American Handbook of Psychiatry

MENTAL DISORDERS WITH HUNTINGTON'S CHOREA

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A. Clinical Aspects

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e-Book 2015 International Psychotherapy Institute

From *American Handbook of Psychiatry: Volume 4* edited by Silvano Arietti

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A. Clinical Aspects[1]

Introductory Remarks

A brief historical review of events since the first edition of the *American Handbook of Psychiatry* is of interest. The first printing of the *Handbook* was in 1959, and it had run through nine printings by 1967. In that year, by coincidence, a remarkable wave of attention was paid to Huntington's disease (chronic progressive hereditary chorea). This was evidenced by the fact that during the decade ending 1959 there had been approximately 120 publications in the scientific literature on the disease. The number had increased to over 350 during the decade ending 1969. Furthermore, the first international symposium on the disease was held in September of 1967 in Montreal. This symposium brought together a group of investigators which reviewed what was known of the disease to that time, and proceedings were subsequently published by the hosting Congress of Neurogenetics and Neuro-ophthalmology of the World Federation of Neurology. In 1967 there was also created the Committee to Combat Huntington's Disease, spurred by the interest of a single individual, Marjorie Guthrie, whose husband died of Huntington's disease. The Committee grew from a single small group in that year to a national organization with headquarters in New York and more than fifty chapters in the United States and other countries by 1974. This Committee was also responsible for assisting the World Federation of

Neurology Research Commission on Huntington's Chorea not only in holding its 1967 symposium but also in holding a centennial symposium in 1972 celebrating the description by George Huntington of the disease and resulting in publication of the first book devoted entirely to its present status. The publication is a comprehensive review to which anyone interested in special aspects of the disease, including those of interest to psychiatrists, may refer.

In the relatively short time since 1967, there has been a great increase in the number of investigators devoting a major part of their efforts to clinical and pathological aspects of Huntington's disease (H.D.). New concepts regarding aspects of the underlying pathological physiology have appeared. The effect of L-Dopa, other chemicals, and of neurotransmitters on the disease has been studied. Development of new techniques and the refinement of previous techniques have progressed, including fluorescence microscopy, electron microscopy, and methods of chemical analysis of human brain obtained at autopsy or by biopsy.

The role of the psychiatrist with regard to the disease varies, depending on the orientation of the patient or family member and the nature and setting of the psychiatrist's practice. Useful previous reports dealing with the role of the psychiatrist in summary manner are available.

Nature of the Disease

The disease is unusual by reason of its genetic mechanism. It passes from one generation to another by a Mendelian pattern of autosomal dominant gene with almost complete penetrance. This means that a parent who carries the gene and lives long enough will ultimately develop the disease. If there are offspring, of either sex, the probability for each of acquiring the disease and passing it to their offspring in the same manner is 50 percent. Although the disease has been thought to "skip" generations there is general agreement that this never occurs. "Skipping" is usually the result of inadequate family history, or of death of a gene-carrying parent prior to the appearance of symptoms. The underlying pathology is that of a slowly progressive atrophy limited to selected sites in the brain only. It is characterized by distinctive neuropathological changes (see section on Neuropathology) in a process usually extending over a period of ten to fifteen years. Onset of more or less blatant symptoms only after the first three decades insures that a pool of individuals "at risk" for the disease is almost always available. In most populations studied to date, a prevalence of six per 100,000 general population is found. Some pockets of exceptionally high prevalence are known, as in Maracaibo, Venezuela, and in the Moray Firth area of Scotland. Knowledge of and attitudes toward the disease by the populations in areas of high prevalence should be of special interest to psychiatrists.

Clinical Picture

The symptoms of the disease may be considered as "usual early patterns" and "usual advanced patterns." The usual early patterns may have an "early onset" form with severe mental retardation, rigidity, and epileptic seizures appearing in the first year of life and rapidly progressing to profound neurological disability and death in three to five years. This early onset form has recently been shown to occur more often when the affected parent of such an offspring was the father. The attention of psychiatrists is usually not drawn to such patients. Other patterns of early onset occur in the juvenile and adolescent period. Here behavior disorders occur, including asocial, antisocial, and withdrawal disorders, emotional lability, depression, a strong tendency to sexual promiscuity, and abuse of drugs and alcohol. These patients are likely to come to the attention of psychiatrists. Recognizing the symptoms either as reactive to the presence of known disease in the family (even in instances where the offspring eventually can be shown to be gene-free by their subsequent course) or as those generated from early influence by the gene in initial stages of the actual disease presents as a challenging situation.

The symptoms in the usual advanced state are the result of years of the slow progressive selective atrophy of the brain which characterizes the disease. Symptoms and signs appear gradually, and are slowly progressive

with onset in the second and third decades. In the fourth and fifth decades they are fully developed. They include psychiatric symptoms such as irritability, hostility, assaultiveness, and depression, and behavioral symptoms including alcoholism, drug abuse, and promiscuity. Neurological symptoms appear, including chorea, incoordination, dysarthria, aphasia, ataxia, pseudo bulbar palsy and bulimia, and defects in memory, orientation and judgment. For psychiatrists it is important to recognize that psychiatric symptoms may long precede the appearance of the neurological symptoms. A tendency for depression and suicide appears to occur more frequently in females, and for assaultiveness and homicide more frequently in males. Despite the relatively low reported prevalence, there are many investigators who believe it is considerably higher. Psychiatrists should always elicit as complete a family history as possible from any patient coming to their attention because of the serious personal, social, economic and other complications arising from a failure to make early diagnosis. Psychiatric symptoms may be the only ones present for many years before the typical choreic symptoms appear. Conversely, chorea alone, late in onset, may exist with very little dementia.

The chorea is typical in pattern, characterized by the occurrence of abnormal involuntary movements (AIMS), caused by contractions of muscle groups occurring at different sites in irregular sequence. Collaboration of contracting and relaxing muscle groups is preserved, so that movements of

body surfaces or segments take place. Contractions may not be of sufficient magnitude or arrangement to cause displacement of a limb or body segment, but they can be detected by careful continuous observation. They do not occur during sleep. Standardized motion picture recording over a period of years has been extremely helpful in distinguishing at risk individuals with abnormal involuntary movements patterned as chorea from at risk individuals with normal involuntary movements (NIMS) resulting from anxiety. When sufficiently forceful and occurring at appropriate sites, the movements produce a sequence of grotesque posturing and distorted or uncoordinated voluntary movements.

Chorea may occur in any part of the visible, voluntary, muscular apparatus such as face musculature, especially perioral and periorbital, and the chest, including diaphragmatic musculature and resulting in markedly irregular breathing patterns which in themselves contribute to speech abnormalities. Speech abnormalities and very slight movements of axial musculature and of fingers tend to occur during the early stages of the disease. The inability to keep the tongue protruded is almost pathognomonic in advanced cases, and reduction in time of maintained tongue protrusion often occurs early in the adult. A tendency to familial stereotype appears not only in the time of onset of the disease (juvenile or adolescent as compared to adult) but also in the sites of choreic activity. A rigid form without chorea is recognized. A tendency also appears for offspring of patients with

Huntington's Disease to display increased frequency of medical disorders unassociated with Huntington's Disease.

A remarkable tendency to promiscuity in both young and old (lack of sexual inhibition, remarked upon in 1872 by Huntington for elderly patients) favors on the one hand illegitimacy with its attendant difficulties in tracing family lines, and, on the other hand, what appears to be a real tendency to high fecundity; families of a parent with the disease tend to be unusually large. This latter observation may very well be related to abnormally high sexual activity by reason of the underlying degeneration of especially caudate and putamen nuclei, whose purpose includes many aspects of inhibition of behavior. The apparently high parental fecundity may also be interpreted, however, as deriving from the denial mechanism which is so common in the disease.

The rate of progression of the disease may vary greatly between individuals. It is much more rapid with early than late onset cases. The influence of stress in some form of other appears unequivocal in causing symptoms to appear for the first time, or in worsening symptoms already present. Pregnancy and head injury have been reported as unusually common stressor events.

Diagnosis

Probably because of the sites of degeneration in the brain and the stress generated even in gene-free at risk individuals with a family history of the disease, an unusually long list of psychiatric and neurological disorders require consideration and exclusion. It must be repeatedly emphasized that only the affirming of a positive family history after energetic tracking of the family line, pursued with such persistence and in such depth as is perhaps done properly only by a geneticist, permits the differentiation of H.D. from other disorders. Psychiatric disorders include anxiety, which is capable of ubiquitous manifestations, and schizophrenic reactions, especially paranoid and catatonic, torticollis, tic (including the syndrome of Gilles de la Tourette), and especially depressions of one or another variety. Perioral, periorbital, and facial choreic movements are occasionally mistaken for schizophrenic grimaces. Among neurological disorders, Huntington's disease is most frequently misdiagnosed as Parkinson's disease or multiple sclerosis. Sydenham's chorea, and chorea occasionally presenting with general medical disorders should provide no diagnostic problem, but the disorders of Creuzfeldt-Jakob and Hallervorden-Spatz, familial paroxysmal choreoathethosis, cerebellar disorders including olivopontocerebellar atrophy, and the diseases of Alzheimer and Pick may present diagnostic problems resolved only by a neurologist.

"Senile chorea" probably is an entity, but can usually be distinguished from Huntington's disease by the pattern of severe AIMS in the presence of

relatively mild or absent dementia, and a well-established negative family history. Posthemiplegic chorea is almost invariably unilateral. A recent review listed eighty-five diseases to be considered in differential diagnosis.

Urgent search is underway for a specific test capable of detecting the disease before the onset of symptoms. The effort has been notably unsuccessful, except perhaps for evidence that an L-Dopa challenge may evoke choreic AIMS in at risk subjects (and worsen chorea if present already). The lack of an early sensitive test prior to onset of recognizable early symptoms has been probably the single most troublesome aspect of the management of Huntington's disease, since the stress of knowledge of its presence in the family and the drive to child bearing precede the signs and symptoms required for diagnosis in at risk individuals. Specifically, lumbar puncture and specialized examination of spinal fluid have had no value. The electroencephalogram has been shown to be without value in early stages of the disease. When disease is advanced, abnormal EEG patterns usually appear as flattening of wave forms. Pneumoencephalography shows dilated lateral ventricles and widened sulci, which characterize the ultimate generalized atrophy of affected brains. Psychological testing offers no diagnostic help. Electromyography has nothing specific to offer. Special applications of tremometry may ultimately be helpful in early diagnosis. Electro-oculography is still in the experimental stage but shows considerable promise. Cineseismography is one of the newer methods for quantifying abnormal

involuntary movements of all types, and may be helpful in a battery of tests for secondary phenomena. By this method, motion-picture records are made of movements and their detection by the sensitive surface of a metabolic scale. Brain biopsy is now being performed, and the tissue studied by a variety of sophisticated methods, but this is not practical for routine purposes, although some abnormalities in cortical tissue may ultimately be accepted as specific.

Management

The way in which psychiatrists become drawn into what is best referred to as a management relation to patients (referred to as probands in the case of the first in the family coming to his attention) and their family depends upon many factors, including the psychiatrist's type of practice, his geographic location, the administrative setting in which he may operate, and the special diagnostic resources available to him. Most patients hospitalized for Huntington's disease are in its advanced stages, and are usually found in state hospitals, Veterans Administration hospitals, or nursing homes.

Patients usually appear as troubled family members either from a direct line who are at risk and have not yet developed the disease or who are showing early signs of the disease. In either case, anxiety and depression and combinations of these may be present.

Collateral members of affected families may come to the psychiatrist's attention with symptoms of anxiety and depression arising from their awareness of the disease if it has only recently come to their attention and they have little knowledge of its nature. In any case, psychotherapy is indicated in whatever form the psychiatrist can offer, and this does not exclude patients with the disease suffering from its nonneurological consequences. The first priority of therapy should be to insure that the patient's knowledge of the disease is as complete as he is capable of

comprehending, the information being communicated by a therapist who is free of anxiety. This may take preliminary exploration of the area, and instruction over a period of time. Indeed this educational process alone may, if properly handled, alleviate much of the symptomatology. If a definite diagnosis has not been made, there should be no hesitation by the psychiatrist to refer to a neurologist or a medical center. Most experience, contrary to what might be expected, is that a positive diagnosis is less likely to generate symptoms than it is to relieve them. This is apparently because uncertainty by itself creates fear or anxiety. It is always desirable to proceed carefully giving knowledge concerning the disease, and especially in conveying the fact that diagnosis has been made. Many patients stoutly assert that they wish to know whether they have the disease when, in fact, at least for the moment, they do not. However, if a patient is asked, why he wishes to know, one can be guided by the answer: "I would find the nearest tall building and jump off it." This carries quite different implication than "At least I would know and be able to plan in advance depending on how bad my condition might become." Psychotherapy should resort to the aid of professional genetic counseling if available, Sometimes it is not; references to detailed reports of management are provided in this chapter. In addition, referral may be made to special resources, such as geographical listing of genetics counseling centers regularly updated by the National Foundation-March of Dimes. The Committee to Combat Huntington's Disease now has chapters in almost every

state, and the national organization in New York can provide information about a nearby chapter. Contact by patients with these chapters usually provides strong additional support for psychotherapy. In some situations, physical, social and economic assistance may be available, as in the Veterans Administration. Legal referral may occasionally be necessary because individuals may have problems relating to vocational, professional, and economic planning, marital and parental situations, or insurance and driving coverage. With regard to application forms, individuals should usually be informed that if they are truthful concerning the presence of Huntington's disease in the family, they may risk rejection or increased insurance premiums, or be subjected to special tests for a driver's license. If they are not truthful, and difficulties arise they may lose insurance coverage and be subject to heavier penalties for damages incurred in accidents. Problems of this nature often require a psychiatrist, but unfortunately they do not always have the information to offer. Very often the expectation is that somebody else will take care of this responsibility, such as a neurologist or a geneticist. The result is that the patient is never provided with the information he requires in order to advance the psychotherapeutic relation which should always include correct information, appropriately presented. The situation is analogous to many of those arising from overspecialization in medicine, unless provision is made for specifying functions in an organization. Of course, in some rural situations a psychiatrist may be the only individual

available to a family either to alert a family to the presence of Huntington's disease or to see that their needs are properly met.

A variety of medications are effective in the psychiatrist's handling of patients, whether they are symptomatic with chorea and non-neurological problems, or at risk. A series of effective antichoreic medications include reserpine in doses increasing from 2 to 12 mg. per day; chlorpromazine in appropriate dosage, usually 50 mg. three times a day or single dose at bedtime, and fluphenazine or halo-peridol, either given in dosage from 2 to 15 mg. per day. All these medications usually are increased by steps over a period of several weeks. Benefit to the chorea, anxiety, and delusions or other mental aberrations should be expected before adverse side effects, usually drowsiness or dystonic reactions. The latter can be appropriately managed with benztropine in dosage of 2 mg. or biperiden (2 mg.) 2 mg. twice a day or more. Diazepam is useful during the day and for sleep, as is the newer compound fluorazepam.

Depression, which is so frequent and common, responds to antidepressant medications, which the psychiatrist should choose as he desires. Imipramine in dosage of 50 mg. three times a day or single dose at bedtime is quite reliable. In some instances antidepressants alone may worsen the chorea.

It is more generally recognized that neurosurgical procedures on brain or peripheral nerves is of no benefit, and may damage a tissue already undergoing progressive handicap.

Complications in early stages include depression of suicidal degree which should be handled appropriately; Huntington's disease is no contraindication of electroconvulsive therapy. As the disease advances, the neurological symptoms singly or in combination usually lead to bedfast state, and watch must be kept for the usual complications of pneumonia, skin ulcers, fractures of long bones or skull, urinary tract infections, and the like.

In conclusion, Huntington's disease can be seen as a condition that may be rightfully judged a paradigm for hereditary medical disorders in general and for psychiatric disorders in particular, complicated by neurological symptoms.

B. Neuropathology

Dunlap supplemented the literature review (See references 1, 2, 8, 9, 33, 38, 39, 40, 43, 45, 47, 48, 51, 82, and 90) with a personal detailed neuropathologic study based on seventeen positive[2] cases of Huntington's chorea, twelve questionable cases, and thirty or more control cases. Many selective destructive lesions in the human striatum had failed to give clear evidence of any definite function of this region. Wilson's experimental work on anthropoid animals "in which the striatum was first electrically stimulated and then in large part destroyed on one side," showed little, if any, difference from normal controls. Therefore Dunlap attempted (in the above mentioned study) to determine whether gross or microscopic changes could be found in the central nervous system "in all cases of Huntington's chorea which would distinguish this disease process from all others."

Grossly, the brains in the "positive" cases of Huntington's chorea were small and of diminished weight. The reduction was chiefly, if not entirely, in the forebrain, with marked general atrophy affecting the convolutions, the deep white matter, and particularly the corpus striatum, which was less than half the normal size. The cerebellum was regarded as essentially normal in all cases except one, and its average weight equaled that of the controls, but further study would have been desirable. No conclusions were reached regarding the other nuclear constituents of the extrapyramidal system.

Microscopically, the corpus striatum showed a remarkable loss of nerve cells in the putamen, especially in the posterior three fourths; less loss in the anterior fourth and in the head of the caudate nucleus; and probably no loss of nerve cells in the globus pallidus. In the majority of cases, an extensive neuroglial proliferation, most marked where the neurons were fewest, was noted. In the red nucleus no constant or definite neuronal or neuroglial changes were identified. The corpus subthalamicum and the substantia nigra were too little studied to justify a definite opinion.

The nerve cells of the cerebral cortex were nearly always "dark staining, small, and shrunken in appearance." The cytoarchitecture was not obviously disorganized, and as a whole, the neurons were "probably" not reduced in number as compared with the control cases. The neuroglial nuclei of the cortex looked smaller, darker, and more abundant than in the control cases. The neuroglial fibers were usually most abundant in the zone of junction of gray and white matter or in the deepest layers of the gray matter, where many of the glial nuclei were large, pale, and vesicular.

The white matter of the cerebral hemispheres, in general, was thought to be considerably more reduced in amount than the gray matter. No abnormality in the gray or white matter of the cerebellum or in the dentate nucleus was observed, with the exception of one case (see further comments on pp. 421-422; electron-microscopic observations on pp. 425-432, and H.C.

in children on p. 422).

In conclusion, Dunlap felt that there were constant lesions of a definite type in the corpus striatum and in the gray and white matter of the cerebrum. Several authors (See references 34, 49, 57, 59, and 60) have found changes similar to those described by Dunlap. Some authors, in addition, have described areas of tissue necrosis which doubtless had a vascular origin but such lesions sometimes appeared distant from the involved blood vessels, being then possibly a sequence to angiospasm. Such findings, however, were not specific or of constant character and were found not to be related to the duration of the disease.

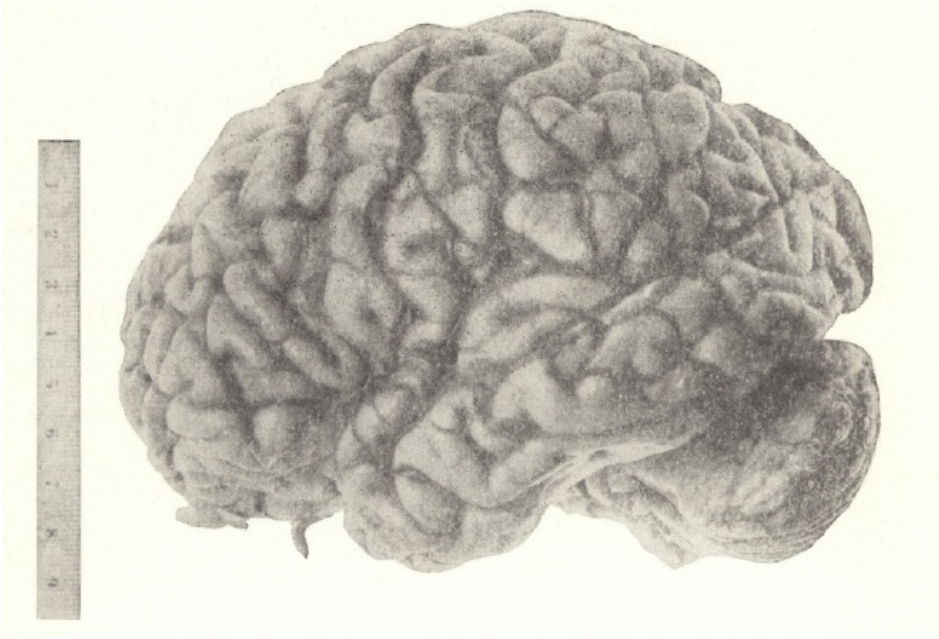
Subsequent studies by Davidson et al. essentially confirmed Dunlap's findings, with the exception that these investigators observed more marked changes in the third cortical layer of the cerebral cortex and changes in the cerebellum in two of the three cases studied. In contrast to Dunlap's cases, but in conformity with Jakob's, they found that the rostral portions of the striatum were more involved than the caudal.

In view of the fact that these minor discrepancies could also be attributed to some individual variability of the disease process and possibly some difference in investigative techniques, we (Roizin and Kaufman) reviewed some of Dunlap's original material and added ten selected

unquestionable cases of chronic, progressive Huntington's chorea. We shall mention only some of the most outstanding neuropathological findings in our series.

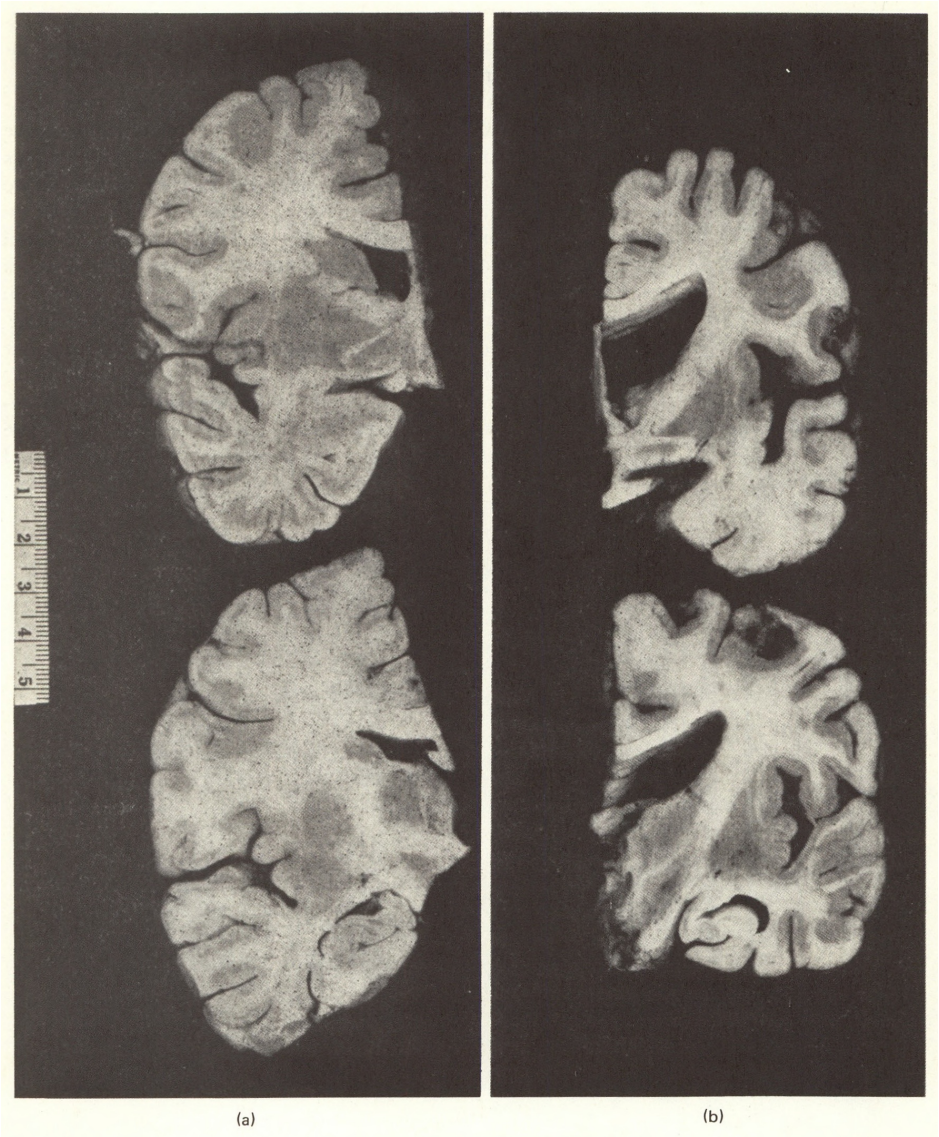
Microscopic examination of the CNS revealed, in general, various degrees of atrophic changes of the cerebrum (Figure 17-1) and loss of weight. The leptomeninges, particularly over the atrophic gyri, often appeared thickened. Coronal or horizontal sections of the brain revealed various degrees of narrowing of the cerebral convolutions, deepening and widening of the sulci, thinning of the gray and white matter of the cerebrum and corpus callosum, variable atrophic changes of the caudate nucleus and putamen, and variable degrees of internal hydrocephalus frequently, but not exclusively, of the anterior horns of the lateral ventricles (Figure 17-2). In some cases the brain stem also appeared somewhat smaller than in comparable controls.

Figure 17-1



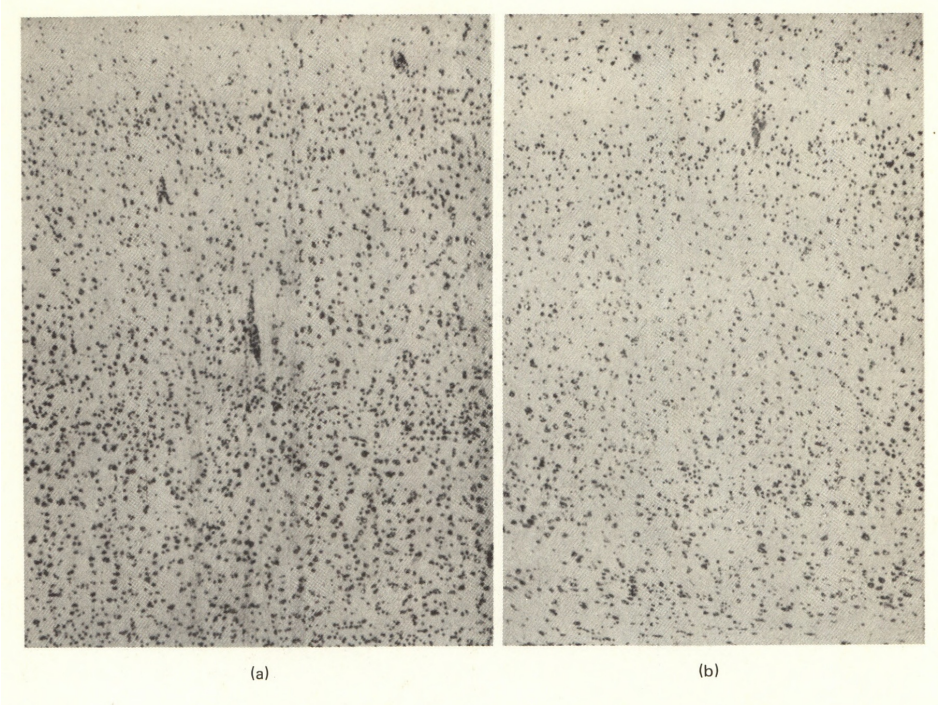
Huntington's chorea. Gross appearance of the brain, revealing pronounced atrophic changes.

Figure 17-2.



(a) Coronal section through a control brain; (b) Huntington's chorea as described in the text.

Figure 17-3.



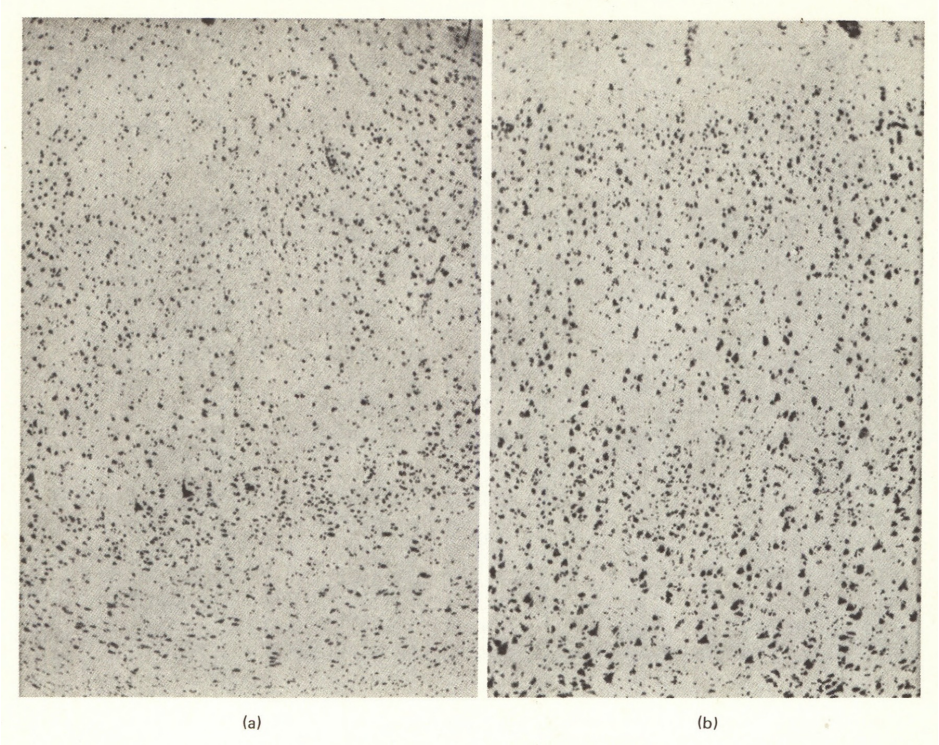
(a) Section from the frontal lobe of a control case; (b) section from the same region (approx.) of a case of Huntington's chorea, revealing prominent reduction in number of the nerve cells in various cyto-architectural areas. Nissl stain. Low-power magnification.

Microscopic examination disclosed a degenerative, generally chronic, process of variable intensity and distribution. In some instances the middle layers appeared more prominently involved (Figure 17-3 (b)), in others the deeper layers; in still others, the involvement appeared more diffuse in

character (Figure 17-4 (a)). Here and there, circumscribed neuronal rarefraction or small acellular areas were also encountered (Figure 17-4 (b)). Though frequently the smaller neurons appeared severely involved, in some instances the large pyramidal cells showed chromatolysis as well as lipid degeneration. Increased neuroglial density (marginal or subcortical) was observed particularly in association with the more pronounced degrees of atrophy. Neuronal degeneration and various degrees of numerical reduction were observed in the putamen and the head of the caudate nucleus. Generally, the most marked involvement was of the smaller nerve cells (Figure 17-5 (a)), but the larger neurons Figure 17-5 (b)) in the putamen and caudate nucleus as well as in the globus pallidus were not always spared. As a matter of fact, Sudan III and Sudan black stains, particularly in long-standing chronic cases, revealed the presence of increased intraneuronal lipid material. Similar changes were also encountered, in various degree, in the hypothalamus, in the different nuclear formations of the brain stem and medulla (particularly the inferior olives), and in the Purkinje cells and dentate nucleus of the cerebellum. In some cases the Ammon's horn also appeared to be involved. Increased satellitosis, pseudoneuronophagia, and neuronophagia were, at times, prominent in the caudate nucleus and putamen. In the same structures, increased gliosis (Figure 17-6), fibrillary as well as protoplasmic, was frequent. In some instances hypertrophic astrocytes were quite prominent and frequently independent of the blood-vessel walls. There was

periaqueductal gliosis in some cases, and in one case marked atrophy and severe gliosis of the inferior olivary nuclei of the medulla were noted. Myelin-sheath stains disclosed in four cases some sub-cortical pallor and myelin rarefaction as well as poor differentiation of the tangential systems. Almost complete status dysmyelinatus was present in two cases. Moderate arteriosclerotic changes with some lipid deposits and perivascular fibrosis were noticed in five cases. In one instance calcium deposits within the walls and in a perivascular location were observed. Abundant deposits of calcium and amorphous material giving an intense iron reaction, involving particularly the basal ganglia, were found in one case. Now and then, amyloid bodies in a periventricular location, in perivascular areas, or in the white matter were also identified. Senile plaques were detected with silver impregnation in one case.

Figure 17-4.

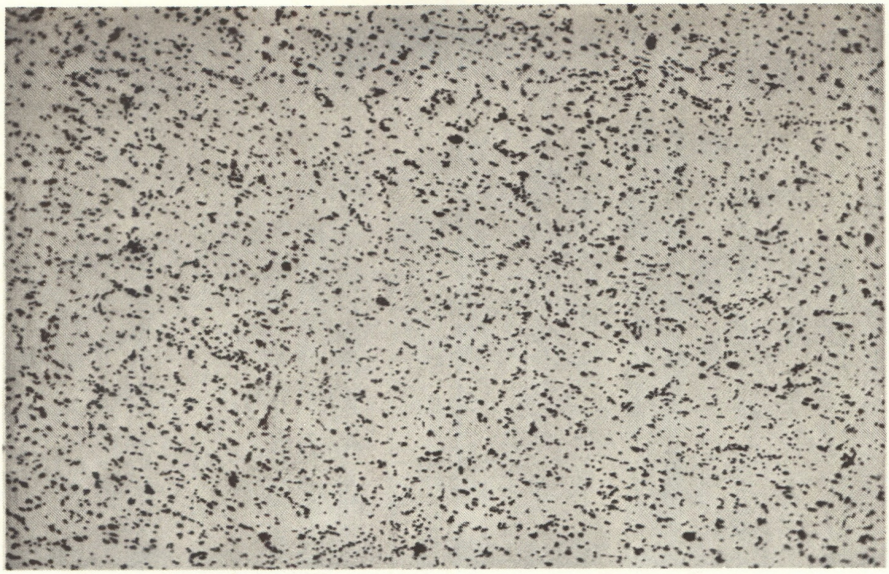


Huntington's chorea. Cortical regions showing (a) diffuse and (b) small, focal areas with reduction in number of neurons. Nissl stain. Medium-power magnification.

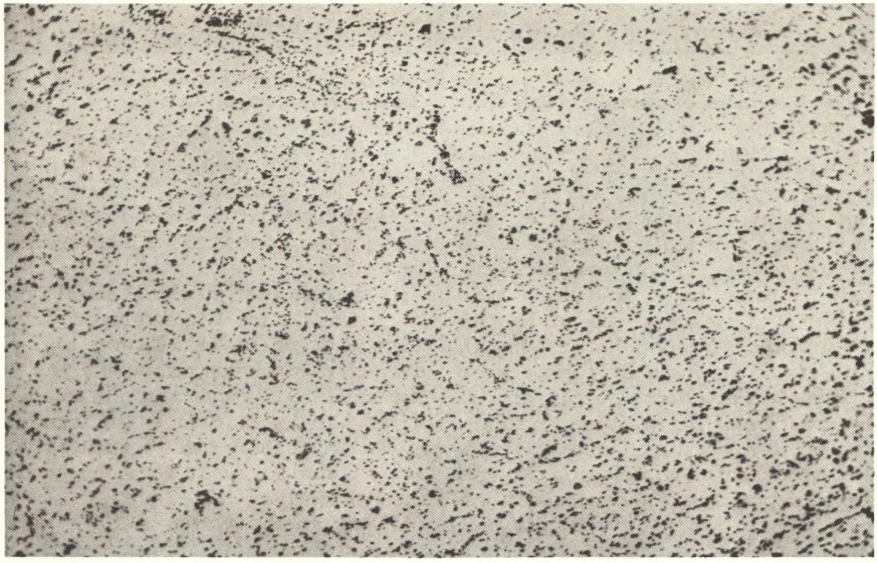
Clinicopathological studies on Huntington's chorea occurring in the first decade are considered to represent about 1 percent of the total number of patients. The incidence of this disease in the general population is one in 24,000. In addition, typical choreatic movements are often absent in children.

Instead they may have hypokinesia, muscular rigidity, epilepsy, cerebellar symptoms, and mental retardation. The cause of death is frequently bronchopneumonia.

Figure 17-5.



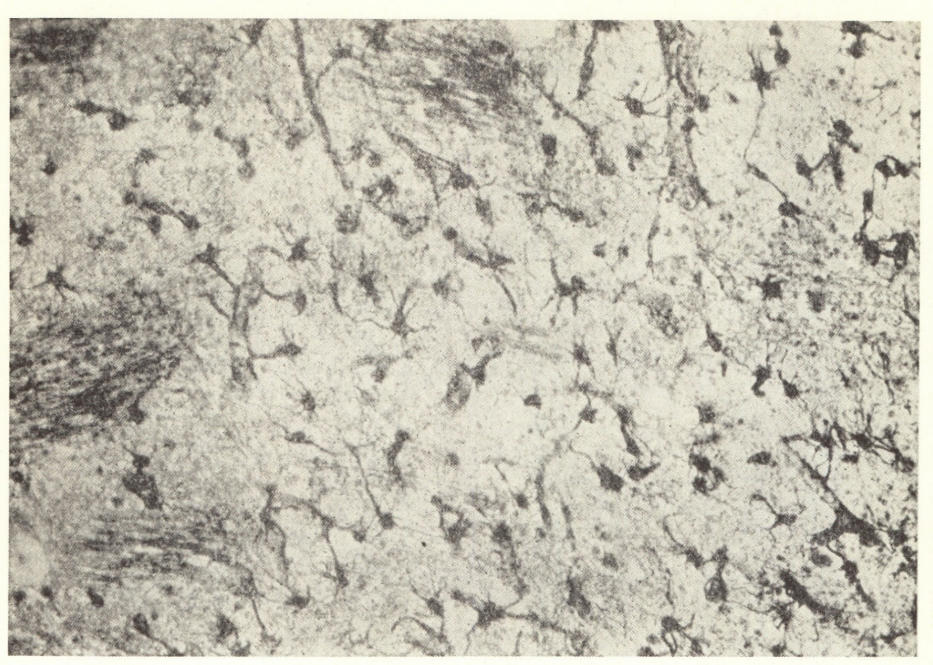
(a)



(b)

Huntington's chorea. Putamen: (a) Various degrees of very pronounced diminution of the neurons (particularly of the small nerve cells) and (b) neuronophagia and increased density of glial nuclei. Nissl stain. Low-power magnification.

Figure 17-6.



Huntington's chorea. Putamen: Astrocytic gliosis as described in the text. Cajal's gold sublimate impregnation. High-power magnification.

Grossly the cerebrum and the cerebellum show various degrees of generally diffuse[3] atrophy (brain weight 940-980 g.). There is a striking decrease in size of the caudate nucleus, less marked reduction of the putamen and slight of the globus pallidus.

The most common microscopic findings consist of various degrees of

decrease in neurons throughout the cerebral cortex. Pronounced to complete loss of neurons in the caudate nucleus is the most frequent feature. In the putamen often only a few large neurons are present with frequent absence of all small ones. The globus pallidus may show some loss of neurons or be well-preserved. Decrease of neurons is also encountered in the subthalamic and red nuclei. The substantia nigra contains less pigment than expected, usually without loss of neurons.

In the cerebellum, the folia are atrophic and the molecular layer reduced in width. The Purkinje cells are particularly depleted. Granular and dentate nuclei neurons are also reduced in number.

In some instances considerable loss of neurons was observed in the inferior olives of the medulla.

Sparse fat-laden cells in the perivascular regions, moderate decrease of myelin in the globus pallidus, very pale or diminished strionigral fibers were prominent in certain cases. Also dense gliosis of globus pallidus, putamen, and Bergmann's layer, as well as increased glial reaction in the molecular layer and dentate nuclei of the cerebellum have been observed in several cases.

It appears from earlier clinicopathological studies that, in the classical type of Huntington's chorea, the neuropathological process is of a

degenerative, chronic, and progressive character, involving principally the neurons of the caudate nucleus and putamen, and to a somewhat lesser degree the cerebral cortex. However, in some cases correlated systems also are affected, though to a lesser degree and inconsistently.

From an etiopathogenetic point of view, some authors have interpreted the lesions as a primary degeneration of the small cells of the putamen caudate system and of the third and fifth cortical layers. The Vogts Jakob, and others assumed that these two sets of structures comprised a "biologically combined organ" subjected to an abiotrophic[4] process As was demonstrated above, however, the lesions in Huntington's chorea are generally diffuse and not specific in character. Other authors regarded the lesions as being due to a "primary progressive gliosis" and the neuronal degeneration as being secondary in character. On the other hand, some investigators believed that vasular involution comes first, and that both parenchymatous and glial changes are secondary. The diversity of opinion seems to indicate that, thus far, specific and consistent data are not available for conclusive determination of the pathogenetic mechanisms in Huntington's chorea (See references 27, 28, 58, 65, 67, 75, and 92). It would appear that the choreic individual is congenitally predisposed to develop, at a certain period of life, the characteristic clinicopathologic syndrome which we have briefly reviewed. Hence, heredity has assumed the role of the principal "etiopathogenetic" factor.

Inborn errors of metabolism in degenerative processes (See references 25, 31, 76, 77, and 84) and mental disorders have been suggested as possible factors, based upon the assumption that the morbid changes may be caused by the lack of specific enzymes. Mental abnormalities as by-products of inborn biochemical errors of different degree have been ascribed to phenylketonuria, porphyria, methemoglobinemia, amaurotic idiocies, gargoylism, and other cerebral lipoidoses, as well as to some involutional degenerative processes such as Alzheimer's and Pick's presenile psychoses, although the pathognomonic enzyme abnormality has not been specifically identified as yet. A similar parallel inborn biochemical abnormality also could be assumed for Huntington's chorea. In support of this suggestion, one should consider that, according to some investigators, hereditary dispositions due to metabolic errors are mainly of two kinds. The first type is almost always genetically homozygous and the affected subject lacks an enzyme because the abnormal genes present in duplicate fail to produce it. These people show signs of a constant abnormality throughout life, or at least from an early age. A carrier with one normal and one abnormal gene is still able to make the necessary enzyme. The second type is less regular in appearance and can have a dominant inheritance. At times, the inborn error gives rise to symptoms only under special circumstances or stress (see below).

During the last two years our combined electron-microscope and histochemical-enzyme studies revealed the following salient findings: (1) The

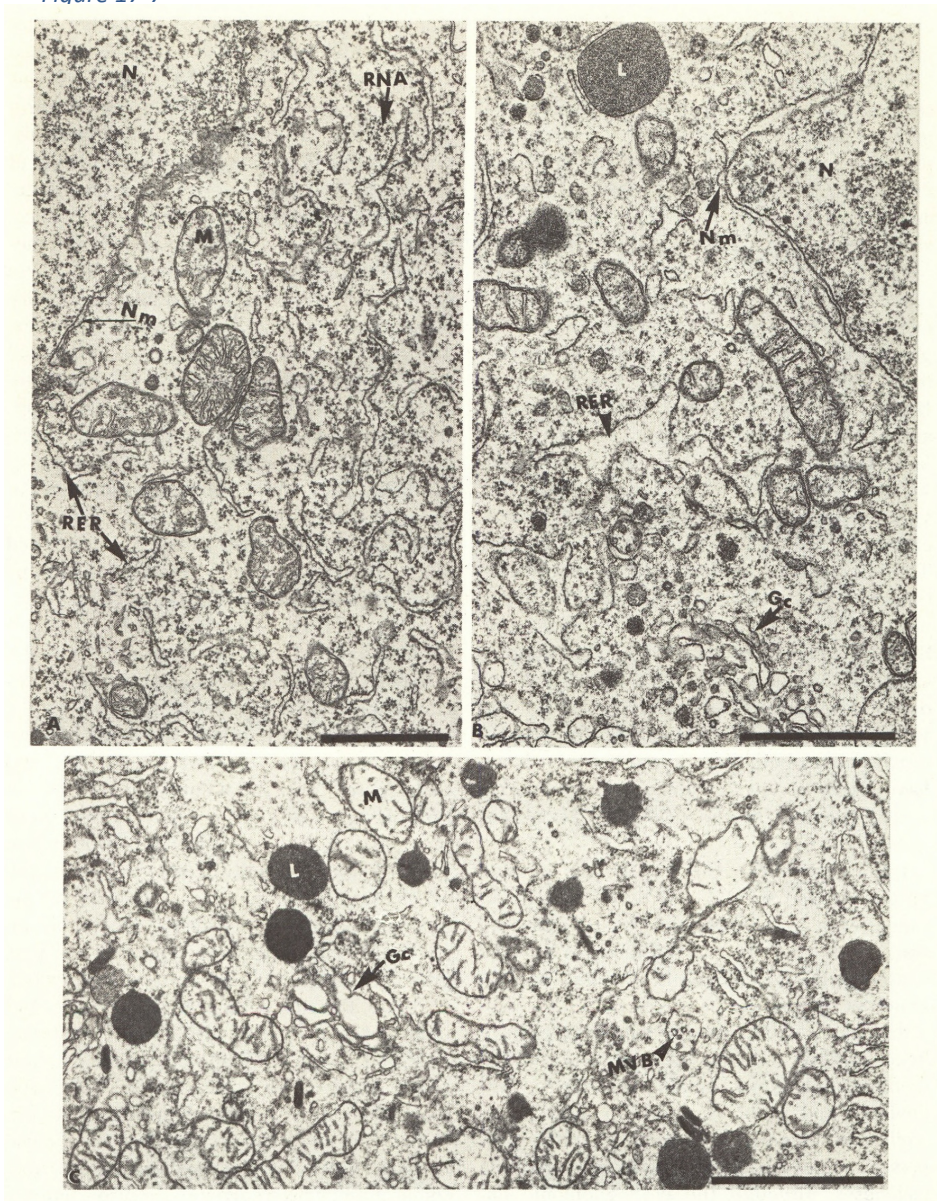
fine structure of the nuclei of cerebral cortical neurons appeared, at times, denser than usual and contained clumps of circumscribed masses of compact osmiophilic granules and/or irregularly dispersed particulate material. The nuclear membranes and their "pores" also show fine structural alterations. Enzyme reaction products of acid phosphatases (AcP) and glucose-6-phosphatase (G-6-P) were usually observed in higher concentrations in the denser regions of the nucleus and at the periphery. (2) Some nucleoli also showed changes and only the pars granulosa and chromosa were differentiated. At times the nucleolus contained dense and light zones composed of granular material.

The rough endoplasmic reticulum was scanty and irregularly distributed. Frequently there were abnormal enlargements of the cisternae. In some instances the cisternae showed varying degrees of degranulation. Free ribosomal granules were irregularly dispersed and often reduced in number (Figure 17-7). (4) The Golgi canaliculi formed irregular patterns and frequently the canalicular outlines were blurred and their lumens not discernible (Figure 17-8). The distribution of AcP, G-6-P, and TPP (thiamine pyrophosphatase) reaction products differed and, at times, they had an extracanalicular location. (5) The lysosomes displayed marked variations in number and many were pleomorphic. They showed various stages of metamorphosis particularly in the vicinity of or within areas containing lipid products and lipofuscin bodies (Figure 17-9). AcP, G-6-P, and, to a lesser

degree, TPP reaction products were distributed in various concentrations and configurations in lysosomes which were in various stages of auto- and heterophagism. (6) Degenerative products showing variations in osmiophilia were frequently observed in contact with or intertwined with multiforme varieties of lipofuscin bodies (Figure 17-10). The latter were most often observed in the cytoplasm of neurons, particularly in the perinuclear regions. They were also encountered in the glial cells (Figure 17-11), in perivascular regions, and in lesser numbers within the blood-vessel walls. AcP, TPP and G-6-P reaction products were irregularly distributed in differing concentrations, except within vacuolated structures where they were lacking (Figure 17-12). (7) Glycogen granules were found particularly in glial cell processes in the neurophil often in perivascular areas. They were occasionally seen in the axoplasm of neurons or in the presynaptic terminals. (8) Mitochondria (polymorphometabolosomes) showed variation in number, shape and size. There were also concomitant variations in the configuration of the cristae and osmiophilia of the matrix. Some mitochondria contained AcP reaction products. (9) Multi vesicular bodies and heterogeneous bodies which varied in number, configuration, and osmiophilia also contained AcP, TPP, and G-6-P reaction products. Centrioles were sometimes seen in the vicinity of the Golgi system. (10) Of the synaptic complex, the presynaptic terminals often showed reduced numbers of vesicles, which, at times, were associated with variable numbers of organelles some of which were undergoing degenerative changes.

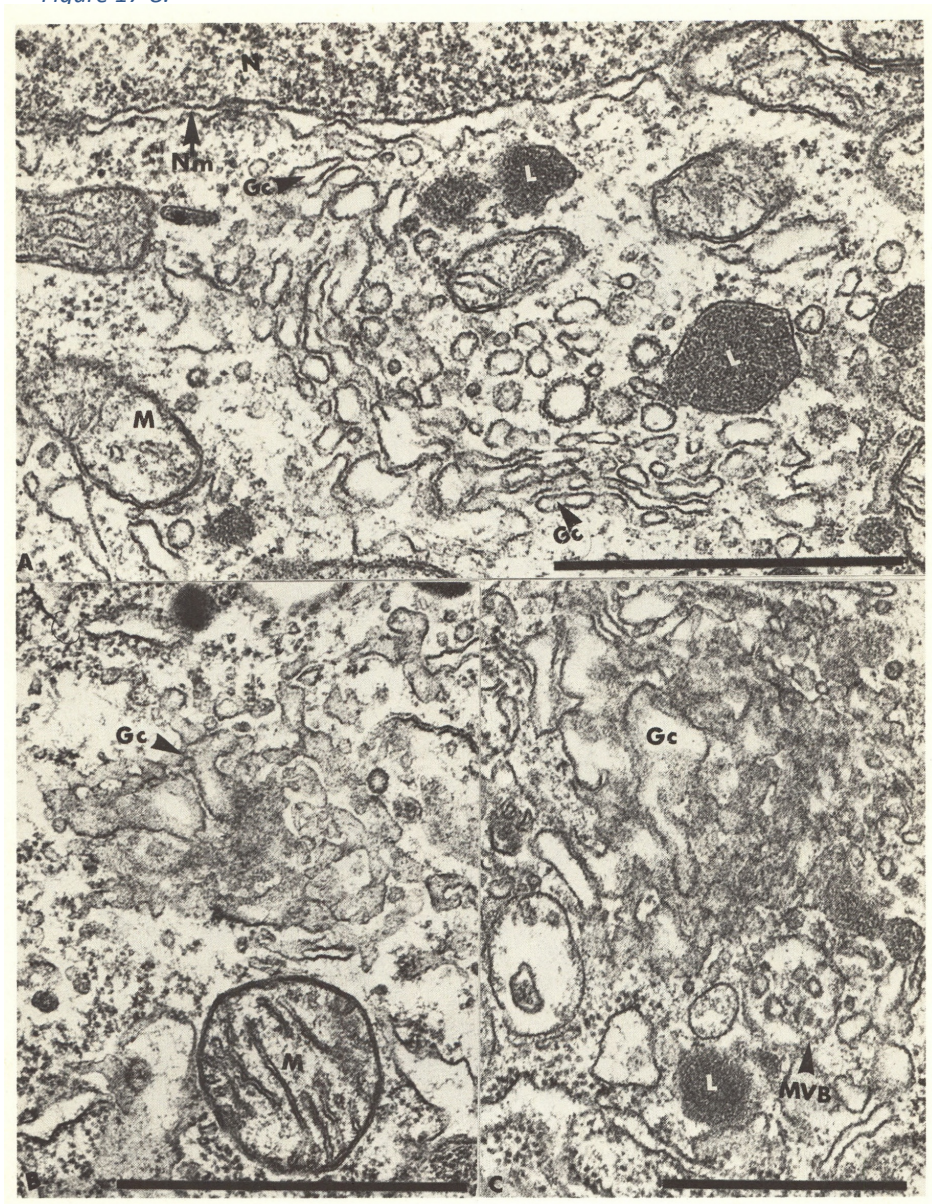
Variations in the fine structure and osmiophilic character of the synaptic cleft and subsynaptic web were observed. (11) In several instances the axoplasm contained variable numbers of mitochondria and organelles which gave an appearance resembling axonal dystrophy (Figure 17-13). In addition, AcP and G-6-P reaction products were found in differing concentrations independent of the presence of organelles (Figure 17-12). (12) Intra- and interlamellar myelin degeneration was observed in some cases. Our control material is still inadequate to make appropriate comparisons. However, these findings in cerebral biopsies of Huntington's chorea[5] augment those reported previously by Tellez-Nagel et al. in that additional histochemical studies were carried out which have enabled us to demonstrate previously undescribed pathological features.

Figure 17-7



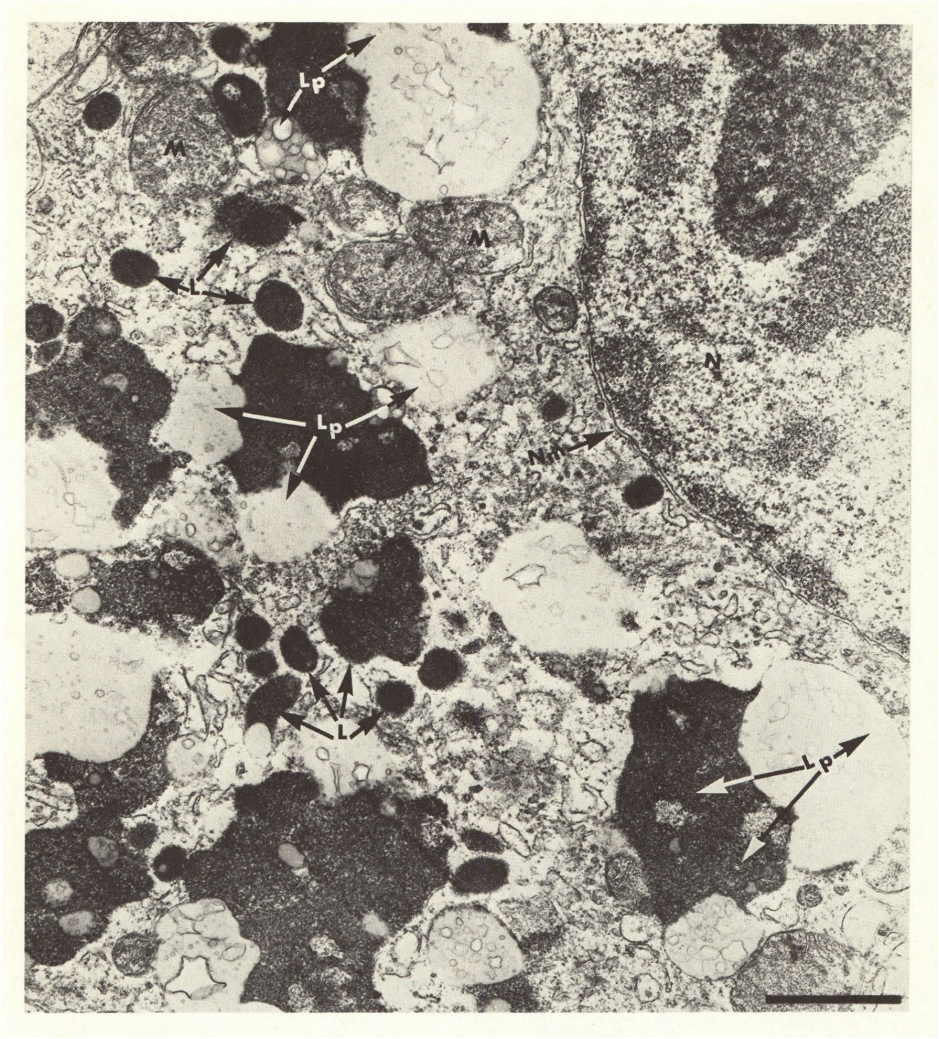
Various degrees of fine structural changes of the rough endoplasmic reticulum and RNA distribution in the cytoplasm of some neurons as described in the text. Magnification: (a) X29,500; (b) X35,400; (c) X39,530. Scale: 1 mm = 1000μ
Explanation of symbols: Gc = Golgi complex or the smooth component of the endoplasmic reticulum; M = mitochondrian; MVB = multivesicular body; Nm = nuclear membrane; N = nucleus; RER = rough component of the endoplasmic reticulum; RNA = ribosomal granules.

Figure 17-8.



Various stages of fine structural changes and disorganization, especially of the Golgi system as described in the text. Magnification: (a) and (b) X64,900; (c) X45,815
Scale: 1mm. = 1000μ
Explanation of symbols: Gc = Golgi caniculi; L = lysosomes; M = mitochondrian; MVB = multivesicular body; N = nucleus; Nm = nuclear membrane.

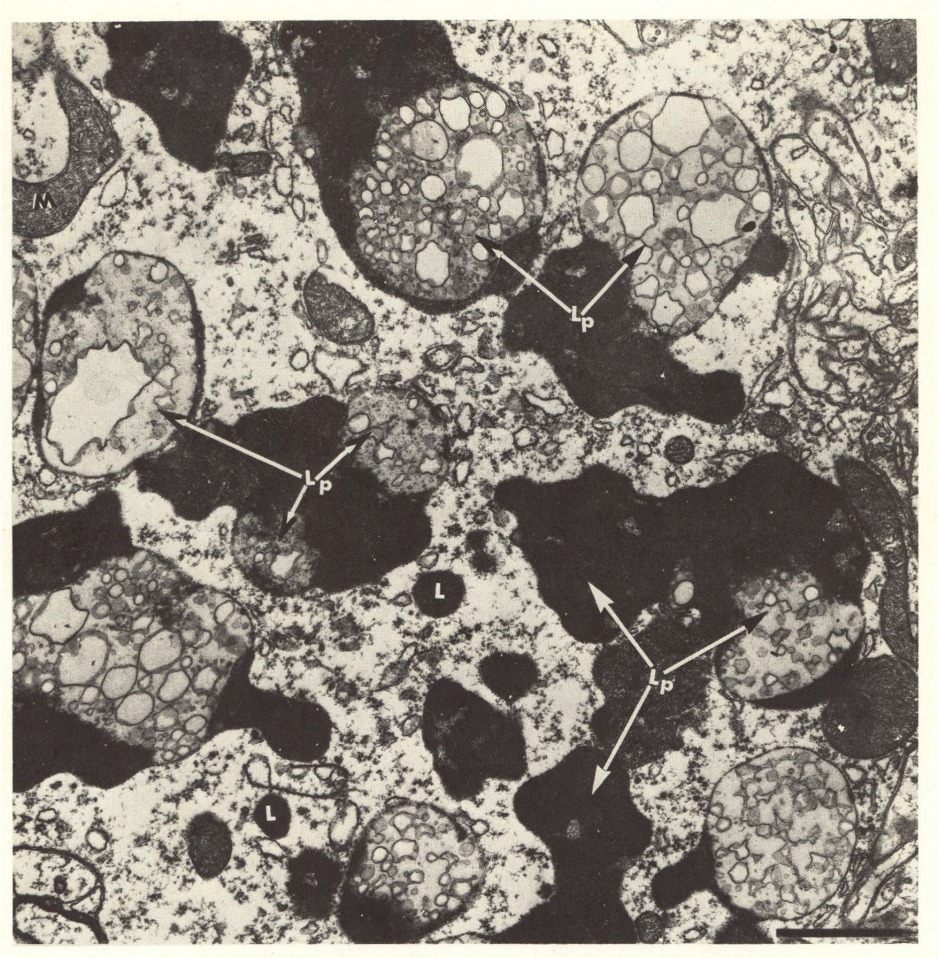
Figure 17-9.



Pronounced degeneration of the neuronal cytoplasm associated with lipid products of degeneration and lipofuscin. Lipid products of degeneration

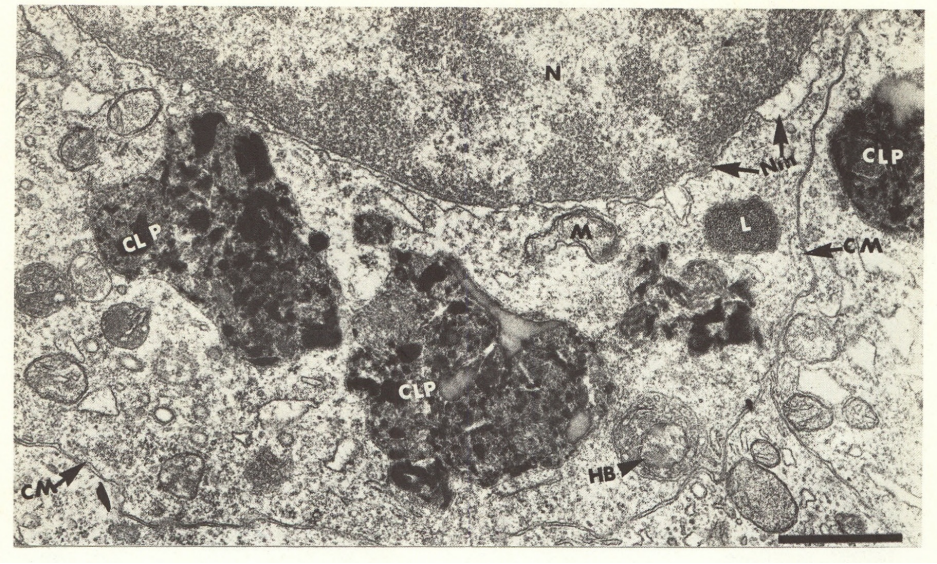
intertwined with lipofuscin pigment associated with increase in number of lysosomes. Magnification: X28,560
Scale: 1mm. = 1000μ
Explanation of symbols: L = lysosomes; Lp = lipofuscin compounds; M = mitochondrian; N = nucleus; Nm = nuclear membrane.

Figure 17-10.



Multivacuolated lipofuscin structures intertwined with degenerative lipid material. Magnification: X 25,960
Scale: 1mm. = 1000μ.
Explanation of symbols: L = lysosomes; Lp = lipid with lipofuscin vacuolated structures; M = mitochondrion.

Figure 17—11.



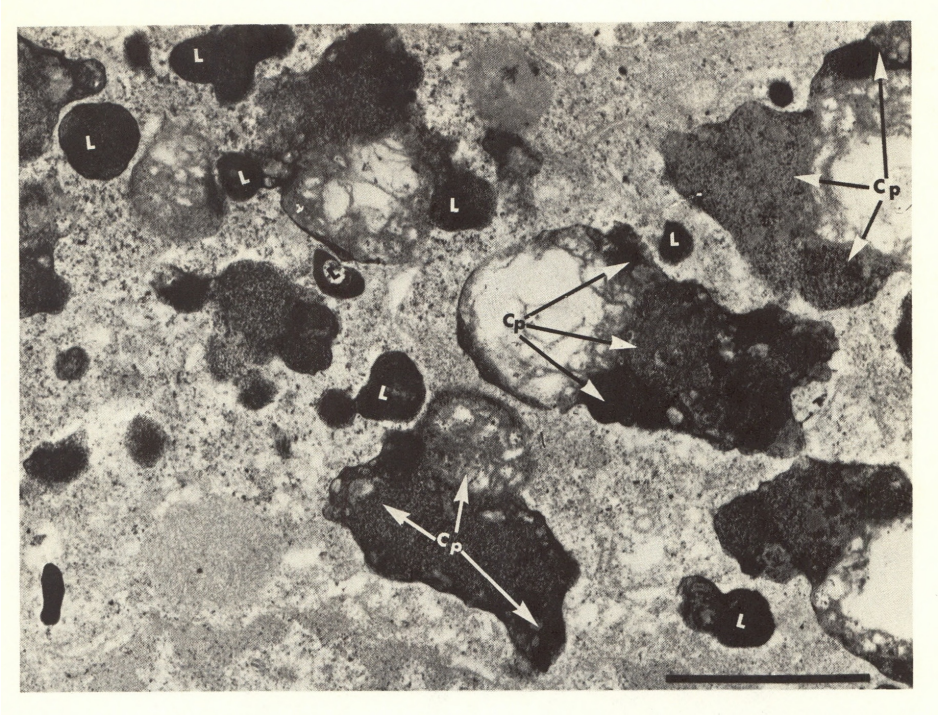
Composite lipid products undergoing digestive processes in cytolysomes as described in the text. Magnification: X26,550.
Scale: 1mm. = 1000μ
Explanation of symbols: CLP = composite lipid products; CM = cellular membrane; HB= heterogeneous body; L = lysosome; M = mitochondria; N = nucleus; Nm = nuclear membrane.

Although our understanding of possible pathogenic mechanisms based on electron-microscope studies is limited, since only the cerebral cortex was examined, similar investigations will be carried out on basal ganglia tissue when it becomes available. With these factors in mind we would like to hypothesize as follows: (1) The ultrastructural alterations in the nucleus and nucleolus, the changes in the endoplasmic reticulum including degranulation,

and the irregular distribution and decrease in the number of cytoplasmic ribosomes may be related to disordered protein metabolism. Further studies are needed to determine whether these findings can be correlated with the protein abnormalities recently reported in Huntington's chorea by Igbal et al. (2) Some investigators (Novikoff et al. and Roizin et al.) have suggested that the endoplasmic reticulum is in communication with the nuclear membranes, lysosomes (and correlated structures), and multivesicular bodies and that it serves as a unitary system concerned with intracellular transport mechanisms. In light of these considerations, it appears possible that the fine structural alterations and irregular distribution of the AcP., G-6P, and TPP reaction products in the Golgi complex and related organelles might be due to a disorder of intracellular transport mechanisms. With respect to the latter it would be of interest to consider its possible significance in lipofuscin body formation in the sense that the degenerative changes of the Golgi canaliculi and its subunits may interfere with or deprive the lysosomes of a continuous supply of the enzyme systems necessary for digestive mechanisms (DeDuve and Wittaux). The subsequent accumulation of the lipofuscin bodies may not only be the result of a failure of cell exocytosis (Brunk and Ericsson10), but it may also be due to the fact that the accumulated "residues" were incompletely digested or metabolized as a result of a lack of some lysosomal enzymes. This might result in a molecule which is too large to pass readily through the membranes. (3) The axonal involvement and some of the fine

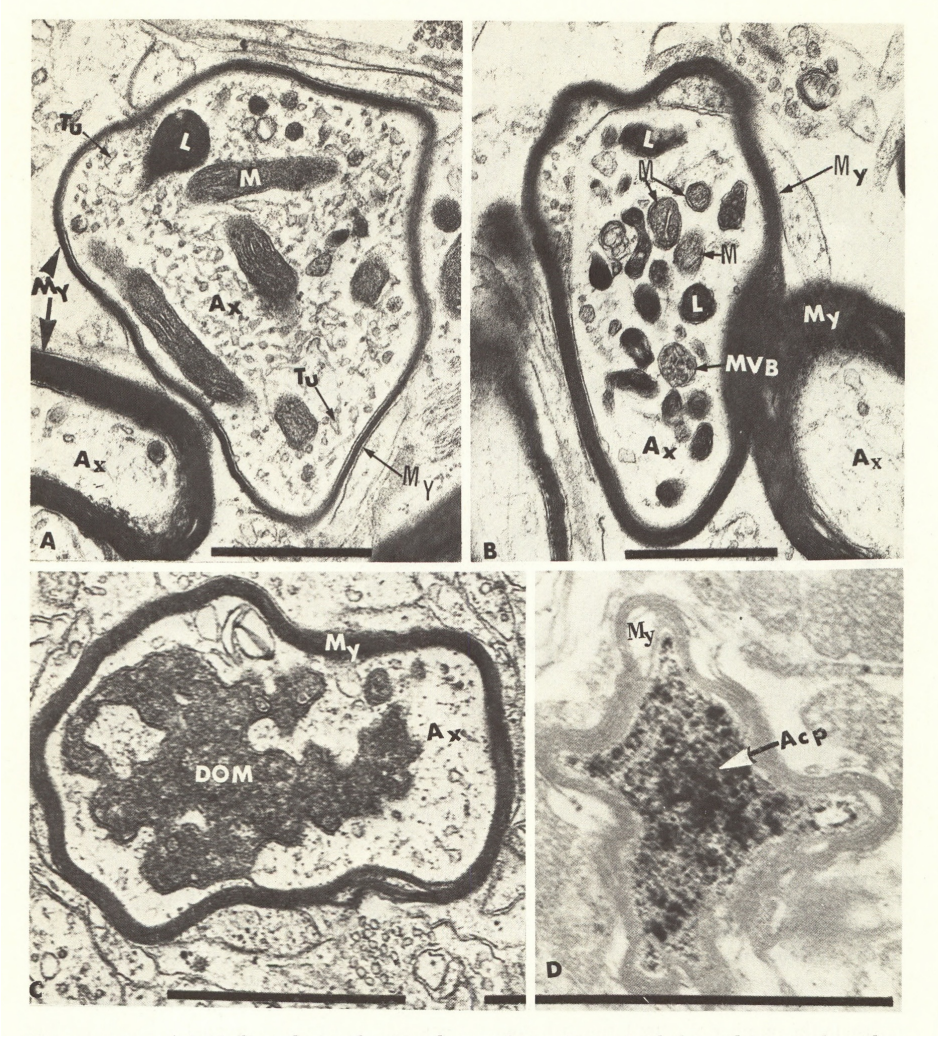
structural alterations of the synapses and their respective subunits may represent some functional and histochemical disorders of the neuronal communication mechanisms.

Figure 17-12.



Combined electron-microscope and histochemical reaction for glucose-6-phosphatase showing presence of various amounts of glucose-6-phosphatase reaction products as described in the text. Magnification: X45,720.
Scale: 1mm. = 1000μ
Explanation of symbols: L = lysosme; Cp = composite lipofuscin, glucose-6-phosphatase enzyme reaction products distributed over portions of dense lipofuscin structures.

Figure 17-13.



(a) Myelinated axon showing pleomorphism of neural tubules and increased number of organelles. Magnification: X30,480. (b) Myelinated axon with

axoplasm containing a large number and variety of organelles undergoing some degenerative changes. Magnification: X28,650. (c) Myelinated axon revealing dense osmiophilic material as described in text. X40,650. (d) Axoplasm field with acid phosphatase reaction products. X77,290.
Scale: 1mm. = 1000µ.
Explanation of symbols: AcP = acid phosphatase reaction product; Ax = axon; DOM = dense osmiophilic material; L = lysosomes; M = mitochondrian; MVB = multivesicular body; My = myelin; Tu = neural tubules.

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Notes

1 The author wishes to acknowledge the assistance of Pearl Band and Roslyn Laiterman in preparation of the clinical aspects of this chapter.

2 Every member of this group had, in addition to the characteristic motor disorders and mental symptoms of Huntington’s chorea, a family history of uninterrupted heredity from parent to child, and was considered free from all objections.

3 In some instances particularly fronto-parietal.

4 This is a term coined by Gowers to indicate an inherent constitutional weakness or a “defective vital endurance” and “premature decay” of the affected parts of the nervous system.

5 This biopsy material is part of a multidisciplinary research investigation on Huntington's chorea carried out in cooperation with S. Stellar, N. Willson, and J. Whittier, supported in part by the St. Barnabas Medical Center Research Foundation for the Neural Sciences.