given the rather low concordance rate for monozygotic twins.

Pathology

The characteristic gross appearance of the brain is a severe, symmetrical, and diffuse atrophy with associated flattening of gyri and widening of the sulci. The entire ventricular system is uniformly enlarged. The histologic findings in general are a diffuse loss of neurons in the cerebral and cerebellar cortices, the basal ganglia, the brainstem, and the spinal cord. In particular, there is prominent neuronal loss in the basal nucleus of Meynert (substantia innominata), the septal nuclei, and the diagonal band of Broca. These basal forebrain nuclei usually provide a diffuse cholinergic input into the cerebral cortex, and their loss is the basis for the significant reduction in acetylcholine throughout the cortex (7,8). Neuritic plaques and neurofibrillary tangles are additional features of Alzheimer's disease brain. For further details, see refs. 9–33.

Molecular Genetics

The most compelling evidence within the last few years is that Alzheimer's disease is the result of a genetic abnormality. The new genetic data are most convincing for a primary pathogenetic mechanism of disease compared to other possibilities, including an infectious etiology (34), toxins, autoimmune disease, heavy metals, a selective neurotransmitter disorder, or a metabolic encephalopathy. Familial Alzheimer's disease is being defined in molecular terms for the first time, and it is probable that nonfamilial or sporadic Alzheimer's disease will share a similar molecular basis.

A most exciting discovery by Glenner and Wong (35) has been the genetic association between Down's syndrome and Alzheimer's disease. The beta-amyloid protein of the neuritic plaque of Alzheimer's disease shares the same amino acid sequence with the protein present in similar neuritic plaques in the brain of patients with Down's syndrome who live past 35 years of age. These investigators surmised correctly that the amyloid gene probably resides on chromosome 21, since it is primarily involved in the pathogenesis of Down's syndrome—which commonly has trisomy 21 as its cytogenetic hallmark. It was suggested that perhaps an early or primary defect in the pathogenesis of Alzheimer's disease is a regulatory disorder involving the amyloid gene on chromosome 21.

Great credit must be given to Selkoe et al. (36) for demonstrating that the aging process of brain that is associated with amyloid deposition in neuritic plaques and blood vessels is not restricted to Alzheimer's disease and Down's syndrome. Rather, as they have shown, it is a biochemical and pathologic feature of aged mammalian brain, including monkey, dog, orangutan, and polar bear. Amyloid deposition is an event that spans millions of years of mammalian evolution. It is a genetic event that is highly conserved, and it represents an essential gene function which has become abnormally regulated in the aged mammal (37,37a).

In 1987, Goldgaber et al. (37) reported the isolation and characterization of complementary DNA (cDNA) clones coding for the beta-amyloid peptide. They point out that the gene is highly conserved in evolution and that it maps to human chromosome 21.

Using unique sequence cDNA probes, St. George-Hyslop et al. (38) have shown genetic linkage of a polymorphic marker with the genetic locus for familial Alzheimer's disease. Four large kindreds with histologically proven early-age-of-onset Alzheimer's disease were studied using banked cell lines from affected, at-risk, and non-at-risk individuals from several generations. Their results indicate that the familial Alzheimer's disease gene from families with early-age-onset disease does map to chromosome 21, but to the q11-12 region and not to the 21q22 region associated with Down's syndrome. Families with late-onset disease do not map to this site, suggesting the possibility of genotypic heterogeneity in this disease as reported by Schellenberg et al. (39), Bird et al. (40) and St. George-Hyslop et al. (40a).

Another major step in this rapid cascade of molecular insights into the basis of Alzheimer's disease was the observation by Tanzi et al. (41) that the regional localization of the beta-amyloid gene by both physical and genetic mapping is near the locus of the genetic defect responsible for familial Alzheimer's disease at q11-12 of chromosome 21. They also measured amyloid mRNA levels on Northern blots from a variety of brain regions and from various organs. Amyloid mRNA is expressed widely, including spleen, thymus, pancreas, muscle, kidney, liver, lung, and heart. It was present in human brain cortex, thalamus, putamen, hipposcampus, and cerebellum. Amyloid mRNA was expressed in organs and brain regions (i.e., cerebellum) that are not associated with pathologic lesions of Alzheimer's disease to a significant degree. The lack of an absolute correlation between regional neuritic plaque density and *in situ* hybridization of brain with ^{35}S-RNA probes to amyloid mRNA was also made recently by Bahmanyar et al. (42). These data imply that mRNA expression per se is necessary but not sufficient to explain the pathogenesis of Alzheimer's disease.

Increased mRNA for amyloid in Down's syndrome brain suggests that the deposition of amyloid in this disorder is the direct result of a dosage-related increase in the gene product. It is not yet clear whether the amyloid plaques in Alzheimer's disease are analogously due to gene overexpression. Tanzi et al. (43) and Van Broeckhoven et al. (44) have independently addressed this point and have concluded that the amyloid and familial Alzheimer's disease loci are separate and distinct and that the amyloid gene is not the site of the inherited defect underlying this disorder.

Duplication of the q11-21 region of chromosome 21 by a meiotic defect during embryogenesis was suggested by Delabar et al. (45) as the mechanism responsible for the molecu-

lar pathogenesis of Alzheimer's disease. Specifically, they cited data indicating a 50% increase in leukocyte DNA per genome for the amyloid gene from patients with sporadic Alzheimer's disease. However, neither Tanzi et al. (41) nor Van Broeckhoven et al. (44) could reproduce the evidence for a gene duplication at the amyloid locus on Southern blots.

Kang et al. (46) have isolated and sequenced an apparent full-length cDNA clone which codes for the amyloid A4 polypeptide. This 43-amino-acid peptide is the major amyloid protein associated with neuritic plaques and blood vessels. They have put forward the view that this peptide is a cleavage product of a larger precursor protein which is 695 amino acids in length and which is characteristic of glycosylated cell-surface receptors.

Recently, Tanzi et al. (47), Kitaguchi et al. (48), and Ponte et al. (49) have independently reported the presence of three separate mRNAs that encode for human brain amyloid. These mRNAs encode for proteins that contain 695, 751, or 770 amino acid residues. Palmert et al. (50), however, have reported that the 695-residue mRNA amyloid devoid of the protease inhibitor is preferentially expressed (twofold) in Alzheimer's disease brain, nucleus basalis, and locus ceruleus neurons, allowing full expression of protease function and thus allowing cleavage of the A4 peptide from the precursor protein. Schubert et al. (51) has described the amyloid precursor protein as a heparan sulfate proteoglycan. The consensus view is that amyloid accumulates as a result of a processing abnormality in the amyloid precursor protein. The methodologies exist to answer these points, and there is an optimism pervading the field that the important issues in Alzheimer's disease will be resolved in the near future and that this devastating illness affecting millions of persons world-wide will be able to be prevented or be treatable (52).

Membrane Phospholipid Changes in Alzheimer's Disease

Recent *in vitro* ^{31}P nuclear magnetic resonance (^{31}P-NMR) studies have demonstrated alterations of membrane phospholipid metabolism in Alzheimer's disease (AD) brain obtained at autopsy and biopsy (53–59). In particular, AD brain contains elevated levels of phosphomonoesters (PME), a class of molecules that are normally found in abundance only in developing brain (54,56,60). It is remarkable that a degenerative disease should bear such striking molecular/metabolic resemblance to the normal developing brain. For further details, see refs. 61–98.

Clinical Manifestations

The disease is characterized by the progressive and insidious development of intellectual impairment, going on to a profound dementia over several years' time. The disease begins usually in the fifth or sixth decade of life and is usually sporadic in its occurrence in a family. Familial involvement is recorded in 25–40% of cases, and an autosomal dominant mode of inheritance in 10% of families has been documented. The patient is usually aware of problems in memory or judgment in the early stages of the disorder, and as it becomes more advanced, he loses insight and appreciation of his deficits. Marked swings in mood may occur, including difficulty in controlling manic behavior alternating with depression. Judgment, insight, introspection, and memory gradually become impaired, producing a total dementia with dissociation from the environment and eventual virtual mutism. In the late stage of the disease, aphasic syndromes and, rarely, signs of extrapyramidal involvement (including bradykinesia and rigidity) may appear. Rosenberg et al. (154) have described a new syndrome with Alzheimer-type dementia and parkinsonism in a family having unusual non-Alzheimer-type plaques and no neurofibrillary tangles in two examined brains. Seizures and myoclonus may also occur. There is no evidence for a difference between early-onset and late-onset disease and the rate of change on mental status testing (99).

In addition to the dementia, the neurologic examination may indicate the presence of primitive reflexes inducing a snout reflex, a palmomental reflex, and the presence of symmetrical mild hyperreflexia. The cerebrospinal fluid (CSF) and routine blood chemistry studies are negative. The electroencephalogram (EEG) during the advanced stages of the disease will show diffuse and symmetrical slowing. A computerized axial tomographic (CAT) brain scan shows both ventricular enlargement and gyral atrophy, with increased sulcal markings. This diffuse atrophy can be confirmed by pneumoencephalography showing both ventricular enlargement and cortical atrophy. Brain blood-flow studies with inhaled ^{133}Xe often shows a biparietal symmetrical reduction in blood flow.

At the terminal stage, the patient appears dissociated, demented, mute, and decorticate. Death is usually from pulmonary or urinary tract infection. Unfortunately, no specific treatment is available. Oral treatment of patients with lecithin, choline, or physostigmine has not been useful. Preliminary reports regarding intrathecal or intraventricular infusion of bethanechol, a cholimimetic, suggested some mental improvement (100,101).

Pick's Disease

Pick's disease is a circumscribed brain atrophy with predilection for the frontal and temporal lobes. It spares the more posteriorly located structures. In 1984 Morris et al. (102) described an autosomal dominant disorder which could be considered as part of a Pick–Alzheimer spectrum of cortical neuronal degenerations. They referred to their class of disorders as *hereditary dysphasic dementia* and the *Pick–Alzheimer spectrum.* Clinical manifestations include in late adulthood the occurrence of progressive dementia and severe dysphasia. Neuropathological examination shows (a) typical Pick's disease or asymmetrical focal cerebral atrophy, (b) Alzheimer's disease with typical plaques, and (c) neuronal loss in the substantia nigra, indicative of Parkinson's disease. The disorder needs to be included in the spectrum of the inherited dementias, and the precise classification will require further cases to be studied.

Pathology

The neuropathologic changes can be clearly seen by examining the gross brain, which shows prominent atrophy involving the frontal and temporal lobes with preservation of the posterior regions of the brain. The frontal and temporal horns of the lateral ventricles are similarly focally enlarged. The hippocampal formation in the medial ventral portion of the temporal lobes is preserved, but there may be atrophic changes in basal ganglia, thalamus, and brainstem. Neurons contain a large amorphous cytoplasmic basophilic structure referred to as a *Pick body.*

Clinical Manifestations

It is difficult to differentiate Alzheimer's disease from Pick's disease by neurologic examination. Alzheimer and Pick patients both show a dementia, but the Pick patient may have a better preservation of memory and insight.

Familial Amyotrophic Lateral Sclerosis, Parkinsonism, and Dementia

Families have been described in which there occur progressive dementia, parkinsonism, and amyotrophic lateral sclerosis inherited in an autosomal recessive manner. Neuropathologic examination has found Alzheimer-type neurofibrillary tangles in the substantia nigra, innominata, locus ceruleus, and parahippocampal gyrus, as well as in the hippocampus and cerebral cortex. Complex forms of dementia involving these other neurologic features have been reported in natives of Guam, New Guinea, Europe, and the Kii peninsula of Japan (103,104).

BASAL GANGLIA DISEASES

Huntington's Disease

In 1872 George Huntington, a physician living on Long Island in New York, noted a family expressing a disorder which included progressive dementia and chorea. Much has been learned about this disorder in the past 118 years, but yet the precise molecular defect remains unknown; however, a DNA polymorphism associated with the disease has now been described, and the mutant gene has been mapped to chromosome 4 (105). It is characterized by an autosomal dominant mode of inheritance with almost uniformity of clinical expression. An excellent review of the pathogenesis, restriction fragment length polymorphism studies, and management aspects was published by Martin and Gusella (106) in 1986. The most recent mortality rate study, performed by Lanska et al. (107), indicated a rate of 2.27 per million per year in the United States. Rates were similar for both sexes and were higher in whites than in non-whites. The leading causes of death were pneumonia and heart disease. For further details, see refs. 108–121.

Clinical Manifestations

The clinical manifestations are those of progressive dementia, including impaired judgment and insight, bizarre behavior, and a personality change. These behavioral changes also may be present in other affected family members in an autosomal dominant mode of expression. In association with the mental change is the occurrence of involuntary choreiform movements described as quick, random, jerking movements. At times there may be more rhythmic, twisting, and slow movements that are characteristic of athetosis. If the disorder occurs in childhood, it may present with progressive rigidity, especially if it is the paternal gene that expresses the disease. As mentioned, the disorder begins in the fourth, fifth, or sixth decades of life and runs a progressive and relentless course of dementia and chorea. Late in the course, the occurrence of corticospinal deficits, including hyperreflexia, clonus, Babinski's signs, and decortication, may result. The children of affected women have significantly older mean ages of onset than do offspring of affected men. The absence of increased father–daughter similarity indicates that modification is not X-linked (121). Autosomal dominant non-Huntington's chorea has been reported (122). Chorea in this family commenced in childhood and progressed up to the eighth decade without intellectual impairment.

Molecular Genetics

A dramatic advance has been achieved by Gusella et al. (105), who found a DNA polymorphism associated with the disease. It was achieved by testing their eighth unique sequence cDNA probe with the restriction endonuclease Hind III on genomic DNA obtained from large, informative kindreds from Indiana and Venezuela. A specific genetic haplotype co-segregated with the presence of disease in these two families, offering a means to identify the presence of disease in at-risk persons. It is a precise and powerful approach and one which offers the means to eliminate this disorder in families who utilize it along with careful genetic counseling (105). Careful screening of additional families is now underway to see if all families ascribe to the same polymorphism or if other allelic or nonallelic forms of the disease exist. The probe used would not be useful if nonallelic forms exist, and great care must be taken to avoid false-negative determinations. By somatic cell hybrid studies and *in situ* hybridization, Gusella has been able to map the Huntington's disease gene to chromosome 4 near the locus for the Wolf–Hirschhorn syndrome at 4p16 to pter (105,123,124). Of considerable interest is the recent report of Folstein et al. (125), who found linkage of the HD locus to the G8 probe, provided by Gusella, in two families with differing clinical features. Wexler et al. (126) have identified persons with a high probability of being homozygous, and they do not differ in clinical expression or course from typical heterozygotes. Thus one mutant allele in the heterozygote shows full penetrance of disease, with no additional effect contributed by the second mutant allele found in the

homozygote. Hayden et al. (127) has attempted prenatal diagnosis with polymorphic DNA probes.

Treatment

There is no specific treatment to stop the progression of the disease process, but the use of haloperidol (1–5 mg, 3–4 times daily) or chlorpromazine (20–100 mg, 2–3 times daily) may be very effective in reducing the involuntary movement and calming the patient. Perry et al. (128) reported several patients in whom choreoathetosis resolved with treatment of INH (isonicotinic acid hydrazide).

Wilson's Disease: Hepatolenticular Degeneration

In 1861 Von Frericks probably described the first case of Wilson's disease when he reported on a young boy who had severe liver disease, violent tremors, and convulsions and who, at autopsy, exhibited cirrhosis of the liver (129). In 1902 Kayser (130) described a greenish ring at the limbus of the cornea in a patient who was diagnosed as having multiple sclerosis. In 1903 Fleischer (131) reported the corneal ring as an integral part of a neural disease associated with cirrhosis of the liver. In a series of papers between 1903 and 1912, Fleischer (131) proposed that the changes in the eye, brain, and liver were all caused by a common metabolic factor. In 1912 Wilson (132) published his monograph entitled *Progressive Lenticular Degeneration: A Familial Nervous Disease Associated with Cirrhosis of the Liver.* In 1913 Rumpel (133) was the first to demonstrate the increased copper content in a patient with "pseudosclerosis," and in 1922 Siemerling and Oloff (134) suggested that the pseudosclerosis of Westphal and Strümpell was caused by copper deposition in liver, eyes, and brain. In 1945 Glazebrook (135) firmly established the role of copper in the pathogenesis of Wilson's disease. In 1948 Cummings (136) first recommended the use of the copper chelating agent dimercaprol [also known as "British anti-lewisite" (BAL)] to remove excess copper from tissues. In 1952 Scheinberg and Gitlin (137) and Bearn and Kunkel (138) independently reported a deficiency of circulating ceruloplasmin in Wilson's disease. Penicillamine was discovered by Walshe (139) in 1956, and in 1968 Sternlieb and Scheinberg (140) suggested that presymptomatic diagnosis was possible, leading to early therapy and thereby preventing organ damage (see ref. 38).

Genetics

It is an autosomal recessively inherited disorder. It has been linked to the esterase D locus on chromosome 13 (141). Two studies utilizing restriction fragment length polymorphisms have confirmed the Wilson's disease locus to be at 13q (141,142). The locus for ceruloplasmin maps to chromosome 3q. Thus the impairment in serum ceruloplasmin is a secondary effect of the primary mutation at 13q.

Clinical Features

Wilson's disease presents with the triad of neurologic deterioration (movement disorder and psychiatric symptoms), cirrhosis of the liver, and Kayser–Fleischer rings of the cornea. The age of onset is variable, with most patients exhibiting signs and symptoms in adolescence or early in adulthood. The onset may be as early as 4 years or as late as the fifth decade. It has an incidence of 1 in 10,000 and is inherited as an autosomal recessive disorder.

There are two neurologic forms of the disease, with clinical intermediates. In one form, the major manifestations are spasticity, rigidity, dysarthria, and dysphagia with drooling of saliva. This form occurs predominantly in young adults. The other neurologic form has flapping tremors of the wrists and shoulders as the major feature, with rigidity and spasticity much less marked. This form occurs at any age in either sex.

Psychiatric manifestations are common, but they are variable in type and degree. Behavioral changes include aggressiveness, childishness, or euphoria. In spite of these changes, the intellect remains quite intact. Patients may present with frank schizophrenia. For further details, see refs. 143 and 144.

The diagnosis of Wilson's disease can be accurately made on clinical findings. Confirmatory laboratory findings include lowered serum ceruloplasmin levels, lowered total serum copper, elevated urinary copper excretion, and elevated liver copper content by needle per cutaneous biopsy.

Families that include a patient with Wilson's disease should be screened for ceruloplasmin levels in order to identify asymptomatic patients. The identification of asymptomatic patients is very important so that therapy can be started to prevent organ damage.

Positron emission tomography (PET) has shown diffusely reduced glucose metabolism in all brain regions compared to controls, with the exception of the thalamus (144).

Therapy

Untreated Wilson's disease is invariably fatal. Treatment is aimed at restricting dietary copper and chelating the excess copper from tissues (145–148).

Parkinson's Syndrome

Parkinson's syndrome is usually thought of as a sporadic disorder, but familial clustering of components of parkinsonism has been reported. It has been estimated that parkinsonism occurs as a familial disorder in 5–15% of patients. An autosomal dominant form of disease has been reported in some of these families (149,150). Rarely, familial parkinsonism has been reported as an autosomal recessive or X-linked recessive disorder. Martin et al. (149) reported a multifactorial polygenic model of inheritance for familial parkinsonism and suggested a genetic defect in tyrosine hydroxylase, the rate-limiting enzyme in the pathway for dopamine synthesis. The risk for an individual to de-

velop familial parkinsonism increases with the number of affected individuals in the at-risk person's family. The occurrence of dementia may be part of the parkinson syndrome, and in these families an increased risk of developing parkinsonism will occur when the onset of the illness occurs earlier in life (151). Nygaard and Duvoisin (152) reported an interesting family with childhood onset of leg and truncal dystonia followed by parkinsonism. There was minimal progression in adult life, with a dramatic response to levodopa therapy. The mode of inheritance was autosomal dominant. Alonso et al. (153) believe a small subset of cases that have an early onset may have an important genetic susceptibility. Rosenberg et al. (154) described a family in which a dominant form of inheritance, probably autosomal dominant, expresses parkinsonism and severe Alzheimer-type dementia as the major clinical features. Neuropathological correlates in two autopsied members of this family consisted of extracellular hyaline eosinophilic amyloid plaques in decreasing order of frequency in the cerebral cortex, basal ganglia, thalamus, and substantia nigra, along with atrophy and gliosis of the basal ganglia and substantia nigra. The brains examined showed no neuronal neurofibrillary tangles. These plaques did not stain with antibody raised against either the A4 peptide or the prion protein. The combination of dominantly inherited dementia with parkinsonism and A4-peptide- and prion-protein-negative extracellular plaques in this distribution has not been previously reported and thus may represent a new neurological disorder.

The Finish Twin Cohort study published in 1988 further substantiated the low concordance for Parkinson's disease in monozygotic as well as in dizygotic twins and indicated that the prevalence of Parkinson's disease in twins compares with the prevalence in the general population. The Finnish study concluded that Parkinson's disease is an acquired disease and not a hereditary disorder (155).

Hallervorden–Spatz Disease

Clinical Findings

Hallervorden–Spatz disease (HSD) includes the development of childhood rigidity and hypertonia resembling parkinsonism associated with dysarthria and dysphagia. Late in the course of disease, dementia and corticospinal degeneration with spasticity and decerebrate posturing occur. Pigmentary retinal degeneration, optic atrophy, and visual loss also occur. Computerized tomography of the brain has been reported to show high-density lesions in the globus pallidus (156).

Pathology

As a result of the excessive deposition of iron, there is a pigmentary degeneration of the pallidum and nigra. Neuronal loss and demyelination in these regions also occur, associated with axonal swellings referred to as *spheroid bodies.*

Genetics

The disease is inherited as an autosomal recessive disorder (157,158). In 1985 Jankovic et al. (159) described a family with autosomal recessive HSD disease in which four of five siblings developed the syndrome presenting as familial parkinsonism. This family presented with late-onset disease, with the propositus dying at 68 years after 13 years of dementia and parkinsonian features rather than a dyskinesia. The disorder thus does not have to present in young adulthood. The cause of the disorder is not known. Perry et al. (160) have, however, reported that the content of cystine and of glutathione-cysteine mixed disulfide were markedly elevated in the globus pallidus in one 19-year-old patient.

Neuroaxonal Dystrophy of Seitelberger

This syndrome overlaps with HSD, and some consider them to be variants of a common disorder. In general, this disorder occurs earlier in life and is more aggressive than HSD. Early dementia with extrapyramidal type of rigidity and dystonia are typical features. The main difference from HSD is the paucity of pigment accumulation. Axonal spheroid bodies and demyelination occur throughout the brain (not limited to the basal ganglia as in HSD) and peripheral nervous system. It is inherited as an autosomal recessive disorder. The cause of the disease is not known (161).

Gilles de la Tourette Syndrome

Clinical Findings

The onset of this syndrome occurs in childhood, with an increased incidence in boys; it is characterized by motor tics of the face, head, and extremities that resemble blinking, facial grimacing, and other muscle twitching. These tics are accompanied by vocal grunting, clearing of the throat, and even spitting movements. Uncontrolled vocal expletives without cause are a cardinal feature of the syndrome but are not necessary for the diagnosis. Other findings include sleep problems, echolalia, tremor, and depression. Stress exacerbates the syndrome (162).

Genetics

The syndrome is probably inherited as an autosomal dominant disorder with variable penetrance, but the precise type of inheritance is not clear (163). Comings and coworkers (164–166) have presented data suggesting that there is an X-linked modifier gene affecting the expression and penetrance of the Tourette syndrome gene located on an autosome to explain the male predominance. The gene may be on the long arm of chromosome 18 (162,167).

Pathogenesis

The cause of the syndrome and its precise pathogenesis are not known. A beneficial response to dopamine receptor blockers such as haloperidol strongly suggests that a hypersensitivity state of the dopamine system may be of primary concern in this syndrome (168).

Therapy

Clonidine was helpful in reducing motor and phonic tics (169). Haloperidol has been used for many years and has been found to be effective in reducing tics and abnormal behaviors. Haloperidol or pimozide are effective forms of therapy for the tic manifestations (170).

Familial Choreoathetosis

A variety of familial syndromes involving progressive choreoathetosis inherited as autosomal dominant traits have been described. They are all essentially benign disorders with late childhood onset of the involuntary movement disorder and with preservation of intellect. Distinctions have been made within this group according to whether the syndrome is associated with (a) progressive or nonprogressive choreoathetosis, (b) involuntary movement induced with a voluntary act, (c) dystonia, (d) acanthocytosis, or (e) the presence of basal ganglia calcifications. Familial Sydenham's chorea associated with acute rheumatic fever must be included in this spectrum as a familial entity that requires antibiotic therapy for streptococcal disease. Sydenham's chorea can be the sole manifestation of an acute rheumatic fever attack, and it may appear in a familial setting (171).

Familial amyotrophic chorea with acanthocytosis is a rare multisystem disorder expressing buccolingual dyskinesia, seizures, facial tics, dysarthria, chorea, muscle atrophy, and pes cavus. Acanthocytosis occurs with normal serum lipids and an elevated serum level of MM-type creatine kinase. Basal ganglia show a severe degeneration with muscle atrophy due to denervation. The disorder is one that is progressive in midlife, and its type of inheritance is uncertain (172).

Benign Essential Tremor

The occurrence of tremor without other neurologic deficits has been reported as an autosomal dominant disorder. There is wide variation in the age of onset in a family and in the degree of severity of the tremor (173). The tremor may be focal, involving only the head as a head-nod, the arms and hands, the legs, or the muscles of speech and swallowing, or it may become generalized, involving the trunk and impairing walking.

Torison Dystonic Syndromes

This group of disorders is characterized by slow involuntary twisting movements due to forceful muscle contractions. The resultant dystonic postures are the cardinal feature of the torsion dystonia. These dystonic postures or muscle spasms may be local, as in writer's cramp, or may involve the neck muscle to produce torticollis of the pelvis and hence tortipelvis. Oromandibular dystonia (Meige's syndrome), which involves spasms of jaw muscles, tongue protrusion, and blinking, may also be a familial disorder. The distribution may be generalized and is therefore known as *dystonia musculorum deformans* (DMD). Recently, an autosomal dominant mode of DMD inheritance was documented among Ashkenazic Jews (174). It has been shown to map to chromosome 9q32-34 (175).

Dystonia Musculorum Deformans

This disorder is inherited as an autosomal dominant trait with marked variation in clinical expression. Four generations of a family of 121 persons, 16 of whom were affected as autosomal dominants, have been reported. It has been described as concordant in twins as an autosomal recessive, with onset in the twins being years apart. Clinical manifestations include dystonia of cervical musculature (torticollis) and dystonia of the trunk (tortipelvis). The disorder may be severe, producing marked deformity of the neck, extremities, and trunk (176). Minor changes, including neuronal loss and reactive gliosis, have been described, involving the striatum, globus pallidus, and dentate nucleus of the cerebellum. Larsen et al. (177) have described a family with dominantly inherited dystonia and intracranial calcifications in the basal ganglia, dentate nucleus of the cerebellum, and frontal lobes. Hornykiewicz et al. (178) reported a markedly reduced concentration of norepinephrine in the lateral and posterior hypothalamus, mamillary body, subthalamic nucleus, and locus ceruleus. Elevated norepinephrine concentrations were present in the septum, thalamus, coliculi, red nucleus, and dorsal raphe nucleus. There were no important histologic changes in the basal ganglia, cerebral cortex, higher brainstem nuclei, locus ceruleus, or raphe nuclei. For further details, see refs. 179–186.

SPINOCEREBELLAR DEGENERATIONS

The spinocerebellar degenerations represent a series of clinical deficits, including ataxia and dysmetria resulting from the predominant involvement of the cerebellum and its afferent and efferent pathways. These disorders are system degenerations, and many of them are specific entities clearly inherited as genetic disease or as familial entities in an autosomal dominant or autosomal recessive manner. Although the clinical manifestations and neuropathologic findings of cerebellar disease are the most predominant in the spinocerebellar degeneration, there may also be characteristic changes in the basal ganglia, optic atrophy, retinitis

TABLE 1. *Summary of the spinocerebellar degenerations*

Type	Age of onset	Development	Reflexes	Sensory change	Cerebellar	Other important clinical features
Spinal syndromes						
Friedreich's syndrome	1st decade	Slowly progressive	Absent myotatic deep tendon reflexes; extensor plantar response	Moderate loss	Severe	Dysarthria; nystagmus; moderate mental retardation; skeletal defects; defect in pyruvate dehydrogenase; defect in mitochondrial malic enzyme; autosomal dominant or recessive or sporadic; cardiomegaly with fibrosis
Hereditary spastic paraplegia	1st or 2nd decade	Slowly progressive	Hyperreflexia; clonus; extensor plantar response	Minimal loss	None	Paraplegia; impaired bowel and bladder function; autosomal dominant or recessive or may occur in families with typical Friedreich's syndrome or olivopontocerebellar degeneration
Roussy–Levy syndrome (included in types I and II hereditary motor sensory neuropathy of Dyck)	1st or 2nd decade	Slowly progressive	Absent myotatic deep tendon reflexes; extensor plantar response	Moderate loss	Moderate	Absence of dysarthria with peroneal muscular atrophy; intermediate between Friedreich's and Charcot–Marie–Tooth diseases
Polyneuropathy	1st or 2nd decade	Slowly progressive	Absent	Moderate loss	None	Predominant peroneal muscle atrophy; nerves may be hypertrophic; usually autosomal dominant; can be autosomal recessive or X-linked; optic-acoustic nerve involvement occurs
Charcot–Marie–Tooth disease (types I and II hereditary motor sensory neuropathy of Dyck)						
Dejerine–Sottas (type III hereditary motor sensory neuropathy of Dyck)	1st or 2nd decade	Slowly progressive	Absent	Moderate loss	None	Tremor; nystagmus; dysarthria; scoliosis; hypertrophic nerves; usually sporadic or autosomal recessive; elevated CSF protein
Ataxia–telangiectasia	1st or 2nd decade	Slowly progressive	Reduced	Minimal loss	Severe	Telangiectatic lesions involving sclerae, face, pinna, and neck; pulmonary infections; increased incidence of lymphoma; hypo-γ-IgA; autosomal recessive
Bassen–Kornzweig syndrome	1st decade	Slowly progressive	Absent	Moderate loss	Severe	May have mental retardation; acanthocytosis; steatorrhea; pigmentary retinal degeneration; a-β-lipoproteinemia; autosomal recessive
Tangier disease	1st decade	Slowly progressive	Reduced	Moderate loss	None	Enlarged yellowish-appearing tonsils; defect in high density lipoproteins; autosomal recessive
Refsum's disease	1st decade	Slowly progressive	Absent	Severe loss	Severe	Nyctalopia; pigmentary retinal degeneration; ichthyosis; cardiac conduction defects; deafness; elevated serum phytanate; defect in lipid α-oxidase activity; autosomal recessive
Cerebellar syndrome, olivopontocerebellar degeneration	1st or 2nd decade	Slowly progressive	Hyperreflexia; clonus; extensor plantar response	Moderate loss	Severe	Late development of optic atrophy and muscle atrophy; may develop a moderate dementia; seizures are rare; may be autosomal dominant or recessive; contrast studies including CT scan show pontine and cerebellar atrophy
Carcinomatosis cerebellar degeneration	Adult	May be progressive	Reduced	Moderate loss	Truncal	Truncal greater than extremity ataxia; dysarthria and nystagmus minimal; lung carcinoma most common association

TABLE 1. *Continued.*

Type	Age of onset	Development	Reflexes	Sensory change	Cerebellar	Other important clinical features
Alcoholic cerebellar degeneration	Adult	Slowly progressive	Reduced	Moderate loss	Severe truncal	Truncal greater than extremity ataxia; dysarthria and nystagmus minimal; peripheral neuropathy present
Dyssynergia cerebellaris of Ramsay Hunt	Adult	Slowly progressive	Reduced	Normal	Moderate	Diffuse myoclonic jerks; generalized seizures; sporadic or recessive; mitochondrial defects
Marinesco–Sjögren syndrome	1st decade	Slowly progressive	Reduced	Normal	Moderate truncal	Associated with mental retardation and cataracts in early childhood

pigmentosa, and peripheral nerve disease (187). There are many gradations in the spectrum, ranging from pure cerebellar involvement to mixed cerebellar and brainstem involvement, cerebellar and basal ganglia involvement, or spinal syndromes including associated peripheral nerve disease. The clinical picture may be rather consistent in one family, but examples do occur in which the disease assumes a characteristic form in the majority of family members and is entirely different in one or several members.

The typical clinical picture and the age of onset of symptoms and signs are used to classify these inherited spinocerebellar diseases. Major categories of disease are included in this designation, but it should be pointed out that these divisions are arbitrary and that gradations between the various entities are encountered. The important and common inherited spinocerebellar degenerations include (a) Friedreich's syndrome, the spinal form of spinocerebellar degeneration, (b) Roussy–Levy syndrome, (c) Refsum's syndrome, (d) Bassen–Kornzweig syndrome, (e) olivopontocerebellar degeneration, (f) Joseph's disease, (g) dyssynergia cerebellaris myoclonica, (h) ataxia–telangiectasia, (i) Marinesco–Sjogren syndrome, (j) hereditary spactis paraplegia, and (k) Charcot–Marie–Tooth disease (Table 1).

These entities, as classified by Greenfield (188), can be grouped into predominantly spinal forms, spinocerebellar forms, and pure cerebellar forms. The olivopontocerebellar degenerations (OPCD) were subclassified by Konigsmark and Weiner (189) into at least five subgroups with both autosomal dominant and autosomal recessive forms of inheritance. The many minor variants of OPCD described—for example, by Brown (190) in 1892, Marie (191) in 1893, Dejerine and Thomas (192) in 1900, Holmes (193) in 1907, and Schut (194) in 1950, as listed by Konigsmark and Weiner (189)—might represent examples of genetic disease in which all the phenotypic variability could theoretically be explained by (a) a single gene mutation transmitted as an autosomal recessive trait and (b) another single gene mutation transmitted as an autosomal dominant trait in which many other host genes modify expression and penetrance of the mutant gene.

Insights into the molecular causes of these diseases are beginning to be described in some of the spinocerebellar diseases, including Friedreich's syndrome, Refsum's disease, and Bassen–Kornzweig syndrome (Table 2). In the remaining spinocerebellar degenerations, although the disorders are well described both clinically and pathologically, the specific cause of disease remains elusive. The spinocerebellar system is highly vulnerable to a series of molecular abnormalities, as evidenced by very different molecular defects such as Bassen–Kornzweig syndrome and Friedreich's syndrome, yet the system can respond only in a limited manner and without a great deal of pathologic variation, as evidenced by the similarity of neuropathologic findings in these various disorders. Common neuropathologic features, from the peripheral nerve through the spinal cord and up to the cerebellum with its associated connections, are seen in the broad spectrum of these spinocerebellar degenerations, and the interesting aspect of these generalized and nonspecific changes is that they represent specific clinical syndromes caused by separate molecular defects inherited in a characteristic autosomal recessive or autosomal dominant manner.

Hereditary Spinal and Cerebellar Ataxia of Friedreich (Friedreich's Syndrome)

Friedreich's syndrome is a collection of spinocerebellar degenerations that occur in childhood as a familial disorder or that may be clearly transmitted as a genetic autosomal recessive or dominant disorder. Sporadic or isolated examples of the syndrome have been reported (195). Friedreich's syndrome represents a series of several specific entities that share common clinical features and pathologic changes. The syndrome includes a variety of inborn errors of metabolism, including several disorders of lipids (phytanic acid storage disease, a-β-lipoproteinemia, moderate β-galactosidase deficiencies, and juvenile arylsulfatase deficiencies), diseases of oxidative metabolism [deficiencies of the pyruvate dehydrogenase complex, defect of mitochondrial malic enzyme, neuromuscular disorders with "ragged red" fibers, and abnormalities of cytochrome b or of nicotinamide adenine dinucleotide (NADH) oxidation], aminoaciduriase (intermittent maple syrup urine disease, γ-glutamyl-cysteinyl transferase deficiencies, and Hartnup disease), and the partial deficiency of hypoxanthine guanine phosphoribosyl transferase (HGPRT) deficiency. The clinical expression of these inborn errors of metabolism includes involvement of cerebellar functions and corticospinal functions that are progressive and symmetrical, compatible with Friedreich's syndrome.

TABLE 2. *Biochemical disorders in the inherited ataxias*

Biochemical disorder	Clinical type	Age of onset	Clinical features
Lipid disorders			
Autosomal recessive			
Storage of phytanate due to defect in α-oxidase	Refsum's disease	20–80 yr	Ataxia; retinitis pigmentosa; deafness; ichthyosis; cardiac arrhythmia; polyneuropathy
a-β-Lipoproteinemia	Bassen–Kornzweig syndrome	5–10 yr	Ataxia; acanthocytosis; retinitis pigmentosa; polyneuropathy; malabsorption of fat
Arylsulfatase A deficiency	Juvenile onset metachromatic leukodystrophy	5–20 yr	Ataxia; mild mental retardation; polyneuropathy
Storage of GM_2 ganglioside due to hexosaminidase A deficiency, α-locus type	Juvenile onset atypical spinocerebellar ataxia	3 yr	Progressive ataxia; spasticity; dysarthria; muscle atrophy; pes cavus; normal intelligence
Storage of GM_2 ganglioside due to hexosaminidase A deficiency, β-locus type	Juvenile onset atypical ataxia with cherry-red spots	2 yr	Progressive ataxia and intention tremor; macular cherry-red spots
Partial deficiency of hexosaminidase A and B	Adult onset spinocerebellar degeneration	20 yr	Gait and limb ataxia; head titubation; dysarthria; tremor grimacing; chorea
Galactosylceramide lipidosis	Late infantile to adult progressive cerebellar deficits	Late infantile	Multiple periventricular hypodense lesions suggestive of leukodystrophy; sural nerve shows demyelination; reduced leukocyte galactocerebrosidase activity
X-linked recessive		5–20 yr	Cortical blindness and spasticity; skin pigmentation; childhood onset of adrenal cortical insufficiency; adult onset with ataxia and polyneuropathy
Storage of long-chain (C24–30) fatty acids	Adrenoleukomyeloneuropathy (Nixon–Blaw disease)		
Carbohydrate disorders			
Autosomal recessive			
Pyruvate carboxylase or pyruvate dehydrogenase deficiencies; cytochrome oxidase defect (complex IV of electron-transport complex)	Leigh's disease (subacute necrotizing encephalopathy)	birth–5 yr	Acute episodic extraocular muscle palsies; optic atrophy; hypotonia; ataxia; mental retardation; somnolence; hyperreflexia; extensor plantar responses; elevated serum pyruvate and lactate
Biotin-responsive multiple carboxylase deficiency	Neonatal or infantile intermittent ataxia	birth–1 yr	Intermittent ataxia responsive to biotin; ketosis; lactic acidosis; infections; hyperammonemia; hypotonia
Lipoamide dehydrogenase deficiency; mitochondrial malic enzyme	Friedreich's ataxia	5–15 yr	Progressive gait and limb ataxia; dysarthria; nystagmus; areflexia; extensor plantar reflex; distal sensory loss
Oxidative metabolism with elevated serum lactate and pyruvate; cytochrome oxidase defect (complex IV of electron-transport complex)	Adult onset neuromyopathy with ataxia, Kearns–Sayre syndrome	20–50 yr	Retinitis pigmentosa; neuromyopathy; ophthalmoplegia; ataxia; cardiac arrhythmias; muscle biopsy shows ragged red fibers
Disorders of amino acid metabolism			
Autosomal recessive			
Deficiency in branched-chain keto acid decarboxylase	Maple syrup urine disease and variants	birth–5 yr	Mental retardation; seizures; failure to thrive; irritability; anorexia; ataxia; maple syrup odor to urine; excretion of branched-chain amino acids and keto acids
Hyperglycinemia	Spastic paraparesis with muscular atrophy and arm dysmetria	2–10 yr	Spastic paraparesis; peroneal muscle atrophy; distal sensory loss; pes cavus; optic atrophy; arm dysmetria
5-Oxoprolinuria due to deficiency of glutathione synthetase	Ataxia and defect in the γ-glutamyl cycle (I) (reduced glutathione synthesis)	10 yr	Progressive mental retardation; spasticity; limb and gait ataxia; tremor; hemolytic anemia with intermittent jaundice
Generalized amino aciduria due to deficiency of γ-glutamyl-cysteine synthetase	Ataxia and defect in the γ-glutamyl cycle (II) (reduced glutathione synthesis)	20 yr	Hemolytic anemia; areflexia; gait and limb ataxia; distal sensory loss; staccato speech; acute psychosis

TABLE 2. *Continued.*

Biochemical disorder	Clinical type	Age of onset	Clinical features
Defect in tryptophan absorption from gut; aminoaciduria	Hartnup disease	5–25 yr	Intermittent ataxia; episodic pellagra-like skin rash; progressive mental retardation; spasticity; choreoathetosis
Deficiency in glutamate dehydrogenase in recessive type only	Olivopontocerebellar degeneration	20–40 yr	Progressive gait and limb ataxia; spasticity; mild extrapyramidal features; late distal amyotrophy and sensory loss; rare mental changes
Disorder or urea cycle metabolism			
Autosomal recessive			
Argininosuccinate synthetase deficiency	Citrullinemia	Infancy	Vomiting; somnolence; tremor; ataxia; seizures; delay in mental and physical development; hyperammonemia
Disorder of immunologic function			
Autosomal recessive			
Reduced serum immunoglobulins (IgA, IgG, and IgM); lymphopenia	Ataxia–telangiectasia (Louis–Barr syndrome)	5–12 yr	Telangiectasia of face and sclerae; Friedreich's phenotype with ataxia; dysarthria; areflexia; extensor plantar responses; oculomotor apraxia
Disorder of protein metabolism (increased amount of glial proteins)			
Autosomal dominant			
Increased glial acidic filamentous protein and a complex of 40,000 MW proteins in cerebellum and basal ganglia seen on 2-D gels	Joseph's disease	20–65 yr	Gait ataxia often with either corticospinal and extrapyramidal findings or late onset polyneuropathy
Disorder of endorphin enkephalin metabolism			
Increased endorphin and enkephalin levels in brain and CSF	Necrotizing encephalopathy (Leigh's syndrome)	1–2 yr	Attacks of coma; miosis; ptosis; clumsiness; pallor; hyperhydrosis; may respond to naloxone; 20-fold increase in brain enkephalins and CSF endorphins
Cytochrome oxidase defect (complex IV defect of electron-transport complex)			

In addition to those inborn errors producing spinocerebellar degeneration (already mentioned), deficiencies of enzymes of the pyruvate dehydrogenase complex that catalyze the conversion of pyruvate to acetyl-CoA and carbon dioxide have also been identified in patients having ataxia and peripheral neuropathy. Pyruvate oxidation defects have also been described in patients with ataxia and peripheral neuropathy caused by nongenetic acquired conditions such as thiamine deficiency, alkylmercury poisoning, and elemental mercury poisoning (196–198).

Stumpf et al. (199) have reported several patients in whom mitochondrial malic enzyme of fibroblast cultures has been reduced by at least 50%, but other patients reported by Chamberlain and Lewis (200), Gray and Kumar (201), and Fernandez et al. (202) had normal levels in fibroblast cultures. Patients in whom a defect in oxidative metabolism can be documented might be referred to as having *Friedreich's disease,* and those patients sharing the same phenotype but not having the oxidative defect might be referred to by the nonspecific designation *Friedreich's syndrome.* Linkage analysis with 36 polymorphic-blood-group and protein markers gave negative LOD (logarithm of the odds) scores and thus excluded at least 20% of the genome for the genetic locus of this disease (203–205). In 1988 Chamberlain et al. (206), using the molecular genetic linkage technique, mapped the gene mutation for this disorder to chromosome 9p22-CEN. The probes used were for an anonymous DNA market MCT112 and the β-interferon gene. Both probes defined MsPI polymorphisms. Although clinical variation is seen in this disorder, these investigators did not observe genetic heterogeneity. The maximal LOD score between the Friedreich's ataxia locus and the locus defined by MCT112, calculated for combined sexes, was 6.41 at a recombination fraction ($\theta = 0$). No recombinations were observed between the Friedreich's ataxia locus and this probe.

Pathology

The primary area of pathology is the spinal cord and the peripheral nerves. The spinocerebellar tracts, lateral corticospinal tracts, and posterior columns are specifically and selectively involved (207).

Clinical Manifestations

Truncal ataxia, as manifested by a discoordination of gait, frequent falling, and titubation, may be the earliest and most severe aspect of this syndrome. Gait instability may be the only manifestation of the disease for many years, but eventually dysarthria of speech and incoordination of arm and hand movements develop. By the second decade of life, the progression in gait ataxia usually develops to the point where assistance in walking becomes necessary (208–210).

The neurologic examination indicates the presence of nystagmus, loss of fast saccadic eye movements, truncal titubation, cysarthria of speech, and dysmetria and ataxia of extremity and truncal movement. Important findings in the motor examination include extensor plantar responses with normal tone in trunk and extremities and absent deep tendon reflexes (211). Weakness and extremity atrophy with fasciculations may be noted. Cardiac disease involving cardiomegaly, murmurs, bundle-branch block, T-wave inversions, and complete heart block, as recorded on the electrocardiogram, may develop (212,213). Congestive heart failure requiring diuretics and digitalis may develop. Cardiomegaly with subsequent cardiopulmonary arrest has been reported. Moderate mental retardation or psychiatric syndromes may be present in a small percentage of patients (214–218).

Hereditary Ataxia with Muscular Atrophy (Roussy–Levy Syndrome)

Roussy–Levy syndrome, originally described in 1926 (219), is an example of an intermediate form between Friedreich's syndrome and Charcot–Marie–Tooth syndrome. It is placed in the intermediate category because it represents a combination of minor cerebellar deficits with atrophy of the muscles of the legs, especially in a peroneal distribution (220,221). Harding and Thomas (220) include it as a form of hereditary motor and sensory neuropathy types 1 (slow conduction velocities) and 2 (normal conduction velocities).

Olivopontocerebellar Degenerations

The olivopontocerebellar atrophy (OPCA) syndromes represent a collection of disorders that produce progressive involvement of cerebellar functions and that share a common impairment or reduction in neurons in the inferior olivary nuclei of the medulla, in the basis pontis, in the cerebellar cortex, and in the deep cerebellar nuclei (222–225).

Clinical Manifestations

Progressive ataxia, dysarthria, dysmetria, dysadiodochokinesia, nystagmus, loss of fast saccadic eye movements, and subsequent development of spasticity, optic nerve atrophy, distal sensory involvement, and late intellectual dysfunction represent the essential clinical features of the olivopontocerebellar degenerations (189,226). As previously mentioned, there may be modifications and new clinical phenomena in different families expressing either an autosomal recessive or a dominant disease as classified by Konigsmark and Weiner (189). It is important that the variants previously described by Holmes, Sanger-Brown, and Marie, among others [as cited by Konigsmark and Weiner (189)], are quite similar as clinical entities and are separated by arbitrary minor differences in clinical features (227). It can be argued that the olivopontocerebellar degenerations inherited as autosomal dominant (189) or autosomal recessive (228) genetic disorders represent a very small number of unique clinical diseases and that the primary gene mutation has its penetrance and expression altered clinically by other modifying genes (229–234).

Gilman et al. (233) studied 30 patients with OPCA and determined their localized cerebral metabolic rates for glucose ($LCMR_{glc}$) using [^{18}F]-2-fluoro-2-deoxy-D-glucose; the results were compared with those of 30 control subjects. In these patients, PET scans showed significant hypometabolism in the cerebellar hemispheres, cerebellar vermis, and brainstem compared to normal controls. Patients had normal $LCMR_{glc}$ for the thalamus and cerebral cortex, thus indicating the selective regional hypometabolic defect present in the cerebellum and its brainstem connections.

Biochemistry and Genetics

Glutamate dehydrogenase (GDH) activity in cerebellar homogenates from dominantly inherited OPCA patients compared to control subjects was normal. GDH has been modestly reduced in leukocyte or platelet homogenates from selected patients with an autosomal recessive form of inheritance. In 1988 Mavrothalassitis et al. (235) reported isolating cDNA clones for human liver GDH; this technique may allow careful mRNA Northern blot studies to be carried out with OPCA brain tissue in order to study this gene's role in OPCA directly.

Benzodiazepine receptors were unchanged in cerebellar cortex in OPCA, but they increased in the dentate nucleus. Muscimol binding was reduced in the granule cell layer. The density of muscarinic cholinergic receptors was reduced in molecular and granule cell layers and was increased in the dendate as reported by Whitehouse et al. (236). Kish et al. (237) reported that choline acetylase (CA) and acetylcholinesterase (AChE) activities in postmortem brain samples of seven patients from one family with dominantly inherited OPCA (Schut-Swier family of Minnesota and South Dakota) were significantly reduced in both cerebral and cerebellar cortices. The loss in cholinergic activity was similar to that in Alzheimer's disease, but OPCA patients had only minimal mental status changes (238,239).

In one black American family with autosomal dominant disease, Zoghbi et al. (240) found linkage to the human leukocyte antigen (HLA) loci on the short arm of chromosome 6. A maximum LOD score of 5.83 was found at a recombination fraction of 0.12. Similarly, in the Schut-Swier family with autosomal dominant disease, Rich et al. (241) reported linkage to the HLA-A locus; this linkage was about 15 cM telomeric to the probe site on the short arm of

chromosome 6. Jackson et al. (242) and Haines et al. (243), studying the Schut-Swier kindred, have presented convincing evidence of linkage between the gene for ataxia and the human lymphocyte antigen complex situated on chromosome 6. These data may become most helpful as a marker of disease for purposes of genetic counseling.

In general, the spinocerebellar degenerations represent syndromes producing progressive and symmetrical involvement in their pathologic and clinical expression and often have a clear genetic basis of inheritance or suggest familial involvement. Rosenberg et al. (244) reported an abnormal organic acid composition in urine from affected patients. An increased incidence of echinocytes (245) and an abnormally low aspartate concentration in the cerebrospinal fluid (CSF) from patients (246) are also reported. Plaitakis et al. (247,248) and Duvoisin et al. (249) reported a 50% reduction in GDH activity in nonneural tissues from recessively inherited and dominantly inherited (with incomplete penetrance) patients, respectively, which could result in toxic levels of glutamate in the cerebellum, producing potential excitotoxic degeneration of cerebellar neurons. Recently, dominantly inherited patients have been reported as having low GDH activities in leukocyte and platelet homogenates (250–252).

Grossman et al. (253) studied the activities of brain GDH and malate dehydrogenase from patients with autosomal dominant OPCA or Joseph's disease. They found that the activities of these two enzymes were the same in patient and control samples. Thus in dominantly inherited OPCA disease as distinct from recessively inherited disease, GDH is not involved in the pathogenesis of disease as judged by measurement of this enzyme directly in brain tissue.

Other, more newly described syndromes resembling OPCA include Joseph's disease, hereditary branchial myoclonus with spastic paraparesis and cerebellar ataxia (254), and myoclonus epilepsy with ragged red fibers (MERRF syndrome); the latter is a mitochondrial encephalopathy resembling the syndrome of Ramsay Hunt. An infantile OPCA with a-lipoprotein disorder and cirrhosis associated with a low cholesterol and elevated triglycerides has been reported by Agamanolis et al. (255). OPCA has been reported with abnormal sleep and rapid eye movement (REM) activity without atonia (256).

Therapy

No specific therapy is available. It is important to be sure that the patient does not either have (a) malabsorption of vitamins A and E secondary to gastric surgery, which would result in a blind loop syndrome and a spinocerebellar syndrome as a secondary event, or (b) other causes of malabsorption (257–260).

Joseph's Disease

A nongenetic form of striatonigral degeneration was described initially by van der Eecken et al. (261) in 1960. The patients involved were diagnosed clinically as having Parkinson's disease, but their symptoms differed neuropathologically in that they had bilateral degeneration of the corpus striatum and substantia nigra, particular the zona compacta portion. No cause has been found in any of these cases.

In 1976 Rosenberg et al. (262) described a family of Portuguese ancestry with autosomal dominant spinocerebellar and striatonigral degeneration. This family numbered 329 persons in eight generations. Romanul et al. (263) described another family of Portuguese-Azorean ancestry with striatonigral degeneration (patient 2) in a clinical setting of parkinsonism and polyneuropathy. The two families are not related and, in fact, are descended from persons from separate and distant Azorean Islands. Joseph's disease has also recently been described [by Lima and Coutinho (264) in Portugal and by Healton et al. (265) in the United States] in two families that have no known relationship to any family in the Azores. The first reports of similar disease were by Nakano et al. (266) and by Woods and Schaumburg (267). It was originally thought that the disorders described by Nakano et al. (266), Woods and Schaumburg (267), and Rosenberg et al. (268) were separate and distinct. After careful epidemiologic studies and case analyses in the United States, Portugal, the Azores, India, and Japan by Rosenberg et al. (268), Coutinho and Andrade (269), Barbeau et al. (270), and Romanul et al. (263), it is concluded these clinical types represent variation in the expressivity and penetrance of the same mutant gene. Preliminary data suggest that the Joseph's disease gene is on chromosome 1 near the amylase locus. A family with autosomal dominant Charcot–Marie–Tooth disease has also been mapped to chromosome 1 because of linkage with the Duffy locus (271).

Three reports also cite the presence of Joseph's disease in Japan (272–275). The clinical features are the same as in the American and Portuguese families, and the neuropathological features are quite similar but have an accentuation of a dentatorubroluysian degeneration (274,276). Joseph's disease has also been described in a family from India by Bharucha et al. (277). It is suggested that Joseph's disease was brought to India and Japan, possibly as early as the 16th century, by Portuguese navigators and clergy who established missionaries in the western Indian state of Goa and in the southern Japanese island of Kyushu, where the disease is found today. Suite et al. (278) reported a family of Sicilian-American origin. The disease was elegantly reviewed in 1987 by a fine anthropologist, Marie Boutte (279). A comprehensive assessment of the natural history of the disease was published by Barbeau et al. (270) in 1984, and current concepts of pathogenesis were published by Rosenberg and Grossman in 1989 (280; also see refs. 281–289).

Ataxia Telangiectasia

Syllaba and Henner (290) in 1926 and Louis-Barr (291) in 1941 described a neurocutaneous disorder that begins in the first decade of life with permanent telangiectatic lesions involving the conjunctivae, malar eminences, ear lobes, and occasionally the upper neck regions; it is associated with cerebellar deficits and nystagmus (292). Although the disorder usually is sporadic in occurrence and isolated in families, it may present in families with a pattern consistent with

an autosomal recessive genetic disorder. A chromosome translocation involving chromosomes 7 and 14, a marked reduction in lymphocyte response to phytohemagglutinin, and increased chromosome breakage have been noted in some patients (293).

Fiorilli et al. (294) have indicated that spontaneous breakages at chromosome bands 7p14 and 14q32 in patient lymphocytes are caused by faulty rearrangements of the T- and B-cell receptor genes, as well as by the immunoglobulin heavy-chain locus which also maps there (294), thus explaining the immunologic defects in this disorder. These breaks could result in an increased occurrence of oncogene translocation and activation, producing T-cell or B-cell neoplasia. There is an increased incidence in lymphomas, Hodgkin's disease, and acute leukemias. The acute leukemias are of T-cell type, in contrast to B-cell neoplasia in other immunodeficiencies; these were reviewed in a *New England Journal of Medicine* Clinical Pathological Conference in 1987 (295). There is also an increased occurrence of breast cancer in women who are also heterozygous for ataxia–telangiectasia, as reported by Swift et al. (296) in 1987. Increased sensitivity of patient G1 chromosomes in stationary fibroblast cultures exposed to x-irradiation has been quantitated. There is a fivefold increase in breaks that do not rejoin in patient cultures compared with control cultures (297). Based on incidence data of Swift et al. (298) in 1986, the minimum frequency of a single hypothetical ataxia–telangiectasia gene in the United States white population was estimated to be 0.0017.

Genetics

Ataxia–telangiectasia is inherited as an autosomal recessive disorder. Genetic characteristics of the disorder include: loss of Purkinje cells; chromosomal rearrangements in lymphocytes; premature aging; insulin-resistant diabetes mellitus; increased incidence of cancer; increased sensitivity of fibroblasts and lymphocytes to ionizing radiation; and thymic hypoplasia with a reduction in serum IgA and IgG. Genetic linkage analysis of 31 families was carried out to identify the genetic defect responsible for this disorder, which was mapped to chromosomal region 11q22-23.

Clinical Manifestations

In the first decade of life there is the onset of progressive telangiectatic lesions associated with progressive deficits in cerebellar function and early nystagmus. The neurologic manifestations correspond to those seen in Friedreich's syndrome, and this entity should be included in that differential diagnostic category. Truncal ataxia, extremity ataxia, dysarthria of speech, extensor plantar responses, myoclonic jerks, areflexia, and distal sensory deficits may develop. There is a high incidence of recurrent pulmonary infections and neoplasms of the lymphatic–reticuloendothelial system in these patients, as reviewed by McFarlin et al. in 1972 (299; also see refs. 300–303).

Parenchymal Cerebellar Degeneration

The syndrome of intrinsic cerebellar degeneration begins with symmetrical cerebellar deficits primarily involving truncal and leg functions in the fifth to seventh decades of life, with males being more frequently involved than females; it is slowly progressive. It may be inherited in a recessive pattern (304), but usually it is sporadic. For detailed reading on this subject and related disorders, see refs. 305–312.

Bassen–Kornzweig Syndrome

Bassen–Kornzweig syndrome, initially described in 1950 (313), was the first entity with specific diagnostic features associated with the typical picture of Friedreich's syndrome (314). Acanthocytosis, steatorrhea, impaired chylomicron formation, and retinitis pigmentosa are the diagnostic features (313,315,316). Furthermore, the electrophoretic pattern of the serum proteins is grossly abnormal because of the absence of β-lipoproteins. Children with this syndrome develop progressive truncal and extremity ataxia, dysarthria, nystagmus, and muscle atrophy and weakness in a peroneal distribution with distal sensory involvement. Mental retardation is rare; when it does occur, however, it is usually mild. Cardiomegaly and progressive cardiac failure may develop. The disease is a rare one and must be considered in a child presenting with a progressive cerebellar deficit (317). An adult onset may be associated with malabsorption of vitamins A and E, resulting in nyctalopia, optic atrophy, and cerebellar deficits, all of which are improved with vitamin A and E therapy.

Marinesco–Sjögren Syndrome

Marinesco–Sjögren syndrome is a rare disorder in which progressive cerebellar deficits begin in early childhood. It is associated with bilateral cataracts and mental retardation, and it is another rare example in which the general Friedreich's syndrome is associated with additional specific features—in this case, cataracts and mental retardation. Using electron microscopy, Walker et al. (318) studied four patients' skin fibroblasts and found numerous enlarged lysosomes that contained whorled lamellar or amorphous inclusion bodies, indicating that this syndrome is probably a lysosomal storage disorder caused by an enzyme defect.

Muscle biopsy specimens from three patients reported by Sewry et al. (319) were abnormal, showing vacuolation and membranous whorls and, in particular, a unique dense membranous structure associated with nuclei by electron microscopy.

Cockayne's Syndrome

Cockayne's syndrome, first described in 1936, is a most rare autosomal recessive disorder associated with multiple features. Mental retardation, optic atrophy, dwarfism, neural deafness, cataracts, and retinal pigmentary degener-

ation are the major findings. Cerebellar, pyramidal, and extrapyramidal deficits and peripheral neuropathy may occur with bird-headed facies and normal-pressure hydrocephalus.

Demyelination, perivascular microcalcification, and gliosis are the neuropathologic findings. In 1980 Kennedy et al. (320) reported a patient with late onset of disease at the age of 19 years, associated with completion of a successful pregnancy. This syndrome must be considered in the evaluation of (a) mental retardation and (b) syndromes with progressive cerebellar or pyramidal degenerations.

In 1985 Lehmann et al. (321) diagnosed the syndrome prenatally. This was accomplished by examining amniotic cells *in vitro*. RNA synthesis following irradiation with ultraviolet light was abnormal in cells from a fetus with the syndrome, but not in cells from a normal fetus.

MOTOR NEURON DISEASES

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) represents a spectrum of motor system degenerations involving the corticospinal and corticobulbar pathways and motor neurons associated with the cranial nerves and anterior horn cells of the spinal cord. It is inherited in about 10% of instances, usually as an autosomal dominant with variable penetrance and expressivity (322). Dysfunctions of motor neurons produce clinical manifestations of spasticity and muscular atrophy, either singly or in combination. The presence of diffuse atrophy, weakness, fasciculations, and reduced myotatic reflexes indicates a variant of the system degeneration known as *progressive spinal muscular atrophy*. Progressive weakness and atrophy of muscles innervated by cranial nerves indicate the development of another variant referred to as *progressive bulbar palsy* (322). A pure expression of corticobulbar and corticospinal involvement (i.e., with signs of upper motor neuron deficits—including weakness and spasticity with hyperreflexia, clonus, and extensor plantar responses, but without evidence of muscular atrophy) corresponds to another variant known as *primary lateral sclerosis* (323,324). For more detailed discussions, see refs. 325–350.

Infantile Progressive Spinal Muscular Atrophy (Werdnig–Hoffman Syndrome)

Werdnig–Hoffman syndrome is to a generalized neurogenic muscular atrophy beginning in the first year of life and progressing to death within the first 2 years of life. The syndrome with onset in the first year of life, characterized by a slower progression and prolonged survival into adolescence or early adulthood, is known as Wohlfart–Kugelberg–Welander syndrome and probably represents a benign form of Werdnig–Hoffman syndrome. Epidemiologic studies have suggested an autosomal recessive mode of inheritance (351). Neuropathologic findings include loss of anterior horn cell motor neurons and bundles of focal glial hyperplasia in relation to the anterior spinal roots (352–354). There is also a predilection for involvement of type 1 muscle fibers. The cause of disease and effective therapy are not known (355).

Fleury and Hageman (356) reported an autosomal dominantly inherited lower motor neuron disorder presenting at birth with arthrogryposis. Walsh et al. (357) found the expression of the cell adhesion molecule N-CAM present in all myofibers in Werdnig–Hoffman patients; in contrast, only the atrophic fibers were positive in the Kugelberg–Welander juvenile-onset patients. Dicarboxylic aciduria was reported in one infant with classic Werdnig–Hoffman disease (358). Patients with either acute or chronic spinal muscular atrophy have recently been mapped by linkage analysis to chromosome Eq 11.2-13.3 by Gilliam et al in 1990 (358a).

Juvenile Progressive Spinal Muscular Atrophy (Wohlfart–Kugelberg–Welander Syndrome)

Wohlfart–Kugelberg–Welander syndrome has its onset in childhood or adolescence and develops as a progressive, usually proximal neurogenic muscular atrophy that may be confused with Werdnig–Hoffman disease or limb girdle muscular dystrophy (359). Since the original descriptions by Wohlfart et al. (360) and by Kugelberg and Welander (361), other investigators have reported (a) over 200 cases with infantile onset of disease beginning at less than 2 years of age and (b) about 133 cases with onset in the juvenile years between 3 and 18 years of age (362). A family history is positive in most cases, and the disease is inherited in an autosomal recessive manner, but several families have been reported as having an autosomal dominant mode of inheritance. In 1970 Namba et al. (363) reported a sex ratio of about one to one for infantile onset of disease. The disease produces weakness and muscular wasting in the proximal muscles of the extremities, usually sparing ocular, facial, and other bulbar musculature. Corticospinal and sensory pathways of the spinal cord are not involved. Fasciculations may be prominent in weak or atrophied muscles. This syndrome is distinguished from Werdnig–Hoffman disease by the later onset and benign course; it is also distinguished from ALS similarly because of the slow progression of disease and the absence of any involvement of corticospinal tracts. The limb girdle form of muscular dystrophy can be distinguished from this syndrome by findings on electromyography and muscle biopsy. The Charcot–Marie–Tooth form of neuropathy is distinguished by the presence of a predominantly distal muscular atrophy and sensory loss, neither of which are characteristic of Wohlfart–Kugelberg–Welander disease.

Fischbeck et al. (364) studied genetic linkage in seven families with X-linked adult-onset spinal muscular atrophy. They found significant linkage to the marker DXYS1 on the proximal X-chromosome long arm, but they found loose linkage or nonlinkage to markers elsewhere. The adult form is similar to the juvenile type, characterized by progressive weakness, atrophy, and fasciculations. In the X-linked recessive form, only men are affected; women who are asymptomatic carriers pass the disease on to their sons.

An interesting and important variant are patients with juvenile-onset spinal muscular atrophy with hexosamini-

dase A deficiency. These syndromes are discussed in more detail in the sections on GM2 gangliosidosis and on hexosaminidase variants and neuromuscular syndromes. In 1988 Karni et al. (365) reported an adult patient with late-onset denervating spinal muscular atrophy who had a deficiency of hexosaminidase A. This patient had clinical and electromyographic evidence of denervation and no clinical cerebellar deficits, but computed tomography of the brain demonstrated cerebellar atrophy. Indeed, some patients do show evidence of both spinal muscular atrophy and clinical cerebellar deficits. There is a wide spectrum of manifestations, including familial psychosis, fasciculations, ataxia, dysmetria, and dysarthria.

Fazio–Londe Disease

Progressive bulbar paralysis in childhood is the hallmark of Fazio–Londe disease, as emphasized by Gomez et al. (366) in 1962. It is a rare syndrome beginning in childhood and resulting in progressive bulbar palsies; there is minimum involvement of extremity musculature, however. It may be inherited in an autosomal recessive manner, and it results in progressive paralysis of the masticatory muscles, facial muscles, and pharyngeal and lingual muscles.

Familial Spastic Paraplegia

Familial spastic paraplegia is characterized by the occurrence, in the first two decades of life, of progressive spastic paraparesis leading to paraplegia. The syndrome is inherited as an autosomal recessive, sex-linked recessive, or familial trait (367). It occurs more frequently in males than in females, and its onset may rarely be delayed so that it occurs in adult life (368). It may be related to the spinocerebellar degenerations, since this familial syndrome may be encountered in large families with other forms of spinocerebellar disease (369–375). Familial spastic paraparesis and deafness inherited in an X-linked manner was reported by Wells and Jankovic (376). Preliminary genetic linkage data regarding an autosomal dominant family with "pure" familial spastic paraplegia was reported by Boustany et al. (377). Recently it has been associated with HTLV-1 infection as a genetic predisposition (377a).

Syringomyelia

Syringomyelia, or cavitation of the spinal cord, was described by Esteinne in 1546 in his treatise entitled "La Dissection du Corps Humain." The precise term "syringomyelia," referring to a cavitation of the spinal cord, is attributed to Charles P. Ollivier D'Angers, who, in 1827, attributed the abnormal dilation of the central canal to a developmental anomaly. Since that time, "syringomyelia" has referred to a chronic and progressive disorder with amyotrophy, pain and temperature sense loss (although position and stereognostic functions are relatively well preserved), paraparesis, skeletal defects including scoliosis, and associated neurogenic arthropathies (378). Syringomyelia occurs more frequently in males than in females, and the first sign of disease begins in the second or third decade of life; it rarely begins in childhood or late adulthood (379). Because of the developmental abnormalities in the cord and its predominance in males, predisposing genetic factors may be involved in the cause of this disorder. Sisters with syringomyelia were reported by Busis and Hochberg (380). For more details, see refs. 381–394.

Hereditary Myasthenic Syndromes

A sporadic case of a congenital myasthenic syndrome associated with acetylcholinesterase (AChE) deficiency was described in 1977 by Engel et al. (395). A defect in acetylcholine (ACh) resynthesis or mobilization was reported as an autosomal recessive myasthenic syndrome in 1979 by Hart et al. (396). In 1982 Engel et al. (397) described an autosomal dominant myasthenic syndrome and suggested that it was associated with an abnormally prolonged open time in the ACh-induced ion channel. Symptoms occurred in the latter syndrome in infancy or later life. There was involvement of cervical, scapular, and finger extensor muscles with ophthalmoparesis. Although there is atrophy of the neuromuscular junction (as detected by electron microscopy), there are no immune complexes at the end-plate.

PERIPHERAL NERVE DISEASES

Peroneal Muscular Atrophy

Charcot–Marie–Tooth disease, or peroneal muscular atrophy, is a genetic disorder of the peripheral nervous system primarily involving the peroneal musculature and other distal muscles of both the upper and the lower extremities. It is most often inherited as an autosomal dominant disorder and less frequently as an autosomal recessive and X-linked dominant or recessive disease (398,399). The specific molecular defect remains unknown.

Pathology

The peripheral nerves in the lower extremities, and subsequently in the upper extremities, undergo degenerative changes that include demyelination and dissolution of the axon. The occurrence of recurrent demyelination and remyelination with the formation of so-called onion-bulb changes in the peripheral nerve may result in a hypertrophied nerve as a variant; this nerve may be palpated on physical examination. Examination of biopsied skeletal muscle may indicate the occurrence of group atrophy indicative of neurogenic denervation (400). Pathologic changes have been described in the dorsal root ganglion cells, motor neurons of the spinal cord, and posterior columns of the spinal cord.

Incidence

Peroneal muscular atrophy is a rare disorder most commonly seen as an autosomal dominant inherited genetic disease in large families in which atrophy of the peroneal musculature is the dominant expression. It may also be seen in the spectrum of the spinocerebellar degenerations. It usually begins in the first or second decade of life, but delayed onset has been reported. Dyck and Lambert in 1968 (401), Dyck in more detail in 1975 (402), and Harding and Thomas in 1980 (220) described an autosomal dominant

variant (type I, dominantly inherited hypertrophic neuropathy) in which slow motor nerve conduction velocities were associated with a hypertrophic form of disease resulting from recurrent demyelination and remyelination. A second form (type II, neuronal form of peroneal muscular atrophy) of autosomal dominant disease was not associated with hypertrophy or with slow conduction velocities but rather with denervation, as evidenced by fasciculations and impaired interference patterns on electromyography (401,403). A minor variant was a form of peroneal atrophy without sensory involvement.

Ouvrier et al. (403) reported clinical and histopathological features in sural nerve biopsies from 10 cases of dominantly inherited type I disease and from six cases of Dejerine–Sottas disease (type III disease). They found a significantly higher incidence of ataxia, areflexia, and nerve hypertrophy in type III. Of note, the functional severity of type III cases was not markedly worse than that of type I patients. Berciano et al. (404) described a large family with type II disease in which 10 affected and 17 unaffected members in three generations were examined. Their view is that type II disease represents a primary neuronopathy affecting motor and sensory neurons (405).

Genetics

Charcot–Marie–Tooth disease type IB has been mapped to chromosome 1 by demonstrating linkage to the Duffy blood group locus (406,407). The Duffy locus is linked to the uncoiler locus (1qh) on the proximal long arm of chromosome 1 and is, in turn, loosely linked to the antithrombin III locus (AT3). A cDNA for AT3 has been isolated and assigned to 1q23-q25, and a restriction fragment length polymorphism (RFLP) has been identified for AT3. Using a DNA RFLP for AT3, Chance et al. (408) investigated the genetic linkage relationship of all three markers (type 1B disease presence, Duffy, and AT3) in two affected families. They could not show that type IB disease was tightly linked to AT3. The loci for both type I disease and Duffy must be close to the centromere on chromosome 1, and its precise localization and gene order will require additional probe sites and more families. Ionasescu et al. (409) studied 169 members of 15 families which were autosomal dominant. Four families were informative for linkage to apolipoprotein A2 on chromosome 1 (1q21-23), with an overall LOD score of 2.45 at a recombination of 0.001. Apolipoprotein A2 has been localized to the q21-23 region of chromosome 1 and is thus the approximate locus for the gene for type 1B patients. An excellent review of the genetics of this disorder was published by Bird (410) in 1989. For more detailed reading, see refs. 411–416. Recently, Vance et al. (416a) mapped the mutation in patients with neuropathy type 1a to chromosome 17. Recently, eight families were also mapped to the centrometric region of chromosome 17 (416b). Families that map either to chromosome 1 or 17 are phenotypically identical.

Hypertrophic Interstitial Neuropathy (Dejerine–Sottas Disease)

Dejerine–Sottas disease (417), or hypertrophic interstitial neuropathy (type III hypertrophic neuropathy of Dyck), is a recessively inherited genetic neurologic disorder producing symmetrical and severe involvement of the peripheral nerves; it is associated with impressive hypertrophy beginning in infancy or early childhood (418–423).

Hereditary Sensory Neuropathy

Hereditary sensory neuropathy is a genetic disease involving the sensory fibers of the peripheral nervous system (424,425). It is inherited as an autosomal dominant trait, and it produces progressive sensory deficits beginning in the first or second decade of life (426–431). There is a progressive loss of sensations of pain, heat, and light touch, accompanied by a loss of proprioceptive functions with associated absence of the deep tendon reflexes and occasional lightning pains. Characteristic painless ulcerations develop in the feet and the digits of the hands.

Familial Dysautonomia (Riley–Day Syndrome)

Riley–Day syndrome presents in early childhood and is inherited in an autosomal recessive manner (432). It occurs almost entirely in Jewish children. It was originally described by Engel and Aring (433) in 1945 and again in 1949 by Riley et al. (434). Smith et al. (435) in 1963, Dancis and Smith (436) in 1966, and Smith and Dancis (437) in 1967 suggested that the disorder was caused by a defect in catechol metabolism, since patients demonstrated (a) an increased concentration in urine of homovanillic acid, which is a metabolic product of dopamine metabolism, and (b) an associated decrease in the concentration of vanillylmandelic acid, which is a metabolic product of norepinephrine. These abnormalities in the urinary excretion of these metabolites suggested a defect in the enzyme dopamine-β-hydroxylase. In 1971 Weinshilboum and Axelrod (438) reported a marked reduction in serum dopamine-β-hydroxylase activity in some (but not all) patients with this syndrome. Ziegler et al. (439) reported on the norepinephrine concentration in serum and the dopamine-β-hydroxylase plasma activity in dysautonomic patients when reclining or after standing as compared with normal control subjects. Dysautonomic patients, after standing, did not have a normal increase in their levels of norepinephrine and dopamine-β-hydroxylase; furthermore, they became hypotensive. Their data supported the view that hypotension and hypertension in dysautonomia were related to abnormal rates of norepinephrine release. Siggers et al. (440) found a threefold increase in serum antigen levels of the biologically active β-subunit of nerve growth factor (NGF) in dysautonomic persons as compared with normal subjects. The beta-subunit of NGF from dysautonomic persons was functionally abnormal as measured by binding assays and radioimmunoassays. Thus it is suggested that the β-subunit of NGF is qualitatively, as well as quantitatively, abnormal in dysautonomia. Such abnormalities might provide the molecular explanation of neuropathologic changes in the peripheral nervous system, the autonomic nervous system, and the central nervous system. Breakefield et al. (441) identified some copies of the β-NGF gene (alleles) in six affected families. Alleles differed in the

length of restriction fragments that hybridized to DNA probes for the NGF gene. They found that in two families the affected children did not inherit the same two alleles at the β-NGF locus. They pointed out that since this disease is inherited as an autosomal recessive, the affected children must share the same alleles at the locus causing the disease, and thus their study excludes the β-NGF gene locus as the cause of the disorder. For more detailed reading, see refs. 442–449.

The important laboratory findings are (a) an increased homovanillic acid–vanillylmandelic acid ratio in the urine, (b) low serum dopamine-β-hydroxylase activity, and (c) impaired norepinephrine release. Characteristic findings on physical examination include the absence of fungiform and circumvallate papillae of the tongue, absence of the deep tendon reflexes, and impairment in normal lacrimation. The intravenous administration of edrophonium chloride under carefully controlled circumstances may demonstrate a transient return of taste and lacrimation accompanied by decrease in dysphagia, indicating that the disorder is, in part, related to an alteration in ACh metabolism (449).

Hereditary Amyloid Neuropathy

Peripheral neuropathy may be a component of generalized primary amyloidosis in about one-fifth of patients. There are two major hereditary forms that have been documented where neuropathy is an important clinical feature (450).

Andrade (451) reported several families from northern Portugal with autosomal dominant amyloid neuropathy. The disease process begins in the third or fourth decade, and there is subsequent development of a progressive and symmetrical impairment in both sensory and motor functions associated with marked autonomic involvement. Typical findings include hyperpathia of the distal lower extremities with an impairment in temperature and pain sensations. A steppage gait caused by a bilateral footdrop subsequently occurs along with areflexia. Evidence for autonomic neuropathy includes distal ulcerations of the lower extremities, sphincter impairment, impotence, pupillary changes, and diarrhea or constipation. The neuropathologic changes include direct deposition of amyloid into the peripheral nerves and also into other organs such as the skin, gastrointestinal tract, tongue, heart, and kidneys. Several patients with primary hereditary amyloid neuropathy inherited as an autosomal dominant have been treated with colchicine, which has resulted in clinical improvement, reduced amyloid on repeated peripheral nerve biopsies, and an improvement in nerve conduction velocities.

A similar form of autosomal dominant amyloid polyneuropathy has been described in the United States. These patients appear to have a milder form of the disease, with an onset occurring as late as the sixth decade. It begins with a slow progression of motor and sensory deficits in the upper extremities, and it may present initially as a carpal tunnel syndrome. The Finnish-type neuropathy is characterized by slowly progressive cranial neuropathy, corneal lattice dystrophy, and distal sensorimotor neuropathy without autonomic dysfunction. In 1986 Darras et al. (452) reported a typical patient with Finnish-type neuropathy in the United States.

In the Japanese-type of autosomal dominant familial amyloid polyneuropathy, as reviewed in 1987 by Ikeda et al. (453), there is also a prealbumin variant with a single amino acid replacement of valine by methionine at position 30, and this mutant protein leads to amyloid fibril formation. Sasaki et al. (454) have cloned and sequence-analyzed the cDNA for normal human prealbumin transthyretin (TTR) and have detected the mutation in the TTR gene for this dominant form of amyloid polyneuropathy. The mutant gene maps to chromosome 18. The presymptomatic diagnosis of disease was made in two sons of an affected mother in one family and in a daughter of an affected father in a second family. The demonstration of two abnormal hybridization signals in the first family at 5.0 and 1.4 kb with NsiI restriction enzyme, indicating unique restriction fragment polymorphism, was sufficient to establish a diagnosis of presymptomatic disease. Similarly, in the second family the signals at 5.0 and 1.4 kb indicated a restriction fragment polymorphism pattern associated with the mutant genotype, although presymptomatic. Both families thus had the same mutation, and the probe was highly effective in diagnosing disease in the at-risk person. These molecular findings originally reported in 1984 were confirmed and extended by Araki and co-workers (455) at Kumamoto University in 1986; this group found a mutation resulting in an adenine for a guanine in the first portion of the codon coding at portion 30 of the TTR molecule. This mutation resulted in the incorporation of a methionine instead of a valine. Recently, Tanaka et al. (456) reported a 47-year-old woman with familial amyloid polyneuropathy without familial occurrence of the disease. Her 81-year-old mother and 53-year-old sister were shown (by radioimmunoassay) to be asymptomatic carriers for variant TTR. Similar families were reported by Nakazato et al. (457) and Saraiva et al. (458) in 1987 and 1986, respectively. It is suggested that unknown factors may play a role in preventing or delaying the onset of the disease. As these investigators pointed out, to establish the diagnosis of nonhereditary primary amyloidotic polyneuropathy, it must be confirmed that variant TTR is absent in the serum of relatives. Surely this approach will be a powerful tool to eliminate this disorder not only in Japan but also in Sweden, Portugal, the United States, and Finland, where it is endemic.

Tangier Disease

Inhabitants of Tangier Island in Chesapeake Bay develop a progressive polyneuropathy in the second or third decade of life that involves distal motor and sensory functions of the extremities (459). A deficiency in high-density serum lipoproteins (a-α-lipoproteinemia) in the serum of these patients has been a consistent feature associated with lipid deposits within lymphoreticular deposits of the tonsillar fossae of the oropharynx. The primary molecular defect has not been determined, but it appears that high-density lipoproteins are abnormally targeted for lysosomes and degraded. The disorder is inherited as an autosomal recessive trait.

Porphyric Polyneuropathy

Acute polyneuropathy may be an important component in the acute intermittent Swedish-type porphyria that is inherited as an autosomal dominant trait. The phenotypic neurologic features include episodes of personality change, depression, psychosis, abdominal pain, and severe generalized polyneuropathy. Skin manifestations do not occur in this form of porphyria. Episodes of polyneuropathy may be precipitated by barbiturates or phenytoin. A characteristic syndrome may occur in individual families, and the variation and severity of disease also differ from family to family. Urinary excretion of porphobilinogen is uniformly present. The enzyme uroporphyrinogen synthetase (porphobilinogen deaminase) has been reported to be deficient in liver and erythrocytes from affected patients. Enzyme activities are reduced by 40–60% of normal, which apparently is sufficient to alter the rate of metabolism of the porphyrin pathway. Thus porphyria is a most rare example of a dominantly inherited disorder resulting from an enzyme deficiency state. As a result of this enzyme deficiency and the reduced synthesis of its product, uroporphyrin-1, there is a release induction of the activity of the rate-limiting enzyme in the pathway, δ-aminolevulinic acid synthetase. This induction, in turn, results in an increase in urinary δ-aminolevulinic acid and porphobilinogen. Several patients have been treated with hematin, which corrects the metabolic defects of δ-aminolevulinic acid and porphobilinogen and leads to a striking improvement in clinical findings, including polyneuropathy. A high-carbohydrate diet may also prevent attacks and reduce morbidity. Hematin is unstable, and its value to reverse the course of disease is dependent on fresh material (460).

The occurrence of acute polyneuropathy is sudden and often without any apparent cause. Drugs, hormones, or infection may trigger an attack. Severe polyneuropathy may develop with predominantly motor findings in an ascending distribution, with proximal accentuation resembling the Guillain–Barré syndrome. In fact, facial diplegia and bulbar paralysis may also occur in an ascending fashion. Patients may also demonstrate an encephalopathy with delirium and seizures. Hyponatremia resulting from the inappropriate secretion of the antidiuretic hormone (ADH) has been reported. Rarely, the presentation of a mononeuritis multiplex syndrome occurs, with random, asymmetric involvement of individual nerves resembling a sacral plexus syndrome with severe pain and weakness. Phenothiazines, glucose, and intravenous infusion of hematin are therapeutically effective. Coproporphyria and variegate porphyria are two other autosomal dominant forms of porphyria that result in acute neurologic deficits. Llewellyn et al. (461) investigated a common two-allele MspI RFLP of the human erythroid porphobilinogen (PBG)–deaminase gene in 33 unrelated patients with acute intermittent porphyria (AIP) and 20 controls. The polymorphism was tightly linked (LOD score 3.14; no recombinants) to the AIP locus as identified by activity of erythrocyte PBG–deaminase. In suitable families, MspI polymorphism provides a more certain way of identifying carriers of the AIP gene than do current enzymatic methods.

Giant Axonal Neuropathy

Giant axonal neuropathy is a rare autosomal recessive disorder described in 1972 by Asbury et al. (462); it is characterized by a symmetrical distal neuropathy, mental retardation, and frizzy, kinky hair. The peripheral nerve axons are dilated segmentally because of the accumulation of 10-nm neurofilaments as seen on nerve biopsies. Similar axonal pathology is seen in the central nervous system (CNS).

Thomas et al. (463) reported on the autopsy findings of an 18-year-old man who had the onset of disease at age 4 years. Histological examination of the brain and spinal cord showed numerous Rosenthal fibers, a distal axonopathy that most severely affected the corticospinal tracts, middle cerebellar peduncles, posterior columns, and olivocerebellar degeneration.

Donaghy et al. (464) reported a 5-year-old patient who had abnormalities within the cerebellar and cerebral white matter on magnetic resonance brain imaging. Myelinated nerve fiber density in the sural nerve was reduced to 6790/mm^2 at age 8 years and had fallen to 3812/mm^2 16 months later, indicating that progressive axonal loss occurs. 2,5-Hexanedione is a toxin that produces an experimental model of giant axonal neuropathy. Using this model system, Monaco et al. (465) reported that the transport of neurofilamentous protein and two other polypeptides was selectively increased. Thus the genetic disorder may result from a similar defect, but the precise biochemical defect is unknown.

PHAKOMATOSES OR NEUROCUTANEOUS SYNDROMES

Neurofibromatosis (von Recklinghausen's Disease)

Neurofibromatosis, or von Recklinghausen's disease, is a genetic disorder inherited as an autosomal dominant trait; it is characterized by the occurrence of pigmented skin lesions, multiple tumors of spinal or cranial nerves, tumors of the skin, and associated gliomas and intracranial meningiomas. There is an increased association with pheochromocytomas, cystic lung disease, renal vascular lesions causing hypertension, fibrous dysplasia of bone, gastrointestinal neurofibromas with chronic blood loss, and medullary thyroid carcinoma and other tumors of the endocrine glands.

A long-term follow-up of 212 affected patients in Denmark was reported by Sorensen et al. (466). Compared with the general population, male relatives with neurofibromatosis had the same rate of neoplasms, whereas female relatives had a nearly twofold higher rate. The malignant tumors in 212 patients with neurofibromatosis according to tissue type, as reported by Sorensen et al. (466), are listed in Table 3. Riccardi (467) and Riccardi and Lewis (468) reviewed the concepts of penetrance and expressivity present in this disorder.

Von Recklinghausen's neurofibromatosis is also referred to as "neurofibromatosis I" (NFI); it is a separate entity from "neurofibromatosis II" (NFII), which is bilateral familial acoustic neurofibromatosis. NFII produces bilat-

TABLE 3. *Malignant tumors in 212 patients with neurofibromatosis according to tissue type*[a]

Type of tumor	Number of tumors reported
Central nervous system	
Gliomas	16
Meningiomas	2
Malignant neurilemoma	1
No histopathology	2
Total	21
Peripheral nervous system	
Neurosarcomas	4
Neuromyxoma	1
Acoustic neuroma	1
Total	6
Other	
Sarcoma fusciellulare	2
Fibrosarcoma	1
Fibromyxosarcoma	1
Osteosarcoma, maxillary bone	2
Pheochromocytoma	3
Squamous-cell carcinoma, lung	2
Carcinoma	
Adrenal	2
Bile duct	1
Colon	5
Ovary	4
Breast	7
Uterus	1
Conjunctiva	1
Left eyelid	1
Nevocarcinoma, skin	1
Cancer	
Stomach	12
Liver	1
Pancreas	1
Kidney	1
Mediastinum	1
Prostate	1
Multiple myeloma	1
Chronic lymphatic leukemia	1
Lymphosarcoma	1
Retiçulosarcoma	1
Unspecified gluteal region	1
Primary site undetermined	1
Total	57

[a] From ref. 466, with permission.

eral eighth nerve tumors as an autosomal dominant disorder and may have the other central and peripheral nervous system manifestations of NFI. In NFII patients, meningiomas–ependymomas were more common among the younger patients, and those who initially presented with acoustic neuromas were nearly a decade older (469).

Genetics

The gene responsible for NFI is located near the centromere on the long arm of chromosome 17 (17q11.2), as reported in 1987 by Barker et al. (470); this was determined by linkage analysis of 15 Utah kindreds. In 1987 Rouleau et al. (471) reported (using linkage analysis) that the gene for NFII is on chromosome 22 and that it is therefore distinct from the NFI gene locus. More precisely, Wertelecki et al. (472) and Martuza and Eldridge (473) reported that the locus for NF2 is near the center of the long arm of chromosome 22 at 22q11.1 to 22q13.1. Deletions of chromosome 22 have been associated with NFII and meningiomas, suggesting that the disease locus encodes a tumor suppressor gene. A transgenic mouse model for NFI has been reported utilizing the tat gene of HTLV-1, which results in tumors resembling human NFI. At the rate of current progress [as reviewed by Collins et al. (474) in 1989], the NFI gene will be cloned in the next few years. For more details, see refs. 475–80. Infact recently, two groups headed by Collins (480a) and White (480b) have sequenced the NF1 gene and believe its normal product is an anti-oncogene suppressing the ras oncogene. The mutation results in abnormal activation of the ras oncogene resulting in tumor production.

Tubulerous Sclerosis (Bourneville's Disease)

Tuberous sclerosis (Bourneville's disease or epiloia) is a neurocutaneous disorder inherited as an autosomal dominant trait. Its triad of findings includes (a) facial nevi (adenoma sebaceum), (b) epilepsy, and (c) mental retardation. Although the clinical and neuropathologic features are well described, the basic biochemical defect remains unknown. Rarely, an astrocytoma may occur in a child; for example, a computerized tomographic (CT) scan will demonstrate an astrocytoma located in the head of the caudate nucleus of a young child.

Clinical Manifestations

The clinical appearance of the patient is characteristic. Patients develop mental retardation and epilepsy during the first decade of life. The first manifestation of disease is usually focal or generalized major motor seizures without other focal neurologic deficits. The occurrence of mental retardation is not evident until age 6 years. Several years after the development of seizures, the characteristic cutaneous facial lesions first develop. The facial nevi or sebaceous adenomas occur in a symmetrical distribution on the malar and nasal regions, and they appear yellow or orange-red in color, varying from several millimeters to a centimeter in size. Areas of roughening of the skin (shagreen patches) in the shape of small spheres caused by fibrous hyperplasia, cafe au lait spots, areas of depigmented nevi, and, rarely, subungual neurofibromas are characteristic of tuberous sclerosis and are evidence for its being genetically related to von Recklinghausen's disease.

Neoplasms of the kidneys are common but usually not clinically evident. Tumors of endocrine organs and the liver occur rarely, and true rhabdomyomas occur in a small percentage of patients. Papilledema and other focal neurologic deficits signal the presence of a large intracranial tumor.

The electroencephalogram (EEG) may show facial slowing and multifocal spikes resulting from associated cerebral phakomas. Hypsarrhythmia has been reported in a small number of patients. Roentgenograms of the skull may indicate the presence of calcifications in a periventricular distribution.

Genetics

This disorder is inherited as an autosomal dominant with a high degree of penetrance. Linkage analysis was performed by Fryer et al. (481) in 19 families using 26 polymorphic markers. Maximum LOD scores were 1.20 for adenylate kinase at zero recombination and 3.85 for the ABO blood group at zero recombination. These data indicate that the gene for tuberous sclerosis is on the distal long arm of chromosome 9. There may be heterogeneity as some families apparently map to 11q 23 (481a).

Sturge–Weber Disease

Sturge–Weber disease is a neurocutaneous disorder that produces a port-wine-colored capillary hemangioma on the face; this is accompanied by a similar vascular malformation of the underlying meninges and cerebral cortex. The etiology is unknown, although the defect has been reported in more than one family member, which indicates a genetic predisposition.

Clinical Manifestations

The diagnosis is easily made by the presence of a port-wine facial nevus following the sensory dermatomal distribution of the first, second, or third portion of the trigeminal nerve. Generalized or focal motor seizures may also occur and may be associated with mental retardation. The patient may develop hemiplegic atrophy with shortening of the extremities, which occurs contralateral to the atrophic hemisphere with calcification. Exophthalmos, glaucoma, buphthalmos, optic atrophy, and other cutaneous port-wine nevi and retinal angiomas may also be present.

In the differential diagnosis, Sturge–Weber disease must be distinguished from von Hippel–Lindau (VHL) disease. The latter disorder is autosomal dominant with an inherited susceptibility to various forms of cancer, including hemangioblastomas on the central nervous system, pheochromocytomas, pancreatic neoplasms and renal cell carcinomas. Seizinger et al. (482) reported in 1988 that the VHL gene is linked to the locus encoding the human homologue of the RAF 1 oncogene mapping to chromosome 3p25. It is suggested that sporadic and VHL-associated forms of renal cell carcinoma might both result from alterations causing loss of function of the same "tumor suppressor" gene on chromosome 3p.

Incontinentia Pigmenti

Incontinentia pigmenti, recognized as early as 1906 by Garrod (483), is a rare neurocutaneous disorder inherited in an X-linked dominant manner. It must be differentiated from neurofibromatosis, which is a more common neurocutaneous disorder but which is inherited as an autosomal dominant. Pigmented skin lesions begin in the first 6 months of life and initially appear as vesicular or bullous eruptions. The skin lesions then become pigmented, forming brown linear patterns or whorls on the face, extremities, and abdomen. There may be mental retardation, seizures, dystrophy of the fingernails, and alopecia, in addition to the skin hyperpigmented lesions. Microcephaly, hydrocephaly, microphthalmia, chorioretinitis, and spastic or flaccid quadriparesis may also be associated features of the disease. The spectrum of findings was recorded by Sulzberger et al. (484) in 1938 and Carney (485) in 1976. Miller and Parker (486) reported a depigmented form of incontinentia pigmenti achromians (hypomelanosis of Ito) with a chromosome defect. A 6-month-old girl had seizures, the Wolf–Parkinson–White cardiac conduction defect, and a whorled pattern of hypopigmentation over the trunk and limbs. The patient had a balanced translocation between chromosomes 2 and 8. Parental karyotypes were normal. The patient was 46.

Xeroderma Pigmentosum

Xeroderma pigmentosum is a rare but severe disorder of the skin and nervous system. Patients have extreme sensitivity to sunlight or ultraviolet light, resulting in skin freckling, atrophy, and telangiectasia. The nervous system involvement can result in microcephaly, chorea, athetosis, ataxia, deafness, and mental retardation (487,488,488a). Recently, peripheral neuropathy has been described in several patients in 1990. Patients readily develop skin cancers, including basal cell malignancies and melanomas. Medulloblastomas and neuromas also occur. The basic defect involves an impairment in DNA repair. This defect involves the removal of pyrimidine dimers because of deficient endonuclease activity. The patients whose cells in culture show the highest percentage of defect in DNA repair are the ones that develop neurologic disease. The patients with neurologic abnormalities (DeSanctis–Cacchione syndrome) have neuronal death of the pyramidal cells, Purkinje cells, and basal ganglia neurons. It is inherited as an autosomal recessive disorder with an incidence of between 1 per 65,000 and 1 per 250,000 births (489).

DISORDERS OF PURINE METABOLISM

Lesch–Nyhan Syndrome

Historical Perspective

In 1964 Lesch and Nyhan (490) described a familial disorder of uric acid metabolism with CNS dysfunction, and in 1966 Shapiro et al. (491) reported an X-linked recessive inherited syndrome of mental retardation and hyperuricemia. In 1967 Seegmiller et al. (492) reported an enzyme defect associated with an X-linked human neurologic disorder (Lesch–Nyhan syndrome) with excessive purine synthesis in erythrocyte lysates and cultured skin fibroblasts. In 1968 the first *in utero* diagnosis of a heterozygous individual was achieved.

Incidence and Prevalence

The true incidence and prevalence are not known at this time, but this is a rare entity.

Genetics

This disorder is transmitted in an X-linked recessive fashion.

Clinical

Patients with Lesch–Nyhan syndrome are usually normal for the first 1–3 months of life, although some exhibit recurrent vomiting, feeding difficulties, and hypotonia. By 3–4 months the infants show signs of slowed motor development, and by 8–12 months they develop extrapyramidal signs. The extrapyramidal signs usually consist of combinations of chorea, athetosis, and dystonia of the extremities. These signs, however, are not specific for Lesch–Nyhan syndrome. At around 12 months of age, the patient begins to develop signs of pyramidal tract involvement such as hypertonia, hyperreflexia, and extensor plantar responses. The extrapyramidal and pyramidal signs become more prominent with the passage of time. Between 2 and 6 years of age, many patients develop a striking compulsive, self-destructive type of behavior, consisting of biting their lips, buccal mucosa, and accessible parts of their extremities, such as fingers and toes. These patients also exhibit head-banging and place their extremities in dangerous places. The urge to perform self-mutilation can be strikingly asymmetrical. Patients also exhibit unusual aggressiveness toward others, and the aggressiveness and self-mutilation can be quite varable from day to day. It has been suggested that the aggressiveness is similar to "sham rage." The aggressiveness, agitation, episodes of opisthotonic posturing, and self-mutilation are all increased by placing the patients in stressful situations.

Approximately 50% of patients with Lesch–Nyhan syndrome have been reported to have seizures. Routine I.Q. testing methods have revealed I.Q. scores in the 39–65 range. When trying to assess intelligence of these patients, one has to take into consideration their dystonia and movement disorders.

Routine neurologic laboratory studies, including CSF studies, electromyography, and nerve conduction velocities, are normal. EEGs can either be normal or reveal diffuse slowing.

All patients exhibit excessive uric acid production, with excretion ranging from 25 to 143 mg/kg/day, compared with an upper limit of 18 mg/kg/day in normal children. The serum urate concentration ranges from 7 to 18 mg/dl in the absence of renal insufficiency. Because of this variability, determination of serum uric acid concentration is not a reliable screening test. The uric acid/creatinine ratio in urine is a nonspecific but valuable screening test. The normal uric acid/creatinine ratio in urine is up to 2.8 under 1 year of age and less than 1.0 for ages greater than 10 years. In Lesch–Nyhan syndrome the ratio may be greater than 5.0 for patients less than 10 years old and is usually in the range of 2.0 to 3.0 for patients older than 10 years. Other disorders that are associated with excessive uric acid production include type I glycogen storage disease and lymphoproliferative disorders.

Because of increased urinary uric acid excretion, uric acid cystalluria usually develops at some time in most patients and can lead to the finding of orange crystals on an infant's diaper. The excessive uric acid excretion can also lead to symptomatic uric acid nephrolithiasis and obstructive uropathy. Elevated serum uric acid can lead to gouty arthritis and tophaceous deposits of monosodium urate. The diagnosis is confirmed by finding virtual absence of activity of HGPRT in tissues, erythrocyte lysates, leukocytes, or cultured skin fibroblasts (493,494). For further details, see refs. 495–504.

Adenosine Deaminase Deficiency

An infantile syndrome caused by a deficiency of the purine salvage enzyme adenosine deaminase (ADA) has been clearly recognized, which includes severe combined immunodeficiency and severe motor and mental retardation. It is inherited as an autosomal recessive disorder. Pendular nystagmus, headlag, increased extensor muscle tone, dystonic and athetoid movements, absent deep tendon reflexes, and mental retardation are some clinical features. Profound lymphopenia, the absence of a thymic shadow, rib concavity, and flattened acetabula are other features. Serum IgA and IgM can be absent, and IgG is very low. Peripheral blood lymphocytes do not respond to *in vitro* stimulation with phytohemagglutinin, and T and B cells may be absent. Delayed skin tests for reactivity to dinitrochlorobenzene (DNCB) are nonreactive. ADA deficiency is confirmed by measurement of the enzyme in red blood cells. Neurologic abnormalities have been reported in three of 23 ADA-deficient patients. Importantly, neurologic abnormalities disappeared in one patient during treatment with multiple partial-exchange transfusions of irradiated normal erythrocytes, thus providing enzyme replacement (505). A child with this disorder was the first patient to be treated with gene therapy, but as of yet, no formal publication in a scientific journal has yet appeared.

Familial Pyrimidinemia and Pyrimidinuria Associated with Fluorouracil Toxicity

Recently, an autosomal recessive disorder has been described in which patients manifest pyrimidinemia or pyrimidinuria with impairment in level of consciousness progressing to coma and associated with cerebellar deficits when treated with fluorouracil. A 27-year-old woman with a breast malignancy was treated with modest doses of fluorouracil and rapidly developed a severe leukopenia, thrombocytopenia, stomatitis, hair loss, diarrhea, fever, weight loss, dysarthria, cerebellar ataxia progressing to confusion, and semicoma. Her neurological symptoms gradually improved when the drug was stopped, but she continued to excrete high amounts of uracil and thymine. Plasma levels of uracil and thymine were also elevated. Her normal brother also had pyrimidinemia, indicating that the patient just described had a genetic defect in pyrimidine metabolism which was made clinically manifest when treated with fluorouracil. A defect in the degradation of uracil and thymine

is postulated in these individuals and was responsible for an impairment in the degradation of fluorouracil as well. Dihydropyrimidine dehydrogenase, the rate-limiting enzyme in pyrimidine metabolism, is postulated as being defective in this patient and her brother, as described by Tuchman et al. (506).

Hereditary Cerebral Angiopathy with Cerebral Hemorrhage and Amyloidosis

Hereditary cerebral hemorrhage due to an angiopathy associated with amyloidosis is an uncommon event compared with hypertension-induced cerebral hemorrhage. In 1935 Arnason (507) published a report showing 10 families with a high incidence of cerebral hemorrhage. More recently, the fibrillar components of the amyloid deposits in cerebral arteries were isolated and were found to consist of large fragments of the alkaline microprotein gamma-trace (508). For more details, see refs. 509–511.

DISORDERS OF AMINO ACID METABOLISM

Phenylketonuria

Phenylketonuria is the most common disorder of amino acid metabolism in our society; the incidence of this disease in the United States is 1 in 14,000 births, and fortunately it is treatable. It was originally described by Folling (512) in patients who were retarded and who excreted urinary phenylpyruvic acid. Based on this excretion product, Penrose and Quastel (513) called it "phenylketonuria" (PKU). The enzyme defect for this autosomal recessive disorder involves hepatic phenylalanine hydroxylase (514). The therapeutic value of diet restricted in phenylalanine was reported by Bickel et al. (515), and heterozygote identification with a phenylalanine challenge was reported by Hsia et al. (516).

Clinical Features

In general, children at birth are normal, although neonatal disorders, especially vomiting and eczema, have been cited as being increased in incidence. A characteristic odor due to elevated phenylacetic acid in perspiration has been emphasized. During the first 12 months of life, progressive mental retardation and hypopigmentation of hair, skin, and the ocular iris occur. It has been suggested that this hypopigmentation is due to inhibition of tyrosine by the high titers of phenylalanine in tissues. If patients are not treated early, a very high percentage of them will be severely mentally retarded.

A simple diagnostic test is the ferric chloride test, which produces a vivid green color in the presence of phenylpyruvic acid. A more reliable test is the Guthrie test (517), which gives a more quantitative assessment of blood phenylalanine levels and avoids the false-negative assessment of the ferric chloride test in some patients. An abnormal serum phenylalanine level is that above 20 mg% in a child who is older than 1 week and who is on an average protein and calorie diet.

An adult form occurs in which patients have mental retardation, chorcoatretosis, spasticism ataxia and show white matter changes on brain scan (517a).

Genetics

A major advance occurred in 1983 when Woo et al. (518) cloned the gene for phenylalanine hydroxylase and demonstrated its usefulness in diagnosing affected persons, carriers, and noncarriers by showing distinctive patterns of hybridization signals on Southern blots.

In 1985 DiLella et al. (519) observed two variations of PKU at the mRNA level. The liver from one PKU patient contained abundant phenylalanine hydroxylase mRNA, whose size was identical to that of normal mRNA. Thus the low levels of enzyme activity in this patient were the result of defective or unstable enzyme rather than that of a transcriptional error from the gene level into its mRNA. Another patient had rarely detectable liver levels of phenylalanine hydroxylase mRNA. Thus this patient has a transcriptional error, and minimal enzyme protein would be synthesized. Hence there is now evidence for molecular variability for the clinical expression of this disorder. In 1985 a full-length cDNA clone of human phenylalanine hydroxylase was inserted into a eukaryotic expression vector and transferred into mouse NIH3T3 cells, which usually do not express this enzyme. The transformed mouse cells expressed enzyme mRNA. Thus a single gene contains all of the necessary genetic information to code for functional enzyme (520).

Lidsky et al. (521) reported diagnosing classic PKU prenatally in two at-risk families by means of a cloned phenylalanine hydroxylase gene probe that was used to analyze DNA isolated from cultured amniotic cells. The diagnoses of a PKU fetus in one family and a heterozygous fetus in another family were confirmed after birth.

In 1988 DiLella et al. (522) identified single base substitutions in two mutant phenylalanine hydroxylase alleles that cause PKU. Amplification (via polymerase chain reaction) of a subgenomic DNA fragment containing both mutation sites was used to identify carriers of the mutant alleles. See refs. 523 and 524 for further details.

Homocystinuria

Homocystinuria is a common aminoacidopathy, with an incidence of 1 in 200,000 births in the United States. It was described in patients who were retarded and who excreted homocystine (525). Mudd et al. (526) described the enzyme defect to be cystathionine β-synthase for this autosomal recessive disorder. Holowell et al. (527) demonstrated that pyridoxine (vitamin B_6) could increase enzyme activity and lower excretion of homocystine in selected patients.

Clinical Features

Patients develop a characteristic clinical picture that includes mental retardation, ectopia lentis, scoliosis, genu val-

gum, pectus carinatum or excavatum, a high arched palate, pes cavus, thromboembolism, a malar flush, and prominent livido reticularis. Seizures may be present in a small percentage of patients, and about 10% of patients are mentally normal.

Several hereditary disorders of intracellular cobalamin metabolism—usually noted because of homocystinuria (cobalamin E and G mutations) or methylmalonic aciduria (cobalamin A, B, and F mutations), or both (cobalamin C and D mutations)—have been reported. Homocystinuria occurs when methylcobalamin and its cofactor, 5-methyltetrahydrofolate, cannot be used in the methylation of homocysteine to methionine (methionine regeneration shuttle), mediated by methionine synthase. Cystathionine β-synthase activity is normal. Neurological symptoms and megaloblastic anemia may develop in late childhood or in adulthood and may be misdiagnosed as multiple sclerosis. Screening must be done for homocystinuria and methylmalonic aciduria. Carmel et al. (528) reported a 21-year-old woman who had myelopathy and neuropathy due to methionine synthase deficiency. In this disorder, 5-methyltetrahydrofolate, which acts as a methyl donor to cobalamin to generate methyl cobalamin, cannot be used. A few patients present in childhood or early adulthood with a schizophrenic-like behavior, homocystinuria, and hypomethioninuria. Their cystathionine β-synthase activity is normal, and they have a methionine regeneration shuttle that is defective because of vitamin B_{12} or folic acid synthesis or reductase enzyme defects. See refs. 529 and 530 for further details.

Methylmalonic Aciduria

Patients with methylmalonic aciduria have a marked motor and mental retardation, often with generalized seizures and ketoacidosis (531,532). Adult patients with a progressive myelopathy should be screened for methylmalonic aciduria caused by an inborn error of cobalmin metabolism (cobalamin A, B, and F mutations). Methylmalonic aciduria results when the conversion of methylmalonyl-CoA to succinyl-CoA by methylmalonyl-CoA mutase, mediated by 5′-deoxyadenosylcobalamin, becomes impaired. Patients may improve biochemically and clinically with high doses of vitamin B_{12} (532). Defects in the enzymes methylmalonyl-CoA synthase and mutase as well as in vitamin B_{12} synthetic enzymes have been reported as being associated with this syndrome. It is presumed to be inherited as an autosomal recessive disorder. Another subset of patients consists of those in which methylmalonic aciduria was also present with homocystinuria, cystathioninuria, and hypomethioninemia, and these patients were not ketoacidotic. A 19-month-old child with vitamin B_{12} responsive disease was noted to have low-density lucencies in the globus pallidi as shown by CT (533).

Treatment consists of a low-protein diet and high doses of vitamin B_{12} for those who respond biochemically with reduced methylmalonic acid excretion and improved mental status. L-Carnitine oral therapy has been advocated in a loading dose of 100 mg/kg, followed by 100 mg/kg/day divided into three or four doses (534,535).

Propionic Acidemia

During the neonatal period, patients with propionic acidemia present with obtundation, coma, dehydration, and ketoacidosis. Propionic acidemia and aciduria with a deficiency of the enzyme propionyl-CoA carboxylase in fibroblasts or leukocytes are diagnostic of the syndrome, which is inherited as an autosomal recessive disorder. Therapy includes a low-protein diet, vigorous rehydration, and correction of acidosis with bicarbonate. Biotin, a cofactor of propionyl-CoA carboxylase, is given to patients whose response is both biochemically and clinically favorable. L-Carnitine oral therapy has been advocated in a loading dose of 100 mg/kg, followed by 100 mg/kg/day divided into three or four doses (534,535).

Hyperglycinemia

Hyperglycinemia is an autosomal recessive disorder whose clinical features include neonatal to early childhood onset of episodic ketoacidosis with motor and mental retardation and with hyperglycinemia and hyperglycinuria. During acute episodes, urinary excretion of α-methyl-β-hydroxybutyrate, α-methyl acetoacetate, and butanone increases. If the disorder is diagnosed promptly and proper therapy of protein restriction and correction of acute attacks of acidosis is implemented, it is possible for relatively normal development to occur in patients (536,537).

Glutaric Acidemia

Glutaric acidemia is an autosomal recessive disorder that presents as infantile (type 1)- or childhood (type 2)-onset mental and motor retardation with glutaric acidemia and aciduria. There may be clinical hypotonia, dystonic posturing, and choreoathetosis. The enzyme defect involves glutaryl-CoA dehydrogenase (538). Minor improvement has been reported with a diet low in lysine and tryptophan, which produces a significant reduction in serum and urinary levels of glutaric acid. Siblings who have absent enzyme activity in both but who exhibit clinical disease in only one have been reported. Unidentified mechanisms must spare or delay the onset of disease. Low plasma carnitine levels have been reported. Riboflavin therapy and a fat-restricted, carbohydrate-enriched diet resulted in dramatic improvement in one 17-year-old girl with a lipid storage myopathy and glutaric aciduria type 2 (539–541).

Maple Syrup Urine Disease

In 1954 Menkes et al. (542) described a family in which four of six siblings in early neonatal life presented with a syndrome of vomiting, hypertonia, and a urinary odor resembling that of maple syrup. In 1957 Westall et al. (543) described a child with elevated serum and urine levels of leucine, isoleucine, and valine. A late-onset form of the disorder was described by Morris et al. (544) in 1961. The

incidence of disease is about 1 in 290,000 births. It is an autosomal recessive disorder caused by a defect in the enzyme branched-chain amino acid decarboxylase as measured in leukocytes or fibroblasts. Clinical features include neonatal failure to thrive, vomiting, lethargy, and maple syrup odor of the urine. Patients may also develop hypotonicity and seizures. Occasionally, hypoglycemia will develop that is probably secondary to elevated serum leucine, isoleucine, and valine. There is considerable heterogeneity in clinical severity (545).

Treatment consists of a diet reduced in branched-chain amino acids with careful monitoring of serum leucine, isoleucine, and valine to maintain them within a normal range.

Hypervalinemia

To date, a single patient has been reported who presented with vomiting and failure to thrive. The child, who was of Japanese extraction, was mentally retarded, had hypervalinemia (546), and had a disorder of valine transamination (545). The child improved with a low-valine diet. This is an autosomal recessive disorder caused by a defect in the transamination reaction converting valine to a α-keto-isovaleric acid.

Isovaleric Acidemia

Isovaleric acidemia is an autosomal recessive disorder in which young children present with mental retardation, a body odor resembling sweaty feet or cheese, and increased levels of isovaleric acid in serum and urine. Such a syndrome was originally reported by Tanaka et al. (547) in 1966 in siblings who were 2.5 and 4 years of age. The initial presentation is similar to that of maple syrup urine disease, with a severe acidosis, failure to thrive neonatally, neurologic deterioration leading to coma, and a high mortality in the first 3 months of life. The abrupt onset of acidosis and neurologic deterioration is often induced by acute infections.

It is presumed that the enzyme defect is isovaleryl-CoA dehydrogenase.

Therapy includes a diet low in leucine enriched with lipid, carbohydrate, and vitamins until the isovaleric acid levels achieve a normal value. With acute therapeutic intervention the outcome is significantly improved.

The differential diagnosis for this entity and maple syrup urine disease includes (a) multiple carboxylase deficiency due to a deficiency in the neonatal-onset form of holocarboxylase synthetase and (b) a later-onset form due to biotinidase deficiency. Patients with the biotinidase deficiency form develop life-threatening episodes of acidosis and ketosis leading to coma. Alopecia and lesions of the skin and mucous membranes may also occur. Treatment with oral biotin in moderate doses results in significant and sustained improvement. Basal ganglia calcifications have been reported in a case of biotinidase deficiency (548–550).

Methylcrotonylglycinuria

Methylcrotonylglycinuria is an autosomal recessive disorder first reported by Eldjarn et al. (551) in a $4\frac{1}{2}$-month-old girl whose parents were first cousins. The child presented a clinical picture of spinal muscular atrophy and excreted excessive levels of β-hydroxyisovaleric acid and β-methylcrotonylglycine. Subsequently, Gompertz et al. (552) reported a second case in a 5-month-old infant with acidosis, rash, and vomiting who also had increased urine excretory levels of β-methylcrotonylglycine and diglyglycine. The child improved clinically and biochemically when treated with biotin at 10 mg/day.

Therapy consists of leucine restriction in the diet and biotin administration, and when treatment is begun early in the course, the prognosis is favorable.

Glutamyl-Ribose-5-Phosphate Storage

Historical Perspective

Williams et al. (553) described a 6-year-old boy with seizures, neurologic deterioration, and proteinuria.

Genetics

This is presumably an X-linked recessive disorder with storage of glutamyl-ribose-5-phosphate caused by a postulated defect of an ADP-ribose protein hydrolase.

Clinical Presentation

A 2-year-old boy developed normally, but then his speech and language deteriorated. He developed seizures at 3 years of age and was microcephalic. He developed proteinuria, and a renal biopsy showed focal segmental and global glomerulosclerosis. There was progressive deterioration in neurologic and renal function, and he died at 8 years of age. A maternal uncle had a similar clinical presentation and died at 7 years of age after having suffered from seizures, mental retardation, nephrotic syndrome, optic atrophy, hypertension, and hyporeflexia (553).

Pathology

The brain of the 8-year-old boy described by Williams et al. (553) was atrophied, weighing 860 g (normal weight for age: 1273 g). The cerebral cortex, basal ganglia, cerebellum, dentate nucleus, and pontine and roof nuclei had moderate-to-marked neuronal loss affecting all layers. There was end-stage renal disease. Electron microscopy of connective tissue cells in a conjunctival biopsy showed lysosomes containing granular and multilamellar material.

Biochemistry

The activities of enzymes in leukocytes and cultured skin fibroblasts known to be responsible for lysosomal storage disease were normal. Chromatography of an acetic acid extract of brain and kidney showed an abnormal carbohydrate-containing peak. The structure of the stored material was shown to be glutamyl-ribose-5-phosphate. The postulated enzyme defect is ADP-ribose protein hydrolase.

Diagnosis

This disorder is identified by the early childhood progressive deterioration of neurologic and renal functions, normal lysosomal enzymes for the common storage disorders, and identification of glutamyl-ribose-5-phosphate on a renal biopsy.

Treatment

No specific therapy is available.

Histidinemia (Histidase Deficiency)

Histidinemia is rare autosomal recessive aminoacidopathy characterized by elevated histidine in serum and urine, along with reduced activity of the enzyme histidase. Clinical features include partial deafness, delayed speech development, and moderately severe mental retardation. The metabolic defect is an inability to convert histidine to urocanic acid because of a deficient activity of histidase. A positive urine ferric chloride test is caused by elevated levels of imidazole pyruvic acid. It has an incidence in the United States of about 1 in 18,000 newborns. Some patients have shown some histidase activity in skin, suggesting a heterogeneous syndrome. A dominant pedigree has also been reported. For practical purposes, therapy is limited to a diet low in histidine (554,555).

Triosephosphate Isomerase Deficiency

Triosephosphate isomerase (TPI) (E.C. 5.3.1.1) deficiency results in a syndrome characterized by chronic hemolytic anemia with progressive neurological dysfunction. It may also be associated with an increased susceptibility to infection. TPI catalyzes the interconversion of glyceraldehyde phosphate and dehydroxyacetone phosphate in the glycolytic pathway. This disease was first described as an enzyme deficiency disorder in 1965 by Schneider et al. (556), and its inheritance is autosomal recessive. About 18 cases have now been reported. Clinical features include dystonia, tremor, corticospinal deficits, and muscle atrophy due to anterior horn cell disease. Optic disk pallor may be present. Intelligence is usually maintained. These neurological deficits begin at about 2 years of age and continue on a progressive basis throughout childhood (557). No treatment is available.

Hartnup's Disease

Hartnup's disease is an autosomal recessive disorder caused by an intestinal transport defect for tryptophan that results in ataxia, mental retardation, and a pellagra-like skin rash. It was named after the first patient with this disease, reported by Baron et al. (558). It has as its characteristic amino acid pattern the excretion of increased amounts of neutral amino acids. It occurs in about 1 in 16,000 newborns, thus indicating that the mutation is not a rare one. Treatment with nicotinamide (50–30 mg/day) has resulted in improvement in the skin rash and neurological deficits.

Lowe's Syndrome (Oculocerebrorenal Syndrome)

Lowe et al. (559) described an X-linked recessive syndrome associated with mental retardation, hypotonia, cataract, corneal lesions, glaucoma, and rickets. Renal hypophosphatemic rickets with low normal or decreased serum phosphate and elevated alkaline phosphatase, accompanied by normal serum calcium with metabolic acidosis, are typical features. Life span is limited to the late childhood years, and death results from renal insufficiency, metabolic acidosis, or infection.

UREA CYCLE ENZYME DEFECTS

Overview

For each of the five enzymes of the urea cycle, an inherited deficiency has been described. The overall prevalence of these combined diseases is 1 in 30,000 live births. A child who is born with an absolute deficiency of one urea cycle enzyme appears normal at 24 hr of life, but the symptoms of hyperammonemia begin in about 1 week. These include feeding difficulties, impaired level of consciousness, vomiting, and seizures.

Msall et al. (560) studied the neurologic outcome in 26 children with inborn errors of urea synthesis. There was a 92% survival rate at 1 year with nitrogen restriction therapy and stimulation of alternative pathways of waste nitrogen excretion. Seventy-nine percent of the children had one or several developmental disabilities between 12 and 74 months of age, and their mean I.Q. was 43 ± 6. These investigators also found (a) a direct negative linear correlation between duration of stage 3 or 4 neonatal hyperammonemic coma and I.Q. at 1 year and (b) a significant correlation between CT abnormalities and duration of hyperammonemic coma. There was also a good correlation between CT abnormalities and concurrent I.Q. They concluded that a poor outcome for children can be prevented by early diagnosis and aggressive therapy.

The urea cycle was described by H. A. Krebs and K. Henseleit in 1932, and a 20-year perspective on it was republished by Krebs (561) in 1951. In summary, the ammonia nitrogen of the body is generated by aspartate, glutamate, glutamine, and asparagine, and the amino derivatives are generated by the purines adenine and guanine. In general,

the cycle includes five separate enzyme steps and converts two amino nitrogen moieties and one mole of carbon dioxide to yield one molecule of urea. For practical purposes, it is a hepatic cycle since only the liver has a significant urea production rate. Brain does possess carbamyl phosphate synthetase, ornithine transcarbamylase, and arginase, but in general their activities are too low for practical clinical purposes.

Carbamyl phosphate synthetase and ornithine transcarbamylase are associated with mitochondrial membrane, and the last three cycle enzymes are present in the cell's cytoplasm. Energy-specific transport systems are utilized for ornithine transport into the mitochondria and for citrulline transport from it. Shih and Efron (562) reported that acetylglutamate synthesis may be regulatory for ammonia entry into the urea cycle initially. This subject was recently reviewed by Brusilow and Horwich (563).

Carbamyl Phosphate Synthetase Deficiency

It was relatively recently that Freeman et al. (564) reported the first case of carbamyl phosphate synthetase (CPS) deficiency in a patient who at 5 weeks of age had an elevated blood ammonia of 480 μg/dl and CSF ammonia of 550 μg/dl and who clinically by the second week of life was hypotonic, obtunded, and dehydrated. This is a rare syndrome, with fewer than 10 patients reported.

It is inherited as an autosomal recessive disorder.

Ornithine Transcarbamylase Deficiency

Ornithine transcarbamylase (OTC) deficiency is more common than CPS deficiency, since 38 patients in 33 families had been described by 1972 (562).

Clinical Features

Patients appear normal at birth, but rapidly a syndrome of obtundation, failure to thrive, seizures, and altered muscle tone develops. Coma and neurologic deterioration to death may rapidly ensue in the first week of life. It is inherited as an X-linked dominant disorder, with a severe clinical expression and total absence of OTC activities in males and a variation in clinical severity and enzyme activity in heterozygous women. Short et al. (565) described two populations of hepatic cells in a heterozygous female; one of these did not have OTC activity, and the other had normal OTC activity. Presumably the variation in clinical severity in heterozygous women is related to random inactivation of the X chromosome by the Lyon hypothesis, which, in turn, determines cell population distributions for normal and OTC-deficient cells. Reports on the natural history of symptomatic partial OTC deficiency in female patients have emphasized early protein restriction to prevent neurologic impairment.

Neuropathology

Two brains have been reported by Brutton et al. (566) in which there was ventricular enlargement associated with cerebral cortical neuronal loss, white matter loss, and increased numbers of Alzheimer type II astrocytes, which are a reflection of hyperammonemia.

Biochemistry and Genetics

The mammalian hepatic enzyme OTC (E.C. 2.1.3.3) is a nuclear-coded mitochondrial protein. It is synthesized on cytosolic ribosomes as a precursor molecule (40 kD) and is then transported into the mitochondria and processed into its final, active form (36 kD). It is a trimer of identical subunits and catalyzes the second step of the urea cycle, namely, the condensation of carbamyl phosphate with ornithine to form citrulline. The structural gene is located on the X chromosome in human and mouse. The transport of precursor OTC is energy-dependent, and cleavage of the leader sequence is catalyzed by a Zn^{2+}-dependent matrix protease (567). For further details, see refs. 568–576.

Argininosuccinic Acid Synthetase Deficiency (Citrullinemia)

Clinical Features

Citrullinemia is an autosomal recessive disorder caused by the deficiency of the enzyme argininosuccinic acid synthetase (ASA). The clinical syndrome which emphasized severe vomiting and mental retardation was described initially by McMurray et al. (577) in 1962, and the enzyme abnormality was described by Tedesco and Mellman (578) in 1967.

The clinical manifestations include neonatal-, late-infantile-, childhood-, and early-adult-onset forms. The onset of the neonatal form occurs in the first few days of life and is characterized by lethargy, tachypnea, vomiting, irritability, and failure to thrive; these symptoms eventually lead to seizures, coma, and death. Citrulline is significantly elevated in serum, urine, and CSF. Hyperammonemia is also an important feature. Associated laboratory findings include metabolic acidosis, hypocalcemia, hypoglycemia, elevated serum glutamic-oxaloacetic transaminase, and hyperammonemia. Episodes of lethargy, acidosis, and hyperammonemia may be severe and carry a high mortality. Similar presentations have been reported in the late infantile period. A 4-year-old child with normal development was detected by a routine screening program. A 21-year-old patient with ASA deficiency and hyperammonemia was evaluated for episodes of dysarthria, irritability, insomnia, visual defects, and delirium. Mental evaluation indicated a normal intelligence and a minor hand tremor. He developed a spastic paraparesis but no episodic neurologic dysfunction while being treated with a protein-restricted diet along with neomycin and L-arginine.

Biochemistry and Genetics

ASA was reduced in activity and had an altered Michaelis constant, K_m. The enzyme has been mapped to chromosome 9. A cDNA probe for ASA (579) was developed, and 10 gene copies have been found per haploid genome, spread over eight chromosomes, including the X and the Y.

Argininosuccinase Deficiency

Clinical Features

Argininosuccinase deficiency is an autosomal recessive disorder caused by argininosuccinase deficiency with associated argininosuccinic aciduria (580,581). It has been diagnosed antenatally (582), and normal brain and kidney enzyme activity have been reported, along with absent liver enzyme activity (583).

Neonatal, subacute, and late-onset forms have been reported. The neonatal type begins in the first few weeks of life, and its features include failure to thrive, lethargy, seizures, coma, hepatomegaly, and dry brittle hair, referred to as *trichorrhexis nodosa.* The hair disorder may be related more directly to the low-protein diet. Older children develop delayed motor and mental milestones, with I.Q. scores usually in the 30–60 range. Ataxia of gait and seizures develop in one-third of patients.

Patients have hyperammonemia with elevated amounts of argininosuccinic acid in serum, urine, and CSF. Argininosuccinase is deficient in liver, fibroblasts, and amniotic fluid cells.

Therapy

The conventional therapy for acidosis, dehydration, and hyperammonemia is employed. Use of arginine has been successful to aid in the formation of argininosuccinic acid.

Genetics

The several clinical forms are probably caused by allelic modifications of the enzyme. The enzyme locus has been assigned to chromosome 7 by Naylor et al. (584).

Arginase Deficiency (Argininemia)

Clinical Features

Argininemia is an autosomal recessive disorder, and patients present with seizures, vomiting, and failure to thrive; these symptoms eventually lead to mental retardation, spastic paraplegia, ataxia, and hepatomegaly. The syndrome was reported initially by Terheggen et al. (585), who described two sisters with hyperargininemia and arginase deficiency. Arginine values were intermediate in both parents and in two normal siblings. Arginase activity was also intermediate in the parents.

Therapy

The fact that research workers using the Shope virus had low blood arginine levels led to the use of the Shope virus as a means of therapy (586). Although Shope virus can induce arginase activity in patient fibroblast cultures, its practical value apparently is limited, and the mainstay of therapy is to treat hyperammonemia in the conventional manner.

GLYCOGEN STORAGE DISEASES

A series of enzyme defects involving glycogen degradation have been described in a group of autosomal recessive or X-linked recessive disorders. As a result of these enzyme abnormalities, glycogen accumulates in liver to values much in excess of the normal 5–7 g/100 g wet weight, or it accumulates in muscle to values greater than 2 g/100 g wet weight. The human fetus begins to store some glycogen in liver in the last trimester of pregnancy, and adult glycogen values are achieved by 1 month of age (587–589). Hers et al. (588) have recently reviewed this subject in detail.

Type I Glycogen Storage Disease (Glucose-6-phosphatase Deficiency; von Gierke's Disease)

In 1929 von Gierke (590) described a rare autosomal recessive disorder (von Gierke's disease) caused by a defect in the enzyme glucose-6-phosphatase. The incidence of this disease is 1 in 50,000.

Clinical Features

During the newborn period, patients present with severe hepatomegaly, hypoglycemia, seizures, and failure to thrive. Older children are short in stature and tend to appear slightly obese with muscle hypotonia. Yellow-appearing, paramacular retinal lesions are noted in some patients. Some patients have a bleeding disorder caused by reduced platelet adhesiveness and prolonged bleeding time. Patients have significant hypoglycemia that is nonresponsive to epinephrine and glucagon but that results in elevations in blood lactate, pyruvate, triglycerides, phospholipids, cholesterol, and uric acid. Hyperlipidemia is a significant finding in the disorder. Glycogen deposition in the renal tubules can also result in a Fanconi's syndrome of glucosuria, aminoaciduria, and phosphaturia.

A diabetic type of glucose tolerance test, with reduced basal plasma insulin levels and reduced output of insulin to stimuli of glucose or arginine, is reported. Hyperuricemia with attendant gouty arthritis and gouty nephropathy is described in older children.

Genetics

This is an autosomal recessive disorder caused by a defect in the activity of the enzyme glucose-6-phosphatase, as confirmed by liver biopsy.

Therapy

Frequent feedings to avoid hypoglycemia are recommended. Diazoxide has been useful to increase glycogenolysis, depress insulin release, and inhibit glucose uptake by the liver. A surgical approach may be necessary in some patients to produce a portacaval shunt to reduce variceal bleeding, reduce liver size, and reduce serum lipids and uric acid. Some patients have had a meaningful improvement in growth postsurgically (591). Schwenk and Haymond (592) concluded that the minimal nocturnal nasogastric infusion rate of carbohydrate needed to maintain plasma glucose concentrations and minimize organic acidemia is approximately 8–9 mg/kg/min.

Type II Glycogen Storage Disease (α-1,4-Glucosidase Deficiency, Acid Maltase Deficiency; Pompe's Disease)

Pompe's disease is an autosomal recessive disorder caused by a defect in the enzyme α-1,4-glucosidase; the incidence of this disease is 1 in 50,000.

Clinical Features

The disease has been described in infantile, early childhood, and adult forms. The infantile type begins in the first year of life with muscular atrophy, hypotonia, hyporeflexia, cardiomegaly, and heart failure. An early childhood type progresses more slowly, and muscle atrophy and weakness are less severe, but eventually all patients expire by age 20 from severe atrophy and weakness leading to aspiration pneumonia. The adult variety presents with a slowly evolving proximal myopathy with weakness and atrophy. Glycogen storage occurs in skeletal muscle, heart, tongue, and liver. Motor neurons present in cranial nuclei and anterior horn cells of the spinal cord are also involved in storage of glycogen; this results in the dysfunction and demise of these motor neurons, producing a denervating neurogenic process.

Danon et al. (594) reported two brothers with a gait disorder due to acid maltase (AM) deficiency. Their asymptomatic mother had AM activity in the homozygote range. The asymptomatic mother may be homozygous for the adult-onset variant by AM disease. Alternatively, either the mother or the children may be genetic compounds for both the childhood and adult form of disease.

Genetics

This is an autosomal recessive disorder with glycogen storage resulting from reduced activity of the enzyme α-1,4-glucosidase. Fibroblasts obtained from amniocentesis can be cultured and assayed for enzyme activity and can provide a prenatal diagnosis (595). Miranda et al. (596) examined immunocytochemically infantile- and adult-onset muscle cells for AM enzyme activity. Adult muscle cultures showed normal intracellular localization of enzyme activity, and infantile patient cultures showed no activity. Adult-type patients show about 20% enzyme activity compared with controls.

Therapy

There is no specific therapy available; however, two reports have found clinical improvement in two adult patients on a high-protein diet (597,598).

Type III Glycogen Storage Disease (Amylo-1,6-glucosidase or Debrancher Deficiency; Cori's Disease)

Cori's disease is an autosomal recessive disorder with an incidence of 1 in 50,000, caused by a defect in the enzyme amylo-1,6-glucosidase or debrancher enzyme. It was Cori (599) in 1954 who showed that the form of glycogen stored was an abnormal type with very short outer branches.

A 42-year-old man with adult-onset type 3 glycogenosis developed a gradually progressive polyneuropathy with markedly reduced activity of muscle amylo-1,6-glucosidase and glycogen accumulation within all elements of biopsied sural nerve, including axons, as demonstrated by electron microscopy (600).

Clinical Features

Patients develop hepatomegaly early in life; eventually (in early adulthood), muscle atrophy and weakness develop, along with cardiomegaly due to glycogen storage. Occasionally, hypoglycemia and seizures develop. Serum lipids may become elevated, but serum urate levels are usually normal (601).

Genetics

This is an autosomal recessive disorder in which glycogen is significantly stored in skeletal muscle, heart, and liver. Glycogen is of an abnormal form, having short outer branches because of a deficiency in the activity of amylo-1,6-glucosidase as measured in liver.

Type IV Glycogen Storage Disease (α-1,4-Glucan-6-glucosyl Transferase or Brancher Deficiency; Anderson's Disease)

Anderson's disease is an autosomal recessive disorder with an incidence of 1 in 50,000. The disease process is caused by the storage of an abnormal form of glycogen, which has long outer chains as a result of a deficiency in α-1,4-glucan-6-glucosyl transferase (brancher) enzyme in liver. Alternatively, this disease has been referred to as *amylopectinosis* (602,603). A defect in the activity of this enzyme has been found and measured in fibroblasts, thereby making prenatal detection of disease feasible (604).

Clinical Features

During infancy, patients present with hepatosplenomegaly, failure to thrive, and hypotonia. Cirrhosis, portal hypertension, and liver failure occur, with death resulting in the first few years of life.

Genetics

This is an autosomal recessive disorder caused by the storage of an abnormal form of glycogen, which has long outer chains because of a deficiency in brancher enzyme, amylo-(1,4 to 1,6)-transglucosidase.

Therapy

Therapy is directed at improvement of liver failure and ascites.

Type V Glycogen Storage Disease (Muscle Phosphorylase Deficiency; McArdle's Disease)

McArdle's disease is an autosomal recessive disorder with an incidence of 1 in 50,000, caused by a deficiency in the enzyme muscle phosphorylase (604–607).

Clinical Features

Patients begin to have symptoms of easy fatigability in childhood, followed by muscle cramps and myoglobinuria with exercise in the second to fourth decades. Thereafter, progressive muscle weakness and atrophy occur. Ischemic exercises, such as forearm and hand exercises with an inflated cuff on the upper arm, characteristically produce an electrically silent contracture in which no lactate rise occurs in sampled venous blood. Normal exercising muscle releases alanine, but these patients take up alanine, probably so that it can be a substrate for the tricarboxylic acid cycle. An increase in muscle phosphoenol-pyruvate supports such a view (608).

It is interesting that phosphorylase activity is present in muscle cultures from patients with McArdle's disease and also in biopsied samples containing regenerating fibers. It is felt that this enzyme activity is due to a fetal isoenzyme under different regulatory control than the adult species (609,610).

Clinical features of this disorder are virtually identical with those of phosphofructokinase deficiency.

Basilar artery aneurysm formation occurred in three siblings with AM deficiency, perhaps due to glycogen deposition in vascular smooth muscle (611).

Muscle carnitine levels may be abnormally low in the infantile form.

Genetics

This is an autosomal recessive disorder caused by a defect in muscle phosphorylase assigned to chromosome 11 (612). Muscle glycogen levels are significantly increased. Schmidt et al. (613) reported a family in which the mother with an affected son had myalgia and weakness after exercise; she also had 20% of normal muscle phosphorylase activity. Thus she was a manifesting heterozygote.

In 1987 Mineo et al. (614) studied the mechanism of hyperuricemia that is present in the glycogenoses (types 3, 5, and 7). They found that the plasma concentrations of ammonia, inosine, and hypoxanthine increased markedly in all the patients after mild exercise. Plasma urate concentrations also increased. Urinary excretion of inosine, hypoxanthine, and urate increased significantly after exercise. These investigators concluded that the excessive increases in blood ammonia, inosine, and hypoxanthine were due to an accelerated degradation of muscle purine nucleotides and that these purine metabolites served as substrates for the synthesis of uric acid and thus hyperuricemia.

Argov et al. (615) studied muscle energy metabolism *in vivo* by analyzing ^{31}P-NMR spectra of exercising arm muscle. 2,4-Dinitrophenol (DNP) has been used as a means to simulate exercise in muscle biopsy preparations. DNP provocation in a muscle biopsy sample from a patient with McArdle's disease showed an absence of lactate and high levels of inosine monophosphate correlating with clinical findings (616).

Therapy

In 1985 Slonim and Goans (617) hypothesized that the myopathy in this syndrome was caused, in part, by an increased demand (by muscles) for amino acids as fuel, thereby precluding the availability of these amino acids for normal synthesis of muscle protein. Thus a decrease in synthesis of muscle protein with a normal rate of muscle protein degradation produces muscle weakness and atrophy. These investigators postulated that a high-protein diet would provide adequate amounts of amino acids for both energy and protein synthesis. They fed a patient a high-protein diet and compared the result with that of diets high in carbohydrate or fat. On the high-protein diet the patient had a marked increase in muscle endurance. If this observation by Slonim and Goans on a single McArdle's patient can be extended to others, it will be a significant advance in providing the first effective treatment for this rare metabolic myopathy, and it may open the way to provide therapy for other disorders of muscle carbohydrate metabolism.

Type VI Glycogen Storage Disease (Hepatic Phosphorylase Deficiency; Hers' Disease)

Hers' disease is an autosomal recessive disorder with glycogen storage in liver, caused by a deficiency of liver phosphorylase (604,618). It has an incidence of about 1 in 50,000.

Clinical Features

It presents in a manner similar to that of type I glycogenosis, but in a milder form.

Genetics

It is inherited as an autosomal recessive disorder caused by a defect in hepatic phosphorylase with an increase in liver glycogen.

Type VII Glycogen Storage Disease (Muscle Phosphofructokinase Deficiency; Tarui's Disease, Layzer's Disease)

Layzer's disease is an autosomal recessive disorder with an estimated incidence of 1 in 50,000, caused by a defect in the muscle enzyme phosphofructokinase (619–621).

Clinical Features

The presenting symptoms are identical to those of McArdle's disease, with childhood onset of easy fatigability followed by muscle cramps and myoglobinuria. In the early adult years, muscle weakness and atrophy develop. Servidei et al. (622) reported a fatal infantile form in a girl who died of respiratory failure at the age of 7 months. ^{31}P-NMR spectroscopy shows that ATP levels are lower than normal and continue to decline during exercise. Exercise increases plasma uric acid (623,624).

Genetics

This is an autosomal recessive disorder caused by a defect in muscle phosphofructokinase. The enzyme defect causes (a) an increase in muscle glucose-6-phosphate and fructose-6-phosphate and (b) a marked reduction in fructose-1,6-diphosphate. Muscle glycogen is increased. Phosphofructokinase is absent in activity in muscle, has 50% of normal activity in red blood cells, and is normal in activity in leukocytes. It is thought that the muscle enzyme is composed of identical muscle type (M) subunits, whereas the red blood cell isoenzyme is composed of both muscle and red blood cell type (R) subunits. Thus the absence of enzyme activity in muscle is caused by a defect in the M subunit and a partial loss of activity in erythrocytes. A late-onset adult form of the disease has also been recently described (625).

Type VIII Glycogen Storage Disease (Hepatic Phosphorylase Kinase Deficiency)

Hepatic phosphorylase kinase deficiency is an X-linked recessive disorder in which glycogen is stored in liver because of a 90% deficiency in phosphorylase b kinase activity; this disease has an incidence of 1 in 50,000 (604,626).

Clinical Features

Patients present with an asymptomatic hepatomegaly. The diagnosis depends on finding low activity of phosphorylase b kinase in liver.

Genetics

This is an X-linked recessive disorder caused by a deficiency in the activity of phosphorylase b kinase in liver, with resultant glycogen storage of normal structure in liver.

Clinically, adult muscle phosphorylase b kinase deficiency is identical to muscle phosphorylase deficiency. Their muscle phosphorylase activity is normal, but the active form "a" is markedly reduced in activity as a result of low phosphorylase kinase activity. A typical patient was described in detail by Abarbanel et al. (627).

Phosphoglucomutase Deficiency

Thomsom et al. (628) reported the first case of possible phosphoglucomutase (PGM) deficiency in a 4-year-old boy with toe-walking. Illingworth and Brown (629) and Brown and Brown (630) reported the second case of PGM deficiency in a 17-month-old boy with hepatomegaly. Liver and muscle PGM activities were markedly reduced. In 1988 Sugie et al. (631) reported a 5-month-old boy with recurrent vomiting, lethargy, and failure to thrive. He had severe metabolic acidosis and nonketotic dicarboxylic aciduria. Of note, this patient had low muscle and serum carnitine levels and showed some improvement with oral carnitine therapy. A quadriceps muscle biopsy showed intrafiber lipid droplets and a mild increase in glycogen. An anaerobic glycolysis *in vitro* study showed a block after glucose-1-phosphate and before glucose-6-phosphate. PGM in muscle was 13% of the control mean. PGM deficiency is a newly recognized cause of secondary systemic carnitine deficiency.

PGM has three isozyme types as detected by starch gel electrophoresis. PGM-1 maps to chromosome 1, PGM-2 maps to chromosome 4, and PGM-3 maps to chromosome 6.

Galactosemia (Galactose-1-phosphate Uridyltransferase Deficiency)

Galactosemia is an autosomal recessive disorder caused by a deficiency of the enzyme galactose-1-phosphate uridyltransferase. Its incidence varies between 1 in 35,000 and 1 in 190,000. It was described clinically in 1935 (632), and the increase in erythrocyte galactose-1-phosphate was reported in 1956 (633). The enzyme defect was first reported by Isselbacher et al. (634) in 1956, and an erythrocyte uridine diphosphate glucose consumption test was described by Anderson et al. (635) in 1957. This test made it possible to identify heterozygotes for carrier detection purposes, in addition to identifying homozygotes. Variation in clinical and biochemical features of the disorder has been noted (636,637).

Clinical Features

The disease presents early in infancy with jaundice, hepatomegaly, ascites, vomiting, diarrhea, and failure to thrive. These clinical features have their onset shortly after mild ingestion occurs. Nascent cataracts can be detected in the

neonatal period, and progressive mental retardation is noted in the first few months of life. Associated clinical chemical abnormalities include galactosemia, galactosuria, hyperchloremic acidosis, albuminuria, and, occasionally, aminoaciduria; other routine liver chemical studies may be abnormal.

Genetics

This is an autosomal recessive disorder caused by a deficiency in the activity of the enzyme galactose-1-phosphate uridyltransferase. It has been mapped to chromosome 9p12-p13. Cataract formation occurs because of accumulation (in the lens) of dulcitol, which is the product of aldose reductase (in the lens) and the substrate galactose. Dulcitol and galactose-1-phosphate are stored in liver, kidney, and brain as well. The neural toxicity of galactose feeding has been described by Wells and Wells (638), and effects include decreased brain ATP, glucose, and glycolytic metabolic intermediates and a decrease in fast axoplasmic transport.

Therapy

This is one neurogenetic disorder that responds to specific therapy—in this instance, the elimination of dietary galactose. The casein hydrolysate nutramigen and soybean milks are used early in life to avoid the development of mental retardation and cataracts. Dietary galactose should also be eliminated by women who already have one galactosemic child, so that fetal toxicity can be eliminated. The earlier the onset of the galactose dietary restriction, the better the clinical outcome.

Galactokinase Deficiency

This is an autosomal recessive disorder with an incidence of 1 in 40,000, caused by a deficiency in the enzyme galactokinase.

Clinical Features

The main feature is juvenile cataract formation without mental retardation and liver disease. The absence of liver and gastrointestinal disease separates it from the transferase deficiency. Elevated galactose levels in serum and urine, normal activity of galactose-1-phosphate uridyltransferase, and absence of galactokinase activity in erythrocytes or fibroblasts establish the diagnosis. The formation of cataracts is caused by dulcitol, and the absence of mental retardation is probably caused by the lack of galactose-1-phosphate production.

Genetics

This is an autosomal recessive disorder caused by galactokinase deficiency and the resultant presence of elevated amounts of galactose in body tissue. The enzyme has been mapped to chromosome 17 near the thymidine kinase locus.

Therapy

As with the transferase deficiency, dietary elimination of galactose is effective to reduce tissue levels of galactose and prevent cataract formation.

Glucokinase Deficiency

In 1988 Poulton and Nightingale (639) reported a 34-year-old man with intermittent sharp pains in his knees exacerbated with exercise. Brisk walking in a cold environment produced leg muscle tightness. A severe defect in glucose phosphorylation of his skeletal muscle was found to be associated with an electrophoretically abnormal hexokinase: The block in glucose metabolism was bypassed via an enhanced phosphorylation of fructose by the abnormal hexokinase. This is a most unique biochemical abnormality, and it remains to be seen if its presence is more widespread; what also needs to be determined is the precise molecular defect.

Unverricht–Lundborg Syndrome (Myoclonus Epilepsy)

This is a rare glycoprotein–mucopolysaccharide storage disease described as an autosomal recessive disorder. Clinical features include myoclonus epilepsy, mental retardation, spasticity, extrapyramidal rigidity, and ataxia. Life span is usually limited to the second decade of life. Inclusion bodies are abundant in apocrine sweat gland duct cells of the axillary skin (640,641). The neuronal inclusions are referred to as *Lafora bodies.* A Hartung variety has been inherited as an autosomal dominant trait. It has also been referred to as *Lafora's disease* when the inclusions are present. In 1986 Logigian et al. (642) reported two brothers with myoclonus epilepsy, supranuclear ophthalmoplegia, progressive visual loss, and embolic strokes due possibly to cardiac valvulopathy. It is a rare autosomal recessive form of progressive myoclonus epilepsy of unclear etiology. There is no known biochemical defect described, and no specific metabolic therapy is available (643,644).

Mannosidosis

Mannosidosis is a very rare autosomal recessive disorder caused by an enzyme defect in mannosidase. Wenger et al. (645) reported a well-studied 46-month-old boy who had an impairment in neurological development at 16 months. He developed coarsening of facial features, mild bone disease, delayed development of speech, hyperactivity, mental retardation, and a deficiency of β-mannosidase activity. This patient also had a low level of heparin sulfamidase activity in cultured skin fibroblasts. The exact relation between these two enzyme defects remains unknown. The defect in β-mannosidase results in tissue storage and urinary excre-

tion of incompletely catabolized oligosaccharide chains. The effects of the disease have been reported to vary according to time of onset: The infantile-onset form is usually fatal, whereas the adult-onset form is usually mild. Noll et al. (646) reported three brothers with very low enzyme activity but with only mild mental deficits that were stable during a 2-year period. Also, Cooper et al. (647) reported a 44-year-old man with mental retardation but with no other neurological abnormalities.

Dominantly Inherited Cardioskeletal Myopathy with Lysosomal Glycogen Storage and Normal Acid Maltase Levels

Byrne et al. (648) described a family in which there were seven persons in three generations that were affected with a cardioskeletal myopathy. These patients had a vacuolar myopathy with increased free and lysosomal glycogen in both skeletal and cardiac striated muscle. These patients had normal enzyme activities for acid maltase, phosphorylase, debrancher, and lysosomal glycolytic enzymes. It is an interesting and unique syndrome, being dominantly inherited among the glycogenoses.

DISORDERS OF LIPID METABOLISM

For a detailed discussion on the disorders of lipid metabolism, see ref. 649.

LIPID STORAGE DISORDERS

GM_1 Gangliosidosis

This is an autosomal recessive disorder caused by a deficiency of the enzyme β-galactosidase, resulting in the storage of the lipid GM_1 ganglioside. Norman et al. (650) first described it clinically as a variant of Tay–Sachs disease with visceral involvement. Infantile, juvenile, and adult forms have been described (651–653).

Infantile Form (Type I Disease)

Clinical Features

The disorder has as its main features severe mental retardation, seizures, early hypotonia, and hepatosplenomegaly. Hurler-like features also occur, both clinically and roentgenographically. The newborn is hypoactive, hypotonic, and has coarse facial features. These facial abnormalities include hirsutism, macroglossia, prominent maxilla, frontal bossing, depressed nasal bridge, long philtrum, and hypertrophied alveolar ridges.

The infant gradually develops motor and mental retardation. Gradually increased tone, increased deep tendon reflexes, and Babinski signs develop, indicating impairment of the corticospinal tract. Seizures occur early in development as well. By 12 months of age the child is severely retarded, has optic atrophy and blindness, may be deaf, and shows spasticity, quadriparesis, and often decortication or decerebration. Hepatosplenomegaly and skeletal defects are also present. Malformations of the wrist and ankles occur, and a progressive dorsolumbar kyphosis also develops.

Roentgenographic findings are those of a dysostosis multiplex. The long tubular bones are shortened and widened in the midshaft area and tapered at the proximal and distal ends. The lumbar vertebrae are hypoplastic and beaked anteriorly. The ribs are spatula-like and thickened. The ilea are flared and the sella turcica is elongated and shallow, giving it a shoe-shaped appearance.

Laboratory findings include vacuolated lyphocytes in the peripheral blood, foam cells in the bone marrow, and a normal or slightly elevated quantity of mucopolysaccharides in the urine.

The deteriorating clinical course continues until death, which occurs at about 2 years of age.

Genetics and Biochemistry

GM_1 gangliosidosis is an autosomal recessive disorder in which a deficiency of the enzyme β-galactosidase occurs, resulting in the storage of GM_1 ganglioside in neurons and glia of the brain, brainstem, and spinal cord. In addition, all organs contain foam cells. Their cytoplasm is filled with periodic acid–Schiff- and Alcian blue-positive metachromatic granules, which are probably keratin sulfate. Gangliosides are glycolipids that contain sialic acid moieties attached to their oligosaccharide chains. Gangliosides are localized primarily in neuronal synaptic membranes (654), although they are found in most cell types.

The biosynthesis of GM_1 gangliosides is by a multiglycosyltransferase system, which has highest activity in synaptosomal membranes. On the catabolic side, all the glycosidases appear to be localized in lysosomes, except for some sialidases, which are extralysosomal (655,656).

The stored material in brain is identical to normal GM_1 ganglioside and is elevated to 10 times normal in the gray matter in types I and II and to 20–50 times normal in the liver of type I patients. The asialo-derivative of GM_1 accumulates to 10 times normal in the brain, and galactose-containing glycoproteins accumulate in viscera of both types I and II.

There are two acid β-galactosidase isoenzymes: A and B. Both are sialoglycoproteins with an acid pH optimum (4.2–4.4), and both are heat-labile and stimulated by chloride. The enzyme is mapped to chromosome 22q13-22qter.

In 1981 Farrell and Ochs (657) suggested more precisely that the phenotypic variation found in GM_1 gangliosidosis resulted from different allelic mutations affecting the GM_1 ganglioside β-galactosidase locus, and that different combinations of these mutations determined the clinical heterogeneity of this illness. They reported a family in which both the infantile and juvenile forms of GM_1 gangliosidosis were found, thus supporting their heterogeneity hypothesis. They reported that acid β-galactosidase activity could be separated into multiple molecular forms by isoelectric focusing on cellulose acetate membranes. The residual acid β-galactosidase in the juvenile form of GM_1 gangliosidosis had three bands of enzyme activity with an apparent isoelectric pH (pI) range from 4.9 to 5.2. The infantile form of the

enzyme had a single band with an apparent pI of 5.2. Thus they were able to show that separation of residual acid β-galactosidase into multiple molecular forms by isoelectric focusing demonstrated that enzymatic differences can be correlated with the allelic mutations that affect the GM_1 ganglioside β-galactosidase locus (658).

Therapy

There is no specific therapy that has been useful.

Late Infantile–Juvenile Form (Type II Disease)

This is similar to type I disease, but it is less aggressive and less severe, beginning at about 1 year of age and progressing to death at about age 5 years or even extending one to two decades in some patients. Motor and mental retardation occur associated with mild Hurler-like features of facial coarsening. Seizures, spasticity, and mental retardation complete the clinical picture. The biochemical, enzymatic, and pathologic features are similar to those of type I disease.

Adult Dystonic Form (Type III Disease)

An adult type of disease presenting as dystonia was reported by Goldman et al. (659) in 1983. In 1988 Guazzi et al. (660) reported a family with autosomal recessive type III GM_1 gangliosidosis presenting with choreoathetotic dementia. They reported three sisters with progressive neurological disease characterized by athetoid movements, spastic tetraparesis, and dementia without seizures. Their biochemical studies showed abnormal urinary oligosaccharide excretion and β-D-galactosidase deficiency in serum, leukocytes, and cultured fibroblasts. It is of note that these patients also had a deficiency of β-D-fucosidase. The combined deficiency of β-D-fucosidase and β-D-galactosidase indicates that there may be a genetic linkage between these two enzymes. Guazzi et al. (660) also suggest another possible interpretation in that β-D-galactosidase also possesses β-D-fucosidase activity against artificial substrates. Thus they are not separate enzymes, but rather a single enzyme having both β-D-galactosidase and β-D-fucosidase activities.

Ohta et al. (661) reported a 51-year-old Japanese man presenting with dementia, dysarthria, gait defect, and limb rigidity. Similarly, Mutoh et al. (662) reported three adult patients in a single family with severe myoclonus, ataxia, and pyramidal signs. A dog model of GM_1 gangliosidosis with β-galactosidase deficiency has been reported (663).

Tay–Sachs Disease (GM_2 Gangliosidosis Type I)

This is an autosomal recessive disorder first described as a clinical entity by Tay (664), who reported the retinal degeneration, and by Sachs (665), who described the neurologic and neuropathologic findings in an affected infant having blindness and dementia. It was Klenk (666,667) who first showed increased concentrations of gangliosides in brain tissue from patients, and in 1961 Svennerholm and Raal (668) found that the stored ganglioside was a monosialoganglioside. Hexosaminidase A was first reported as being the specific molecular defect in this disorder almost simultaneously by Sandhoff et al. (669) in 1968, Sandhoff (670) in 1969, Hultberg (671) in 1969, and Kolodny et al. (672) in 1969. There have been other, similar reports. Further characterization of the enzyme defect was provided by Sandhoff and Jatzkewitz (673) in 1972. The mutant gene has a frequency of 0.016 in the New York City Jewish population, with a carrier rate of 1:30 in the Jewish population and 1:300 in the non-Jewish population.

Clinical Features

Seizures, blindness, and motor and mental retardation are cardinal features. These features begin within the first 6 months of life, and the child gradually loses interest in visual stimuli, moves less, and startles easily to sound. Milestones for sitting and standing are delayed, and the child usually never learns to walk. Optic atrophy and macular degeneration, with the generation of a cherry-red spot when increased vascularity becomes visible as the ganglion retinal cells are lost, appear early. Seizures, which are absence, fragmentary motor, myoclonic, or generalized major-motor, occur in the first year of life. By 1 year, spasticity with decortication or decerebration may develop. Because of progressive lipid storage, megalencephaly develops but hepatosplenomegaly does not occur.

Neuropathology

Neurons are characterized by the lysosomal storage of ganglioside. The presence of a lipidosis is evident in all neurons of the central and peripheral nervous system, but the degree of storage is most evident in Ammon's horn of the temporal lobe.

Neuronal loss, gliosis, demyelination, and brain atrophy are features of the disorder. Elevated levels of gangliosides are present in liver.

Genetics and Biochemistry

GM_2 monosialoganglioside is increased in brain between 100 and 300 times normal. Asialo-GM_2 is elevated about 20 times normal. Hexosaminidases A and B are isoenzymes possessing both β-D-*N*-acetylglucosaminidase and β-D-*N*-acetyl-galactosaminidase activity. Both isoenzymes are found in all normal human tissues except erythrocytes. Hexosaminidase A is more heat-labile and more negatively charged than hexosaminidase B. These hexosaminidase isoenzymes act on the widely used artificial fluorogenic and chromogenic substrates and on all of the natural substrates except GM_2 ganglioside. GM_2 ganglioside is cleaved rapidly only by hexosaminidase A in the presence of a heat-stable cofactor protein or activator protein. The activator protein binds to GM_2 ganglioside in such a way that it can be rapidly cleaved by hexosaminidase A (674). In GM_2 gangliosi-

dosis type I, hexosaminidase A activity is nearly absent, but activity of hexosaminidase B in brain is increased 10 times normal, possibly because of lysosomal stimulation secondary to ganglioside storage. A heat-denatured serum assay for hexosaminidase A is 96% accurate in detecting homozygotes as well as heterozygotes. False positives in the heterozygote range may occur in patients with diabetes mellitus, myocardial infarction, hepatitis, and pancreatitis. False positives also occur in normal pregnant women as well as in women taking birth control pills. Leukocyte hexosaminidase A activity, however, remains unaltered in these disorders and is accurate in more than 99% of patients tested. For the most reliable results, and especially for some of the variants, the natural GM_2 ganglioside should be used as substrate. Hexosaminidases A and B both cleave asialo-GM_2 and globoside (Cer-Glc-Gal-Gal-Gal) (NAc), but kinetic studies indicate that only hexosaminidase A cleaves GM_2 ganglioside. Hexosaminidase A has a molecular weight of 100,000 daltons, and hexosaminidase B has a molecular weight of 108,000 daltons. Both isoenzymes may be dissociated into four subunits with hexosaminidase A (composed of two α and two β polypeptide chains) and hexosaminidase B (four β chains). At this time it appears that the α chain is coded by chromosome 15 and that the β chain is coded by chromosome 5. This would indicate the genetic defect is on chromosome 15 for GM_2 gangliosidosis type I and on chromosome 5 for GM_2 gangliosidosis type II.

Cashman et al. (675) reported a patient with partial deficiency of *N*-acetyl-β-hexosaminidase who developed a progressive motor neuron syndrome at age 7 years. Hexosaminidase B activity in serum, leukocytes, and fibroblasts was nearly absent, and there was partial hexosaminidase A activity in serum and leukocytes and low normal hexosaminidase A activity in fibroblasts. These data are consistent with a β-locus defect. Kotagal et al. (676) reported a child with AB variant GM_2 storage. Hexosaminidase A and B activities were normal in this child, but soluble activator protein responsible for initiating GM_2 gangliosidosis degradation was deficient. Two unique adult sisters with severe spinocerebellar degeneration were deficient in hexosaminidase A and B. Data suggested a destabilizing mutation in the β locus preventing precursor β chains from forming mature β chains (677).

Apaia et al. (678) identified a single base mutation in a cloned fragment of the Hex A gene from an Ashkenazic Jewish patient. By virtue of this change, the substitution of a C for G in the first nucleotide of intron 12 resulted in a defective splicing of the messenger RNA. This case and two others cited by Apaia et al. (678) indicated that the infantile form of Tay–Sachs disease is heterozygous for at least two different mutations.

Treatment

At the present time, no definitive treatment is available. Enzyme infusion intravenously, intracisternally, and intrathecally has produced no clinical improvement (652). Screening for heterozygotes and genetic counseling is the most logical approach. Since the enzyme deficiency is manifest in amniotic fluid cells, therapeutic abortion is possible. Supportive care is all that is presently available for the affected homozygote.

GM_2 Gangliosidosis Type II (Sandhoff's Disease)

Sandhoff et al. (679) described a form of GM_2 gangliosidosis in 1968 in a non-Jewish infant in which the clinical features and natural history of disease were almost identical to GM_2 gangliosidosis type I, or Tay–Sachs disease. The one clinical difference between the two syndromes is that some GM_2 type II patients may have hepatosplenomegaly. The enzyme defect is characterized by decreased activity of both hexosaminidase A and B in serum, fibroblasts in culture, white blood cells, and amniotic fluid cells.

GM_2 Gangliosidosis Type III

This is a rare clinical entity first reported by Bernheimer and Seitelberger (680) in 1968. Children, all of whom are reported to be non-Jewish, begin with cerebellar ataxia between 3 and 7 years of age with slowly progressive psychomotor retardation, spasticity, and seizures. These children develop optic atrophy, retinitis pigmentosa, and clinical blindness. The course is progressive with decortication, decerebration, and death within the first decade of life. Hexosaminidase A activity is about 25% of normal, and serum levels are severely reduced.

Hexosaminidase Variants and Neuromuscular Syndromes

In recent years, Johnson (681) has described disorders of the neuromuscular system in association with deficiencies of β-D-*N*-acetylhexosaminidase and β-methylcrotonylglycinuria I. Hexosaminidase deficiencies have been associated with recognized clinical phenotypes, including infantile encephalopathy, late infantile or juvenile encephalopathy, cerebellar or spinocerebellar ataxia, Kugelberg–Welander syndrome, a disorder similar to ALS, and even an adult-onset type of dementia. Johnson pointed out that motor neuron syndromes are encountered mainly in α-locus defects of hexosaminidase rather than in β-locus or protein activator disorders. However, he pointed out that α-locus disorders are more common than β- or activator-locus defects.

A patient reported by Johnson (681) as having the Kugelberg–Welander disease phenotype was in actuality a true genetic compound, since the patient had a severe deficiency in hexosaminidase A and a partial deficiency in both parents. The father of this patient carried the Hex α_2 allele, since a paternal relative had classic infantile Tay–Sachs disease and the mother carried a milder hexosaminidase α-locus allele (681). Rectal ganglion cells from the patient contained classic membranous cytoplasmic bodies seen in the other GM_2 gangliosidoses, and most likely spinal cord anterior horn neurons were similarly affected to explain the denervating clinical syndrome.

Another patient reported by Johnson (681) had an ALS-

like syndrome with hexosaminidase A deficiency. He was a 22-year-old man with a 20-year history of progressive weakness and proximal muscle-wasting with increased reflexes and bilateral Babinski signs. Electromyographic studies and a muscle biopsy were consistent with the diagnosis. He had a severe deficiency of hexosaminidase A, and partial deficiencies were present in his parents. Thus he had upper and lower neuron involvement clinically and a rectal ganglion cell disorder caused by inclusions of membranous cytoplasmic bodies typical of GM_2 gangliosidoses, and presumably his motor neurons were similarly affected. It is important to point out that most patients with motor neuron disease do not have a hexosaminidase A deficiency, especially those who have rapidly advancing disease and who are over 40 years of age. It should be considered in younger patients with a slowly progressive form of disease and a recessive pattern of inheritance.

A cerebellar ataxia syndrome has been associated with an α-locus defect of hexosaminidase A, and a juvenile cerebellar ataxia form (a Ramsay Hunt phenocopy) and an adult-onset spinocerebellar ataxia syndrome have been associated with a β-locus defect. A protein activator-locus defect has been described with adult GM_2 gangliosidosis with dementia, seizures, and normal pressure hydrocephalus.

Mitsumoto et al. (682) have recently described two families that have an adult hexosaminidase A deficiency syndrome with a multisystem degeneration. The clinical picture included mild dementia, ataxia, and an axonal motor-sensory peripheral neuropathy associated with a juvenile ALS syndrome. Marked cerebellar atrophy was detected by head scans in all patients.

Navon and Proia (683) described a point mutation in the α-chain gene that resulted in the substitution of Gly^{309} with serine in eight adult GM_2 patients from five different families.

Thus the clinical spectrum seen in various hexosaminidase deficiencies has widened considerably in recent years, and the story has become more complex. About two dozen hexosaminidase deficiency types now exist, and the number is bound to increase. Similar allelic mutations, activator defects, and genetic compounds exist for other lysosomal enzymes as well; thus Johnson (681), by making us aware of the multiple genotypes and associated phenotypes for this enzyme (in particular, as a model approach to other lysosomal enzymes), has made an extremely important contribution that has moved molecular neurogenetics forward in a most elegant fashion.

One interesting clinical note along these lines is the report by Johnson et al. (684) regarding a child who developed classic late infantile GM_2 gangliosidosis; the biological father was a donor for artificial insemination, and both he and the mother were carriers of an α-locus hexosaminidase deficiency. Thus here is another gene product for which insemination screening is needed to avoid a lethal genetic disease.

Gaucher's Disease (Glucosyl Ceramidase Deficiency)

Gaucher (685) published a description of a chronic, progressive disorder characterized by hepatosplenomegaly that he believed was caused by an epithelioma of the spleen. Tuchman et al. (686) reported elevation of serum acid phosphatase in patients with Gaucher's disease. Brady et al. (687) demonstrated glucocerebrosidase deficiency in Gaucher's disease, and later they demonstrated that both the heterozygote carrier and the intrauterine presence of Gaucher's disease could be diagnosed. The adult form of the disease is approximately 30 times more frequent in Ashkenzic Jews, and the incidence in this population has been reported to be as high as 1 in 2500, with a reported frequency in Ashkenazic Jews ranging from 1 in 100 to 1 in 20. It is an autosomal recessive disorder.

Clinical Features

Gaucher's disease has been divided into three clinical forms: type I (chronic, nonneuronopathic), type II (acute neuronopathic), and type III (subacute neuronopathic).

Type I Disorder

The type I disorder usually presents late in the first decade or early in the second decade, frequently with the onset of episodic pains in the legs, arms, or back, which may be accentuated by fever or by a minor illness. There is also abdominal distention with hepatosplenomegaly, hypotonic colon, respiratory difficulties, and the beginning of yellow pallor and a diffuse yellow-brown discoloration of the face and legs. A mild microcytic anemia with thrombocytopenia may occur. The hematologic abnormalities may be severe at times. Bone marrow examination reveals many Gaucher's cells. The course is one of frequent painful and hemorrhagic episodes that progress in severity over the years. The hepatosplenomegaly increases but is usually associated with normal liver function tests. There is worsening of pulmonary function and appearance of bony changes, including rarefaction of the bony cortex, pathologic fractures of the femur, and compression fractures of the vertebral bodies. The brain of a 17-month-old boy with infantile Gaucher's disease showed (by electron microscopy) intraneuronal cytoplasmic inclusions containing twisted tubules in both the oculomotor nucleus and cerebral cortex.

Type II Disorder

Type II infants are usually normal up to 6 or 7 months of age, after which they develop hepatosplenomegaly, pulmonary deterioration, and marked brain degenerative findings. It involves the brainstem neurons and clinically is manifested by strabismus, retroflexion of the head, dysphagia, and laryngeal stridor. Hypertonicity, hyperreflexia, Babinski signs, and seizures occur. The course is progressively downhill, with death usually occurring at 9–12 months of age.

Type III Disorder

The type III disorder includes a small number of patients who have been described with hepatosplenomegaly and

Gaucher's cells in their bone marrow and in whom the onset of brain deterioration occurs in the childhood years.

The diagnosis is suspected in the presence of the constellation of hepatosplenomegaly, brain degenerative findings, hemorrhagic tendencies, a marked increase in the serum non-tartrate-inhibitable acid phosphatase, and the presence of Gaucher's cells in the bone marrow.

The diagnosis is supported by the finding of increased glucocerebroside levels in tissues and markedly decreased glucocerebrosidase activity in leukocytes, skin fibroblasts, and amniotic fluid cells. Heterozygotes may be identified by enzymatic assay of either skin fibroblasts or leukocytes, and intrauterine diagnosis is possible.

Molecular Genetics

Tsuji et al. (688) reported in 1988 that the nucleotide sequence of a genomic clone from an Ashkenazic Jewish patient with type I Gaucher's disease had a single base mutation (adenosine-to-guanosine transition) in exon 9 of the glucocerebrosidase gene. This change results in the amino acid substitution of serine for asparagine. Allele-specific hybridization with oligonucleotide probes demonstrated that this mutation was found exclusively in the type I phenotype. None of the six type II patients, 11 type III patients, or 12 normal controls had this allele. Furthermore, these investigators found that there are multiple allelic mutations responsible for type I Gaucher disease in both the Jewish and non-Jewish populations. They have concluded that RFLP studies are now able to determine (at about an 80% level of accuracy) the at-risk status of patients to be affected or the status carriers (689).

Gaucher's Cells

A Gaucher cell is an enlarged, lipid-laden histiocyte that stains positively with periodic acid–Schiff stain, indicating the presence of glycolipid. The cells range from 20 to 100 μm in diameter, with an eccentrically placed nucleus. The cytoplasm has the appearance of crinkled tissue paper. The cells react readily with phenylphosphate, demonstrating the presence of acid phosphatase. Gaucher's cells contain spindles or rod-shaped membrane-bound inclusions, which in cross section appear to be tubules with a diameter of between 130 and 150 Å (690).

Therapy

Patients with Gaucher's disease need careful follow-up and supportive care of any hematologic difficulties that may arise. Splenectomy may become necessary for hypersplenism, but it is usually postponed as long as possible because of the danger of accelerating bone and liver involvement after splenectomy. Corrective orthopedic surgery may be indicated in certain cases.

Enzyme replacement therapy has been shown to be inconsistently effective in ameliorating the nonneurologic signs and symptoms in patients with type I disease. In the first two patients there was a 26% reduction in the quantity of glucocerebroside in liver, and serum concentrations returned to normal in 3 days in both patients. By modifying glucocerebrosidase through deglycosylation, it has been possible to increase the amount of enzyme delivery to Kupffer's cells fivefold and thus more effectively mobilize substrate (652). Preliminary evidence in one patient using modified enzyme again shows significant clinical improvement in patients in terms of reduction of the glucocerebroside burden of hepatic Kupffer's cells, normalization of serum concentrations of glucocerebroside, and improvement in the patients' hematologic status (Dr. Robin Ely Berman, *personal communication*).

As reviewed by Brady (652), most Gaucher's patients have type I disease, in which the nervous system is minimally, if at all, involved. There is extensive brain damage in types II and III Gaucher's patients, and thus special considerations must be employed to possibly mobilize substrate on the brain side of the blood–brain barrier. As has been mentioned previously for Tay–Sachs disease, intravenous, intrathecal, and intracisternal administration of enzyme is not effective for this purpose. Brady (652) approached this problem by attempting to open the blood–brain barrier with hyperosmolar solutions of mannitol or arabinose just prior to enzyme infusion. This approach is being attempted for both Tay–Sachs and Gaucher's patients (types II and III), and the results, although preliminary, are probably not going to indicate meaningful clinical improvement. Additional new approaches, such as plasmapheresis and bone marrow transplantation with recombinant DNA techniques that transfect the normal gene into patient cells, will be necessary for therapy to be effective. There is no evidence that replacement enzyme crosses the blood–brain barrier, and therefore replacement therapy is not effective against the neurologic manifestations (691).

Niemann–Pick Disease (Sphingomyelinase Deficiency)

Niemann, a German pediatrician, described an 18-month-old infant of Jewish extraction with hepatosplenomegaly, lymphadenopathy, edema, pigmentation of the face, and brain impairment (692). The infant died before 2 years of age. Pathologic examination revealed yellow deposits in the liver, spleen, lymph nodes, kidneys, and adrenals, and large sudanophilic cells were seen throughout these organs. Between 1922 and 1927, Pick (693) provided histologic evidence that differences existed between this disease and Gaucher's disease. Brady et al. (694) presented evidence that the deficient enzyme was sphingomyelinase. The incidence of this disorder is high for Ashkenazic Jews, but the disorder has been described in other ethnic groups. It is an autosomal recessive disorder.

Clinical Features

Five clinical types of Niemann–Pick disease are now recognized: type A (acute neuronopathic), type B (chronic nonneuronopathic), type C (chronic neuropathic), type D (Nova Scotia variant), and type E (adult nonneuronopathic) (695).

Type A Variant

The type A patient presents with visceral and brain involvement in early infancy, with rapid deterioration. Hepatosplenomegaly is usually recognized by 6 months of age with concomitant feeding difficulties and failure to thrive. A brownish-yellow discoloration of the skin may be observed, and approximately 50% of the patients have a cherry-red spot in the macula. Neurologically, there is a rapidly progressive deterioration with loss of motor and intellectual functions.

Type B Variant

In the type B variant, visceromegaly may appear as early as in type A, but there is no brain involvement. Splenomegaly is usually apparent first, followed by hepatomegaly, with little or no impairment in liver function tests. There is often a diffuse infiltration of the lung fields with secondarily increased susceptibility to pneumonia.

Type C Variant

The patient with type C variant is usually normal for the first 1–2 years of life. There is then a gradual onset of neurologic degeneration originally manifested by moderate ataxia, grand mal seizures, and loss of language. The hepatosplenomegaly is less striking than in the type A or B variants. There is progressive gray matter deterioration followed by the onset and progression of white matter deterioration.

Type D Variant

The patients with the type D variant share a common ancestry and live in a coastal area in western Nova Scotia. Clinically, they have the onset of a neurologic gray matter deterioration between 2 and 4 years of age which resembles that of type C. Progressive hepatosplenomegaly occurs with progression of neurologic degeneration.

Type E Variant

The type E variant is represented by adults with moderate hepatosplenomegaly without brain abnormalities. These patients also have foamy lipid-laden cells in their bone marrow.

Type C–E Hybrid

This variant is represented by adults with minimal hepatosplenomegaly but with foam cells in their bone marrow, cerebellar ataxia, and cherry-red spots in the macula. The presumptive diagnosis can be made on the basis of clinical presentation and presence of lipid-laden cells with foamy cytoplasm in the bone marrow. The diagnosis is supported by finding increased levels of sphingomyelin in tissues.

Niemann–Pick Cell

The Niemann–Pick cell is a large, foamy, lipid-laden cell found throughout the reticuloendothelial system. Brain neurons undergo similar changes. Niemann–Pick cells range from 20 to 90 μm in diameter, with an eccentric nucleus and cytoplasm filled with many droplets, giving these cells a "mulberry" appearance.

Neuropathology

The brain is usually reduced to 50–90% of its normal weight, and there is marked firmness in its consistency. Neurons in the brain are swollen with foamy cytoplasm, within which are found membrane-bound inclusions. These may appear loosely arranged or in concentric lamellar structures. With neuronal cell loss there is disorganization of the cerebral and cerebellar architecture. The neuronal cell loss is followed by gliosis and secondary demyelination.

Genetics and Biochemistry

This is an autosomal recessive disorder. The predominant lipid accumulating throughout the reticuloendothelial system and the CNS is sphingomyelin. There is also a substantial increase in unesterified cholesterol and lyso-bisphosphatidic acid. The latter two lipids may be derived from uncatabolized membrane fragments.

The underlying biochemical abnormality is a result of sphingomyelinase deficiency. At the present time, on the basis of isoelectric focusing studies, there appear to be two sphingomyelinase isoenzymes. Further studies have revealed a virtual absence of both isoenzymes (I and II) in type A, a marked decrease in both I and II in type B, and absence of isoenzyme II in type C. Additional studies are needed to confirm and further clarify this point. However, if different isoenzyme preponderances are found in different organ systems, one can begin to understand the variety of clinical presentations in Niemann–Pick disease.

Therapy

At the present time there is no specific treatment available for Niemann–Pick disease. Splenectomy is occasionally performed for the rare Niemann–Pick patient with symptomatic hypersplenism.

Cerebrotendinous Xanthomatosis

Cerebrotendinous xanthomatosis is a rare familial autosomal recessive disease characterized by elevated plasma cholestanol and accumulation of cholestanol in xanthomas of the tendons, lungs, and brain in spite of a normal or low plasma cholesterol level. The neurologic manifestations include subnormal intelligence, progressive cerebellar ataxia, dementia, paresis, and cataracts. Schneider (696) described xanthomatous lesions in the nervous system of a mentally retarded and epileptic patient. Menkes et al. (697) reported

greatly increased cholestanol levels in the cerebellum and cerebrum of two patients with cerebrotendinous xanthomatosis. Since then, cholestanol has been found in the blood and tissues in greatly increased amounts in several patients.

Clinical Features

Cerebrotendinous xanthomatosis has an insidious onset and unpredictable course and was arbitrarily divided into three stages by van Bogaert et al. (698). For more details, see refs. 699–704.

Therapy

Specific treatment for cerebrotendinous xanthomatosis was recently described by Berginer et al. (701), who reported that after 1 year of treatment with oral chenodeoxycholic acid (750 mg/day), dementia cleared in 10 of 13 patients and pyramidal and cerebellar signs resolved in five and improved in another eight of a total of 17 patients studied. Cerebral CT scans improved in seven patients. Thus, as commented on by Grundy (702) in an accompanying editorial, Berginer et al. have provided evidence that therapeutic intervention can reverse the entire process by changing the course of sterol deposition in the nervous system. Cataract extraction may partially relieve the visual symptoms, and surgical removal of tendon xanthomas may help relieve pain and discomfort. Chenodeoxycholic acid also reduced CSF cholesterol by 34% and reduced cholestanol threefold (703).

This disease has a deteriorating course that eventually leads to death, usually between the fourth and sixth decades, unless long-term therapy with chenodeoxycholic acid is instituted. This therapy may correct, and even possibly reverse, the progression of disease (704).

Acid Cholesterol Ester Hydrolase Deficiency (Wolman's Disease) and Cholesterol Ester Storage Disease

Wolman's disease and cholesterol ester storage disease are two disorders in which there is tremendous storage of cholesterol esters (and often triglycerides) in lysosomes secondary to a deficiency of an acid lipase or acid esterase enzyme. Wolman's disease is the more severe of these disorders; cholesterol ester storage disease follows a more benign protracted course.

Wolman's disease is an abnormality of lipid metabolism that usually becomes clinically evident in the first weeks of life and is characterized by gastrointestinal symptoms, failure to thrive, hepatosplenomegaly, steatorrhea, and adrenal enlargement and calcification. It is inherited as an autosomal recessive disorder. This disease is invariably fatal, usually by 6 months of age. Nearly every organ contains cells loaded with neutral lipids, particularly cholesterol esters and glycerides. The presence of calcified adrenals associated with tissue lipid storage in a seriously ill infant is nearly pathognomonic of Wolman's disease. For more details see refs. 705–707.

Cholesterol Ester Storage Disease

Cholesterol ester storage disease is a rare familial autosomal recessive disease characterized by hepatomegaly and accumulation of cholesterol esters and triglycerides mainly in lysosomes in liver, spleen, intestinal mucosa, lymph nodes, and other tissues. Cholesterol ester storage disease is believed to be an allelic disorder related to Wolman's disease. The distinction between Wolman's disease and cholesterol ester storage disease is that the latter has a much more benign course because of a lesser defect in lysosomal acid lipase. In 1972 it was reported that patients with cholesterol ester storage disease were severely deficient in acid lipase or cholesterol ester hydrolase activity (708).

Clinical Features

Of the cases reported to date, hepatomegaly appears to be a common early clinical finding that may not manifest until the adult years, although it may be discovered within the first decade of life. Hypercholesterolemia is common, and premature arteriosclerosis may be severe. A child with marked hepatomegaly and hyperlipidemia without splenic enlargement, with otherwise normal mental and physical development, should be considered a possible candidate for cholesterol ester storage disease.

Mevalonic Aciduria

In 1986 Hoffman et al. (709) described a family in which one child had mevalonic aciduria due to an inherited deficiency of mevalonate kinase. They were able to diagnose prenatally an affected fetus in a subsequent pregnancy in this same family. They studied a 2-year old boy with mental retardation, cataracts, failure to thrive, anemia, hepatosplenomegaly, and dysmorphic features. He had a massive excretion of mevalonic acid, a metabolic precursor of cholesterol and nonsterol isoprenes. The mevalonic acid concentration in plasma was increased to 440 μmol per liter (normal value < 0.05). The activity of mevalonate kinase, the enzyme that catalyzes the first step in mevalonate metabolism, was generally deficient in the patient's fibroblasts, lymphocytes, and lymphoblasts.

Neuronal Ceroid Lipofuscinoses

Neuronal ceroid lipofuscinoses present with progressive mental retardation, blindness, and seizures. This class of disease was first recognized by Batten (710) in 1903 and was reclassified and established as separate and distinct from the gangliosidoses by Zeman (711) in 1976. This is a group of heterogeneous genetic diseases inherited as autosomal recessive disease, although autosomal dominant inheritance has been reported in the late-onset form (712).

Clinical Features

Santavuori or Finish Form

This form begins as an autosomal recessive disease between 6 months and 2 years of age with insidious mental

retardation, hypotonia, and ataxia. Seizures eventually occur with early-onset amaurosis. Optic atrophy and vascular discoloration occur. The course is one of rapid deterioration with severe brain atrophy.

Jansky–Bielschowsky Form

This form is also inherited as an autosomal recessive disease with onset between 2 and 4 years. Seizures, blindness, and mental retardation with associated optic atrophy, retinitis pigmentosa, and a rapid deterioration in neurologic function characterize the disorder.

Spielmeyer–Vogt–Sjögren Form

This form has a later onset, with a range between 2 and 10 years. Seizures and blindness with subsequent mental retardation occur, with associated vascular degeneration and pigmentary retinal degeneration. This form of disease is more slowly progressive, and patients survive to puberty.

Kufs Form

This form presents in young adulthood as an autosomal recessive or dominant disorder with mental retardation and seizures. The optic fundus usually is normal, and blindness does not occur. The course is slowly progressive and compatible with life until about age 40 years. The main clinical deficits are those of a progressive dementing disorder with seizures. In 1988 a thorough comprehensive review regarding 50 patients was published by Berkovic et al. (713). Their hypothesis is that this disorder is due to a defect in the intracellular processing of lysosomal and related membranes.

Biochemical Findings

All of these forms have in common the presence of autofluorescent lipopigments in neurons, glia, and endothelial cells of cerebral cortex, cerebellum, and hypothalamus. Liver and kidney also contain lipopigments. These two pigments, ceroid and lipofuscin, have different chemical properties and probably represent peroxides of cross-linked polymers of polyunsaturated fatty acids. The basic biochemical defect in these disorders that results in the deposition of the lipid peroxides remains unknown. In 1984 Ivy et al. (714) reported that injections of leupeptin (a thiol proteinase inhibitor) or chloroquine (a general lysosomal enzyme inhibitor) into the brains of young rats induced the formation of lysosome-associated granular aggregates or dense bodies that closely resembled the ceroid lipofuscin that accumulates in the ceroid lipofuscinoses. These observations provide insights into the origin of these syndromes and a means to study them experimentally. Perhaps endogenous inhibitors of lysosomal enzymes or processing defects that prevent their lysosomal addressing might be areas for future research based on these findings. Wolfe et al. (715) reported that long-chain polyisoprenol alcohol (dolichols) levels are significantly increased in the urinary sedient of patients with infantile, late-infantile, and juvenile forms of neuronal ceroid lipofuscinosis. Antioxidant treatment of patients with juvenile neuronal ceroid lipofuscinosis has no effect on dolichol values.

Neuropathology

The neuropathology is characterized by neuronal loss, spongiform change of the brain, and the cytoplasmic inclusion of lipopigments. By electron microscopy the lipopigments appear as lamellar aggregates referred to as *curvilinear bodies,* and others appear as fingerprint bodies. Often a limiting membrane suggestive of tertiary lysosomes can be identified around these bodies. Several reports have described that the lipopigment bodies have acid phosphatase activity.

Lymphocytes can be of diagnostic value, since they may contain cytoplasmic lipopigment inclusions. Three patients with juvenile disease reported by Goebel (716) had fingerprint lipopigments in the absence of vacuoles in their lymphocytes. Similarly, as shown by Farrell and Sumi (717), epithelial cells in the urinary sediment, peripheral nerve, skin, and muscle biopsies may contain cells with lipopigment inclusions.

Phytanic Acid Storage Disease (Refsum's Syndrome)

In 1946 Sigvald Refsum published a monograph (reviewed in ref. 718) identifying a new familial neurologic syndrome that he designated *heredopathia atactica polyneuritiformis,* and in 1963 the postmortem tissues from a 7-year-old girl diagnosed with Refsum's syndrome were biochemically analyzed. The liver and kidneys were grossly infiltrated with lipid, mostly neutral lipid. Gas chromatographic analysis revealed a 20-carbon branched-chain fatty acid that was fully characterized as phytanic acid. Whereas normal human plasma contains only traces of phytanic acid (less than 0.3 mg/dl), patients with Refsum's syndrome have 5–30% of their total plasma fatty acids present as phytanic acid. A series of studies has pointed to an exogenous origin for the accumulated phytanic acid and has also pointed to a defect in its catabolism as a basis for its accumulation. Steinberg and co-workers (cited in ref. 718), in a series of studies, established that the major pathway for phytanic oxidation in human subjects and experimental animals involved the unusual initial α-oxidation to yield α-hydroxyphytanic acid and then the $(N-1)$ fatty acid pristanic acid. Through a series of successive β-oxidation steps, pristanic acid is further degraded. Evidence from clinical observation and cell culture studies now indicates that the primary enzyme defect lies at the first step in this metabolic pathway, the α-oxidase. It is inherited as an autosomal recessive disorder (718).

Clinical Features

Refsum's disease presents with the tetrad of retinitis pigmentosa, peripheral polyneuropathy, cerebellar ataxia, and

high CSF protein concentration in the absence of pleocytosis.

The onset of the disease has been detected in early childhood in some, but not until the fifth decade in others. The most frequent initial manifestation is night blindness. This is followed by decreased vision, signs of peripheral polyneuropathy, and cerebellar ataxia.

The course of the disease is one of gradually progressive deterioration, interrupted in approximately half of the patients by unexplained and sometimes lengthy periods of remission. Dramatic exacerbation associated with an ill-defined febrile illness, a surgical procedure, or pregnancy has been noted. Gradual recovery of function following such episodes is the rule, but residual neurologic deficits may remain.

At the present time, the diagnosis is based on the constellation of clinical findings, demonstrated accumulation of phytanic acid in serum and tissue, or demonstrated reduction in capacity to oxidize phytanic acid. The carrier state can be diagnosed using the fibroblast cell culture methods. Normal amniotic cells have the capacity to oxidize phytanic acid, so intrauterine diagnosis is possible.

Genetics and Biochemistry

This is an autosomal recessive disorder. Biochemical studies to date have revealed that there is little or no endogenous biosynthesis of phytanic acid and that phytol and phytanic acid are potential dietary precursors, since the metabolic error in Refsum's disease lies in a degradative pathway of phytanic acid. It has also been shown that the defect in phytanic acid storage disease persists in cultured fibroblasts. Normal human fibroblasts derived from skin biopsies oxidize added phytanate at rates comparable to those for added palmitate. Cells derived from patients with phytanic acid storage disease, however, oxidize palmitate at a normal rate but oxidize phytanate at only approximately 1% of the normal rate. Further biochemical studies have shown that the metabolic defect is localized to the initial α-oxidation of phytanate and probably to the α-hydroxylation step itself. The α-hydroxylation step has been shown to occur in mitochondria. The reaction is stimulated by NADPH and requires molecular oxygen. The reaction shows a marked stimulation by added ferric iron, whereas ferrous iron inhibits this reaction. This further distinguishes the phytanate oxidizing system in the liver from the straight-chain α-oxidation system in the brain, since the latter is primarily a microsomal enzyme and is stimulated by ferrous iron.

Recently, Skjeldal et al. (719) have reviewed the literature indicating that phytanic acid has also been found to accumulate in the peroxisomal disorders (Zellweger's syndrome, neonatal adrenoleukodystrophy, infantile Refsum's syndrome, rhizomelic chondrodysplasia punctata). Alpha-oxidation of phytanic acid in skin fibroblast cultures showed a defective capacity in all groups mentioned above, with a residual activity similar to that of Refsum's disease. The distinction between Refsum's disease and the peroxisomal disorders can easily be determined on a clinical basis.

At the present time it is not known how the accumulation of phytanic acid leads to clinical manifestations of the disease. Indeed, it is not firmly established whether or not phytanic acid accumulation per se is necessary and sufficient for the clinical manifestations.

Therapy

If it is true that stored phytanate is exclusively of exogenous origin, then elimination of phytanate and its potential precursors from the diet should prevent further accumulation. Patients adhering well to a rigorous diet have brought plasma phytanate levels down to 10% of pretreatment values and even normalized them in some instances. In those patients responding with a good fall in plasma phytanate, there has been an arrest in the progress of the peripheral neuropathy. Improvement in nerve conduction velocity has been documented in five patients followed in three different clinics. Cranial nerve functions have not shown improvement. Two patients have been studied whose symptoms and ulnar nerve conduction velocities improved on the diet, worsened when they went off the diet, and again improved when they went back on the diet.

Lundberg et al. (720) called attention to a potential hazard in dietary management. They followed two patients whose plasma phytanate levels paradoxically increased and whose neurologic status deteriorated markedly over a period of 1–2 months on a reduced caloric and reduced phytanate diet. This was attributed to the marked rise in plasma phytanate secondary to mobilization of tissue storage during rapid weight loss. At this time, the evidence available indicates that any patient with a diagnosis of phytanic acid storage disease deserves an intensive trial of dietary treatment.

The untreated disease has a progressive course, with periods of exacerbation followed by improvement. The extent to which dietary management will alter the progression of this disease is not clear at the present time, but hopefully it will slow the long-term deterioration.

N-Acetyl Neuraminidase Deficiency [The Cherry-Red Spot–Myoclonus Syndrome (CRSM)]

The presence of action myoclonus is a disabling symptom as part of the CRSM or sialidosis type I, as described by Gonatas et al. (721) in 1963. *N*-Acetyl-neuraminidase (E.C. 3.2.1.1.8) shows low levels of activity in patient tissues and is the basis for the disease. When used in combination, 5-hydroxytryptophan (5-HTP) and dantrolene have been effective in reducing the degree of action myoclonus (721,722).

LEUKODYSTROPHIES

Krabbe's Disease (Galactosyl Ceramidase Deficiency, Globoid Cell Leukodystrophy)

Krabbe (723) described clinical and histologic findings in two siblings who presented with early onset of spasticity culminating in a rapidly fatal course. He also described the

globoid cells that are a hallmark of the disease. In 1970 Suzuki and Suzuki (724) demonstrated that galactocerebroside β-galactosidase is deficient in this disorder and that it is autosomal recessive. In 1971 Suzuki et al. (725) made the first intrauterine diagnosis and were subsequently able to detect the heterozygous condition by enzymatic assay. Hagberg et al. (726) reported 32 Swedish cases during the period from 1953 to 1967 and calculated the incidence for that series as 1.9 per 100,000 births. Although the geographic distribution of the cases is widespread, the incidence in Scandinavian countries appears to be higher than in the rest of the world.

Kobayashi et al. (727) recently reported that galactosyl sphingosine (psychosine) in somatic organs from a patient and from the twitcher mouse, an animal model, was increased as in the nervous system, but to a lesser degree. Their findings indicate that globoid cell leukodystrophy is a generalized galactosyl sphingosine storage disease.

Clinical Features

In the majority of patients, this disorder manifests between 3 and 6 months of age and presents as a degenerative disease involving predominantly the CNS. Hagberg et al. (726) have divided the disease into three arbitrary stages:

Stage 1. A child who has been normal for the first few months of life develops hyperirritability, hypertonia, and hypersensitivity to tactile, visual, and auditory stimuli. There are episodes of fever of unknown origin. Psychomotor delay becomes apparent, with feeding difficulties appearing and seizures occasionally being manifested. The CSF protein level is elevated without pleocytosis, even at this early stage.

Stage 2. There is an acceleration of the brain degeneration with marked hypertonia, hyperreflexia, and optic atrophy. Minor motor seizures may occur.

Stage 3. This stage is characterized by decerebration, blindness, and, sometimes, complete deafness. Patients rarely survive for more than 2 years. The head is usually microcephalic, reflecting the destruction of brain myelin, although macrocephaly may occasionally occur.

Peripheral nerve involvement may be demonstrated electrophysiologically by diminished nerve conduction velocities and findings of denervation on electromyography. The peripheral neuropathy is almost always completely overshadowed clinically by the prominent brain white matter degeneration. There is no visceral involvement in this disorder.

A later-onset form of the disease has been described in more than 10 patients, who also have a slow progression of this disorder. Again, the clinical manifestations are those of a white matter degeneration, with the brain manifestations being visual impairment secondary to optic atrophy and/or cortical blindness, hypertonia, hyperreflexia, and pathologic plantar responses. A peripheral neuropathy may be demonstrated by nerve conduction velocity studies but is clinically almost always overshadowed by the brain white matter degenerative findings. The CSF protein level is usually normal. The diagnosis is confirmed by finding decreased galactosyl ceramide-β-galactosidase activity in serum, leukocytes, cultured fibroblasts, or cultured amniotic fluid cells.

Computerized tomographic and magnetic resonance brain scans have been reported as showing rather specific findings in three patients (727–729).

Neuropathology

All the important pathologic findings are limited to the nervous system, both central and peripheral. Peripheral nerve lesions consist of minimal-to-severe axonal degeneration, myelin breakdown associated with endoneural fibrosis, and accumulation of foamy histiocytes around endoneural blood vessels and endoneural trabeculae. Although typical globoid cells are not seen, straight or curved tubular inclusions are ultrastructurally seen within histiocytes.

Two types of globoid cells occur in the brain: mononuclear and multinuclear. At the present time, available evidence strongly suggests that globoid cells originate from nonneural mesodermal cells, which is in keeping with their predominantly perivascular location and numerous fine tortuous cytoplasmic processes.

Genetics and Biochemistry

The disease is inherited as an autosomal recessive disorder. The most consistent finding in the white matter is an increased ratio of galactocerebroside to sulfatide, although both are much lower than normal. This is because there is more of an increase in galactocerebroside than a decrease in sulfatide. Another important observation has been the presence of 10–100 times the normal amount of galactosyl sphingosine (psychosine), which is galactosyl ceramide minus the fatty acid. Galactosyl sphingosine has been shown to be highly cytotoxic. Further studies have shown that the myelin formed in globoid cell leukodystrophy is normal ultrastructurally and biochemically.

Galactocerebroside is characteristically a lipid of the nervous system. The kidney is the only extraneuronal organ with significant amounts of this glycolipid. In brain, galactocerebroside is almost exclusively localized in oligodendroglial cell membranes and therefore in myelin. It is now postulated that during the period of active myelination, both galactosyl ceramide and galactosyl sphingosine accumulate owing to the deficiency of galactocerebroside β-galactosidase. Galactosyl sphingosine is highly cytotoxic and leads to oligodendroglial cell death, since the oligodendroglia are predominantly exposed to this toxic glycolipid.

Kobayashi et al. (730) assayed galactosyl ceramide and galactosyl sphingosine in tissues from patients. They found that galactosyl sphingosine, but not galactosyl ceramide, accumulates in tissue of patients as a result of the fact that galactosyl ceramide, but not galactosyl sphingosine, is readily hydrolyzed by an intact galactosyl ceramidase II.

Therapy

At this time there is no effective treatment for this disorder.

Metachromatic Leukodystrophy (Sulfatide Lipidosis)

In 1910 Alzheimer (731) reported a patient with diffuse sclerosis and metachromatic staining of the tissues, Austin (732) and Austin et al. (733) demonstrated a large excess of sulfatides in the tissues of patients with metachromatic leukodystrophy. Austin et al. (733) demonstrated markedly low activity of arylsulfatase A and cerebroside sulfatase in the tissue of patients with metachromatic leukodystrophy. It is inherited as an autosomal recessive disorder.

Gustavson and Hagberg (734) reported an incidence of approximately 1 in 40,000, and in the juvenile form they reported an incidence between 1 in 160,000 and 1 in 200,000.

Clinical Features

Late-Infantile Form

This form of metachromatic leukodystrophy presents as a peripheral and central white matter degenerative disorder with onset usually between 12 and 18 months of age. Hagberg (735) has divided the clinical course into four stages:

Stage 1. This stage is represented by weakness, hypotonia, and hyporeflexia, which may involve all four extremities. Corticospinal tract and cerebellar findings may occasionally be present at this time. The mean duration of this stage is about 1 year.

Stage 2. This stage is characterized by further progression of white matter degeneration, resulting in dysarthria, ataxia, and onset of hypertonia. The deep tendon reflexes remain diminished to absent. Mental deterioration becomes apparent. Intermittent pain in the arms and legs is a frequent feature that may be a manifestation of peripheral nerve root involvement. This stage usually lasts from 3 to 6 months.

Stage 3. At this stage the child is usually bedridden and quadriplegic, with decorticate, decerebrate, or dystonic posturing. Bulbar and/or pseudobulbar palsies are present, and the mental deficiency is severe. The deep tendon reflexes are almost always absent, and optic atrophy may occur. The optic atrophy appears as a gray macula with a red center. This stage lasts from 3 months to 3.5 years in Hagberg's series.

Stage 4. The patients in this final stage are characterized by loss of contact with their surroundings. They must be fed through a nasogastric or gastrostomy tube.

Juvenile Form

This form of metachromatic leukodystrophy has onset between 3 and 21 years of age, usually between 5 and 10 years. The initial symptom usually involves difficulties in mental functioning, such as school problems or emotional lability, or the disorder may appear initially as a gait disorder. Extrapyramidal dysfunction and cerebellar findings are fairly common.

Adult Form

The clinical manifestations of this form have their onset between 19 and 46 years of age in the cases described to date. The earliest symptoms are usually in the intellectual or emotional areas. Corticospinal and extrapyramidal symptoms develop and outweigh the peripheral nerve findings. Cerebellar findings of truncal ataxia, intention tremor, and nystagmus are also common. Seizures may occur during the later stages. An excellent review of the subject is available (736).

The diagnosis of metachromatic leukodystrophy is suspected on the basis of the clinical presentation of the three forms as outlined above. The diagnosis is greatly strengthened by finding decreased activity (almost undetectable in homozygotes and 50% reduced in heterozygotes) of arylsulfatase A in serum, urine, leukocytes, cultured skin fibroblasts, or cultured amniotic fluid cells. Because arylsulfatase activity has been found to be either normal or only slightly diminished in two patients with definite clinical symptoms, and has been found to be in the homozygous range in two other clinically normal individuals, one cannot rely entirely on arylsulfatase A activity to make the diagnosis. Therefore, it has been suggested that before the diagnosis is firmly established, one or more of the following confirmatory assays must be positive: (a) nonspecific abnormalities such as decreased peripheral nerve conduction velocity, impaired gallbladder function, or elevated CSF protein; (b) above-normal sulfatide excretion in the urine; or (c) the accumulation of glycolipid with metachromatic properties in tissues, preferably in peripheral nerve obtained by sural nerve biopsy. Magnetic resonance imaging showed an increased T2 weighted signal of periventricular white matter adjacent to frontal and occipital horns (737).

Adult Metachromatic Leukodystrophy

Our patient is a 23-year-old man with a 6-year history of poor coordination, gait impairment, and mild mental regression. He had ankle hyperreflexia with clonus and extensor plantar responses.

He had ataxia on finger-to-nose and heel-to-shin maneuvers and also had a broad-based ataxic gait. He could not tandem-walk. A T2 weighted magnetic resonance scan showed a bilateral homogeneous increase in the white matter signal intensity at the frontal and occipital poles. His serum arylsulfatase A was 0.40 units/liter (normal value: 0.4–1.29 units/liter). A 24-hr urine arylsulfatase was 0.39 units/liter, which is very low (normal value: 1–20 units/liter). Frozen sections of the sural nerve biopsy stained with cresyl violet showed metachromatic material in the endoneurium. Plastic embedded sections stained with toluidine blue showed red metachromatic globular cytoplasmic inclusions within Schwann cells (738). Electron micrographs of sural nerve showed general myelinated fibers undergoing active demyelination.

Genetics and Biochemistry

This is an autosomal recessive disorder caused by a deficiency of arylsulfatase A. This enzyme has been mapped to

chromosome 22q13. The chemical pathology of metachromatic leukodystrophy caused by this enzymatic defect is the accumulation of sulfatide up to 3–10 times normal in the late infantile form, with other myelin lipids, such as cholesterol and sphingomyelin, decreased by 30–50%. Cerebroside levels in white matter are decreased by 10–50% of normal, and this gives rise to an abnormal cerebroside/sulfatide ratio. In normal white matter the ratio is approximately 4. In the late-infantile form of metachromatic leukodystrophy, the cerebroside/sulfatide ratio may be decreased to 0.5. All evidence indicates that the chemical structure of sulfatide is normal in metachromatic leukodystrophy (739,740).

The adult form of metachromatic leukodystrophy shows chemical abnormalities similar to, but less severe than, those of the late-infantile form. The one exception is that in the adult form of the disease, the gray matter sulfatide levels are increased to a greater extent than in the late-infantile form. This is interesting in light of the more prominent intellectual and emotional findings (noted above) in the adult form of the disease.

Immunoassay techniques have revealed slight but significant antigenic differences between normal arylsulfatase A and the mutant enzyme found in metachromatic leukodystrophy.

Porter et al. (741) and Farrell et al. (742), using intact fibroblasts in culture, showed that the amount of arylsulfatase activity in cells from patients with metachromatic leukodystrophy was directly correlated with the age of onset of clinical symptoms and severity of disease. Fibroblasts from patients with the late-infantile form of metachromatic leukodystrophy had no detectable cerebroside sulfatase activity, whereas fibroblasts from patients manifesting the disease later in life had appreciable amounts of enzyme activity. One explanation of this finding is that the residual arylsulfatase A may be structurally different in the various clinical forms of the disease, so that in the adult form of the disease the arylsulfatase A may either be physically more stable or possess greater substrate affinity.

In 1983 Hizeidarsson et al. (743) reported low arylsulfatase A levels in two siblings. One sibling had a neurologic disability not typical for metachromatic leukodystrophy, and the other was a healthy 18-year-old woman with a normal developmental history. In both siblings, arylsulfatase A levels in white blood cells were 7–8% of control values. Other family members had enzyme levels consistent with heterozygote or normal status. Hizeidarsson et al. (743) concluded that the neurologic abnormalities in the one sibling were not the result of the low enzyme activity and that both persons represent examples of "pseudo-arylsulfatase A" deficiency (arylsulfatase A deficiency without metachromatic leukodystrophy). This is an unusual disorder caused by a mutation allelic to the mutation responsible for true metachromatic leukodystrophy.

Therapy

At the present time there is no specific therapy for this disorder. Bone marrow transplantation to provide donor cells capable of enzyme production has not been of clinical value.

Adrenoleukodystrophy

Historical Perspective

Adrenoleukodystrophy (ALD) was first described in 1923 by Siemerling and Creutzfeldt (744), who pointed out that skin pigmentation and a progressive leukodystrophy were central features of the disorder. Blaw (745), Schaumburg et al. (746–748), and Moser et al. (749) have provided the important clinical and pathological features.

Genetics

This is an X-linked disease (Xq28) with expression beginning in early childhood, teenage years, or early adulthood. Males are principally affected, but carrier females may also show clinical evidence of disease.

Clinical Features

Several phenotypes of ALD are reported. Progressive cerebral degeneration with cortical blindness, spinal cord involvement with spastic quadriparesis, and cutaneous hyperpigmentation in young males are typical features. Variants of the ALD syndrome include (a) X-linked Addison's disease without any neurologic involvement and (b) spasticity and weakness caused by spinal involvement in female carriers (750). In the adrenomyeloneuropathy variant, symptoms begin later in the second and third decades and the disease process develops slowly over more than two decades. A peripheral neuropathy, azoospermia, and hypotestosteronemia complete the picture. A neonatal ALD variant has also recently been described that shows the same biochemical defect as in typical ALD but that involves girls as frequently and as severely as boys; it is suggested that it is inherited as an autosomal recessive trait (751,752). Cellular peroxisomes in X-linked ALD are normal in number and size, and the peroxisomes have a characteristic coarsely fibrillar, moderately electron-opaque matrix and are often in clusters. In neonatal autosomal recessively inherited ALD, the peroxisomes are sparse, scattered, and small in size compared with normals. There was a 10-fold decrease in the number and mean volume of hepatocellular peroxisomes in a patient with neonatal ALD. Thus the basis for impaired long-chain fatty acid oxidation in ALD, whether it be X-linked or autosomally recessively inherited, is a defect in peroxisomal availability or function (753). Predilection for parietal lobe and occipital lobe white matter is the basis for early-onset cortical blindness. The CT brain scan shows decreased density of cerebral white matter. Clinical and laboratory evidence of hypoadrenalism can be demonstrated at some time during the illness (745) and can precede by many years the onset of neurologic symptoms (754).

O'Neill and Moser (755) reported one family having X-linked recessively inherited Addison's disease in men with no other neurologic disease. Carrier heterozygous females may have mild-to-severe myelopathic findings of a spastic paraparesis without cerebral manifestations (755). Presumably, the presence of clinical disease in female carriers is explained by the Lyon hypothesis of random inactivation of

the X chromosome (756). A female heterozygote presented with a chronic nonprogressive spinal cord syndrome secondary to the ALD heterozygote state. The disease is inexorably progressive and uniformly fatal. Excellent reviews are offered by Blaw (745), O'Neill and Moser (755), and Goto et al. (759).

Moser et al. (749,757) reported on 303 patients with ALS in 217 kindreds. Their patients showed a broad spectrum of phenotypic variation. Sixty percent of patients had childhood ALD and 17% had adrenomyeloneuropathy, a form showing progressive leg spasticity, paralysis, and polyneuropathy without mental status changes. Both ALD and adrenomyeloneuropathy are X-linked recessive and map to Xp27-28. Linkage has been reported between the ALD locus at Xq27-28 and a cloned DNA fragment (St14). The LOD score is 13.766 at a recombination of 0.0 (758). These investigators found that neonatal ALD, a distinct entity with autosomal recessive inheritance and a resemblance to Zellweger syndrome, was present in 7% of the cases. They concluded that ALD and Zellweger's cerebrohepatorenal syndrome belong to a newly formed category of peroxisomal disorders, since in both syndromes the peroxisomal ability to degrade C26:0 very-long-chain lipids is defective (ALD) or absent (Zellweger's). Goto et al. (759) reported that the increase in saturated very-long-chain fatty acids was found not only in sphingomyelin but also in phosphatidylcholine and phosphatidylserine and in erythrocyte membrane phospholipids. Sakai et al. (760) found a deficiency in plasmalogen in cultured skin fibroblasts from neonatal ALD patients. Suzuki et al. (761) treated two patients with a diet low in very-long-chain fatty acids. There was biochemical improvement in one patient, with a lowering of very-long-chain fatty acids in erythrocyte membranes and plasma; however, there was no clinical improvement. Sakai et al. (762) reported an accurate method of carrier detection by measuring total fatty acids with acetonitrile-HCl extracted from cultured skin fibroblasts using high-performance liquid chromatography.

Pathology

The cerebral hemispheres undergo a diffuse, symmetrical loss of myelin in the white matter pathways and especially in the posterior quadrants of the hemispheres. There is a sparing of the subcortical U fibers. Similar demyelination affects the thoracic spinal cord. There is an associated perivascular mononuclear cell infiltration (747,748,763). Lamellar lipid profiles are found in adrenal cortical cells and macrophages in brain white matter, indicating a lipid storage disorder. The adrenal cortices are atrophic with relative preservation of the zona glomerulosa.

Biochemistry

Brain white matter and adrenal cortex from patients have cytoplasmic inclusions that contain cholesterol esters of saturated very-long-chain fatty acids with a carbon chain length of C23 and longer (764,765). Hexacosanoic acid (C26:0) is the most significantly elevated. Cultured fibroblasts accumulate very-long-chain fatty acids as well (766–768). O'Neill et al. (769) studied 21 women from four ALD kinships, nine of whom had a spastic paraparesis, including two with peripheral neuropathy. Fifteen women were assigned heterozygote status based on abnormal very-long-chain fatty acid elevations in plasma, fibroblasts, or both. Singh et al. (770) concluded that ALD patients have a defect in the oxidation of very-long-chain fatty acids (C24:0 and longer), but not in the degradation of fatty acids with a chain length of 18 carbons or less. Lazo et al. (771) reported that the enzymatic basis of the accumulation of very-long-chain fatty acids in ALD is due to a deficiency of peroxisomal very-long-chain (lignoceric acid) acyl-CoA ligase.

Therapy

Patients have been treated unsuccessfully by (a) dietary restriction of very-long-chain fatty acids, (b) use of carnitine and clofibrate, (c) immunosuppression, and (d) plasma exchange (772). Adrenal steroid therapy has no effect on neurologic progression. One 13-year-old boy was treated with an allogeneic bone marrow transplant from a normal HLA-identical sibling donor. Complete hematologic recovery occurred, but neurologic deterioration continued (766). At present, no specific form of therapy exists to treat the progressive neurologic deterioration. Although the excess C26:0 in the brain of patients with ALD is partially of dietary origin, dietary C26:0 restriction did not produce clear benefit (772,773).

Cerebrohepatorenal Syndrome (Zellweger's Syndrome)

Cerebrohepatorenal syndrome (CHRS) has clinical features similar to those of ALD. The two disorders affect the same general age group, both involve cerebral cortex and white matter, both have similar eye lesions, and peroxisomes are absent in CHRS and defective in ALD (753,774). CHRS includes craniofacial abnormalities, severe hypotonia, mental retardation, cerebral dysgenesis, cortical renal cysts, and hepatomegaly. It is inherited in an autosomal recessive manner. In 1984 Moser et al. (775) reported that CHRS patients also have abnormalities of very-long-chain fatty acids similar to those of ADL. They found a fivefold increase of C26:0 in plasma, cultured skin fibroblasts, or postmortem brain tissues of 20 CHRS patients. In 1984 Datta et al. (776) reported a marked reduction in the activity of dihydroxyacetone phosphate acyltransferase, a peroxisomal enzyme, in fibroblasts and leukocytes from CHRS patients. Thus the role of peroxisomes in the metabolism of very-long-chain fatty acids is an important one and depends on the integrity of the acyltransferase pathway. Both ALD and CHRS are the result of defects in peroxisomal oxidation of very-long-chain fatty acids (753,777).

In 1988 Santos et al. (778) indicated that the peroxisomal membranes could be assembled in Zellweger's syndrome but that the importation of matrix proteins is defective. This defect would result in empty (or nearly empty) membrane ghosts, which would not be recognizable by electron microscopy or cytochemistry.

Fabry's Disease (α-Galactosidase A Deficiency)

Anderson (779) in England and Fabry (780) in Germany independently described patients with angiokeratoma corpus diffusum. In 1947 Pompen et al. (781) described the pathologic findings in two patients known to have angiokeratoma corpus diffusum. The most consistent finding was the presence of vacuoles in the media of abnormal blood vessels throughout the body, along with the presence of similar vacuoles about the nuclei of hypertrophied myocardial fibers.

After a number of reports of a more limited form of the disease in heterozygous females, Opitz et al. (782) studied the kindred of 21 carrier females and affected males and confirmed the X-linked transmission of the disease.

On renal autopsy of hemizygote patients, two neutral glycosphingolipids—galactosyl-galactosyl-glucosyl ceramide (Gal-Gal-Gluc-Cer) and digalactosyl ceramide (Gal-Gal-Cer)—have been isolated and characterized. Other studies have shown increased levels of Gal-Gal-Gluc-Cer in brain, plasma, urinary sediment, cultured skin fibroblasts, and most viscera in these patients.

Brady et al. (783) demonstrated that the enzymatic defect was absence of α-galactosidase A, which can be assayed for in plasma, urinary sediment, cultured skin fibroblasts, and cultured amniotic fluid. The disease has an incidence of 1 in 40,000.

The disease is inherited in an X-linked recessive manner. This mode of transmission is supported by the absence of parental consanguinity, absence of male-to-male transmission, occurrence of female-to-male transmission, measurable linkage between the α-galactosidase loci and the X_g^a blood-group antigen, the absence of any sign of the disease in more than 35 known sons of affected fathers, and the presence of three pedigrees in which two affected sons were born to the same mother by different fathers.

Clinical Features

Male Hemizygote

The clinical manifestations are (a) periodic episodes of fever and severe distal extremity pain, with associated vascular lesions of the skin, conjunctiva, and oral mucosa, and (b) crystalline deposits in the conjunctiva. The onset is from childhood to adolescence.

Pain is often the initial symptom and may have an excruciating burning or lightning character. The pain most commonly involves the fingers and toes and is accompanied by paresthesias; with time it spreads proximally. Fever, changes in environmental temperature, and physical exercise may all initiate the painful episodes. Since many of the painful episodes are associated with fever and an elevated erythrocyte sedimentation rate, the children are often erroneously diagnosed as having rheumatic fever.

Telangiectases (angiokeratomas) may be one of the initial signs; classically, these are clusters of dark red angiectasias in the superficial layers of the skin. The skin lesions are usually bilaterally symmetrical in their placement and show a predilection for the hips, buttocks, back, thighs, penis, and scrotum. The oral mucosa and conjunctiva are also commonly involved. With progressive accumulation of glycosphingolipids in the kidneys, progressive renal failure is manifested by azotemia.

Diffuse deposits of glycosphingolipids in the vascular system and myocardium may manifest as hypertension, cardiomegaly, myocardial ischemia or infarction, and brain signs and symptoms of ischemia and/or infarction. The brain manifestations may be seizures, motor or sensory impairment, aphasia, various brainstem syndromes, or intracranial mass lesions secondary to intracranial hemorrhage. The characteristic ocular lesions are aneurysmal dilation of veins in the conjunctiva and retina. Corneal opacities are also commonly found. Progressive vascular disease of the brain, heart, and kidneys usually leads to death in the fourth or fifth decades of life.

Female Heterozygote

In general, all the clinical manifestations found in the hemizygous male are also found in the heterozygous female but are less severe and have a later onset in the heterozygote. However, the disease becomes more severe in middle life in the heterozygous female, and death can usually be attributed to renal or cardiac complications of the disease. In 1988 a 21-year-old woman who was a carrier of Fabry's disease was reported presenting with dysfunction of the autonomic nervous system as expressed by severe orthostatic hypotension (784).

The diagnosis is based on the clinical presentation of widespread small-vessel pathology and is confirmed by the absence of activity of α-galactosidase A in plasma, leukocytes, fibroblasts, and tissues of these patients. The diagnosis may also be made *in utero* from enzymatic analysis of amniotic fluid cells.

Genetics and Biochemistry

The disease is inherited as an X-linked recessive disorder, and the pathology results from an accumulation of cerebroside trihexoside caused by α-galactosidase deficiency. Affected hemizygous individuals have 10–25% of the normal α-galactosidase A activity. The enzyme deficiency in hemizygous individuals appears to be limited to the thermally labile α-galactosidase A, whereas any residual α-galactosidase activity appears to be caused by α-galactosidase B. Most heterozygous females have intermediate levels of α-galactosidase A activity. The complete nucleotide sequence has been determined for a cDNA clone containing the full-length coding region for the mature lysosomal form of human α-galactosidase A (785).

This circulating cerebroside trihexoside is thought to gain access to vascular endothelial cells and to endothelial and adjacent epithelial cells in the renal glomeruli by receptor-mediated uptake. This accumulation within blood vessels gives rise to narrowing, dilatation, instability, and motor unresponsiveness of the blood vessels. These are major physiologic features of the disorder (786).

Therapy

Fabry's disease is characterized by a chronic debilitating course that extends over many years. The single most debilitating aspect is the excruciating pain.

Various drugs have been tried for relief of the pain, including the α-adrenergic blocking agent phenoxybenzamine to increase peripheral vascular flow. In one patient, phenoxybenzamine did appear to provide pain relief on several occasions, but epistasis and priapism were early complications in two other patients. The combination of diphenylhydantoin and carbamazepine can significantly reduce the pain.

Because renal insufficiency is a very common late complication, chronic hemodialysis and renal transplantation may be lifesaving. So far, the use of renal allografts to alter the progression of the disease remains controversial.

In the future, enzyme replacement therapy may hold promise in this disorder. Studies of fibroblasts in tissue culture from hemizygous subjects have shown that α-galactosidase A exogenously supplied to the media is capable of gaining access to fibroblasts and catabolizing the accumulated Gal-Gal-Gluc-Cer. Furthermore, it was demonstrated that less than 5% of exogenous enzyme was capable of causing substantial substrate metabolism.

Brady et al. (787) administered α-galactosidase (purified from human placenta) to two hemizygous individuals. It was shown that the enzyme was rapidly cleared from the blood, was taken up by the liver, and caused a decrease in the circulating level of Gal-Gal-Gluc-Cer.

Canavan's Disease

This syndrome is characterized by megalocephaly in infancy, mental retardation, seizures, cortical blindness, flaccidity, and failure of neurologic development because of abnormal cerebral edema inherited as an autosomal recessive trait. It is sometimes referred to as *spongy sclerosis.* There is extensive demyelination and astrocytic edema throughout the white matter. The life span of affected children is usually less than 5 years. There is no specific therapy.

A CAT brain scan of a 6-year-old girl with Canavan's disease demonstrated bilateral low-density lesions in the globus pallidae suggestive of a degenerative process. There was also diffuse white matter disease present by virtue of the clinical signs of early-onset mental retardation with corticospinal deficit associated with hypodensity of the white matter pathways seen on her CAT scan.

Alexander's Disease

Megalocephaly in the first year of life, failure of neurologic development, spasticity, and decerebration are the features of this poorly characterized disorder. Impaired myelination, presence of Rosenthal fibers within astrocytes, and eosinophilic hyaline bodies are the characteristic features. The mode of inheritance is not clear, since most cases are sporadic. There is no specific therapy, and patients live only a few years.

Pelizaeus–Merzbacher Disease

Pelizaeus–Merzbacher disease is a rare disorder characterized by spasticity, ataxia, coarse ocular nystagmus, optic atrophy, and head tremor. It is thought to be X-linked when it presents in early childhood, but it is believed to be autosomal dominant when it presents in early adulthood. There is moderate-to-severe demyelination of central white matter with an impairment in the formation of compact myelin.

It has been suggested that the mutation for this disease has many features of an inborn error of myelination analogous to the murine jimpy mutation. A cDNA to one of the two major myelin proteins, myelin proteolipid protein (also referred to as *lipophilin*), has been used with Southern blot analysis of somatic cell hybrid DNA to map the human proteolipid protein to the middle of the long arm of the human X chromosome (Xq13-22). Comparison of the gene maps of the human and mouse X chromosomes suggests that myelin proteolipid protein may be involved in X-linked mutations at the mouse jimpy locus. In support of this view, Koeppen et al. (790) reported on the proteolipid protein (lipophilin) content of an 18-year-old patient and found it to be absent in brain but normal in the peripheral nervous system by immunocytochemistry and enzyme-linked immunosorbent assay (788–790).

Hereditary Adult-Onset Leukodystrophy Simulating Chronic Progressive Multiple Sclerosis

In 1984 Eldridge et al. (791) reported a large kindred with a chronic progressive neurologic disorder affecting 10 men and 11 women in four generations in an autosomal dominant pattern of inheritance. In examining an individual patient without access to family history or CAT findings, one would conclude that the disease process was multiple sclerosis. Patients present in the fourth or fifth decades with progressive cerebellar, pyramidal, and autonomic abnormalities. The CAT scan shows symmetrical reductions in white matter density involving all cerebral lobes as well as cerebellar white matter. On pathologic examination, the white matter shows severe degeneration with microscopic vacuolation, preserved subcortical U fibers, and no inflammatory changes or reactive gliosis. The primary genetic defect is unknown, and there is no specific therapy.

DISORDERS OF MUCOPOLYSACCHARIDE METABOLISM

The mucopolysaccharides are a diverse set of compounds containing polysaccharide, alternating amino sugars, and uronic acids (Table 4). Dermatan sulfate and heparan sulfate are two major mucopolysaccharides that increase, are stored, and are excreted in the mucopolysaccharidoses. The compounds are sequentially degraded by specific lysosomal enzymes (exoglycosidases or exosulfatases), and an enzyme

TABLE 4. *Mucopolysaccharides of connective tissue*[a]

Name	Amino sugar	Uronic acid	Sulfate	Amino substitution	Linkage: Uronide hexosaminidic	Linkage: Linkage to protein	Occurrence
Dermatan sulfate	D-GalN	L-IdUA D-GlcUA	$O\text{-}SO_4$	N-Ac	$\alpha 1 \rightarrow 3\beta 1 \rightarrow 4$	Gal-Gal-Xyl-Ser	Skin, lung
Heparan sulfate	D-GlcN	D-GlcUA L-IdUA	$N\text{-}SO_4$ $O\text{-}SO_4$	N-Ac $N\text{-}SO_4$	$\beta_1 \rightarrow 4$ $\alpha 1 \rightarrow 4\alpha 1 \rightarrow 4$	Gal-Gal-Zyl-Ser	Lung, spleen, liver, muscle
Keratin sulfate I (cornea)	D-GlcN	Gal(mann)	$O\text{-}SO_4$	N-Ac	$\beta 1 \rightarrow 4\beta 1 \rightarrow 3$	GalcNAc-AspNH_2	Cornea, nucleus pulposus, cartilage
Keratin sulfate II (skeletal)	D-GlcN D-GalN	Gal(mann)	$O\text{-}SO_4$	N-Ac	$\beta 1 \rightarrow 4\beta 1 \rightarrow 3$	GalNAc-Ser GalNAc-Thr	

[a] From Rosenberg and Pettegrew in Rosenberg, RN, ed: Neurology, New York, Grune and Stratton, 1980 with permission.

deficiency results in an increased degree of cellular lysosomal storage of mucopolysaccharide.

The first clinical description of Hurler's syndrome was probably provided in 1900 by John Thompson from the Royal Infirmary, Edinburgh. In 1917 Hunter's syndrome (792) was reported in two brothers, and in 1920 Hurler (793) reported two boys having the stigmata of the disorder associated with that eponym. The first organized nosologic classification was provided in 1952 by Brandt (794), who used the term "mucopolysaccharidosis" (MPS) for the first time. Excessive urinary excretion of these compounds was reported by Dorfman and Lorinez (795), Brown (796), and Meyer et al. (797). The concept of an MPS caused by an enzyme defect resulting in a lysosomal storage disorder was put forth initially in 1964 by van Hoff and Hers (798), and the *in vitro* accumulation of mucopolysaccharide by fibroblasts in culture was reported by Danes and Bearn (799) using cells from MPS patients. The McKusick classification of MPS was published in 1965 (800).

It was Elizabeth Neufeld (801) who made a brilliant series of enzymatic observations in the early 1970s showing that MPS was caused by specific catabolic enzyme defects resulting in accumulation of substrate, not by increased synthetic rates. She and her colleagues demonstrated that [^{35}S]-mucopolysaccharide accumulated in fibroblasts from MPS patients in cell culture and that a corrective factor, which later was shown to be normal lysosomal enzyme, could prevent [^{35}S]mucopolysaccharide storage; this study led to the identification of the enzyme defects involved. Fratantoni et al. (802–804) demonstrated that cocultured fibroblasts from Hurler and Hunter patients did cross-correct and prevented [^{35}S]mucopolysaccharide storage. This corrective effect was due to complementary enzymatic replacement by the MPS cell line from the Hurler patient on the Hunter patient cells, and vice versa. These disorders have been reviewed by McKusick and Neufeld (805).

Alpha-L-Iduronidase Deficiency

This enzyme deficiency has been associated with Hurler's syndrome (MPS I H), Scheie's syndrome (MPS I S), and a genetic compound form, Hurler–Scheie syndrome (MPS I H/S).

Hurler's Syndrome (MPS I H)

This autosomal recessive disorder was first described in 1920 by Gertrud Hurler (806); it has an incidence of approximately 1 in 100,000 and an estimated carrier rate of 1 in 150.

Clinical Features

Children develop an unrelenting, progressive syndrome caused by mucopolysaccharide storage in the CNS, cornea, bone, heart, liver, and spleen. Severe mental retardation, corneal clouding, hepatosplenomegaly, and skeletal deformities progressively occur, with death occurring before the first decade of life. Characteristic facial coarsening occurs associated with hypertelorism, hirsutism, shallow orbits producing proptosis, and scaphocephaly caused by early sagittal suture closing. Other skeletal defects include a J-shaped sella turcica, joint malformations, chest defects, lumbar lordosis, a widened medial end of the clavicle, vertebral hypoplasia with a hooked appearance to the apical dorsal vertebrae, iliac wing flaring, claw-hand deformities, hip flexion, contractures, and dwarfism.

The clinical diagnosis is established by the increased urinary excretion of dermatan and heparan sulfate (2:1), in association with the typical skeletal deformities, mental retardation, corneal clouding, and hepatosplenomegaly. The enzyme defect is α-L-iduronidase, which can be measured in fibroblast cultures (807).

Therapy

Enzyme replacement therapy has not been useful, and at present there is no specific therapy (808).

Scheie's Syndrome (MPS I S)

This is an autosomal recessive disorder described by Scheie et al. (809) in 1962; it has an estimated incidence of 1 in 500,000.

Clinical Features

These patients present in adulthood with hirsutism, joint stiffening, claw hand, genu valgum, pes cavus, aortic valve disease, and prominent corneal clouding. The syndrome resembles a mild, incomplete presentation of Hurler's syndrome. It is an allelic disorder of Hurler's syndrome, since it is caused by a milder degree of deficiency of α-L-iduronidase.

Therapy

Corneal transplantation and the surgical repair of nerve entrapments are the principal forms of therapy. There is no specific therapy for the underlying disease.

Hurler–Scheie Genetic Compound (MPS I H/S)

Since McKusick et al.'s (810) report in 1972, a series of patients have been reported who are deficient in α-L-iduronidase and who phenotypically are intermediate between Hurler and Scheie patients. We also have reported one such interesting genetic compound patient (811). These patients inherit 50% of their enzyme from one parent, which represents the Hurler allelic defect, and inherit the other 50% from the other parent, which represents the Scheie allelic defect.

Clinical Features

In early adulthood these patients develop progressive mental retardation, skeletal defects, and cardiac and hepatic disease. Associated corneal clouding, joint stiffening, and cardiac valvular disease occur.

Our report described for the first time the storage of mucopolysaccharide material in neurons of the brain and spinal cord, with their characteristic lysosomal storage pattern as demonstrated by electron microscopy (811).

Therapy

No specific therapy is available.

Hunter's Syndrome (Iduronate Sulfatase Deficiency, MPS II)

Hunter's syndrome is an X-linked recessive disorder with an unknown incidence. Hunter (812) first described the syndrome, and Wolff (813) and Njaa (814) suggested the X-linked mode of inheritance.

Clinical Features

The disease presents with a spectrum of severity, which may be caused by allelic defects at the iduronate sulfatase locus on the X chromosome.

It bears a strong resemblance to MPS IH, but it is separated clinically from MPS IH by the absence of corneal clouding, perhaps a more placid personality, and a longer life span. Patients are identified by the typical clinical phenotype, the excretion of equal amounts of dermatan sulfate and heparan sulfate, and a deficiency of iduronate sulfatase in serum and cultured fibroblasts.

Iduronate sulfatase increases in the serum of pregnant women, reaching a three- to fourfold increase from prepregnancy levels toward the end of pregnancy. In pregnancies with Hunter-affected fetuses, enzyme levels did not change in the serum of heterozygous mothers. Thus, a prenatal diagnosis of Hunter syndrome might be made in maternal serum in the early phase of pregnancy (815).

Therapy

There is no specific therapy.

Sanfilippo's Syndrome (Heparan Sulfatase Deficiency, MPS III Type A; *N*-Acetyl-α-glucosaminidase Deficiency, MPS III Type B; Acetyl-CoA:α-Glucosaminide *N*-Acetyltransferase Deficiency, MPS III Type C; *N*-Acetylglucosamine-6-sulfate Sulfatase Deficiency, MPS III Type D)

Sanfilippo's syndrome (816) is inherited as an autosomal recessive disorder, and the different enzyme defects are indistinguishable clinically. It was Harris (817) who first described this new form of MPS, which subsequently turned out to be type B disease (818). Type A disease was shown to be caused by a deficiency of heparan sulfatase (819,820).

Clinical Features

During childhood, patients develop a severe form of mental retardation with minimal skeletal defects and hepatosplenomegaly. Corneal clouding does not occur. Epilepsy may occur. The diagnosis is established by the increased excretion of heparan sulfate and a deficiency of heparan sulfatase or *N*-acetyl-α-glucosaminidase in cultured fibroblasts or amniotic fluid cells for types A and B, respectively. Types C and D are identified by finding a deficiency in the two enzymes reported for them as listed in the main heading of this section. A first-trimester diagnosis was made by chorionic biopsy along with assay of heparan sulfatase which was markedly deficient in activity as reported by Kleijer et al. (821) in 1986.

Therapy

There is no specific therapy.

Morquio's Syndrome (Galactosamine-6-sulfatase Deficiency Type A; β-Galactosidase Deficiency, Type B) (MPS IV)

Morquio's syndrome is an autosomal recessive disorder that was described initially in 1935 by Morquio (822), who reported the disorder in four Swedish children whose parents were first cousins.

Clinical Features

Patients have serious skeletal defects and coarsening of facial features but normal intelligence. Chest deformities with a pectus carinatum occur. The odontoid process of the axis is malformed, hypoplastic, or absent, which results in atlantoaxial subluxation and cervical cord compression in many patients (823). Joint instability, deafness, and corneal clouding occur.

The diagnosis is based on the severe, characteristic skeletal defects, normal intelligence, and increased excretion of keratan sulfate. Deficiency of one of the two enzymes mentioned firmly establishes the type, since types A and B are clinically indistinguishable.

Therapy

The one form of therapy that must be emphasized is identification and correction of the unstable atlantoaxial joint, which may produce cervical cord compression and thus significant morbidity.

Maroteaux–Lamy Syndrome (Arylsulfatase B or Galactosamine-4-sulfatase Deficiency) (MPS VI)

Maroteaux–Lamy syndrome is an autosomal recessive disorder described initially by Maroteaux and Lamy (824,825) as a Hurler's variant in which intellect is preserved and in which there is increased urinary excretion of dermatan sulfate.

Clinical Features

This is a highly variable disorder, with a spectrum of severity resembling Hurler's at one end and Scheie's disorder at the other. McKusick et al. (810) pointed out that these patients are uniformly short but that Scheie's syndrome patients (MPS I S) are in the normal range for height, and it is this feature that has differentiating value. Intelligence is preserved, which is also an important separating point.

Patients excrete high levels of dermatan sulfate exclusively, and assays of leukocytes, fibroblasts, and amniotic cells in culture show very low levels of arylsulfatase B (*N*-acetylgalactosamine-4-sulfatase) activity.

This enzyme has been mapped to a locus on chromosome 5.

Therapy

An encouraging report in 1984 by Gasper et al. (826) demonstrated that a bone marrow transplant corrected the hereditary enzyme deficiency in a 2-year-old male Siamese cat with advanced MPS VI. Leukocyte arylsulfatase B activity increased 30-fold by 232 days after transplantation. Corneal clouding, mobility, and demeanor all improved, suggesting that similar therapy for a child with this syndrome might be useful. In fact, in 1984 Krivit et al. (827) reported a 13-year-old girl with a severe form of Maroteaux–Lamy syndrome who underwent a successful bone marrow transplant. Arylsulfatase B activity increased to normal levels in peripheral lymphocytes and granulocytes, and it increased from 3% to 16% of the mean normal level at 680 days post-transplant in a liver biopsy sample. Hepatosplenomegaly was substantially decreased, and cardiopulmonary function was normal. Visual acuity and joint mobility also improved, and she returned to school. Thus a bone marrow transplant did provide a source of enzymatically normal cells, which significantly improved this single patient. This therapy will be attempted in future children because of this very positive, exciting result. Clearing of the corneal opacity following keratoplasty was reported in 1985 by Naumann (828).

Sly's Syndrome (β-Glucuronidase Deficiency, MPS VII)

Sly's syndrome is an autosomal recessive disorder with considerable clinical variation between reported patients. It was described by Sly et al. (829) in 1973, and Hall et al. (830) described β-glucuronidase in patient fibroblast cultures as being deficient. In 1975 it was mapped to a locus on chromosome 7 by Grzeschik (831) and Lalley et al. (832) using somatic cell hybrid techniques.

Clinical Features

Patients may develop severe skeletal defects and progressive mental retardation. In their index case, Sly et al. (829) reported a child who at 7 weeks had dysmorphic facies, hepatosplenomegaly, umbilical hernia, a thoracolumbar gibbus, and puffy hands and feet. An anterior chest defect subsequently developed, and bilateral inguinal hernias required surgical reduction. By age 3 years there was obvious mental retardation.

The diagnosis is made on the basis of this clinical phenotype along with minimal increases of dermatan and heparan sulfate in urine. It is confirmed by finding reduced activity of β-glucuronidase in cultured patient fibroblasts or in leukocytes or serum.

Therapy

There is no specific therapy.

DiFerrante's Syndrome (MPS VIII, Glucosamine-6-sulfate Sulfatase Deficiency)

DiFerrante's syndrome is a rare entity that resembles Morquio's and Sanfilippo's syndromes, both clinically and biochemically. The one reported patient was a 5-year-old mentally retarded boy who was short in stature and who had hepatomegaly, mild dysostosis multiplex, odontoid hypoplasia, and a clear cornea (833). He excreted keratan and heparan sulfate. The enzyme glucosamine-6-sulfate sulfatase was deficient in the patient and partially so in both parents, thus showing it was inherited as an autosomal recessive disorder (833).

Mucolipidoses

There are three principal mucolipidoses (designated types I, II, and III) with a spectrum of clinical forms. Their characteristic feature is the storage of mucopolysaccharide, but without the occurrence of mucopolysaccharidiuria. Multiple catabolic, degradative mucopolysaccharide enzymes are deficient within their normal lysosomal site in types II and III because of a loss of a lysosomal recognition signal by lysosomal enzymes, but there is a significant increase in the acidity of these enzymes in extracellular fluid spaces (serum). They are inherited as autosomal recessive disorders.

Clinical Features

Mucolipidosis I (Lipomucopolysaccharidosis)

Mucolipidosis I is characterized by mild Hurler features, moderate mental retardation without mucopolysaccharidiuria, and fibroblast inclusions. Levels of fibroblast lysosomal enzymes are normal rather than the low values reported in mucolipidosis II. Patients develop moderate dwarfism, coarse facies, pectus carinatum, thoracic kyphosis, mental retardation, muscle atrophy, hypotonia, choreoathetosis, inability to walk at puberty, and death in early adulthood.

Mucolipidosis II (I Cell Disease)

Mucolipidosis II has a phenotype similar to that of classic MPS I H, Hurler's disease, but differs from it by an earlier age of onset (in fact, it can be present at birth), by the absence of corneal clouding, and by the lack of mucopolysaccharidiuria. A severe psychomotor retardation develops, and patients usually die by age 6 years.

N-Acetylglucosamine-1-phosphotransferase is absent in type II patient fibroblast lysosomal fractions and reduced in type III patients. It is an enzyme that phosphorylates mannose residues of glycoprotein-lysosomal enzymes, thereby providing a needed signal to recognize binding sites on the lysosome. Absence or deficiency of it would explain the low lysosomal enzyme activities and high serum levels simply as a result of lack of lysosomal uptake of these degradative enzymes. Apparently, types II and III mucolipidoses are allelic disorders. Electron microscopy shows that fibroblast inclusions are dilated lysosomes filled with mucopolysaccharide and membrane; this occurs because the lysosomes lack the enzymes needed to degrade mucopolysaccharide.

Mucolipidosis III (Pseudo-Hurler's Polydystrophy)

In most respects, mucolipidosis III is similar to mucolipidosis II but is less aggressive and less severe in its manifestations.

Patients manifest disease between 2 and 4 years of age, presenting with stiffness of hands and shoulders suggestive of juvenile rheumatoid arthritis. Subsequently, a claw hand, dwarfism, facial coarsening, corneal clouding, and aortic or mitral valve lesions with valve murmurs occur. Progressive mental retardation develops in the early elementary school years. There are characteristic roentgenographic changes of the hips. The disorder is similar to MPS I S or mild forms of MPS VI.

This disorder exhibits the clinical features of an MPS, no mucopolysaccharidiuria, and increased levels of activity of lysosomal enzyme hydrolases in extracellular fluid spaces (serum), with deficiencies of these same enzymes in lysosomal fractions of fibroblasts in cultures. A partial deficiency in *N*-acetylglucosamine-1-phosphotransferase is present in cellular lysosomal fractions, resulting in storage of mucopolysaccharide, as explained under mucolipidosis type II. McKusick (833) has suggested that types II and III represent homozygosity for different mutant genes at the same locus, one that is responsible for a lysosomal recognition marker or receptor for multiple lysosomal enzyme uptake.

Lysosomal enzymes that are reduced within the lysosome and increased in serum include α-L-iduronidase, iduronidate sulfatase, β-glucuronidase, *N*-acetyl-β-hexosaminidase, arylsulfatase A, β-galactosidase, α-mannosidase, and α-L-fucosidase. Activities of acid phosphatase and β-glucosidase are normal. It has been suggested that a two- or three-fold increase in *N*-acetyl-β-hexosaminidase or arylsulfatase A activity in serum is a useful screening procedure for both mucolipidosis II and III.

Fibroblasts from mucolipidosis I and II patients contain inclusions which, under the electron microscope, appear to be enlarged lysosomes containing mucopolysaccharide and membranous whorls.

Therapy

There is no specific therapy. Orthopedic correction of skeletal defects may be useful in selected patients.

FUCOSIDOSIS

The fucosidoses are a group of disorders caused by a defect in the lysosomal enzyme α-L-fucosidase resulting in the storage of glycolipids, glycoproteins, and mucopolysaccharides containing fucose. These disorders are inherited as au-

tosomal recessives, and at least three forms are described clinically. Type I disease begins in early infancy and produces severe mental retardation, occasional hepatosplenomegaly, and a rapidly fatal course. Type II disease begins in the late infantile period and produces mental and motor retardation, skeletal malformations typical of gargoylism, and prominent skin lesions of angiokeratoma corporis diffusum. Type III disease is less aggressive and can continue into adulthood. Severe mental retardation with spasticity and skeletal defects was present in three young adult patients reported by Ikeda et al. (834) in 1984. Rectal biopsy has been used to show neuronal storage material, which is rather specific for the fucosidoses.

α-L-Fucosidase (E.C. 3.2.1.51) is encoded by a single locus on the short arm of chromosome 1 (1p34). In 1985, it was reported that a cDNA was obtained that coded for at least 80% of the mature enzyme (835).

TABLE 5. *Inherited mitochondrial encephalomyopathies*

Alper's syndrome (cerebral poliodystrophy)
Canavan's disease (spongy degeneration of white matter)
Carnitine deficiency syndrome or carnitine palmityltransferase deficiency (long-chain fatty acid oxidation defect)
Kearns–Sayre syndrome (ophthalmoplegia plus ragged red fibers)
Leber's optic atrophy
Leigh's disease (subacute necrotizing encephalopathy)
Mitochondrial encephalomyopathy with lactic acidosis and stroke (MELAS syndrome)
Myoclonus epilepsy with ragged red fibers (Ramsay Hunt syndrome variant) (MERRF syndrome or Fukuhara syndrome)
Menkes' kinky hair disease (trichopoliodystrophy)
Refsum's disease (lipid α-oxidase defect)
Zellweger's syndrome (cerebrohepatorenal syndrome)

MULTIPLE SULFATASE DEFICIENCY

Multiple sulfatase deficiency (MSD) is a rare genetic disorder inherited as an autosomal recessive trait which causes a reduction in the activity of several lysosomal sulfatases, including: arylsulfatase A, B, and C; iduronate-2-sulfate sulfatase; heparan *N*-sulfatase; *N*-acetylgalactosamine-6-sulfate sulfatase; and *N*-acetylglucosamine-6-sulfate sulfatase. These patients also accumulate sulfatides, glycosaminoglycans, sphingolipids, and steroid sulfates in tissues and body fluids. Patients express features of two diseases: late infantile metachromatic leukodystrophy and mucopolysaccharidosis. At least 20 patients have been reported. In 1988, Soong et al. (836) recorded in detail a 9½-year-old girl with short stature, microcephaly, mild facial dysmorphism, dysphagia, retinal degeneration, developmental arrest, and ataxia. Her cultured skin fibroblasts after several passages had a marked reduction in multiple sulfatases (837).

MUSCLE DISEASES

Genetic muscle diseases (i.e., the muscular dystrophies) have been a vigorous area of investigation in recent years. The biochemical genetics of many specific disorders have been solved, and a meaningful start into the molecular genetics of these disorders using recombinant DNA methods has already begun. See refs. 838–895 for more details; also see Chapter 13 in this volume.

Mitochondrial Encephalomyopathies

Rowland (896), Rowland et al. (897), Pavlakis et al. (898), Zeviani et al. (899), and DiMauro et al. (901) have reviewed a controversial, complex, and recently emerging literature and have defined several new inherited syndromes associated with mitochondrial metabolic defects (Table 5).

Petty et al. (901) described the clinical features and biochemical defects in 66 patients with histologically defined mitochondrial myopathies. There was a broad range of symptoms from birth to 68 years, but over 60% had the onset of disease before 20 years of age. Only 19 patients had affected relatives. These investigators defined three separate clinical groups: (i) Fifty-five percent had a combination of progressive external ophthalmoplegia and weakness of their extremities which was produced or exacerbated by exercise; (ii) 18% had only extremity weakness; and (iii) 27% exhibited symptoms of CNS disease, including ataxia, deafness, involuntary movements and seizures, and dementia. Biochemical studies of mitochondrial metabolism was carried out in 33 patients, and defects most commonly involved the mitochondrial respiratory chain localized to complex I (NADH-CoQ reductase) (18 patients) or complex III (ubiquinol-cytochrome c reductase) (nine patients). Of importance is that no clinical syndrome was characteristic of any of the defined mitochondrial biochemical defects. Holt et al. (902) studied muscle mitochondrial DNA in 25 patients, nine of whom had defined deletions of restriction fragments up to 7 kb in length. Leukocyte mitochondrial DNA in these same patients did not show these deletions. They showed that mitochondrial DNA defects can be tissue-specific (heteroplasmy) in humans and are associated with human diseases.

Cytochrome c oxidize deficiency (complex IV) has been associated with several syndromes: (i) fatal infantile mitochondrial myopathy with severe limb weakness, hypotonia, hyporeflexia, lactic acidosis, de Toni–Fanconi–Debre syndrome, and respiratory failure; (ii) a fatal infantile myopathy and hepatopathy in second cousins; (iii) a benign infantile mitochondrial myopathy in a 2-week-old boy with weakness of extremities, hyporeflexia, macroglossia, and lactic acidosis or a benign limb myopathy in adult years; (iv) a Leigh's disease complex characterized by respiratory failure, impaired vision and hearing, ataxia, hypotonia, and psychomotor retardation, along with focal, bilateral, symmetric necrotic lesions extending from thalamus to pons as often seen on CT scans; and (v) Menkes' disease (trichopoliodystrophy), which consists of infantile seizures, psychomotor delay, abnormal hair, fragile bones, and temperature instability with low serum copper and ceruloplasmin levels. ^{31}P-NMR spectroscopy of exercising muscle has been able

to detect high-energy phosphate defects, including an abnormally low phosphocreatine/inorganic phosphate ratio in selected patients (903–907).

Mitochondrial Encephalomyopathy with Lactic Acidosis and Stroke (Melas Syndrome)

At least 11 patients with a syndrome consisting of normal development in early life, with symptoms starting between ages 3 and 11 years, were described by Rowland et al. (897) and Pavlakis et al. (898). These patients were short and had seizures. All patients except one had a stroke-like illness with hemiparesis, hemianopia, or cortical blindness. Nine had hemiparesis or hemianopsia, and six had episodes of cortical blindness. Nine patients developed dementia. Vomiting and sensory neural hearing loss were present in several. Two pairs of siblings were affected. Prominent in their absence were cerebellar deficits, interictal myoclonus, heart block, ophthalmoplegia, and retinal changes. This clinical complex is referred to as "MELAS syndrome," as defined in the section heading above. In 1984, NADH-CoQ reductase (complex I) deficiency was found in one patient with this syndrome. Oxygen uptake by isolated mitochondria with NAD-linked substrate such as pyruvate is low, whereas flavin-linked substrates such as succinate and ascorbate support normal respiration (908).

In 1988 Ichiki et al. (909) measured enzymatic activities of the respiratory chain, as well as the content of immunochemically detectable subunits in NADH-ubiquinone oxidoreductase (complex I), in mitochondria from the skeletal muscles of four patients with the MELAS syndrome. The rotenone-sensitive NADH-cytochrome c reductase activity was extremely reduced, ranging from 0% to 27% of the control value. Montagna et al. (910) emphasized that severe prolonged migrainous symptoms and prolonged status epilepticus are characteristic features of the MELAS syndrome.

A 22-year-old man with the MELAS syndrome and cytochrome c oxidase deficiency was treated with CoQ10 (90 mg/day). There was a reduction of previously elevated plasma lactate, but cerebrospinal fluid lactate did not change (911).

Myoclonus Epilepsy with Ragged Red Fibers (MERRF Syndrome)

Fukuhara et al. (912,913) described a syndrome that was different from the MELAS complex of Rowland et al. (897), but there are similarities. At least 16 patients have now been described with normal early development, myoclonus, and a cerebellar syndrome. Eleven patients had seizures, 11 became demented, and six had hearing loss. Ten of the 16 patients had a positive family history. All patients had myoclonus and ataxia, and none had hemiparesis, hemianopia, or cortical blindness, as did MELAS patients. Twelve patients had an intention tremor. Optic nerve atrophy was present in eight patients. No patient in this group had ophthalmoplegia, pigmentary retinal degeneration, or heart block. The acronym MERRF (myoclonus epilepsy with ragged red fibers) was applied to this group of patients. This syndrome resembles the one described by Ramsay Hunt (914), which consists of dyssynergia cerebellaris myoclonica with myoclonus, tremor, and a cerebellar syndrome. A deficiency of the enzyme CoQ-cytochrome c reductase (complex III) was reported in a single patient with proximal weakness, ataxia, myoclonus, and dementia, presumably a MERRF syndrome patient. The patient had a low oxygen uptake with NADH and flavin-linked substrates but had normal oxygen uptake with ascorbate (915). In 1985 Rosing et al. (916) described a family with familial myoclonic epilepsy associated with a mitochondrial myopathy. The disorder followed a maternal inheritance pattern consistent with a mitochondrial DNA mutation.

In several cases a muscle biopsy has shown (a) ragged red fibers (under the light microscope) and (b) the presence of mitochondrial proliferation of cristae with paracrystalline inclusions (under the electron microscope) (917). Feit et al. (918) reported a patient with progressive myoclonus, ataxia, mild mental retardation, abnormal muscle mitochondria, and exquisite hypersensitivity to anticonvulsant medication with respiratory insufficiency. Both hypoventilation and myoclonus responded favorably to L-5-hydroxytryptophan for a limited period.

A novel 0.4-kb deletion in mitochondrial DNA of a patient with the MERRF syndrome was reported by Noer et al. (919) in 1988. The patient had an identical twin, and both were affected by a similar disorder. Electrophoresis of DNA fragments produced by digestion with BamHl-HpaI or AvaI showed that the deletion was 0.4 kb and was in the ND5 gene, which codes for a protein subunit of the mitochondrial respiratory complex I (NADH-CoQ reductase). A marked mitochondrial respiratory complex I deficiency was found in the skeletal muscle of this patient. Most recently, Shoffner et al demonstrated in 1990 a tRNA mutation in mitochondria which subsequently resulted in a deficiency of the enzyme extochrome oxidase, complex A, (919a).

Kearns–Sayre Syndrome

This entity is usually an acquired disorder, although a positive family history was reported twice (898). Clinical features include ragged red fibers on muscle biopsy, ophthalmoplegia, pigmentary retinal degeneration, heart conductive block, elevated CSF protein (100 mg/dl), and a cerebellar syndrome.

As pointed out by Rowland et al. (897), all three syndromes—MELA, MERRF, and Kearns–Sayre syndrome —have spongy degeneration of the brain, giving them some basis of neuropathologic commonality.

The cause of these syndromes is not clear. Nonmendelian maternal inheritance or an X-linked recessive mendelian trait may be the mode of heredity. All have abnormal ragged red fibers, morphologic mitochondrial abnormalities, and an elevated blood lactate concentration. Thus major biochemical defects in muscle and brain mitochondria are postulated. Several biochemical abnormalities have been associated with (a) ragged red fibers and mitochondrial morphologic defects (including defects in cytochrome c oxidase, cytochrome b and aa_3, cytochrome b–NADH-CoQ reductase complex, or ATPase) and (b) loose coupling of oxidative phosphorylation. A defect in succinate-cytochrome c reductase was found in two siblings with the

MERRF syndrome, and one patient with the MELAS complex had deficiencies of cytochrome c oxidase and pyruvate dehydrogenase (898).

Both X-linked and nonmendelian maternal modes of inheritance may be present in the MELAS syndrome, since both sets of twins reported with it may have had a mother partially affected with the syndrome. One mother is said to have had neurosensory hearing loss and diabetes mellitus, and the other is reported to have had night blindness and an abnormal electrocardiogram. Mendelian inheritance involves the transmission (to successive generations) of DNA contained in genes in the nucleus, but DNA is also contained in mitochondria, where it is responsible for the encoding of certain mitochondrial enzymes. Because almost all mitochondrial DNA is maternally transmitted, a nonmendelian pattern of inheritance is possible in a mitochondrial disorder. These disorders may include a structural membrane mitochondrial defect or an enzyme defect that is coded in the nucleus or by mitochondrial DNA. The latter is becoming better understood because some studies have provided evidence that subunits of respiratory enzyme complexes are encoded solely by mitochondrial DNA (920–922).

In recent years, several types of treatment have been used, including: (a) vitamins K_3 and C for a 19-year-old woman who had muscle weakness since late childhood and who experienced several attacks of lactic acidosis due to a complex III deficiency; and (b) CoQ10 (i.e., ubidecarenone plus CoQ10) therapy (120–150 mg/day) in 12 patients (in two separate reports) with Kearns–Sayre syndrome, causing improvement in strength and a reduction of serum lactate and pyruvate levels (924–926).

Zeviani et al. (927,928) identified large-scale deletions in muscle mitochondrial DNA (mtDNA) in seven of seven patients with Kearns–Sayre syndrome. Moraes et al. (929) reported similar patients in 1989. The reported deletions ranged in size from 2.0 to 7.0 kb and were not restricted to any single region of the mitochondrial genome. In each patient the proportion of mutated genomes ranged from 45% to 75% of total mtDNA. Of the six mitochondrial enzyme activities studied, only cytochrome c oxidase was decreased. Based on their results, these investigators concluded that the Kearn–Sayre syndrome is not an autosomal dominant mutation, but rather a genetically lethal mitochondrial mutation. Their data support the view that this syndrome is a unique disorder that is genetic in origin. Rowland et al. (930) reported an interesting set of twin brothers who met all the diagnostic criteria for the syndrome. This cohort raises the issue that the condition can be inherited as a lethal dominant trait, thus explaining why there is an observed small number of familial cases. They hastened to mention that these twin cases do not exclude the possibility of an acquired cause such as a persistent viral injection of the brain.

Alper's Syndrome (Cerebral Poliodystrophy)

Alper's syndrome occurs in children and is associated with seizures, myoclonus, optic atrophy, and motor and mental retardation with spasticity. There is severe brain atrophy with impressive cortical neuronal loss. There is also neuronal loss in thalamus, basal ganglia, brainstem, and cerebellum (931).

Hemispheric demyelination is prominent, and there may be a spongiform change in white matter because of glial vacuolation. Lactic acid may be elevated in concentration in the CSF and serum. Serum pyruvate dehydrogenase in brain has been reported to be low in some patients (932,933). The presence of large mitochondria in neurons of some patients provides linkage of this syndrome with other described mitochondrial encephalopathies. The mode of inheritance is not clear and could be either X-linked recessive or nonmendelian maternal for the mitochondrial genome. No effective therapy is available, and the syndrome inexorably progresses.

Leigh's Disease (Necrotizing Encephalomyelopathy and Lactic Acidosis)

The clinical features are those of an acute encephalopathy in infants or young children, with loss of mental and motor development, extraocular muscle palsies, nystagmus, ataxia, hypotonia and quadriparesis, seizures, and feeding and breathing difficulties. Acute attacks or the insidious development of the above symptom complex may occur. The spectrum of these features has been widened in recent years to include older children and even adults (934–937). A hallmark of the syndrome is an elevated lactate and pyruvate in CSF and serum, indicating a defect in pyruvate metabolism. The CT brain scan sometimes shows lucent areas in the basal ganglia or thalamus. The neuropathology resembles Wernicke's disease, with necrosis present in (a) the periaqueductal regions of the midbrain, (b) the pons, and (c) the periventricular regions of the pons and medulla. Neuronal loss, necrosis, demyelination, and blood vessel proliferation are prominent in the brainstem, with sparing of the hypothalamus and mamillary bodies; this distinguishes Leigh's disease from Wernicke's disease, in which necrosis is prominent in hypothalamus and mamillary bodies.

Defects in the enzymes pyruvate carboxylase, succinate-cytochrome c reductase, and cytochrome c oxidase (complex IV) have been reported in some patients (938). An inhibitor of the enzyme ATP-thiamine triphosphate transferase has been reported in some Leigh's disease patients, and low levels of thiamine triphosphate in patient brain—but not liver—have been found. The precise defect or family of oxidative disorders for pyruvate metabolism has not been completely described for each of the clinical forms of this syndrome. It is probably inherited as an autosomal recessive disorder and may overlap with other mitochondrial encephalopathies such as Alper's disease, Kearns–Sayre syndrome, and the MELAS and MERRF syndromes (939–945).

Dystonia, Optic Atrophy, Putaminal Atrophy, and Maternal Inheritance Syndrome

In 1985 Novotny et al. (946) described a kindred with features of dystonia, mild mental retardation, short stature, optic atrophy, and myopathic findings. CT brain scans

showed putaminal atrophy. The mode of inheritance was compatible with maternal transmission or cytoplasmic inheritance. Preliminary DNA polymorphism studies of mitochondrial DNA indicated that segregation of patterns on Southern blots was appropriate for those affected.

Menkes' Disease

In 1962 Menkes et al. (947) first recognized and characterized this disease. In 1972 Danks (948) demonstrated that these patients were unable to absorb copper, leading to a severe copper deficiency state.

Danks (948) has estimated the incidence to be as high as 1 in 35,000. This disorder is inherited in an X-linked recessive fashion.

Clinical Features

Many patients are premature, with a birth weight appropriate for gestational age. As neonates they demonstrate poor feeding, poor weight gain, transient jaundice, and instability of body temperature. Seizures, usually myoclonic, develop early, and a progressive delay in psychomotor development occurs.

The hair is normal at birth, but the secondary hair growth lacks luster, is somewhat depigmented, and breaks off easily. Microscopic examination reveals pili torti (trichopoliodystrophy).

Arteriography reveals the vessels to be elongated and tortuous with irregularity of the lumen and sometimes arterial occlusion. Radiologic examination reveals spurs on the metaphyses of long bones and subperiosteal calcifications. Wormian bones appear in the posterior sagittal and lambdoidal sutures. The clinical course is one of progressive neurologic deterioration, with death usually between 6 months and 3 years of age.

The diagnosis is suspected on the basis of the clinical findings and confirmed by the demonstration of low total serum copper and even lower liver copper. Cytochrome oxidase deficiency has been reported in a few patients. This is a copper-dependent enzyme, and reduced activity may be secondary to the copper transport defect.

Pathology

It appears that the absorptive defect is not in the uptake of copper by mucosal cells, but rather in the mucosal intracellular transport or in the transport of copper across the mucosal cell serosal membrane.

The main pathologic findings are in the brain and consist of extensive neuronal degeneration and gliosis. The arteries are fragmented, with splitting of the internal elastic lamina and intimal proliferation; narrowing and occlusion also occur. Structurally abnormal mitochondria are found on muscle biopsy, along with decreased activity of cytochromes a and a_3 in brain, muscle, and liver. The disease is thus a member of the mitochondrial encephalomyopathies related to copper metabolism.

Therapy

The present treatment regimen is parenteral copper administration, which must be started early to prevent organ damage. Although this may help the nonneurologic aspects of the disease, it is not clear if the neurologic findings are altered.

Leber's Disease

This neuroretinal disorder was initially described by Leber in 1871. A loss of vision occurs in males during early adult years, accompanied by associated optic neuropathy and optic atrophy. The mode of inheritance is not clear, but an X-linked recessive disorder or a maternal form of inheritance has been suggested. Putaminal lesions have been reported in patients with dystonia. Novotny et al. (949) have reported eight members of a family with Leber's disease. Fourteen persons had a progressive, generalized dystonia thought to be the result of striatal degeneration as shown on CT scans. Novotny et al. (949) and Holt et al. (950) suggested the mode of inheritance to be maternal, with a mitochondrial DNA transfer of disease from carrier mothers to their sons. Novotny et al. (949) and Holt et al. (950) studied RFLPs of mitochondrial DNA from these affected persons and could not detect an associated linkage of a fragment pattern with presence of disease. It has been theorized that the disease is due to an inborn error of cyanide metabolism, and therefore the mitochondrial matrix enzyme thiosulfate:cyanide sulfurtransferase (Rhodanese) was studied. This enzyme detoxifies cyanide by converting it to thiocyanate. Pallini et al. (951) found no difference in enzyme activity in leukocytes from control subjects and patients with Leber's disease. Wallace et al. (952) identified a mitochondrial DNA replacement mutation that correlated with this disease in multiple families. This mutation converted a highly conserved arginine to a histidine at codon 340 in the NADH dehydrogenase subunit 4 gene and eliminated an SFani restriction enzyme site, thereby providing a diagnostic test. Thus Leber's optic atrophy is due to a mitochondrial gene defect maternally inherited in these families.

In 1989 Singh et al. (953) reported that a specific point mutation in mitochondrial DNA is the cause of Leber's optic atrophy.

Fumarase Deficiency

In 1986 Zinn et al. (954) reported that fumarase deficiency is a cause of mitochondrial encephalopathy. They described a male infant with failure to thrive, developmental delay, hypotonia, and cerebral atrophy with lactic and pyruvic acidemia and fumaric aciduria. The patient died at 8 months of age. Skeletal muscle mitochondria had selective defects in the oxidation of glutamate and succinate, and liver mitochondria oxidized these and other substrates normally. Fumarase (E.C. 4.2.1.2) activity was almost entirely absent in both liver and skeletal muscle mitochondria. Fumarase activity was also very low in homogenates of liver tissue and skeletal muscle, indicating a deficiency of both mitochondrial and cytosolic fumarases. Organ differences

in the intramitochondrial accumulation of furamate may have been responsible for the selective oxidative defects in skeletal muscle mitochondria but not in liver mitochondria.

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THE WHITE HOUSE

WASHINGTON

September 9, 1991

Dear Dr. Rosenberg: Roger

Thank you for sending a copy of your chapter on genetic neurological diseases from your new book. I did indeed find the chapter interesting and have passed it along to my staff in OSTP's Life Sciences office for their review.

I appreciate your thinking of me. My best wishes,

Sincerely,

D. Allan Bromley
The Assistant to the President
for
Science and Technology

Roger N. Rosenberg, M.D.
Department of Neurology
Southwestern Medical School
The University of Texas at Dallas
5323 Harry Hines Blvd.
Dallas, Texas 75235-9036

"CORRESPONDENCE TRACKING"

TYPE: INFORMATION DOCUMENT NUMBER: 9124216
ORIGINATOR: 02 STATUS C DIRECTORATE STATUS

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FROM: RIPLEY, S. Dillon: SMITHSONIAN INSTITIUTE

TO: DR. D.A. BROMLEY

DATE OF
CORRESPONDENCE: 08/20/91

SUBJECT: RE: DR. BROMLEY'S LETTER CONCERNING THE OIL WELL FIRES.

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DIRECTORATE ASSIGNED:

STAFF ASSIGNED:

ACTION REQUIRED:

STAFF ACTION:

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SENDER'S DUE DATE:

OSTP DUE DATE:

STAFF DUE DATE

DATE COMPLETED:

DATE COMPLETED/DEPT:

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COPIES TO: D. Allan Bromley
LIFE SCIENCES
ENVIRONMENT

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WHITE HOUSE TRACKING #:

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REMARKS:

OSTP RECEIVED: 09/27/91

FILE: P-LIFE SCIENCES

DEPT RECEIVED:

4216

NHB Room 336
SMITHSONIAN INSTITUTION
Washington, D.C. 20560
U.S.A.

20 August 1991

The Honorable Allan Bromley
Chairman
Office of Science and Technology Policy
for the President
The White House
Washington, D.C. 20500

Dear Alan,

Thank you so much for your kind and important letter regarding the oil fires in Kuwait. I appreciate it very much, having received it, and also enjoy your delightfully constructed letter in itself. With regard to a minor item, I, too, hope very much that it may be possible to achieve a reunion of the Dissenters in Washington during the fall and winter season. The last one that I attempted to attend, briefly, was organized in connection with a visit of Bart Giamatti, to the Four Seasons Hotel, and it was a delight to have a brief glimpse of old friends.

Regarding the oil fires, I can state that the Darwin Scientific Foundation, of which I am Chairman, has just played host to an interesting group of mostly Arab participants in Boston, on this subject. Delegates came from Japan and France as well as the Middle East, and the general consensus appeared to be somewhat more pessimistic and different from that expressed in your letter. Perhaps we (in the USA) have underestimated the long-term Chernobyl-like effects of such a monumental event. I know that everyone is very worried about the recent volcanic eruption in the Philippines, which, of course, hits a bit more close to home to us with our important investments and history of participation in Philippine affiars. However, it is high time that we made ourselves aware of the extraordinarily different situation in the Middle East, where pressures of the oil in itself are so severe - rather like a huge multiple of Artesian well pressures, so that oil erupted in flames or burning, achieves an aerosol-like spray effect, covering everything with minute quantities of high pressure fragments of oil.

People's innards, lungs and other ingested sources,

will surely be heavily contaminated over the long run, with innumerable side effects, I suspect. I do hope that this is all being taken into account at the present time, although it may be of less interest to the Administration in contrast to the immense pressures generated in politics and other human events at the moment. So, we shall see, but it is wise to be alerted and to keep tabs on matters once we can anticipate that they will have achieved such a mega-effect. If I can be of any assistance or otherwise, through my personal experience, I, of course, would be glad to at least be on your back list.

With warm regards, I am,

Always sincerely yours,

Dillon

S. Dillon Ripley
Secretary Emeritus

"CORRESPONDENCE TRACKING"

TYPE: ACTION DOCUMENT NUMBER: 9123901
ORIGINATOR: 02 STATUS I DIRECTORATE STATUS

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FROM: SINCLAIR, Rolf M.: AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

TO: DR. D.A. BROMLEY

DATE OF CORRESPONDENCE: 08/30/91

SUBJECT: RE: THE PROPOSAL THAT WOULD ELIMINATE THE PARTICIPATION BY GOVERNMENT-EMPLOYED SCIENTISTS IN THE AFFAIRS OF THEIR PROFESSIONAL SOCIETIES. [FEDERAL REGISTER 56, #141]

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DIRECTORATE ASSIGNED: LIFE SCIENCES

STAFF ASSIGNED:

ACTION REQUIRED: AS NECESSARY

STAFF ACTION:

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SENDER'S DUE DATE:

OSTP DUE DATE: 09/19/91 STAFF DUE DATE

DATE COMPLETED: DATE COMPLETED/DEPT:

****

COPIES TO: D. Allan Bromley

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WHITE HOUSE TRACKING #: CONTACT PERSON:

PHONE: EXT:

REMARKS:

OSTP RECEIVED: 09/05/91 FILE: P-LIFE SCIENCES-MISCONDUCT

DEPT RECEIVED:

3901

American Association
for the Advancement of Science

SECTION ON PHYSICS—B
ROLF M. SINCLAIR, Secretary

PHYSICS DIVISION
NATIONAL SCIENCE FOUNDATION
WASHINGTON, D.C. 20550
(202) 357-7997

August 30, 1991

Dr. D. Allan Bromley
Assistant to the President
for Science and Technology
Room 358,
Old Executive Office Building
Washington, DC 20506

Dear Allan:

There is a proposal afoot that would eliminate the participation by government-employed scientists in the affairs of their professional societies. [Federal Register 56, #141 (Tuesday, July 23, 1991), pp. 33778-33815; I enclose Section 2635.806, pp. 33811-12].

I find this short-sighted in the extreme. This would reduce our effectiveness in the scientific community, and discourage us from both accepting professional recognition and doing our share of the work in the societies. I myself have accepted from time to time tasks within the American Physical Society and the American Association for the Advancement of Science when asked. I feel it would have been arrogant of me to refuse to do my share of the work.

My colleagues and I spend, on the average, very little time serving on society committees or as officers. But by doing so we improve our credibility with other scientists. They see us as not "just administrators", but also as working scientists. The next time we call them on NSF business, our task is easier.

These tasks we do for professional societies cannot be done "after hours". By their nature they can only be done effectively from our offices. It would be counterproductive for the Government to decide that this is inappropriate. Also, we do bring to the societies unique experiences and viewpoints that help the societies in their task.

Consider the use by the government of scientists in academia, national laboratories, and industry. We ask them to serve on committees and panels with only nominal recompense, and to supply us with detailed reviews, and we get close to 100% cooperation. This is a tremendous use of their time. The scientists and institutions involved see this as a normal responsibility, and in their interest to accept these tasks. How would the government operate if they all refused these duties on narrow grounds of "inappropriateness"? The Government should similarly allow its office hours to be used in the reverse direction.

I am sure that customary participation in the affairs of professional societies can be considered a normal activity for government scientists, without requiring extraordinary justification for each case. It is easy to guard against occasional misuse and abuse and real (or virtual) conflicts-of-interest.

Sincerely yours,

Rolf

Rolf M. Sinclair

Schedule under 5 U.S.C. 5313, as in effect on January 1 of such calendar year. Employees should consult the regulations implementing this limitation, which are contained in §§ 2636.301 through 2636.304 of this subchapter.

Note: In addition to the 15 percent limitation on outside earned income, covered noncareer employees are prohibited from receiving any compensation for: practicing a profession which involves a fiduciary relationship; affiliating with or being employed by a firm or other entity which provides professional services involving a fiduciary relationship; serving as an officer or member of the board of any association, corporation or other entity; or teaching without prior approval. Implementing regulations are contained in §§ 2636.305 through 2636.307 of this subchapter.

(c) *Definitions.* For purpose of this section:

(1) *Outside earned income* has the meaning set forth in § 2636.303(b) of this subchapter, except that paragraph (b)(8) of that section shall not apply.

(2) *Presidential appointee to a full-time noncareer position* means any employee who is appointed by the President to a full-time position described in 5 U.S.C. 5312 through 5317 or to a position that, by statute or as a matter of practice, is filled by presidential appointment, other than:

(i) A position filed under the authority of 3 U.S.C. 105 or 3 U.S.C. 107(a) for which the rate of basic pay is less than that for GS–9, step 1 of the General Schedule;

(ii) A position, within a White House operating unit, that is designated as not normally subject to change as a result of a Presidential transition;

(iii) A position within the uniformed services; or

(iv) A position held by a member of the foreign service which does not require advice and consent of the Senate.

Example 1: A career Department of Justice employee who is detailed to a policymaking position in the White House Office that is ordinarily filled by a noncareer employee is not a Presidential appointee to a full-time noncareer position.

Example 2: A Department of Energy employee appointed under § 213.3301 of this title to a Schedule C position is appointed by the agency and, thus, is not a presidential appointee to a full-time noncareer position.

§ 2635.805 Service as an expert witness.

(a) *Restriction.* An employee shall not serve as an expert witness, with or without compensation, in any proceeding before a court or agency of the United States in which the United States is a party or has a direct and substantial interest, unless the employee's participation is authorized by the agency under paragraph (c) of this section as in the interest of the Government. Except as provided in paragraph (b) of this section, this restriction shall only apply to a special Government employee if he has participated as an employee or special Government employee in the particular proceeding or in the particular matter that is the subject of the proceeding.

(b) *Additional restriction applicable in certain special Government employees.* (1) In addition to the restriction described in paragraph (a) of this section, a special Government employee described in paragraph (b)(2) of this section shall not serve as an expert witness, with or without compensation, in any proceeding before a court or agency of the United States in which his employing agency is a party or has a direct and substantial interest, unless the employee's participation is authorized by the agency under paragraph (c) of this section as in the interest of the Government.

(2) The restriction in paragraph (b)(1) of this section shall apply to a special Government employee who:

(i) Is appointed by the President;

(ii) Serves on a commission established by statute; or

(iii) has served or is expected to serve for more than 60 days in a period of 365 consecutive days.

(c) *Authorization to serve as an expert witness.* Authorization to serve as an expert witness may be given by the designated agency ethics official of the agency in which the employee serves when, after consultation with the agency representing the Government in the proceeding or, if the Government is not a party, with the agency with the most direct and substantial interest in the matter, the designated agency ethics official determines that the employee's service as an expert witness is in the interest of the Government.

§ 2635.806 Participation in professional associations.

Employees are encouraged to participate in the activities of professional associations and similar entities organized to enhance the skills and abilities of their members. Employees may participate through membership in, and may serve as officers of, such organizations subject to the limitations contained in this part and consistent with paragraphs (a) through (c) of this section. Nothing in this section prohibits an agency from designating an employee to serve in his official capacity as its official liaison to a particular organization in which the agency has a specific interest.

(a) *Participation in substantive programs.* An employee may use official time to attend or otherwise to participate in a substantive program sponsored by a professional association or similar organization when authorized by his supervisor on the basis of a determination that the substantive content of the program relates to the performance of the employee's official duties and that the employee's participation is in the interest of the Government.

(b) *Participation in internal or business affairs.* Unless an employee is specifically authorized by statute, executive order or regulation to serve in an official capacity as an officer of a professional association or similar organization, he may not use official time to administer the internal affairs of any such organization or to carry out its business affairs, or to attend or to participate in meetings or events that primarily serve those purposes. Nothing in this paragraph prohibits an employee from using official time to participate in a substantive program that he is authorized to attend under paragraph (a) of this section if only a small portion of the program is devoted to the internal or business affairs of the organization, or from occasionally using a Government telephone for the conduct of organizational affairs if such use is consistent with the requirements of 41 CFR 201.38.007–1.

(c) *Conflict of interest considerations.* An employee who is not simply a member but who serves, other than in his official capacity, as an officer, director, trustee or employee of a professional association or similar organization is prohibited, in accordance with 18 U.S.C. 208(a) and the standards set forth in subpart D of this part, from participating in his official capacity in any particular matter that has a direct and predictable effect on a financial interest of that organization.

Example 1: An attorney with the Defense Logistics Agency is treasurer of the Federal Bar Association and serves on the association's election committee. She may not use DLA wordprocessing or photocopy equipment nor the Government mails to produce and mail bills for association dues or ballots for the election of officers.

Example 2: An accountant employed by the Defense Contract Audit Agency is a member of the Association of Government Accountants. She has been directed by her supervisor to participate in a panel discussion of cost accounting principles to take place at a seminar sponsored by the association. Because she is authorized to participate in her official capacity, she may participate on official time and use her title in

connection with the panel presentation. In addition, she may use her office word processor to prepare her remarks as a panel member.

Example 3: An attorney employed by the Department of Housing and Urban Development serves as an officer of her local bar association. While she must take annual leave to attend a meeting of the association's officers or to run the internal affairs of the association, she may be authorized to use official time to attend an association meeting on problems of the homeless where her participation is determined to be related to her official duties and in the interest of the Government. To improve her professional skills, she may also be authorized to use official time to attend a seminar on professional conduct sponsored by the association. In the absence of a waiver issued under 18 U.S.C. 208(b), however, she may not direct a subordinate to speak at a seminar sponsored by the association for which an attendance fee is to be charged nor could she sign a training form obligating HUD funds to pay the fee for a subordinate to attend the seminar.

§ 2635.807 Teaching, speaking, and writing.

(a) *Compensation for teaching, speaking or writing.* Except as permitted by paragraph (a)(2) of this section, an employee, including a special Government employee, shall not receive compensation from any source other than the Government for teaching, speaking, or writing that relates to the employee's official duties.

(1) *Definitions.* For purposes of this paragraph:

(i) Teaching, speaking, or writing *relates to the employee's official duties* if:

(A) The activity is undertaken as part of the employee's official duties;

(B) The invitation to engage in the activity was extended to the employee because of his official position;

(C) The invitation to engage in the activity was extended to the employee, directly or indirectly, by a person who has interests that may be substantially affected by performance or nonperformance of the employee's official duties;

(D) The information conveyed through the activity draws substantially on ideas or official data that are nonpublic information as defined in § 2635.703(b) of this part; or

(E) The subject matter focuses specifically on the employee's official duties or on the responsibilities, programs, or operations of the employee's agency. A subject matter focuses specifically on agency responsibilities, programs, or operations if:

(1) In the case of a noncareer employee as defined in § 2636.303(a) of this subchapter, it deals in significant part with the general subject matter area, industry, or economic sector primarily affected by the programs and operations of his agency;

(2) In the case of a special Government employee, it deals in significant part with particular matters to which he is or has been assigned as a special Government employee; or

(3) In the case of any other employee, it deals in significant part with particular matters to which he is or has been assigned as an employee of the agency, or with any planned or announced policy of the agency, or with any program or operation of the agency.

Any component of a department designated as a separate agency under § 2635.203(a) of this part shall be considered a separate agency for purposes of this paragraph. No such designation shall be effective as to the head of any such separate agency or as to department-level employees.

Example 1: On his own time, a National Highway Traffic Safety Administration employee prepares a consumer's guide to purchasing a safe automobile that focuses on automobile crash worthiness statistics gathered and made public by NHTSA. He may not receive royalties or any other form of compensation for the guide. The guide focuses specifically on responsibilities and programs of NHTSA.

Example 2: A consultant is employed as a special Government employee by the Department of State for the purpose of providing advice and assistance in multilateral treaty negotiations relating to scientific research on the continent of Antarctica. A speech given by the special Government employee on the subject of scientific advances stemming from research in the Antarctic is not related to his official duties. However, a speech on the status of the treaty negotiations would be related to his official duties. He may receive compensation for the former, but not for the latter. (Note that special Government employees are not subject to the honorarium prohibition on receipt of compensation for speeches, which is implemented in §§ 2636.201 through 2636.205 of this subchapter).

Example 3: A philosophical article on theories of sentencing in felony cases written by a noncareer Senior Executive Service employee of the Department of Justice would be related to his official duties.

(ii) *Compensation* includes any form of consideration, remuneration or income, including royalties, given for or in connection with the employee's teaching, speaking or writing activities. Unless accepted under specific statutory authority, such as 31 U.S.C. 1353, 5 U.S.C. 4111, or an agency gift acceptance statute, it includes transportation, lodgings and meals, whether provided in kind, by purchase of a ticket, by payment in advance or by reimbursement after the expense has been incurred. It does not include:

(A) Items offered by any source that could be accepted from a prohibited source under subpart B of this subpart;

(B) Meals or other incidents of attendance such as waiver of attendance fees or course materials furnished as part of the event at which the teaching or speaking takes place; or

(C) Copies of books or of publications containing articles, reprints of articles, tapes of speeches, and similar items that provide a record of the teaching, speaking, or writing activity.

(iii) *Receive* means that there is actual or constructive receipt of the compensation by the employee so that the employee has the right to exercise dominion and control over the compensation and to direct its subsequent use. Compensation received by an employee includes compensation which is:

(A) Paid to another person, including a charitable organization, on the basis of designation, recommendation, or other specification by the employee; or

(B) Paid with the employee's knowledge and acquiescence to his parent, sibling, spouse, child, or dependent relative.

(2) *Exception for teaching certain courses.* Notwithstanding that the activity would relate to his official duties under paragraphs (a)(1)(i) (B) or (E) of this section, an employee may accept compensation for teaching a course requiring multiple presentions by the employee if the course is offered as part of:

(i) The regularly established curriculum of:

(A) An institution of higher education as defined at 20 U.S.C. 1141(a);

(B) An elementary school as defined at 20 U.S.C. 2891(8); or

(C) A secondary school as defined at 20 U.S.C. 2891(21); or

(ii) A program of education or training sponsored and funded by the Federal government or by a State or local government which is not offered by an entity described in paragraph (a)(2)(i) of this section.

Example 1: An employee of the Cost Accounting Standards Board who teaches an advanced accounting course as part of the regular business school curriculum of an accredited university may receive compensation for teaching the course even though one or more of the twenty classes comprising the course deals with cost accounting principles applicable to contracts with the Government. Moreover, his receipt of a salary or other compensation for teaching this course does not violate the honorarium prohibition on receipt of compensation for any speech, which is

"CORRESPONDENCE TRACKING"

TYPE: INFORMATION DOCUMENT NUMBER: 9123595
ORIGINATOR: 02 STATUS C DIRECTORATE STATUS

****

FROM: BUMPASS, Larry: UNIVERSITY OF WISCONSIN - MADISON

TO: DR. D.A. BROMLEY

DATE OF CORRESPONDENCE: 08/20/91

SUBJECT: LETTER TO LOUIS W. SULLIVAN REGARDING HIS DECISION TO CANCEL THE AMERICAN TEENAGE STUDY AND TO ASK THAT HE RECONSIDER THIS DECISION.

****

DIRECTORATE ASSIGNED:

STAFF ASSIGNED:

ACTION REQUIRED:

STAFF ACTION:

****

SENDER'S DUE DATE:

OSTP DUE DATE:

STAFF DUE DATE

DATE COMPLETED:

DATE COMPLETED/DEPT:

****

COPIES TO: D. Allan Bromley
LIFE SCIENCES

****

WHITE HOUSE TRACKING #:

CONTACT PERSON:

PHONE:

EXT:

REMARKS:

OSTP RECEIVED: 08/26/91

FILE: P-LIFE SCIENCES

DEPT RECEIVED:

3595

University of Wisconsin—Madison

Center for Demography and Ecology
4412 Social Science Building
1180 Observatory Drive
Madison, Wisconsin 53706-1393 U.S.A.
Telephone (608) 262-2182
FAX (608) 262-8400
BITNET NAME@WISCSSC

August 20, 1991

Dr. Louis W. Sullivan
Secretary, Department of Health and Human Services
200 Independence Avenue, SW
Washington, D.C. 20201

Dear Secretary Sullivan:

I am writing to strongly object to your decision to cancel the American Teenage Study and to ask that you reconsider this decision. The need for this study has never been questioned on either scientific or public health grounds. On the contrary, this study had been peer reviewed, approved and recommended at all levels of the Public Health Service, including the NICHD Advisory Council, the Director of NIH, and the Assistant Secretary for Health. What has happened to the assurances that were reportedly given to the new director, Bernadine Healy, concerning the preservation of the independence of NIH from political pressures?

Experts from the biomedical, science, and public health fields agree that new social and behavioral research on sexual behavior is necessary for addressing prevention strategies for unplanned teenage pregnancies and sexually transmitted diseases, including AIDS. Numerous scientific panels have called for the very kind of research reflected in the American Teenage Study. Opponents of this research choose to ignore the nation's public health interest (and accumulated research experience) when they argue that sex is too controversial to study.

As essential as I think the American Teenage Study is, your cancellation of this study raises even graver concerns about the integrity of the scientific funding process and, in turn, the health of the nation's scientific infrastructure. If political interests are going to be allowed to overrule good science, we are in serious trouble indeed. It is certain that there will be other pressure groups--from animal rights activists to those opposed to the frontiers of biotechnology. Are vocal minorities to be given a veto over properly reviewed science?

I currently serve on an NIH peer review committee, and have chaired other such NIH committees in the past. As you know, morale in the scientific community is already impaired. Those of us who conduct NIH funded research, and who devote costly time to the peer review process, feel doubly threatened by this dangerous precedent. I implore you to take the lead in nipping this process in the bud by reversing your decision and preserving the integrity of the scientific funding process.

Sincerely,

Larry Bumpass
N.B. Ryder Professor of Sociology

copy:
D. Allan Bromley, Assistant to the President for Science and Technology
Bernadine P. Healy, Director, National Institutes of Health

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20506

September 16, 1991

MEMORANDUM FOR ALLAN BROMLEY

FROM: **D.A. HENDERSON**

SUBJECT: **TEENAGE STUDY**

Cancellation of this project is to be greatly deplored. As you may know, both Healy and Mason had reviewed its content, designs and provisions with care before agreeing to its funding. I have since talked informally with Mason about it. He is as chagrined as anyone. Basically, the genesis was a question about it to Sullivan (on a talk show, I believe), worded in such a way as to cast it in a poor light. Sullivan indicated he would look into it and implied he would stop it. This he did.

Mason had previously briefed Sullivan on the study during their trip to Africa and thought it had the Secretary's blessing. Whether the Secretary misunderstood or forgot about it or had second thoughts is unclear. The bottom line, however, is that no one sees a way to alter the decision now absent an even more major stir.

"CORRESPONDENCE TRACKING"

TYPE: INFORMATION DOCUMENT NUMBER: 9122958
ORIGINATOR: 02 STATUS C DIRECTORATE STATUS

****

FROM: ROSENBERG, Roger N.: AMERICAN ACADEMY OF NEUROLOGY

TO: DR. D.A. BROMLEY

DATE OF
CORRESPONDENCE: 07/22/91

SUBJECT: RE: MAXIMIZING THE HUMAN POTENTIAL, DECADE OF THE BRAIN REPORT

****

DIRECTORATE ASSIGNED:

STAFF ASSIGNED:

ACTION REQUIRED:

STAFF ACTION:

****

SENDER'S DUE DATE:

OSTP DUE DATE:

STAFF DUE DATE

DATE COMPLETED:

DATE COMPLETED/DEPT:

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COPIES TO: D. Allan Bromley
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WHITE HOUSE TRACKING #:

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PHONE: EXT:

REMARKS:

CLOSED

OSTP RECEIVED: 07/29/91

FILE: P-LIFE SCIENCES*FCCSET

DEPT RECEIVED:

2458

AMERICAN ACADEMY OF NEUROLOGY®

RECEIVED
91 JUL 29 P3:55

July 22, 1991

Office of the President
ROGER N. ROSENBERG, M.D.
University of Texas
Health Sciences Center
5323 Harry Hines Blvd. - J3 - 102
Dallas, Texas 75235
(214) 688-3703

D. Allan Bromley, Ph. D.
Assistant to the President
for Science and Technology
Director, Office of Science
and Technology Policy
The White House
Washington, D.C.

Dear Dr. Bromley:

Thank you for your recent letter and for your kind words about the Rosenbergs and medicine. It was a great pleasure to meet you at the American Academy of Neurology meeting in Boston last April and thank you for your encouraging words about moving forward with the Decade of the Brain. Your book Maximizing the Human Potential is an inspiring document as to what we can now do in the neurosciences for all mankind. I hope it will be possible for OSTP to move ahead with an agenda and recommend funding in the President's Budget so these goals can be realized. I hope what you have been able to accomplish for physics with the superconducting supercollider and for basic biomedical science with the human genome project, you can now do for the neurosciences with a major initiative encompassing basic neuroscience and the major neurological diseases. I enclose a recent chapter I authored which I hope will stimulate you along these lines.

Again, many thanks for your kind letter and all good wishes to you. I remain

Sincerely yours,

Roger N. Rosenberg.

Roger N. Rosenberg, M.D.

RNR:ns
Enclosure

cc: Mr. Jan Kolehmainen
Jack P. Whisnant, M.D.
Sid Gilman, M.D.
Robert B. Daroff, M.D.

To Dr. Brodley -
With my best
wishes,
Roger Brodley

Comprehensive Neurology,
edited by Roger N. Rosenberg,
Raven Press, Ltd., New York © 1991.

CHAPTER 1

Teratology of the Central Nervous System

Robert C. Woody and Michael E. Blaw

The purpose of this chapter is to develop an organized picture of central nervous system development in both normal and abnormal conditions. To accomplish this, three major topics are presented. The first describes the basic principles of organogenesis. The second discusses normal and abnormal morphogenesis of the central nervous system. Factors which govern normal neurogenesis as well as the major morphologic and histologic processes are emphasized. A description of the most common or illustrative disturbances of central nervous system formation is included. In the final section we describe the role of environmental teratogens; in addition, we discuss general principles of teratology and specific chemical, viral, and other environmental agents which have a strong association with abnormal brain formation.

Recognizing the complexity of normal central nervous system formation and its risk for environmentally induced disruptions, the science of teratology has expanded dramatically. Molecular biology has provided elegant tools for exploring these topics. In addition to this, an increasing awareness that gross neurologic malformations probably represent only a small portion of total errors in neurogenesis in humans provides an unending challenge for research into the teratology of the nervous system (40,41).

DEVELOPMENTAL NEUROBIOLOGY

In keeping with the pronounced shift of science toward molecular and cellular biology, the study of neuroembryology now revolves around sophisticated scientific methodologies of molecular genetics and neurophysiology. These approaches have permitted the unraveling of some of the most basic processes of normal and abnormal formation of the nervous system. Victor Hamburger (79) recently wrote that modern developmental neurobiology is the result of the convergence of two different conceptual and methodologic frames of reference: ". . . the histogenetic tradition, was descriptive and became sophisticated through refined technology. The other, experimental neurobiology, was cross-analytical and experimental . . ." Whereas detailed histologic studies of His, Ramon y Cajal, and others in the distant past provided the foundation for the extended investigations of Spemann (220), Sauer (202), and others in the first half of this century, the study of developmental aspects of oncogenes, neuropeptides, and other neuronal and glial growth factors dominate neuroembryology today. The impact of this evolution was predicted by Roth (191):

> . . . the enormous importance of finding a true biochemistry for form cannot be overstated. Even the first trickle of such knowledge would transform the entire field of teratogenesis from purely empirical to predictive. Subsequent information would have important ramifications for neurobiology, neuron circuitry, and ultimately, embryonic morphogenesis in its entirety. Only when such information becomes available will the development of form be explicable in terms of gene activity.

This chapter stresses the recent and concerted shift in neuroscience toward the molecular biologic basis for normal and abnormal formation of the nervous system, and it also stresses the way in which environmental teratogens adversely influence neurogenesis.

Concepts of Cellular Behavior

The concept of cellular behavior, both in the individual cell and in aggregate cells, is fundamental to neuroembryology. It has become increasingly apparent that the behavior of cells derives in part from the permissions and limitations established by cell membranes. Through the cell membrane, complex intracellular interactions develop, eventually translating into division, growth, tissue recognition, and, ultimately, morphogenesis. Despite the number of complex interactions eventually required, a simple concept proposed by Bernfield (14) is useful: "All morphogenesis involves a limited repertoire of cellular behavior." These behaviors include changes in cell shape, cell recognition and adhesion, cell differentiation and proliferation, and cell

R. C. Woody: Departments of Pediatrics, Neurology, and Psychiatry, University of Maryland School of Medicine, Baltimore, Maryland 21201.

M. E. Blaw: Departments of Pediatrics and Neurology, University of Texas, Southwestern Medical Center, Dallas, Texas 75235.

Therapy

Frequent feedings to avoid hypoglycemia are recommended. Diazoxide has been useful to increase glycogenolysis, depress insulin release, and inhibit glucose uptake by the liver. A surgical approach may be necessary in some patients to produce a portacaval shunt to reduce variceal bleeding, reduce liver size, and reduce serum lipids and uric acid. Some patients have had a meaningful improvement in growth postsurgically (591). Schwenk and Haymond (592) concluded that the minimal nocturnal nasogastric infusion rate of carbohydrate needed to maintain plasma glucose concentrations and minimize organic acidemia is approximately 8–9 mg/kg/min.

Type II Glycogen Storage Disease (α-1,4-Glucosidase Deficiency, Acid Maltase Deficiency; Pompe's Disease)

Pompe's disease is an autosomal recessive disorder caused by a defect in the enzyme α-1,4-glucosidase; the incidence of this disease is 1 in 50,000.

Clinical Features

The disease has been described in infantile, early childhood, and adult forms. The infantile type begins in the first year of life with muscular atrophy, hypotonia, hyporeflexia, cardiomegaly, and heart failure. An early childhood type progresses more slowly, and muscle atrophy and weakness are less severe, but eventually all patients expire by age 20 from severe atrophy and weakness leading to aspiration pneumonia. The adult variety presents with a slowly evolving proximal myopathy with weakness and atrophy. Glycogen storage occurs in skeletal muscle, heart, tongue, and liver. Motor neurons present in cranial nuclei and anterior horn cells of the spinal cord are also involved in storage of glycogen; this results in the dysfunction and demise of these motor neurons, producing a denervating neurogenic process.

Danon et al. (594) reported two brothers with a gait disorder due to acid maltase (AM) deficiency. Their asymptomatic mother had AM activity in the homozygote range. The asymptomatic mother may be homozygous for the adult-onset variant by AM disease. Alternatively, either the mother or the children may be genetic compounds for both the childhood and adult form of disease.

Genetics

This is an autosomal recessive disorder with glycogen storage resulting from reduced activity of the enzyme α-1,4-glucosidase. Fibroblasts obtained from amniocentesis can be cultured and assayed for enzyme activity and can provide a prenatal diagnosis (595). Miranda et al. (596) examined immunocytochemically infantile- and adult-onset muscle cells for AM enzyme activity. Adult muscle cultures showed normal intracellular localization of enzyme activity, and infantile patient cultures showed no activity. Adult-type patients show about 20% enzyme activity compared with controls.

Therapy

There is no specific therapy available; however, two reports have found clinical improvement in two adult patients on a high-protein diet (597,598).

Type III Glycogen Storage Disease (Amylo-1,6-glucosidase or Debrancher Deficiency; Cori's Disease)

Cori's disease is an autosomal recessive disorder with an incidence of 1 in 50,000, caused by a defect in the enzyme amylo-1,6-glucosidase or debrancher enzyme. It was Cori (599) in 1954 who showed that the form of glycogen stored was an abnormal type with very short outer branches.

A 42-year-old man with adult-onset type 3 glycogenosis developed a gradually progressive polyneuropathy with markedly reduced activity of muscle amylo-1,6-glucosidase and glycogen accumulation within all elements of biopsied sural nerve, including axons, as demonstrated by electron microscopy (600).

Clinical Features

Patients develop hepatomegaly early in life; eventually (in early adulthood), muscle atrophy and weakness develop, along with cardiomegaly due to glycogen storage. Occasionally, hypoglycemia and seizures develop. Serum lipids may become elevated, but serum urate levels are usually normal (601).

Genetics

This is an autosomal recessive disorder in which glycogen is significantly stored in skeletal muscle, heart, and liver. Glycogen is of an abnormal form, having short outer branches because of a deficiency in the activity of amylo-1,6-glucosidase as measured in liver.

Type IV Glycogen Storage Disease (α-1,4-Glucan-6-glucosyl Transferase or Brancher Deficiency; Anderson's Disease)

Anderson's disease is an autosomal recessive disorder with an incidence of 1 in 50,000. The disease process is caused by the storage of an abnormal form of glycogen, which has long outer chains as a result of a deficiency in α-1,4-glucan-6-glucosyl transferase (brancher) enzyme in liver. Alternatively, this disease has been referred to as *amylopectinosis* (602,603). A defect in the activity of this enzyme has been found and measured in fibroblasts, thereby making prenatal detection of disease feasible (604).

"CORRESPONDENCE TRACKING"

TYPE: ACTION DOCUMENT NUMBER: 9123078
ORIGINATOR: 02 STATUS I DIRECTORATE STATUS

****

FROM: MASON, James O.: HHS AND CLSH

TO: DR. D.A. BROMLEY

DATE OF
CORRESPONDENCE: 07/29/91

SUBJECT: RE: THE AVAILABILITY OF STABLE AND RADIOISOTOPES IN THIS COUNTRY, AND AN OFFER OF ASSISTANCE ON THIS ISSUE.

****

DIRECTORATE ASSIGNED: FCCSET

STAFF ASSIGNED:

ACTION REQUIRED: FOR DAB'S SIGNATURE

STAFF ACTION:

****

SENDER'S DUE DATE:

OSTP DUE DATE: 08/13/91

STAFF DUE DATE

DATE COMPLETED:

DATE COMPLETED/DEPT:

****

COPIES TO: D. Allan Bromley
LIFE SCIENCES
Vickie Sutton
Karl Erb
Leo Macklin

****

WHITE HOUSE TRACKING #:

CONTACT PERSON:

PHONE: EXT:

REMARKS:

OSTP RECEIVED: 07/30/91

FILE: FCCSET*P-LIFE SCIENCES

DEPT RECEIVED:

3078

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of the Assistant Secretary
for Health
Washington DC 20201

RECEIVED
91 JUL 30 P 3:11
OFFICE OF THE DIRECTOR

JUL 29 1991

Dr. D. Allan Bromley
Assistant to the President
for Science and Technology
Office of Science and Technology Policy
358 Old Executive Office Building
Washington, D.C. 20506

Dear Allan:

Thank you for taking time from your busy schedule to attend the July 25 Committee on Life Sciences and Health (CLSH) meeting. The committee found your vision for FCCSET inspiring. Your leadership and enthusiam have achieved a new level of interagency cooperation and are clearly responsible for the success of the FCCSET crosscuts. Additionally, your supportive and thoughtful comments, regarding the activities of our many subcommittees, were encouraging and most appreciated. We were sorry to hear that Mary Anne Bach, who carried the FCCSET process through its period of revitalization, will be leaving. We wish her well in her new position and look forward to working with her replacement, Dr. Sutton.

As you heard during my presentation at the CLSH meeting, there is a crisis in the availability of stable and radioisotopes in this country. The crisis not only affects biomedical research, health treatment and diagnostics, but will also have a serious effect on other public and private sectors. The issue is most complex and so may be the solutions.

The members of the Committee on Life Sciences and Health recommend that this issue be taken to the full FCCSET for discussion. As you know, several prestigious groups have addressed past crises in isotope availability and while they found solutions--those solutions were temporary and have not stabilized the situation. The CLSH encourages the formation of a committee, representing the full spectrum of users of stable and radioisotopes, to address the problem, to determine the demand for these products, and to arrive at long-lasting solutions.

I appreciate your willingness to fully examine this critical issue. Please let me know how I can assist with this important issue.

Sincerely yours,

James O. Mason

James O. Mason, M.D., Dr.P.H.
Assistant Secretary for Health and
CLSH Chairman

"CORRESPONDENCE TRACKING"

TYPE: INFORMATION DOCUMENT NUMBER: 9122675
ORIGINATOR: 02 STATUS C DIRECTORATE STATUS
****

FROM: GRAD, Rae K.: NATIONAL HEALTH/EDUCATION CONSORTIUM

TO: DR. D.A. BROMLEY

DATE OF
CORRESPONDENCE: 07/17/91

SUBJECT: THE MATERIALS TO ACCOMPANY GRAD'S LETTER OF 07/08/91
(which were inadvertently left out).

****

DIRECTORATE ASSIGNED: STAFF ASSIGNED:

ACTION REQUIRED: STAFF ACTION:

****

SENDER'S DUE DATE:

OSTP DUE DATE: STAFF DUE DATE
DATE COMPLETED: DATE COMPLETED/DEPT:

****

COPIES TO: D. Allan Bromley
LIFE SCIENCES

****

WHITE HOUSE TRACKING #: CONTACT PERSON:
PHONE: EXT:

REMARKS: The letter of July 8, 1991 is document #9122053 and was assigned to the Division of Life Sciences. *Enclosures to Life Sciences.

CLOSED

OSTP RECEIVED: 07/24/91 FILE: P-LIFE SCIENCES
DEPT RECEIVED:

2675

Governor Lawton Chiles (FL)
Chairman
National Commission to
Prevent Infant Mortality

NATIONAL
HEALTH/EDUCATION
CONSORTIUM

William S. Woodside
Chairman of the Board
Institute for Educational
Leadership

July 17, 1991

The Honorable D. Allan Bromley
Assistant to the President for Science and Technology
Old Executive Office Building
17th Street and Pennsylvania Ave., NW
Suite 358
Washington, DC 20506

Dear Dr. Bromley:

Enclosed are the materials which were inadvertently left out of the letter sent to you on July 8, 1991. I am also sending a copy of the letter you must have received about a week ago. I am sure the letter will make much more sense with the accompanying reading material.

Sincerely,

Rae Grad

Rae K. Grad
Co-Director

National Commission to Prevent Infant Mortality
Switzer Building, Room 2014 • 330 C Street, SW • Washington, DC 20201 • Tel (202) 472-1364 • Fax (202) 755-0462
Institute for Educational Leadership
Suite 310 • 1001 Connecticut Avenue, NW • Washington, DC 20036 • Tel (202) 822-8405 • Fax (202) 872-4050

Governor Lawton Chiles (FL)
Chairman
National Commission to
Prevent Infant Mortality

NATIONAL
HEALTH/EDUCATION
CONSORTIUM

William S. Woodside
Chairman of the Board
Institute for Educational
Leadership

July 8, 1991

The Honorable D. Allan Bromley
Assistant to the President for Science and Technology
Old Executive Office Building
17th Street and Pennsylvania Ave., NW
Suite 358
Washington, DC 20506

Dear Dr. Bromley:

I have recently learned of your efforts to foster research relating to brain and behavioral disorders. I would greatly appreciate the opportunity to meet with you to discuss a project of the National Commission to Prevent Infant Mortality, a congressional commission chaired by Governor Lawton Chiles of Florida. I believe this project is right in line with the "Decade of the Brain" initiative.

The National Commission to Prevent Infant Mortality has recently joined hands with the Institute for Educational Leadership to convene a consortium of 46 national health and education organizations (including the Society for Neuroscience). The premise of the National Health/Education Consortium is that children must be healthy in order to learn and they must be educated to ensure optimal health. The goal of the consortium parallels the 1989 President's and Governors' National Education goal #1: By the year 2000, all children will begin school ready to learn.

The initial meeting of the National Health/Education Consortium was a symposium of health and education experts who convened in May 1990 at the National Academy of Science (see enclosed booklet, Crossing the Boundaries Between Health and Education). United States Secretary of Health and Human Services Louis Sullivan and former U.S. Secretary of Education Lauro Cavazos attended the meeting and voiced strong support for health and education linkages.

Clinical specialists who presented evidence at the May meeting about circumstances which put children at risk for learning disabilities, emphasized the need to better understand the biology of normal and abnormal brain development, how prenatal and early childhood processes influence later learning, what can be done to support basic research in this area, how to tie developmental research to clinical interventions and ultimately what policy changes will be required.

National Commission to Prevent Infant Mortality
Switzer Building, Room 2014 • 330 C Street, SW • Washington, DC 20201 • Tel (202) 472-1364 • Fax (202) 755-0462
Institute for Educational Leadership
Suite 310 • 1001 Connecticut Avenue, NW • Washington, DC 20036 • Tel (202) 822-8405 • Fax (202) 872-4050

To explore these critical facets of the health/education connection, on December 6, 1990 a meeting of leading neurodevelopmental scientists from across the country was convened by Dr. Joseph Coyle (see Healthy Brain Development: Precursor to Learning). The neuroscientists were asked to define the neurobiologic components of learning and to identify factors that may adversely affect the learning process. Their discussion provided a rare opportunity to move basic research knowledge into the public policy arena.

I would welcome the opportunity to meet with you to discuss how to facilitate a closer working relationship between the scientists doing front-line brain research and the public policy community on the issue of maximizing the health and learning potential of our nation's children. I would be happy to meet with you at your convenience.

Sincerely,

Rae Grad

Rae K. Grad
Co-Director

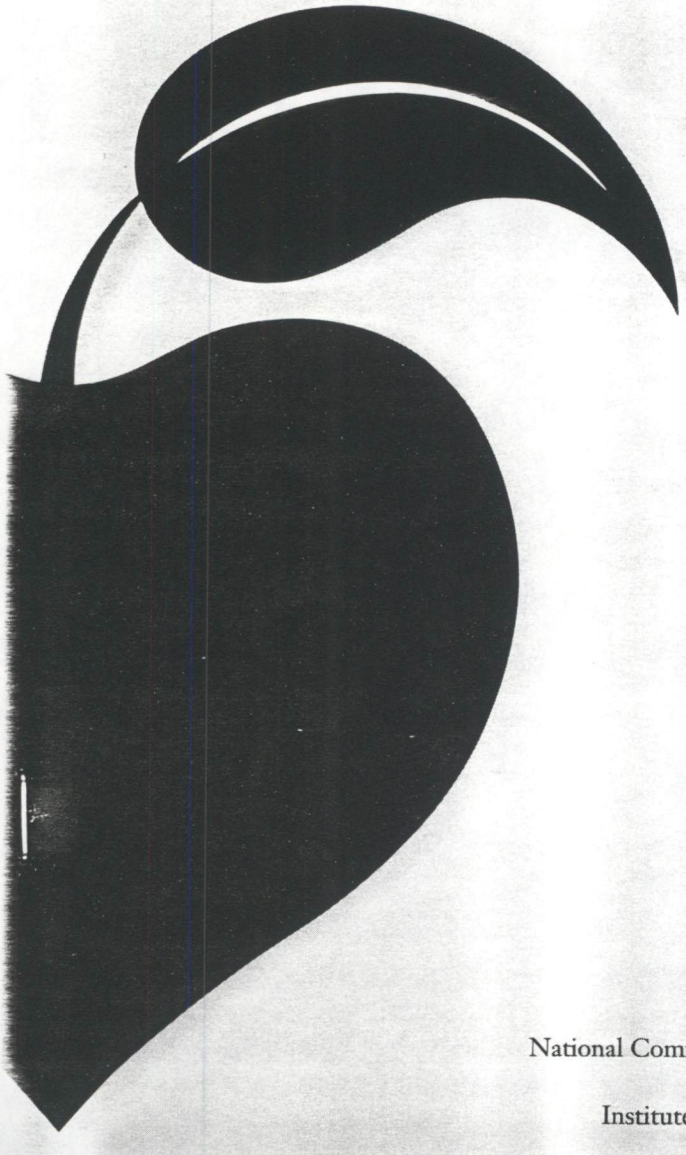
NATIONAL

HEALTH/EDUCATION

CONSORTIUM

Healthy Brain Development:

Precursor to Learning

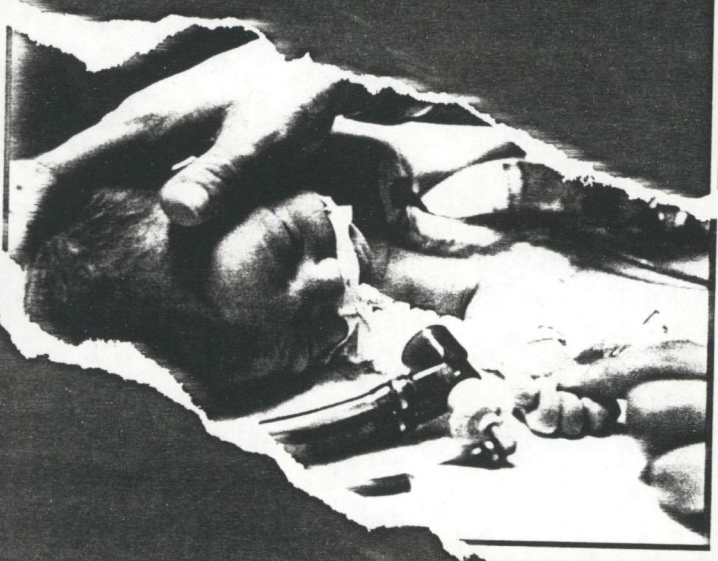


National Commission to Prevent Infant Mortality

Institute for Educational Leadership

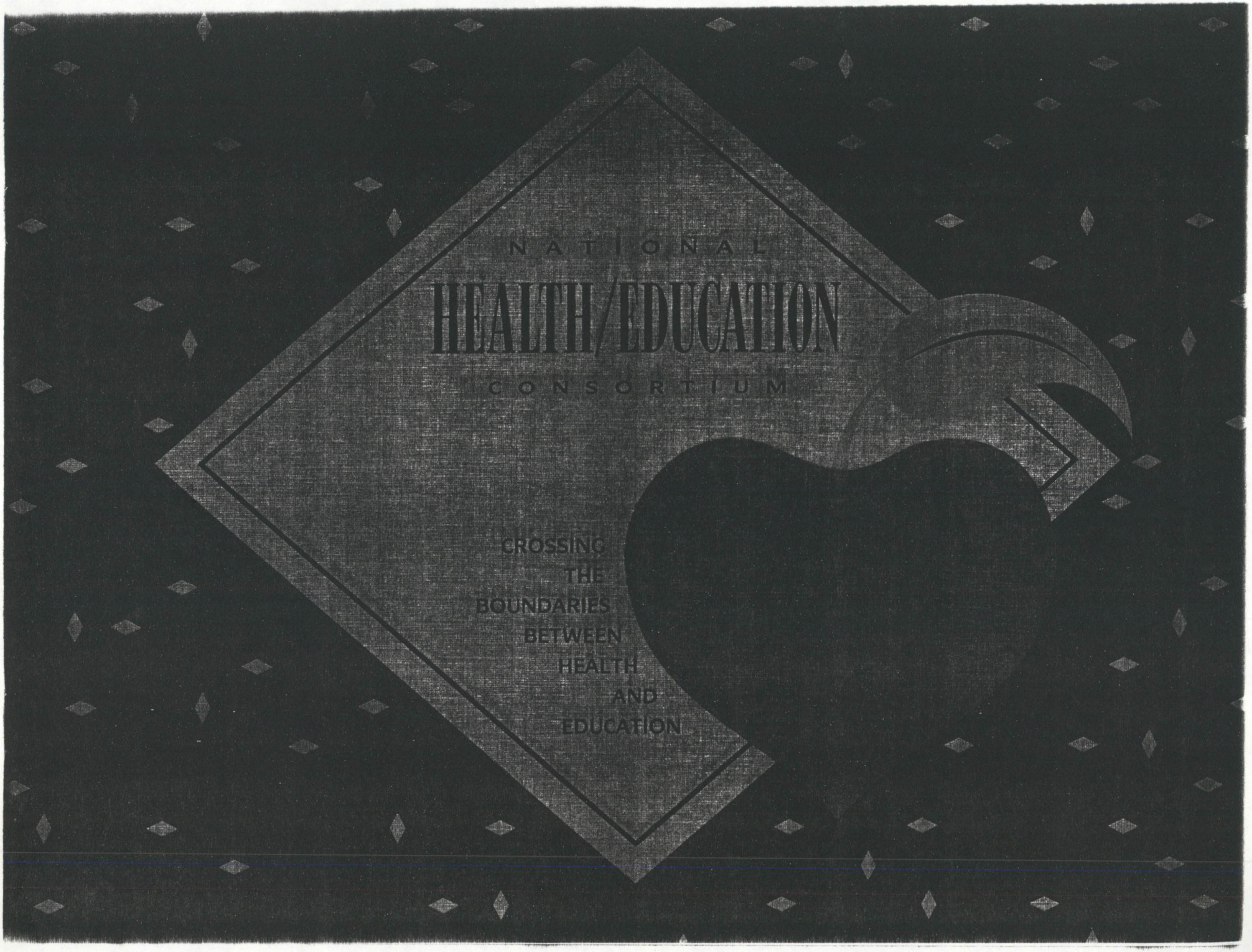
Death Before Life:

THE TRAGEDY OF INFANT MORTALITY



The National Commission to Prevent Infant Mortality

August 1988


NATIONAL
HEALTH/EDUCATION
CONSORTIUM
CROSSING
THE
BOUNDARIES
BETWEEN
HEALTH
AND
EDUCATION

National Commission to Prevent Infant Mortality
Switzer Building • Room 2014
330 C Street, S.W. • Washington, D.C. 20201
202-472-1364

SELECTED CLIPS
NATIONAL HEALTH/EDUCATION CONSORTIUM

PV forum unites forces that help children

> "The education of a child that a teacher deals with, is the justice problem that the judge deals with, is the health problem that the county deals with ...'
>
> — *Maureen Di Marco, state child development and education secretary*

BY JUDY ZUCKERMAN
Sentinel staff writer

WATSONVILLE — Financially strapped health care agencies, education and social services that serve the Pajaro Valley Unified School District (PVUSD) found friends in each other at a forum Saturday that was funded by a new national consortium.

The National Health/Education Consortium, made up of 41 national groups from the three fields, selected Starlight Elementary School to be the first of six sites across the nation to hold a conference.

Pajaro Valley is the only site chosen in California.

Federal, state and local officials joined in discussion with nearly 200 people to cross boundaries between education, health care and family support services.

Gary Bloom, assistant superintendent of personnel for PVUSD, said that there are literally hundreds of agencies, educators and professionals who are committed to helping children and families but don't speak to each other.

"The first step today is communication," said Bloom. "But ultimately we're looking forward to developing a more cooperative relationship between these individuals and schools, and to go from cooperation to collaboration."

With funding streams drying up, the agencies and schools are looking to work together to stretch the few dollars left. However, the conference is not just looking for money-saving solutions, but how to better serve children. This includes children who — more often than realized — fall through the gaps between providers' services.

An early prognosis of the forum was very positive at a noon-time press conference.

Although no policy changes were confirmed, the forum was viewed as a catalyst for holistic reforms in education, health care and social services.

"The education of a child that a teacher deals with, is the justice problem that the judge deals with, is the health problem that the county deals with, etc.," said Maureen Di Marco, state child development and education secretary.

"And it may be the same child."

In the Pajaro Valley, 38 percent of the children are living in poverty, according to PVUSD Superintendent Merrill Grant.

Brochures from various organizations on display ranged from Planned Parenthood and the Campfire Council, to a pamphlet titled "Working with Homeless Families," distributed by the state Department of Education.

Rae Grad, director of the National Health/Education Consortium, said that her organization is trying to effect change on national, state and local levels.

"We are bringing together major national organizations to say, 'We can talk together, we will talk, and we must talk.'"

Some of the groups that belong to the umbrella organization are the National PTA, the Healthy Mothers, Healthy Babies Coalition and the National Coalition of Hispanic Health and Human Services Organizations.

National funding is provided by the Department of Health and Human Services, the Department of Education and the Prudential Foundation, Grad said.

Diane Siri, county superintendent of education, said that changes in how all three fields function -- and how they are funded -- are inevitable. "The current federal and state fiscal crisis isn't going to give us the choice of continuing to do business as usual," she said.

Martin Gerry of the Department of Health and Human Services in Washington, D.C. described how federal funding for any changes that come out of the conference will work differently.

"Rather than doing the traditional federal role, which is to say, 'Here's the money and you figure out how to get it,' what we're trying to say is, 'You tell us what you want to do and we'll figure out a way to get it,'" said Gerry.

"It's a matter of reversing the two, starting with the vision and then finding how to pay for it."

Gary Bloom said that the conference will definitely produce changes down the road.

"I think you will be able to come back in three months, six months, and see where this conference has taken us," he said.

Conference-goers smile at remarks made by one of the speakers at Saturday's meeting.

Health care needs streamlining

By EMILIO ALVARADO
STAFF WRITER

While there are dozens of agencies dealing in health care in Santa Cruz County, often they lack a system of coordinating their services and being more accessible to the community, said organizers of a health-service conference in Watsonville Saturday.

The conference, sponsored by the National Health-Education Consortium, attracted nearly 300 people. It brought county, state and national health-care specialists to Starlight Elementary School to discuss ways of coordinating services that sometimes overlap or don't make themselves readily available to the public.

Most of these services are designed to assist children and their families, said Gary Bloom, Pajaro Valley school district assistant superintendent of personnel.

Bloom, one of the organizers of the conference, said there are about 200 health-care agencies in the county sponsored by federal, state, county and non-profit organizations. The problem is that many agencies get tangled in their own bureaucratic web and many operate in isolation, one agency not knowing what the other is doing. In some cases, agencies don't market themselves effectively and the public doesn't know they are there.

In the Pajaro Valley, 38 percent of families are living in poverty, Bloom said. The plight of these families could be eased, because they are likely to be eligible for assistance from one or more of the agencies, he said.

In the end, children are the ones who suffer, he said, because health problems at home could prevent them from getting the most out of their education.

"Many kids and their families are in trouble," he said. "Kids have to be healthy. We can't be meeting our goals if we don't look at the whole child."

Saturday's conference, which was the first of six to be sponsored by the NHEC nationally, sought not only to bring health-service agencies together but to incorporate schools in a networking plan. Since schools are a central place where parents, children and school officials meet, the idea is to use schools as a bridge that connects health-care agencies and the community.

While Bloom would not discuss details, he said there is a tentative plan under way to select one of the district schools as a "one-stop shopping mall" of health services for parents and children. From this school, representatives from a collection of agencies would assist children and their families. Bloom said the plan could be put into action by 1992.

As the run of state and federal funding slows to a trickle, health-service agencies must be more enterprising with their budgets. Diane Siri, superintendent of the Santa Cruz County Office of Education, said agencies must communicate with each other and coordinate their services to save money. She said these agencies cannot continue with a "business as usual" mindset.

But changes could be difficult because they must be made on a fundamental level, said Sid Gardner, professor of human development at California State

See HEALTH page 9 ▸

HEALTH

▸ From Page 1

University at Fullerton.

"This is about changing institutions," he said, calling health agencies "at-risk-institutions." The idea, he said, is to restructure the manner in which these agencies present their services to the community. Saturday's conference, he said, was "a good start."

A conference report containing ways to coordinate health services will be released in the fall, Bloom said.

Among the speakers at the afternoon session was Maureen DiMarco, Gov. Pete Wilson's chief educational adviser.

The Watsonville Register
Pajaronian
6/5/91

KENNEBEC JOURNAL

AUGUSTA, ME
DAILY 19,000

SATURDAY
MAR 16 1991

1 BURRELLE'S PO

Measures urged to prevent defects

By JEFF NESMITH
Cox News Service

WASHINGTON — Some kids start dropping out of school long before the first day of the first grade.

Prenatal exposure to drugs or lead, nutritional deficiencies that stunt brain cell development and early childhood stress leading to permanent alterations in thought circuits all are precursors to lowered IQ's and learning disabilities.

However, a disconnect between science and education keeps a growing understanding of the brain and its development from being translated into better ways to teach America's youngsters, a private commission reported Wednesday.

"A child's ability to learn and succeed in school is determined well before he or she walks in the school doors," said the National Health/Education Consortium. "It begins with the development of the most basic elements of the brain."

The failure of the health system to prevent early damage to the brain and the failure of the education system to discover and adjust to their special needs condemns many youngsters to failure "through no fault of their own," the consortium said.

The group, which was organized by the National Commission to Prevent Infant Mortality and the Institute for Educational Leadership, is made up of 43 national medical and education organizations.

Officials said the report would be the first of a series of studies of ways to apply health research to the classroom.

The consortium recommended:

✓ Expanded maternity and infant care, so that society might avoid the cost of "the care and treatment of unhealthy children who, through no fault of their own, grow up with long-term disabilities..."

✓ More early childhood screening, along with intervention to deal with learning disabilities.

Rep. Roy Rowland, D-Ga., a member of the National Commission to Prevent Infant Mortality, said he did not know when federal funds for the recommendations would be available.

S. Levy

$8 NHEC File

BENEFITS
Boston Globe; 2-10-91

Robbing baby Peter to pay aging Paul

Entitlements for elderly raise equity questions

By Chris Black

Despite deep dissatisfaction with the governmental status quo, state and federal officials are struggling mightily to maintain status-quo social spending that tilts public benefits to the elderly in the face of rising rates of poverty among children.

While the tilt is more pronounced at the federal level, where one-third of the federal budget goes to the elderly and three-fifths of all entitlements go to those over 65, the item threatening to bust every state budget is Medicaid and the high cost of nursing-home care.

As state and federal legislators begin to grapple with budgets for the upcoming fiscal year, this lopsided allocation of resources raises questions of equity and fairness, cost-effectiveness, and even wisdom, given the high correlation between childhood poverty and costly social problems later in life. Although there is growing pressure to limit public subsidies to those in need, that imperative is pulled up short by 25 years of public-policy decisions to provide benefits, including tax breaks, on the basis of age instead.

In the years after World War II, as many as two-thirds of the nation's senior citizens languished below the poverty line. In response, the federal government dramatically expanded entitlement programs for the elderly in the late 1960s and '70s. The creation of Medicare and Medicaid, major increases in Social Security benefits along with guaranteed annual increases to keep pace with the cost of living lifted the nation's elderly out of poverty. The Census Bureau has estimated that the poverty rate for the old would be more than 35 percent today were it not for federal entitlements.

"Social Security is by far the nation's most effective antipoverty program," says Robert Greenstein, director of the Center on Budget and Policy, a Washington think tank.

As a result of this massive transfer of money, the poverty rate for those over 65 dropped from 24.6 percent in 1970 to 11.4 percent in 1989, the lowest of any age group.

"The term 'elderly poor' has gone from being a redundancy to an oxymoron in the space of 20 years," says Paul Hewitt, vice president of the National Taxpayers Union Foundation and a founder of Americans for Generational Equity.

Chris Black is the Globe's Focus writer.

Safety net for the elderly

While Social Security and Medicare wove an economic safety net for millions of older Americans, the quality of life for poor children deteriorated. Most advocates for children and the elderly dismiss out of hand the suggestion that the children are getting stiffed at the expense of their grandparents. But government entitlement programs for poor families, which include a disproportionate number of young children, have steadily declined at the same time entitlements for the elderly have soared.

The median benefit level for Aid to Families with Dependent Children, the nation's largest entitlement program for poor families, has fallen by 40 percent in the last 20 years when adjusted for inflation. In practice, the AFDC grant has become the sort of income supplement that the architects of Social Security originally envisioned for that entitlement.

In the United States today, a child under 6 has a one in four chance of being in poverty. As many as one-third of the nation's children live in poor families. The poverty rate for children under 18 increased from 14.9 percent in 1970 to 19.6 percent in 1989. In real numbers, that means 12½ million children are living in poverty compared with 3.3 million senior citizens.

According to the National Taxpayers Union Foundation, federal benefits for the elderly rose from less than 3 percent of the Gross National Product in 1965 to nearly 7 percent in 1989. The average benefit per elderly American grew from roughly $3,000 in the early 1960s to $11,000 in inflation-adjusted 1989 dollars. This means that the federal government spends about $10,923 for each elderly person compared with $744 for each child.

While there is growing awareness and concern about poor children, there is no indication that spending priorities will change. The Urban Institute estimates that Social Security and Medicare will account for all of the projected real growth in federal domestic spending in the 1990s. Looked at another way, if the defense budget were cut in half, the growth in Social Security and Medicare would absorb all of the savings.

New budget constraints

Making Social Security and Medicare insurance programs that benefit everyone rather than handouts for the needy has guaranteed both political support and program quality. Many recipients cling to the myth that they are simply collecting money they paid into the system during their working years. In practice, Social Security is now a direct transfer from current workers' FICA taxes to the elderly, and the typical recipient collects far more in benefits than he or she ever contributed.

Yet budgetary constraints are making the practice of subsidizing the affluent elderly more questionable. The federal government will spend about $2.6 trillion on Social Security and Medicare over the next five years, and about 15 percent of that amount,

or $400 billion, will be spent on people with current-dollar incomes of more than $50,000, says Hewitt. Three-fourths of all entitlement dollars are disbursed without regard to financial need and, because payment levels are tied to past earnings, Social Security pays most to families that have the most.

Constraints upon state and federal spending have led Gov. William Weld and President George Bush to cut and paste in an attempt to shift program monies while keeping a lid on spending. Weld has targeted so-called middle-class entitlements and proposed increases in MBTA fares, public college and university tuitions and restrictions on Medicaid eligibility. President Bush's proposed $1.45 trillion federal budget includes modest proposals to limit subsidies that the more affluent get for Medicare, student aid, farm price supports, school lunches and payments to veterans' survivors.

Tinkering, however, has not changed the essential thrust of public spending. The political clout of today's senior citizens rules out radical change.

"This is a generation that felt uniquely entitled to virtually everything," says Hewitt. "At every stage in their lives, government was their friend. Nothing was means-tested. They had a unique relationship to government. All of those programs that benefited the GI generation throughout its life atrophied as the GIs moved on to a new stage of life. Student loans started getting means-tested, mortgage subsidies declined. The government tended to focus on that generation as it moved through life, so it made all the sense in the world for all these programs to narrow down into elderly programs."

Advocates for the elderly and for children take great pains to avoid even the suggestion of intergenerational competition for scarce federal dollars.

Three years ago, about 120 national groups organized into an ad hoc coalition called Generations United to avoid a budgetary dispute. David S. Liederman, director of the Child Welfare League of America, is co-chairman of the group.

"The last thing that we believe ought to happen is we get into intergenerational warfare," he says.

"The problem isn't that we are helping the elderly too much, it is that we are helping children too little," said James Weill, general counsel for the Childrens' Defense Fund.

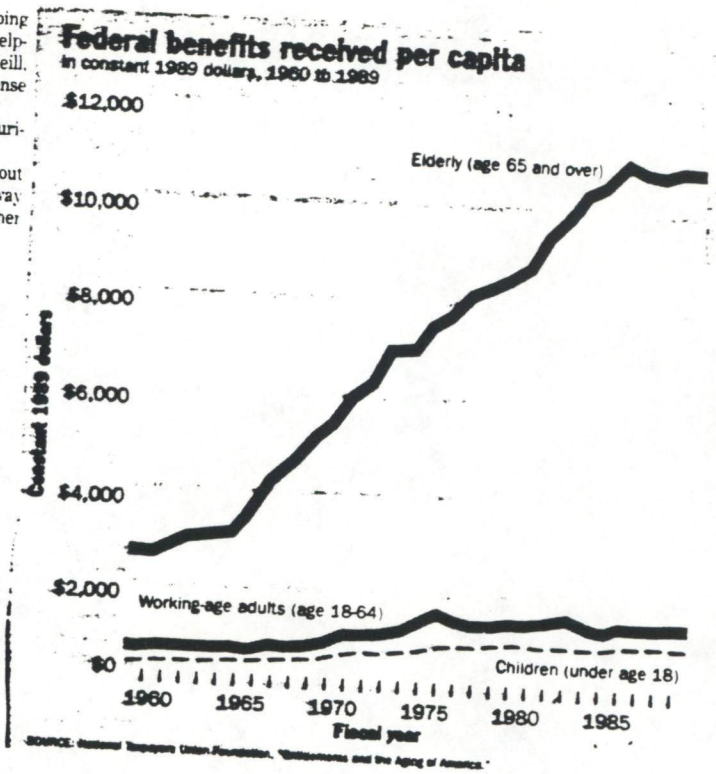
In fact, massive changes in Social Security might backfire.

"It does not make sense to talk about cutting benefits for the elderly in a big way because if you do, you end up with higher poverty rates for the elderly," said Patricia Ruggles, a senior researcher at the Urban Institute.

Budgetary constraints are leading some to question the fairness of benefit programs. Three-fourths of all entitlement dollars are disbursed without regard to financial need and, because payment levels are tied to past earnings, Social Security pays most to families that have the most.

On the other hand, poor children who grow up without enough to eat, without adequate health care or sufficient education impose not only a heavy social burden but also undermine national competitiveness and productivity when they reach adulthood.

"If we allow as many as one-third of American kids to grow up in poverty," said Ruggles, "it really says bad things about what our future is going to be like."



USA TODAY
Life
THURSDAY, JANUARY 31, 1991

Learning, prenatal health linked

By Jeff Kleinhuizen
USA TODAY

Education reforms will fail many U.S. children unless prenatal and infant health care improves, a report released Wednesday suggests.

The report, by the 41-group National Health/Education Consortium, links prenatal health with learning ability.

"Educational reforms — magnet schools, longer days, more science and math, — are inconsequential if you don't consider the child," says Rae Grad, National Commission to Prevent Infant Mortality.

The report cites poor nutrition, prenatal exposure to cocaine and lead. At greatest risk: the poor, says the consortium's Robert Mehl, a school nurse. Half of poor black children have toxic lead in their blood.

"It's an outrage and totally preventable," says Dr. Herbert Needleman, School of Medicine, University of Pittsburgh.

Among recommendations:

▶ Preventive care for every mother and baby.

▶ Early screening to find and treat learning disabilities.

HEALTH & FITNESS

Hobbs Daily News-Sun

Sun., Jan 13, 1991—Page 9A

Health and education inseparable

Excerpted from Crossing the Boundaries
Between Health and Education
A Publication of the National
Health/Education Consortium
Washington, D.C., August 1990

When pediatrician Frank Loda, director of the Center for Early Adolescence at the University of North Carolina, was growing up in southern Arkansas, he remembers hearing the old maxim, "Societies grow great when old men plant trees under whose shade they will never sit." Those are societies that look to the future.

Loda has also worked in Africa. There he experienced the opposite: a society that compromised its future when, during a terrible drought, they found themselves "eating their seed corn."

That, he warned a symposium convened by the National Commission to Prevent Infant Mortality and the Institute for Educational Leadership, is exactly what we are doing. By not responding to the crises faced by our children, we are "eating our seed corn" and putting national survival at risk. That theme resonated throughout the two-day symposium, capturing the sense of urgency felt by many participants.

This sense of urgency was heightened by participants' belief that two critical systems of great importance to children, health and education, need each other to be effective and yet often work in isolation from one another.

A second, more optimistic theme also sounded throughout the two days: available knowledge makes it possible for us to ensure a better future for our children.

Putting that knowledge to use will require fresh new approaches and a greatly expanded level of collaboration between the health and education communities. Both the 25-year-old Head Start program and the relatively new collaborative initiatives under way through Part H of the Education of the Handicapped Act have demonstrated the merit of joining the health and education sectors on behalf of children. Likewise, a number of community and national projects such as teachers working with nurses to help pregnant teens, the establishment of school-based health clinics, and the collaborative effort of the National Association of State Boards of Education and the American Medical Association to examine how learning is affected by health, are also under way — but much more is needed.

The creation of the National Health/Education Consortium represents an important next step, and from the initial symposium came six key points of agreement:

- **Health Affects Education.** Teachers know that learning comes easier to a healthy child. Any health problem — hunger, poor vision or hearing, increased blood lead levels, dental caries and child abuse — can interfere with learning. Physical and mental health problems cause children to miss school, lack energy, be distracted, or have other problems that impair their ability to learn.

Current research supports this notion. For example, as University of Maryland psychologist Stephen Porges pointed out to the symposium, in the past, learning problems were often assumed to be "behavior" problems. New information enables us to know when the underlying cause may be biological and may be treatable.

- **Education Affects Health.** By the same token, health professionals know that education can promote good health. If pregnant women know not to smoke or drink, if children learn the value of good nutrition and exercise, and if parents know how important it is to get their children immunized, the chances for a healthy life improve. The reverse is also true: ignorance can put even a healthy child at risk.

This is not just folk wisdom. San Francisco's Superintendent of Schools Ramon Cortines reviewed the evidence, highlighting examples where educaton is changing attitudes and behavior related to health. Health instruction doesn't just inform young people about which practices to avoid (e.g., drinking, smoking, careless sexual behavior), it slows the rate at which they engage in unhealthy practices.

- **Technological Advances Are Not Enough.** Medical technology can help babies survive, and computers can help children learn, but neither can compensate for growing up homeless or poor in violent neighborhoods or overcrowded schools — all of which affect a child's development.

Even to symposium participants engaged in state-of-the-art research, new knowledge was seen as having limitations. Very similar at-risk children may develop in very dissimilar ways for reasons that have more to do with family and environment (e.g., divorce, separation, poverty, homelessness) than new technology. Technology doesn't determine why a sickly child thrives in a supportive environment, and a healthy child sickens in an unsupportive one.

• **Families Have a Critical Role.** Health and education professionals are essential, but they are no substitute for families. The projects most successful in helping at-risk children are those involving their families. When parents know how to help their ill or learning-disabled children, tangible benefits follow. The same is true for families in crisis, abusing drugs or alcohol, or struggling just to survive.

Involving families can take many forms. Dr. Marilyn Segal of NOVA University's Family and School Center reported effective family-based projects (Family Connections and Even Start) that include home visits. Dr. Rafael Valdivieso of the Hispanic Policy Development Project spoke of a "two-generation approach" in which services are provided to both the preschool child and parent at the same site. Dr. Byron Egeland of the University of Minnesota described the STEEP Program, a preventive intervention program designed to promote healthy parent-infant interaction, and Dr. Margot Kaplan-Sanoff cited three such projects at Boston City Hospital — the Child Development Project, Project Visit, and Women and Infants Program. Another example, Head Start, has successfully integrated parents as everything from teacher aides to board members. Overall, involving families in efforts to help at-risk children makes a significant difference.

• **"At Risk" Does Not Mean "Doomed".** This is the best news. New research has revealed possibilities that were not even contemplated a few years ago. Exciting new research promises a new world of opportunities for very troubled children. Degrees of risk can be changed; I.Q.'s can be raised; school performance, learning ability, and basic functioning can be improved, even for very high-risk children.

Early intervention makes a difference, but research shows that help must be made available as soon as possible after an insult has occurred. That means health professionals need to involve educators and developmental specialists long before school age, and educators need to bring in health professionals as soon as learning disabilities are suspected.

Hobbs Daily News-Sun Sun., Jan 13, 1991

Schools bear weight of dealing with poor health

Reprinted with permission
From the National
Health/Education Consortium

Most of the development of the human brain occurs during pregnancy and the first year of life. If a fetus does not develop normally — if a baby is born prematurely, or at risk because of poor nutrition or maternal substance abuse and if the mother does not get help — the odds of learning difficulties increase substantially. That is why educators and schools have such a major stake in the health care available to pregnant women and infants.

A growing body of research involving both animal and human subjects now makes clear that taking some simple but critical steps can improve the chances for healthy child development and later learning. Three points stand out:

• **Low birthweight is an important predictor of future learning difficulties.** A baby weighing less than five and a half pounds at birth is considered a low birthweight baby. A baby weighing less than three and one-quarter pounds is regarded as very low birthweight. Not all heavier babies are automatically healthy, and not all small babies are automatically troubled, but the evidence leaves no doubt: being born at low birthweight puts a baby at greater risk.

Pediatrician Marie McCormick, Director of the Infant Follow-up Program at Harvard Medical School, gave symposium participants a quick overview of the facts. Compared to babies of normal birthweight, low and very low birthweight babies have seven to 10 times the risk of severe developmental problems (e.g. severe cerebral palsy, blindness, deafness, retardation) and two to three times the risk for school problems. In addition, low birthweight babies are more likely to have chronic health problems necessitating absence from school.

When low birthweight is combined with poverty, the child faces what several symposium participants referred to as double jeopardy. A frail, irritable baby poses problems in any family; however, for a baby born to a mother with a low I.Q. or into a family without steady income, adequate housing, or access to health care, the risks are much greater.

• **Most low birthweight and high-risk births can be prevented by means that are well-known.** As the National Commission to prevent Infant Mortality has documented, much of the low birthweight occurring in the U.S. is preventable. The most effective deterrent is simple: early and regular prenatal care. Women who get prenatal care are more likely to have full-term full-weight babies with less likelihood of learning-related impairments. Despite what is known about its benefits, however, one-third of women in the United States do not get early, regular prenatal care.

• **Health problems affect schools.** In a 1988 national survey of teachers, two-thirds of the responding teachers reported "poor health" among children as a problem. Children who frequently miss school, use drugs, or have trouble seeing or hearing need special attention and often do not do as well as healthy children. Moreover, the problem of children in "poor health" may be increasing as medical science is able to save more and more tiny babies and seriously ill children. Symposium participants agreed that we place an unfair burden on teachers when we send so many children into the classroom with health and developmental problems that could have been remediated with early treatment. Furthermore, many teachers lack the training and experience needed to cope with this influx of learning impaired children.

Just as there are effective and available measures that can lower the incidence of low birthweight, there are equally well-known measures that can improve the health of children entering school. Immunizing children saves lives, avoids days lost from school, and prevents a host of debilitating conditions. Failure to immunize children can result in epidemics, school closings, and life-long learning problems that could have been easily prevented. Although most schools recognize the threat and require proof of immunization, many states do not have blanket immunization requirements for preschoolers. Therefore, preschoolers remain particularly vulnerable to outbreaks of measles, mumps, and whooping cough, diseases that can cause long term impairment.

Lead poisoning is another preventable cause of death, mental illness, cognitive and behavioral problems, and other disabilities in children. Yet three to four million children have dangerously high blood lead levels. Many of the children affected by high blood lead levels will never be diagnosed and treated.

The Hartford Courant
HARTFORD, CONN.
D.221,962
CT-29

MAY 30 1990
BURRELLE'S

Group says healthier learn better

By ROBERT A. FRAHM
Courant Education Writer

When a first-grader at Hartford's Clark School was absent so often that her teacher became worried, a school nurse examined the girl and found she had asthma.

The girl's health and attendance improved markedly after she was treated with medication, nurse practitioner Patricia Sullivan said.

The link between poor health and school failure has been widely documented, but too many children in the nation's poorest cities, including Hartford, arrive at school with poor vision or hearing. Many also suffer from poor nutrition or chronic medical problems, national experts said Tuesday.

Some of the nation's leading experts discussed the issue in Washington, D.C., where officials announced the creation of the National Health/Education Consortium, a project designed to draw closer ties between schools and health-care agencies.

The consortium will report on the connection between health and education and develop recommendations for action by national, state and local agencies. It was introduced at the opening of a two-day seminar attended by officials such as Secretary of Education Lauro F. Cavazos and Health and Human Services Secretary Louis W. Sullivan.

Schools increasingly are enrolling children who have serious illnesses, such as AIDS, or who were born to mothers addicted to alcohol or cocaine. Many believe those conditions lead to long-term problems such as illiteracy, school failure and juvenile crime.

"We're not going to come to grips with these problems unless we deliver a healthy child into the school system," former U.S. Sen. Lawton M. Chiles, a Florida Democrat, said after outlining the consortium's goals at a press conference.

"The whole school system is structured to deal with the normal child. You place upon it these kids that are broken, and it overwhelms the system," said Chiles, chairman of the National Commission To Prevent Infant Mortality, which is a co-sponsor of the consortium.

In a press statement announcing the consortium, officials said:

- A national survey found that more than two-thirds of all teachers report that poor health among children is a problem.
- Babies with low birth weight have an unusual amount of academic difficulty once they reach school age, but half of these risky births could have been prevented by proper prenatal care.

Please see Group, Page D9

Group says health care way to better education

Continued from Connecticut Page

• Every dollar spent in quality preschool education saves nearly $5 in special education, welfare and prison costs.

• Head Start, the federal preschool program for disadvantaged children, leads to improved school performance but reaches only about one-sixth of the children eligible.

Educators and health officials in Connecticut were encouraged by the formation of the consortium, agreeing that schools and health agencies have to work together more closely.

"It's critical, absolutely critical. It's amazing to me that they have remained so separate when the problems have crossed paths," said Leah Fichtner, assistant coordinator of health education and health services for Hartford public schools.

Hundreds of teenage girls give birth each year in Hartford, and their children often suffer from poor nutrition, lack of sensory stimulation and other problems, Fichtner said.

"You see them coming into school already at remedial levels," she said.

Nearly 12 percent of the women who gave birth in Hartford between 1985 and 1987 had babies below 5½ pounds, a rate nearly twice the state and national averages, the state Department of Health Services says.

A recently released study by a consultant assessing the need for a new children's hospital in Hartford painted a bleak picture of health care in the city. The study found that Hartford babies die at a rate twice as high as that for other children in the state, that the pregnancy rate is 50 percent higher than in other cities and that alcohol and cocaine abuse by pregnant women lead to numerous cases of children's having learning disabilities, speech disorders and stunted psychological growth.

"In some respects, some of our cities look worse than Third World countries," state Education Commissioner Gerald N. Tirozzi said.

"There is an inextricable connection between the health of children and their ability to learn," said Tirozzi, whose state Department of Education is leading a state and federal project to identify children under the age of 3 whose development is slower than normal.

The project is operated in Greater Hartford by the Windsor-based Capitol Region Education Council, but there is not enough money to expand to other parts of the state, Tirozzi said.

William S. Woodside, chairman of the board of the Institute for Educational Leadership in Washington, D.C., a co-sponsor of the new national consortium, said financial problems have cut short other efforts to address poor health care and poor school preparation.

"What I find most disturbing is that we have programs that we know are working, and yet we are reluctant to spend adequate amounts of money on them," he said.

WISCONSIN STATE JOURNAL

MADISON, WI
DAILY 83,396

WEDNESDAY
MAY 30 1990

132 BURRELLE'S RZ

Health, learning go hand-in-hand, speakers say

WASHINGTON (AP) — Improved teaching won't mean better schools until curriculum changes are coupled with broader early childhood health screenings, advocates said Tuesday.

"We need to be dealing with the whole child. You're not going to have an educated child until you have a healthy child," said Lawton Chiles, a former senator from Florida and chairman of the National Commission to Prevent Infant Mortality.

His comments came at a news conference that kicked off a two-day symposium designed to persuade health and education professionals to work more closely.

"Nobody is looking at the whole child," said William Woodside, a New York City businessman who chairs the board of the Institute for Educational Leadership. "We've got programs out there, but nobody asks, 'How are all these programs dealing with the children?' "

The organizations headed by Chiles and Woodside form the National Health-Education Consortium.

Chiles said a third of the nation's school-age handicapped children have problems that could have been corrected in their early years. Part of the problem, he said, is that existing programs are under-funded and serve too few.

"We're talking about doing something about curriculum, but if you don't do something on the front end, none of that will make any difference," he said.

While expanded programs might require greater financial commitments from federal, state and local governments, Chiles said the net result is a shifting of costs because children who remain in school are more likely to pay taxes and less likely to need public assistance or end up in prison.

Woodside said the long-term savings could be five times as much as the cost.

Conference participants discussed how a child's learning potential is affected by factors ranging from premature birth, low birth weight and substance abuse by the expectant mother to perinatal, pre-school and school-age health screenings.

ST. LOUIS DAILY RECORD

ST. LOUIS, MO
DAILY 1,300

THURSDAY
MAY 31 1990

376 BURRELLE'S MO

National experts urge link for health and education

62971

By Janet Bass
Of the UPI staff

WASHINGTON (UPI) — Somewhat nostalgic for the days when one federal agency handled health and education, two national experts urged government officials Tuesday to realize the critical role adequate health care plays in children's education.

"Studies ... link good health and better learning, but this knowledge has not resulted in greater coordination to meet the needs of our kids," said Lawton Chiles, chairman of the National Commission to Prevent Infant Mortality and a Democratic gubernatorial candidate in Florida.

"Educational reform has to start at the beginning with good prenatal and early pediatric care. If we only focus on curriculum changes and forget about the brain cells for that youngster ... it all just becomes words on paper," former Sen. Chiles said.

Chiles and William Woodside, chairman of the Institute for Educational Leadership, developed the National Health-Education Consortium, meeting in Washington this week to discuss ways federal, state and local officials can better integrate health and education.

"It's pay now or pay more later," Chiles said.

The consortium said disadvantaged children often end up in a vicious cycle of poor health, poor nutrition, chronic illness and other disabilities that, if untreated or unidentified, impede their ability to learn.

Woodside said the current "compartmentalized approach" of dealing with health and education denies children appropriate attention and could have lasting and costly ramifications.

"It's like walking into a half-completed movie and wondering why we don't understand the plot," Woodside said. "It's imperative that we develop a comprehensive view that looks at the needs of the whole child."

Approaching health and education separately, Woodside said, has been an "atrocious waste of resources."

But he said the nation was "damned both ways" when it split the former Department of Health, Education and Welfare into two separate agencies — the Department of Health and Human Services and the Department of Education.

He indicated education had been getting squeezed by the gigantic social program bureaucracy, yet separating them broke the critical link between the issue.

WATERBURY
REPUBLICAN-AMERICAN

WATERBURY, CT
DAILY 39,856

WEDNESDAY
MAY 30 1990

Need for child health stressed

Vital in the learning process, advocates claim

WASHINGTON (AP) — Improved teaching won't mean better schools until curriculum changes are coupled with broader early childhood health screenings, advocates said Tuesday.

"We need to be dealing with the whole child. You're not going to have an educated child until you have a healthy child," said Lawton Chiles, a former senator from Florida and chairman of the National Commission to Prevent Infant Mortality.

His comments came at a news conference that kicked off a two-day symposium designed to persuade health and education professionals to work more closely.

"Nobody is looking at the whole child," said William S. Woodside, a New York City businessman who chairs the board of the Institute for Educational Leadership. "We've got programs out there, but nobody asks, 'How are all these programs dealing with the children?'"

The organizations headed by Chiles and Woodside form the National Health-Education Consortium.

Chiles said a third of the nation's school-age handicapped children have problems that could have been corrected in their early years. Part of the problem, he said, is that existing programs are under funded and serve too few

"We're talking about doing something about curriculum, but if you don't do something on the front end, none of that will make any difference," he said.

While expanded programs might require greater financial commitments from federal, state and local governments, Chiles said the net result is a shifting of costs because children who remain in school are more likely to pay taxes and less likely to need public assistance or end up in prison.

Woodside said the long-term savings could be five times as much

EDUCATION WEEK

WASHINGTON, DC
40-TIMES/YEAR 57,000

JUN 6 1990

-2230 BURRELLE'S MV

Education and Health Sectors Are Urged To Cooperate To Ensure Child's Success

By Ellen Flax

6297L

WASHINGTON—Even though it is well known that the state of a child's health will affect his ability to learn, the education and health-care systems in this country seldom work together to develop fully a child's potential for learning, experts gathered at a conference here said last week.

The meeting, which brought together more than 50 health professionals, educators, and business leaders, was sponsored by the National Health/Education Consortium. The group was formed jointly last month by the National Commission to Prevent Infant Mortality and the Institute for Educational Leadership to examine the relationship between health and education.

Health researchers at the meeting said that a variety of factors, including maternal drug abuse, prematurity, and poor prenatal care can cause babies to be born with physical impairments that place them at high risk for later school failure.

But given the right circumstances, they added, these babies can thrive and attain a normal academic career.

The factors that cause these high-risk babies and young children to thrive, as well as family and social situations that may cause physically healthy children to do poorly in school, will be the consortium's major focus.

Using information provided by these experts, the consortium will prepare a "white paper" on what is known about the link between learning and health, as well as information about successful intervention programs for at-risk youngsters. No time has been set for the paper's completion.

The consortium is planning afterward, however, to bring together representatives from national associations and agencies in health and education in an effort to identify what can be done at the local, state, and national levels to implement the report's recommendations.

'Never Catch Up'

At the conference, both health researchers and educators stressed the need to begin intervention programs for at-risk children long before they enter school. By creating more prevention-based health programs for the young—and for young women before they become pregnant—the experts said, many future educational and health problems can be avoided.

Photopress

Secretary Cavazos addresses a conference on the relationship between education and health.

Children who suffer from developmental problems or physical or neurological handicaps, they said, have a greater chance of succeeding if they are treated early.

"If children fall behind in the early years, they may never catch up," said former Senator Lawton Chiles of Florida, chairman of the infant-mortality commission.

Many common, and easily correctable health problems, they said, can affect a child's ability to learn. Just as a child with an uncorrected vision problem cannot see the blackboard, a child with a chronic middle-ear infection may be stymied by an inability to master language skills, they said.

To a large extent, participants agreed, children will be able to overcome a host of physical problems if they live in a stable family environment. Dr. Marie McCormick, associate professor of pediatrics at Harvard Medical School, said that though low-birthweight babies are two to three times more likely to have academic problems than are normal-weight babies, two-thirds of these "at-risk" babies have normal academic careers.

But many young children—often those with the most severe physical and developmental difficulties—are in "double jeopardy," said Dr. Judy Howard, professor of clinical pediatrics at the University of California at Los Angeles, because they live in chaotic environments. Even if they were born with no physical impairments, many of the children she sees "would still be in trouble," she said.

'New Alliances'

Dr. Jack P. Shonkoff, professor of pediatrics at the University of Massachusetts Medical School, said there should be "new alliances" between health-care providers and educators. Cultural and economic differences have prevented the two fields from cooperating more closely in the past, he said.

Medicine, Dr. Shonkoff said, is perceived as a high-status, male-dominated field that provides services in both the public and private sectors, whereas education is primarily administered by the public sector and is considered a lower-status field. But the two have to begin cooperating, he said, because "both are in crisis."

Secretary of Education Lauro F. Cavazos said at the meeting that the consortium's work dovetails nicely with the national education goals developed by the President and the governors. The consortium's emphasis on providing high-quality prenatal and early-childhood care, he said, will help the nation realize the goal of having all young children who enter school by the year 2000 ready to learn.

"Your topic of crossing the boundaries between health and education is certainly very timely," the Secretary said.

Group studies ways to plug teaching into health research

By JEFF NESMITH
Cox News Service

6297L

WASHINGTON — Some kids start dropping out of school long before they start first grade.

Prenatal exposure to drugs or lead, nutritional deficiencies that stunt brain cell development and early childhood stress leading to permanent alterations in thought circuits all are precursors to lowered IQ and learning disabilities.

However, a disconnect between science and education keeps a growing understanding of brain development from being translated into better ways to teach America's youngsters, a private commission has reported.

"A child's ability to learn and succeed in school is determined well before he or she walks in the school doors," said the National Health/Education Consortium. "It begins with the development of the most basic elements of the brain."

The failure of the health system to prevent early damage to the brain and its billions of cells and circuits and the failure of the education system to discover and adjust to their special needs condemns many youngsters to failure "through no fault of their own," the consortium said.

The group, which was organized by the National Commission to Prevent Infant Mortality and the Institute for Educational Leadership, is made up of 43 medical and education organizations.

Officials said the report would be the first of a series of studies of ways to apply health research to the classroom.

The consortium recommended:

- Expanded maternity and infant care, so that society might avoid the cost of "the care and treatment of unhealthy children who, through no fault of their own, grow up with long-term disabilities or have difficulty becoming self-supporting adults."
- More early childhood screening, along with intervention to deal with learning disabilities.
- "Demystifying" the discoveries of neuroscience and translating them to policy makers and educators.
- Greater funding for scientific research on the brain.

Conference-goers smile at remarks made by one of the speakers at Saturday's meeting.

Health care needs streamlining

By EMILIO ALVARADO
STAFF WRITER

While there are dozens of agencies dealing in health care in Santa Cruz County, often they lack a system of coordinating their services and being more accessible to the community, said organizers of a health-service conference in Watsonville Saturday.

The conference, sponsored by the National Health-Education Consortium, attracted nearly 300 people. It brought county, state and national health-care specialists to Starlight Elementary School to discuss ways of coordinating services that sometimes overlap or don't make themselves readily available to the public.

Most of those services are designed to assist children and their families, said Gary Bloom, Pajaro Valley school district assistant superintendent of personnel.

Bloom, one of the organizers of the conference, said there are about 200 health-care agencies in the county sponsored by federal, state, county and non-profit organizations. The problem is that many agencies get tangled in their own bureaucratic web and many operate in isolation, one agency not knowing what the other is doing. In some cases, agencies don't market themselves effectively and the public doesn't know they are there.

In the Pajaro Valley, 38 percent of families are living in poverty, Bloom said. The plight of these families could be eased, because they are likely to be eligible for assistance from one or more of the agencies, he said.

In the end, children are the ones who suffer, he said, because health problems at home could prevent them from getting the most out of their education.

"Many kids and their families are in trouble," he said. "Kids have to be healthy. We can't be meeting our goals if we don't look at the whole child."

Saturday's conference, which was the first of six to be sponsored by the NHEC nationally, sought not only to bring health-service agencies together but to incorporate schools in a networking plan. Since schools are a central place where parents, children and school officials meet, the idea is to use schools as a bridge that connects health-care agencies and the community.

While Bloom would not discuss details, he said there is a tentative plan under way to select one of the district schools as a "one-stop shopping mall" of health services for parents and children. From this school, representatives from a collection of agencies would assist children and their families. Bloom said the plan could be put into action by 1992.

As the run of state and federal funding slows to a trickle, health-service agencies must be more enterprising with their budgets. Diane Siri, superintendent of the Santa Cruz County Office of Education, said agencies must communicate with each other and coordinate their services to save money. She said these agencies cannot continue with a "business as usual" mindset.

But changes could be difficult because they must be made on a fundamental level, said Sid Gardner, professor of human development at California State

See HEALTH page 9 ▸

HEALTH

▸ From Page 1

University at Fullerton.

"This is about changing institutions," he said, calling health agencies "at-risk-institutions." The idea, he said, is to restructure the manner in which these agencies present their services to the community. Saturday's conference, he said, was "a good start."

A conference report containing ways to coordinate health services will be released in the fall, Bloom said.

Among the speakers at the afternoon session was Maureen DiMarco, Gov. Pete Wilson's chief educational adviser.

The Watsonville Register
Pajaronian
6/5/91

PV forum unites forces that help children

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[redacted] ZUCKERMAN
Sentinel staff writer

WATSONVILLE — Financially strapped health care agencies, education and social services that serve the Pajaro Valley Unified School District (PVUSD) found friends in each other at a forum Saturday that was funded by a new national consortium.

The National Health/Education Consortium, made up of 41 national groups from the three fields, selected Starlight Elementary School to be the first of six sites across the nation to hold a conference.

Pajaro Valley is the only site chosen in California.

Federal, state and local officials joined in discussion with nearly 200 people to cross boundaries between education, health care and family support services.

Gary Bloom, assistant superintendent of personnel for PVUSD, said that there are literally hundreds of agencies, educators and professionals who are committed to helping children and families but don't speak to each other.

"The first step today is communication," said Bloom. "But ultimately we're looking forward to developing a more cooperative relationship between these individuals and schools, and to go from cooperation to collaboration."

With funding streams drying up, the agencies and schools are looking to work together to stretch the few dollars left. However, the conference is not just looking for money-saving solutions, but how to better serve children. This includes children who — more often than realized — fall through the gaps between providers' services.

An early prognosis of the forum was very positive at a noon-time press conference.

Although no policy changes were confirmed, the forum was viewed as a catalyst for holistic reforms in education, health care and social services.

"The education of a child that a teacher deals with, is the justice problem that the judge deals with, is the health problem that the county deals with, etc.," said Maureen Di Marco, state child development and education secretary.

"And it may be the same child."

In the Pajaro Valley, 38 percent of the children are living in poverty, according to PVUSD Superintendent Merrill Grant.

Brochures from various organizations on display ranged from Planned Parenthood and the Campfire Council, to a pamphlet titled "Working with Homeless Families," distributed by the state Department of Education.

Rae Grad, director of the National Health/Education Consortium, said that her organization is trying to effect change on national, state and local levels.

"We are bringing together major national organizations to say, 'We can talk together, we will talk, and we must talk.'"

Some of the groups that belong to the umbrella organization are the National PTA, the Healthy Mothers, Healthy Babies Coalition and the National Coalition of Hispanic Health and Human Services Organizations.

National funding is provided by the Department of Health and Human Services, the Department of Education and the Prudential Foundation, Grad said.

Diane Siri, county superintendent of education, said that changes in how all three fields function -- and how they are funded -- are inevitable. "The current federal and state fiscal crisis isn't going to give us the choice of continuing to do business as usual," she said.

Martin Gerry of the Department of Health and Human Services in Washington, D.C. described how federal funding for any changes that come out of the conference will work differently.

"Rather than doing the traditional federal role, which is to say, 'Here's the money and you figure out how to get it,' what we're trying to say is, 'You tell us what you want to do and we'll figure out a way to get it,'" said Gerry.

"It's a matter of reversing the two, starting with the vision and then finding how to pay for it."

Gary Bloom said that the conference will definitely produce changes down the road.

"I think you will be able to come back in three months, six months, and see where this conference has taken us," he said.

Forum addresses children's health issues

By Cheryl Fincher
The Macon Telegraph

It was an auditorium filled with both frustration and hope for the future Monday as health professionals, educators, business people and parents voiced their concerns about school-age children.

Consider the following statistics about Georgia's future:

- One in five children grows up in poverty;
- At least 60,000 children go to bed hungry every night;
- More than 18,000 teen-age girls become pregnant each year before graduating from high school;
- And 39 percent of Georgia's youngsters never earn a high school degree.

J. Roy Rowland

"The best way to address this crisis concerning our children ... is to bridge communication among those in the health, education and social services field," U.S. Rep. J. Roy Rowland told the gathering at Macon College.

Rowland was part of a series of symposiums sponsored by the National Health Education Consortium called "Crossing Boundaries Between Health and Education." The purpose of the meetings is to identify the problems of poor health among the state's school age population.

A diversified panel representing various segments of the health, educational and business community addressed the audience about what they see and what type of help they need.

For example, June Bradfield, superintendent of schools in Telfair County, said schools could be the sites for a wide range of health services for both children and their parents. More school nurses provide help with physical and mental problems.

Panel member Raynette Evans, director of health and physical education for the Bibb County school board, said school-based clinics could help keep pregnant teen-agers in school.

But problems — protecting turf, state budget cuts and parental misinformation — prevent public health departments from making inroads into the school system.

"We have a lot of programs in place" at the Macon-Bibb County Health Department, said Carolyn Gibson, director of nurses. "But we need nurses. And then you try to get nurses into the school, and the first thing that comes to mind are foam and condoms" for birth control.

Although there were no firm answers about linking health care and education, Rowland reminded the audience that the symposium was intended to gather information and stimulate dialogue between health care professionals and the education community.

Children's health concerns

The following is a roundup of concerns about school children's health as it affects their ability to learn:

- **Health:** Children must be healthy to be educated and educated to be healthy.
- **Failing children:** A child who fails in school and enters adulthood unable to be a part of the work force is a threat to Georgia's economic future.
- **More nurses:** More school-based nurses are needed in more schools for longer hours.
- **Wellness:** Children need to be taught the "wellness" concept, how to take care of themselves, to reduce employer health-care costs. Physical education should be a daily priority.
- **Networks:** Educators and health professionals should make better use of community resources and network their strengths.
- **Health education:** Families should be involved in their children's health education. Health providers — nurses, doctors, chiropractors, dentists — must be health educators.
- **Volunteerism:** Volunteerism is one way to counter the demands on overworked educators and health professionals.
- **Rewards:** Physicians and patients need to be rewarded for preventing disease.
- **Dental care:** Needy children have little access to dental care.

— Cheryl Fincher

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See HEALTH page 9 ▸

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NEWS AND FARMER

LOUISVILLE, GA
WEEKLY 2,988

JUN 12 1991

163 BURRELLE'S XL

Symposium seeks ways to improve children's health

6297L

A symposium will be held in Macon to explore ways to improve the learning capabilities of school children through better health.

The forum, sponsored by U. S. rep. J. Roy Rowland with assistance from the Washington-based National Health/ Education Consortium, is scheduled for 2 p.m. on Monday, June 17, at the Macon College Auditorium.

The Eighth District Congressman said the purpose of the symposium is to identify the health problems of school children and discuss strategies for addressing those problems. He explained that the program is planned for all communities within the Eighth District.

He said health, education and social welfare professionals will join with community, business and religious leaders for the discussion. Parents and the public at large are invited, he noted.

"Children must be healthy to learn, and they must be educated to keep themselves healthy," Rowland said. "Teachers and school officials have learned that children tend to do much better in school when their health needs are met."

The Macon symposium is one of a number planned around the country by the National Health/Education Consortium, which was jointly formed by the National Commission to Prevent Infant Mortality and the Institute for Educational Leadership.

The Congressman said the goal is to bring about better coordination and cooperation between health, education and social services professionals, and sources in the private sector, in providing health services to school children. When school children are healthier, he said, they can better concentrate on school work. This, he added, can lower the school drop-out rate and increase the graduation rate.

Rowland said former U. S. Surgeon General C. Everett Koop is helping inform the public about the relationship between good health and the ability of young people to learn, telling communities they should incorporate health into education rather than making it a satellite that skirts around education. He said he agrees with Koop that the country's future economy can be seriously undermined if a generation of teenagers drops out of school in large numbers because of health problems.

"CORRESPONDENCE TRACKING"

TYPE: ACTION DOCUMENT NUMBER: 9122690
ORIGINATOR: 02 STATUS I DIRECTORATE STATUS

****

FROM: STONEHILL, David L.:MARINE BIOLOGICAL LABORATORY

TO: DR. D.A. BROMLEY

DATE OF
CORRESPONDENCE: 07/19/91

SUBJECT: REQUEST FOR OSTP TO CONSIDER POLICIES FOR COMMUNICATING FEDERALLY SPONSERED RESEARCH.

****

DIRECTORATE ASSIGNED: LIFE SCIENCES

STAFF ASSIGNED: DAH

ACTION REQUIRED: AS NECESSARY

STAFF ACTION:

****

SENDER'S DUE DATE:

OSTP DUE DATE: 08/06/91 STAFF DUE DATE

DATE COMPLETED: DATE COMPLETED/DEPT:

****

COPIES TO: D. Allan Bromley
INTERNATIONAL/POLICY

****

WHITE HOUSE TRACKING #: CONTACT PERSON:

PHONE: EXT:

REMARKS: Reassigned to International (Perrella)

OSTP RECEIVED: 07/25/91 FILE: P-LS-RESEARCH FUNDING*INT-POLI

DEPT RECEIVED:

2690

MARINE BIOLOGICAL LABORATORY

WOODS HOLE MASSACHUSETTS 02543 (508) 548-3705

DAVID L. STONEHILL

Director
MBL / WHOI Library

Director
Scientific Information
Research Center

July 19, 1991

Dr. D. Allan Bromley
Assistant to the President for Science and Technology
Executive Office of the President
Washington, D. C., 20500

Dear Allan,

Since leaving the EOP, I have been enjoying learning the facts of life as the head of a scientific library. One issue is of common concern across the field and may be of interest to national science policy.

The past five years have seen an increasing copyright of United States scientific information by foreign firms: the bulk of formal scientific publication is now held in this manner. The same period has seen a yearly 15% escalation in the cost of information and a yearly reduction of scientific library holdings by 5%. Data that are of specialized interest cannot be communicated and newer methods for rapid, widespread, scientific communication are inhibited.

Although current results are transmitted informally or at meetings, the problems of formal communication may be important in the long run. They make it difficult to assemble larger bodies of data from published findings, to disseminate large bodies of data widely, to bring scholars into new fields, and to support interdisciplinary work. These issues are particularly germane to larger initiatives, such as the human genome project, that involve many investigators working over a long period.

It does not add up. Publicly supported authors are required to pay publishers to print their work -- and the public must buy it back again. At the same time, technology has radically lowered the cost of distribution and printing. It may be that copyright laws are being used to support a system that is no longer essential, does not benefit the authors, and may be inhibiting research.

It would be helpful for the Office of Science and Technology Policy to consider policies for communicating federally sponsored research.

Yours truly,

David L. Stonehill

David L. Stonehill

"LIFE SCIENCES (CORRESPONDENCE TRACKING)"

TYPE: INFORMATION DOCUMENT NUMBER: 9122958

ORIGINATOR: 02 STATUS C DIRECTORATE STATUS C

****

FROM: ROSENBERG, Roger N.: AMERICAN ACADEMY OF NEUROLOGY

TO: DR. D.A. BROMLEY

DATE OF CORRESPONDENCE: 07/22/91

SUBJECT: RE: MAXIMIZING THE HUMAN POTENTIAL, DECADE OF THE BRAIN REPORT

****

DIRECTORATE ASSIGNED:

STAFF ASSIGNED: Alicia K. Dustira

ACTION REQUIRED:

STAFF ACTION: DAB Signature

****

SENDER'S DUE DATE:

OSTP DUE DATE:

STAFF DUE DATE 08/06/91

DATE COMPLETED:

DATE COMPLETED/DEPT:08/13/91

****

COPIES TO: D. Allan Bromley
LIFE SCIENCES
FCCSET

D.A. Henderson

****

WHITE HOUSE TRACKING #:

CONTACT PERSON:

PHONE: EXT:

REMARKS: Originally sent to DLS FYI, on 07/30/91 Bromley asked DLS to create an acknowledgement for his signature.

OSTP RECEIVED: 07/29/91

DEPT RECEIVED: 07/30/91

FILE: P-LIFE SCIENCES*FCCSET

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20506

August 13, 1991

Dear Roger:

Enclosed please find an article sent to me by Dr. Roger Rosenberg, President of the American Academy of Neurology, which may be of interest to the Subcommittee on Brain and Behavioral Sciences (SBBS).

Sincerely,

D. Allan Bromley
Director

Enclosure

Roger J. Porter, M.D.
Deputy Director
National Institute for Neurological
Disorders and Stroke
Building 31, Room 8A-52
National Institutes of Health
Bethesda, MD 20892

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20506

August 13, 1991

Dear Dr. Rosenberg:

Thank you for the words of encouragement in your letter of July 22, 1991, as well as the article by Drs. Woody and Blaw on the Teratology of the Central Nervous System, which I will pass along to Dr. Roger Porter, chairman of the Federal Coordinating Council for Science, Engineering and Technology (FCCSET) subcommittee responsible for developing the implementation plan for Federal activities related to the Decade of the Brain.

Sincerely,

D. Allan Bromley
Director

cc: Dr. Roger Porter

Roger N. Rosenberg, M.D.
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