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CHEMICAL PATHOLOGY OF HUNTINGTON'S DISEASE

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INTRODUCTION

The primary genetic defect in Huntington's disease has not yet been identified, but some new insight into the brain abnormalities that exist in this tragic disorder has come from recent findings of histopathological and neurochemical changes in postmortem brain.

George Sumner Huntington became aware of chorea in certain families of his father's practice in Easthampton, Long Island, and his description of the clinical characteristics of this disorder were so accurate and clearly described that his name has been associated with this disease ever since (1). Charles Waters observed hereditary involuntary movements in certain afflicted individuals in New York State and noted that families with the disease became financially impoverished by the expense of treating the disease (2). The amount of medical care and attention required for the choreic continues to drain the financial and physical resources of afflicted families in the 20th century.

Huntington's disease (HD) is an autosomal dominant inherited disorder that can be followed through many generations. Vessie (3) traced the ancestors of many choreics in the eastern United States to three immigrants who left Bures, England, in 1630 with the John Winthrop fleet that sailed from Yarmouth to Salem, Massachusetts. In Venezuela, families with HD in villages around Lake Maracaibo have been traced to a German sailor who settled there between 1860 and 1870 (4). Similarly, HD in Tasmania was found to originate in Somerset, England (5).

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GENETICS

Abnormal movements usually begin about the age of 42 years in both males and females, although the disorder may be exhibited either in childhood or late life. Children with the disease most often inherit the disease from their father (6); however, when inherited from an affected mother, chorea in the mother will usually appear earlier than usual. In a large study of HD cases in England, anticipation was noted when the disease was inherited through the male (7). Although further confirmation of anticipation is needed, there appear to be sex-related modifying factors that influence the age of onset for the disorder.

Among siblings, onset of choreiform movements usually occurs within the same decade, and apart from the degree of anticipation mentioned above, usually within a decade of the onset in their parents. No predictive tests are available to diagnose those "at risk" for HD. Genetic linkage studies have failed to define a marker for this disorder, and electroencephalogram (EEG) (8) and computerized axial tomography (CAT-scan) cannot detect abnormalities in those at risk. After the administration of L-dopa to at risk cases, 50% developed choreiform movements and are suspect, although it will take a number of years to determine whether these cases develop HD (9). However, there are ethical reasons why this procedure should not be generally used.

CLINICAL

Age of Onset

Although the onset of abnormal movements occurs in the greatest majority of patients between the ages of 37 and 47 years, many patients will manifest behavioral changes before the onset of movements. A woman married to a choreic will often suspect which of her children are affected long before choreiform movements occur. It has been my impression that in those families where the onset of choreiform movement is in the late twenties or early thirties, behavioral disturbances appear to be more prevalent, presenting a decade before the choreiform movement. Many patients will be admitted to a mental hospital with a diagnosis of schizophrenia, and some years later the correct diagnosis is clarified when abnormal movements occur. It is, therefore, difficult to assign an exact age of onset for this disease.

In the majority of cases, the abnormal movements begin in the extremities along with slight twitching of the face, occurring rather infrequently at first, and then progressively involving more muscle groups throughout the whole body until the patient is unable to stand. Patients will often sit on one hand

or clasp their hand or leg in order to prevent such movements. Patients may initiate a voluntary movement over and above an abnormal movement in order to distract the attention of observers. Patients have difficulty speaking, impairing their ability to communicate. As a result of the involvement of the muscles used for deglutition, a number of choreics have died by choking on food. Aspiration pneumonia often occurs in the terminal phases of their disease usually some 15 years after the onset of the choreiform movements.

Dementia is a feature of HD that occurs in most cases, and the earlier the onset of chorea the more progressive and severe the dementia. Young children may appear to be retarded, and if they do not have abnormal movements or a family history of chorea, the diagnosis of HD may not be made.

Juvenile Chorea

In approximately 10% of HD cases the onset may occur under the age of 15 years, and diagnosis may be difficult when there is a negative family history. A child with HD may present with epilepsy or choreiform movements, although the movements may be myoclonic or dystonic in nature rather than choreiform. The course of the illness is more rapid than in the adult, so muscle rigidity occurs early and is usually present throughout the terminal stages of the disease. The disorder in children has sometimes been called the Westphal variant after Westphal noted rigidity in children with this disorder (10). The difficulty in making the diagnosis is compounded by the fact that the parent, usually the father, may not show choreiform movement until some years after the child presents with any one of the above neurological manifestations or even after the child has died. When a child presents with bizarre neurological features, an extensive examination of the father and his family for early signs of HD is warranted.

Late Onset Chorea

The onset of choreiform movement in some families may occur in the sixth or seventh decade, and when this happens, the progress of the disease is slower than usual. These patients may have their choreiform movement for 20–25 years and usually die of other causes than those usually associated with HD. It is of interest that these patients do not show the dementia that occurs with the onset of choreiform movement in earlier decades. Diagnosis of HD in the elderly may sometimes be difficult, since frequently there is no family history of chorea. This is understandable, since the age of natural death in earlier generations was lower in the general population than it is today, and such ancestors probably would have died before the onset of the choreiform movement.

Neurologic Examination

The neurologic examination reveals abnormalities mainly in the motor system, with the sensory system remaining intact. There may be "doll's eye" phenomenon (11), and patients have difficulty maintaining a protruded tongue. Muscle strength is generally good, but the tonicity may vary from hypotonia early in the disease to hypertonia in the later stages of the disease. Many patients with HD will have generalized rigidity in the terminal stage of their disease. Reflexes are always exaggerated even in the early stages of the disease and ataxia is usually present.

In the early stages of the disease, the diagnosis can, at times, be difficult. Some patients may first have predominantly ataxia and with a positive family history of ataxia, it may be difficult to differentiate HD from autosomal dominant cerebellar ataxia. The initial onset of dementia with a positive family history for dementia associated with myoclonic movements may make it difficult to differentiate the disorder from familial Alzheimer's disease. However, the rapid progress of the dementia out of proportion to the abnormal movements will usually differentiate these two conditions. Similarly, the abnormal movements that occur with Jakob-Creutzfeldt disease may be mistaken for HD; however, the rapid progress of this disease will usually differentiate it from the slower progress of Huntington's disease.

Patients with HD frequently fall and fracture various bones, and at postmortem, chronic and subacute subdural hematomas are frequently present.

Behavior

Huntington (1) in his original paper commented on the bizarre sexual behavior of two married men with severe chorea who were having sexual relations with various women in their village. Increased libido may occur in both male and female choreics and that, no doubt, accounts for the apparent increased rate of illegitimacy among such families.

Subjects "at risk" for HD may present with catatonic features in their late teens or early twenties and may be diagnosed as schizophrenic. Others may exhibit paranoid features and occasionally both visual and auditory hallucinations have been reported. Aggressive outbursts sometimes occur and can, on occasion, lead to being retained in a penal institution. Occasionally, in spite of the prognosis of this disease, some patients may remain quite euphoric throughout most of their course. Suicide is more common among choreic families than the population as a whole, and may occur in those at risk for HD or in patients in the early stages of their disease. Suicide is unusual in the late stages of HD.

Neuroendocrinologic Disturbances

Reed & Palm (12) noted that the fertility rate of choreic women was greater than that of their nonchoreic siblings. This may be associated with the altered production of the neuropeptide, gonadotrophic releasing hormone (GnRH) in the hypothalamus (13). Metrorrhagia occurs in some women and may be severe enough to require hysterectomy.

Increased appetite is a common phenomenon in choreic patients right up to the time of death. In spite of the increased appetite and increased caloric intake, these patients show progressive weight loss and in the final stages of the disease appear cachectic.

PATHOLOGY

Alzheimer (14) was the first to associate the loss of neurons in the caudate nucleus and putamen with this clinical disorder. There is a general atrophy of neurons throughout the brain, but the greatest atrophy occurs in the basal ganglia. Earl (15) noted that often there was remarkable preservation of neurons, even though a patient might be described as having advanced choreiform movements. Campbell et al (16) noted that the brain from children with chorea had a greater degree of atrophy in the basal ganglia than in adult cases.

Brain biopsy of the frontal cortex in cases of HD reveal proliferation and hypertrophy of astrocytes containing large amounts of lipofuscin and a high activity of acid-phosphatase (17). Electromicroscopy on frontal cortex biopsy tissue revealed that the lipofuscin granules, although increased, were not unusual in appearance. Other ultrastructural features noted were increased amounts of smooth endoplasmic reticulum and vesicles associated with Golgi complexes (18).

The whole brain weight is usually reduced by 20%, whereas the basal ganglia weight is usually less than 50% of normal. On a coronal section at the level of the anterior commissure the striatal complex is less atrophic when compared to the more posterior regions of the caudate and putamen. This anterior striatal complex contains the nucleus accumbens, a part of the limbic system.

The brain stem is also atrophic, and this is most marked in the region of the substantia nigra where the atrophy is greater in the more ventral pars reticulata. The substantia nigra generally appears more deeply pigmented than normal. The cerebellum may be reduced in size along with the reduction in size of the brain stem. The skull may reveal the presence of one or more chronic subdural hematoma, as a result of frequent falls in the latter years of life.

Microscopically the loss of tissue is most marked in the caudate, putamen, globus pallidus, and substantia nigra. There appears to be an increased number of glial cells seen in the basal ganglia, and gliosis has often been reported. However, Lange et al (19) counted glial cells in choreic and normal brain and found that the total glial cell number in each nucleus was the same as in normal brain; however, the concentration of glial cells is increased because of the loss of neuronal cells.

Professor Corsellis and his colleagues carried out histopathological examinations on our group of 250 postmortem choreic brains and found that 7% of the cases diagnosed as having Huntington's disease actually had other neurological conditions. The condition most often misdiagnosed clinically as Huntington's disease was Alzheimer's disease. Other cases were found to have the cerebellar changes consistent with autosomal dominant cerebellar ataxia. One case of Jakob-Creutzfeldt disease was uncovered.

In view of the implication for the at risk members of choreic families, it is obviously important that every case with the diagnosis of Huntington's disease be confirmed eventually by autopsy, and that the neuropathological report be subsequently filed in the clinical notes.

NEUROCHEMISTRY

The measurement of certain neurotransmitter substances and their related biosynthetic enzymes in postmortem brain tissue from patients dying with extrapyramidal disorders has provided a better understanding of the clinical manifestations and neuropharmacological basis of such conditions. The decrease in dopamine concentration in the basal ganglia in Parkinson's disease (20) and the decreased concentration of γ-aminobutyric acid (GABA) in the same nuclei in Huntington's disease (21) may reflect essential neurochemical differences between these two conditions, and these correlate well with the opposing clinical syndromes.

Several chemical transmitters and related enzymes are fairly stable in postmortem brain. Brain cooling has been shown to start immediately after death and, provided the cadaver has been placed in refrigerator, this rate of cooling progresses until the center of the brain reachers 4°C, usually about 24 hr after death (22). Enzyme activities usually decline to some stable level during this first 24 hr. Control tissues are handled similarly and since it usually takes 24 hr to complete the administrative postmortem details, cases will usually be autopsied after stability has been attained. Choreic patients are often in a psychiatric hospital receiving neuroleptic drugs for some months or years before death and they often develop bronchopneumonia prior to death. Most of the control brain tissues used for comparison in the past have been from non-neurological cases dying from

natural causes, although among the controls there is a subgroup of control cases that died from bronchopneumonia. Also, a recent large collection of brain tissues from patients dying in mental hospitals with the diagnosis of schizophrenia may serve as another group for comparison with the choreic group (23).

γ-Aminobutyric Acid (GABA)

GABA is widely distributed throughout the mammalian CNS and is considered to be an important inhibitory neurotransmitter at virtually all levels of nervous system function (24). Studies on the regional distribution of GABA and its biosynthetic enzyme, glutamic acid decarboxylase (GAD), in the mammalian CNS, including that of man, have shown that the highest levels of each are in the pallidum and substantia nigra, with high values in the striatum (25).

Perry et al (21) reported that the concentration of GABA was decreased in the caudate nucleus and putamen of postmortem brain from patients dying with HD. Bird & Iversen (26) found that the activity of GAD was decreased in the striatum and substantia nigra but not in cortex of the brain from choreics (see Table 1). This selective loss of enzyme activity does not appear to be related to chronic hospitalization or neuroleptic drug administration as normal GAD values are observed in long-term psychotic inpatients (23).

However, Bowen et al (27) noted low postmortem brain GAD values from patients dying with conditions likely to lead to cerebral hypoxia. Perry et al (28) also pointed out the influence

GAD activity was significantly lower in several brain regions from a group of chronically hospitalized patients than in a group of normal people who had suffered sudden deaths. This suggests that spuriously low GAD activities may easily be recorded in various pathological conditions in which postmortem brain samples are obtained from elderly patients dying after chronic hospitalization, in whom the immediate cause of death is often bronchopneumonia or a related condition likely to lead to terminal hypoxia.

Iversen et al (29) compared the GAD activities in postmortem brain from both controls and choreics that suffered either an acute death or a prolonged death with bronchopneumonia and, although there is within the control group a significant decrease in the GAD activities in brain from controls that die from bronchopneumonia, there is still a significant decrease in GAD activity in both the acute and prolonged death choreic groups when compared to respective control groups.

Recently Perry et al (30) and Spokes et al (31) have found that GABA concentrations appear to be fairly stable in postmortem tissues and, unlike GAD, are not influenced

Table 1 Glutamic acid decarboxylase, choline acetyltransferase, and tyrosine hydroxylase in control and choreic postmortem brain[a]

	Control[b]	Huntington's chorea[b]	P
GAD[c] caudate	25.9 ± 3.8 (23)	13.0 ± 1.6 (52)	< 0.001
Nucleus accumbens	40.9 ± 6.3 (15)	39.1 ± 6.6 (30)	NS
Cortex	22.7 ± 5.5 (9)	23.9 ± 2.3 (27)	NS
CAT[d] caudate	270.9 ± 11.7 (72)	153.8 ± 16.1 (52)	< 0.001
Nucleus accumbens	226.3 ± 10.6 (50)	186.8 ± 17.1 (30)	< 0.05
Cortex	5.8 ± 0.4 (26)	5.9 ± 0.4 (27)	NS
T-OH[e] caudate	24.5 ± 4.49 (30)	34.4 ± 10.1 (23)	NS
Substantia nigra	28.3 ± 3.57 (39)	75.21 ± 17.2 (40)	< 0.02

[a] NS = not significant.
[b] All values are means ± SEM for the number of brains shown in parentheses.
[c] Glutamic acid decarboxylase (μmol/hr/g protein).
[d] Choline acetyltransferase (μmol/hr/g protein).
[e] Tyrosine hydroxylase (μmol/hr/g protein).

CSF measurements of GABA in control and choreic subjects have yielded conflicting results. Some workers have reported an approximate 50% reduction in choreic patients (32), whereas others have failed to detect GABA in CSF samples from normal subjects (33).

We have focused considerable attention on the substantia nigra in HD, an area which has had little histopathological examination in the past, since it is always normally pigmented. The substantia nigra is divided into two regions, the more dorsal region being the zona compacta which is normally darkly pigmented and contains the cell bodies of the dopamine neurons whose axons form a pathway to the striatum (see Figure 1). Dendrites extend from the dopamine cell body throughout both regions of the substantia nigra. The less pigmented ventral region of the substantia nigra, the zona reticulata, receives axons from neuroinhibitory GABA cells in the striatum, and the terminals of these axons are in contact with the dendrites from the dopamine cells. The dopamine concentration in the zona compacta is normally twice that of the zona reticulata, and concentration of GABA

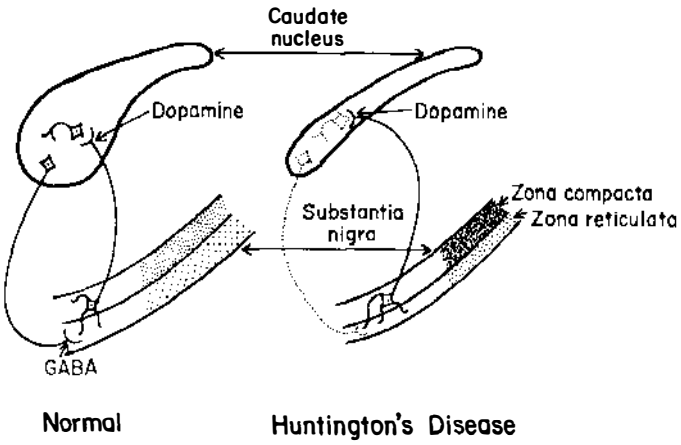

Figure 1 Schematic representation of the striatal-nigral connections showing the dopaminergic pathways from the zona compacta of the substantia nigra to the striatum, and the GABAergic pathways from the striatum to the zona reticulata in both the normal and choreic brain.

is twofold higher in the reticulata zone than in the compacta zone. The substantia nigra in the brain from a patient with Huntington's disease is often more darkly pigmented than normal and the zona reticulata is much more atrophic than the zona compacta because of the loss of striatal afferents.

Dopamine

The activity of tyrosine hydroxylase (T-OH), the biosynthetic enzyme for dopamine (DA), was found to be increased in both the striatum and substantia nigra (34) (see Table 1), and more recently significant increases in dopamine concentrations were found in the corpus striatum, substantia nigra, and nucleus accumbens (35) (see Table 2). These increases could not be attributed to chronic neuroleptic drug administration, which is common clinical practice in the treatment of chorea, as normal striatal dopamine values were found in patients dying with a hospital diagnosis of schizophrenia (23). Moreover, drug-treated choreic subjects had dopamine values similar to their drug-free counterparts (35). Animal studies also support the view that chronic treatment with neuroleptic drugs does not influence striatal dopamine levels (36, 37).

The most likely explanation for the increases in dopamine concentrations is that they are secondary to the increased density of dopaminergic terminals in the striatum and substantia nigra, which are undergoing shrinkage. However, since there is approximately a 50% loss of tissue in the corpus

striatum, this would be expected to produce a 150% increase in the dopamine concentration of the remaining tissue, if the net content of dopamine were unchanged. However, the increases found were only about 70% in the putamen and pallidum, and only 32% in the caudate nucleus (Table 2). The total content of dopamine in the choreic corpus striatum is, therefore, likely to be considerably reduced. However, it should be noted that the greatest increases in dopamine were found in the nucleus accumbens, a region that exhibits less atrophy than the body of the caudate (Table 2). Therefore, it would appear that there may be three possible factors affecting the absolute concentrations of dopamine found in the brain. First, there may be functional increases due to the loss of neuroinhibitory control by GABA. Second, there may be a relative increase due to loss of surrounding neurons. Finally, there may be absolute decreases due to a retrograde loss of dopamine terminals in the body of the caudate where the greatest loss of neurons is occurring.

A useful method of estimating the functional activity of dopamine-containing neurons is to measure the brain concentrations of the major dopamine metabolite, homovanillic acid (HVA), formed from the metabolism of dopamine released at synapses. Reduced CSF HVA concentrations have been found in Huntington's disease (38, 39), suggesting that the turnover of the remaining dopamine in the corpus striatum is normal or slightly reduced. However, HVA concentration in CSF may also depend on ventricular volume and the decreased HVA concentrations in CSF from

Table 2 Dopamine, substance P, and gonadotropic releasing factor from control and Huntington's disease patients

	Brain region	Control[a]	Huntington's disease[a, b]
Dopamine	Caudate	18.5 ± 0.9 (72)	24.4 ± 1.8*** (48)
	Nucleus accumbens	12.2 ± 1.0 (50)	22.8 ± 1.7**** (29)
	Substantia nigra (Pars compacta)	5.0 ± 0.4 (29)	6.7 ± 0.5** (28)
Substance P	Globus pallidus	18.0 ± 3.3 (18)	9.7 ± 1.9*** (15)
	Substantia nigra (Pars reticulata)	42.9 ± 4.9 (14)	29.1 ± 3.8*** (9)
GRF	Median eminence	314 ± 84 (11)	1,231 ± 410* (9)

[a] All values are means ± SEM for the number of brains in parentheses.
[b] *P* values: * < 0.05, ** < 0.01, *** < 0.005, **** < 0.001.

choreic subjects may, to some extent, be related to ventricular enlargement (40). CSF levels of HVA have been shown to be particularly low in rigid choreic patients (41) and it has been shown that rigid cases have marked atrophy of the corpus striatum (42).

Receptor hypersensitivity has been proposed as a mechanism for the choreiform movements in the face of normal or decreased total dopamine (43). However, measurements of the density of dopamine receptors on autopsied striatal tissue have shown a significant decrease in Huntington's disease (44).

Acetylcholine

The enzyme choline acetyltransferase (CAT), responsible for the biosynthesis of acetylcholine, is considered to be exclusively localized in cholinergic neurons and it is present in high activity in basal ganglia tissue, especially in the putamen. Although there is an average loss of more than 50% in the activity of CAT per unit weight in putamen and caudate nucleus from choreic brains (see Table 1), a substantial portion of the choreic cases show CAT activities in basal ganglia which are within the normal range (26). The remaining cases have severely reduced basal ganglia CAT activities (approximately 85% reduction). The finding that in some choreic cases CAT activity was only slightly reduced in caudate nucleus may support the suggestion of McGeer et al (45) that the degeneration of the cholinergic innervation in choreic basal ganglia occurs in a "patchy" manner. This has also been noted by Aquilonius et al (46).

The finding of only slightly reduced CAT activity in the choreic nucleus accumbens (Table 1) is consistent with other reports (46, 47) and again emphasizes the relative sparing of this region compared with the striatum.

Normal values were obtained in the striatum and other brain regions from long-term psychotic in-patients, indicating that neither hospitalization nor neuroleptic drug treatment is responsible for these changes in HD (23).

Serotonin

Serotonin-containing nerve fibers arise from cell bodies in the midbrain raphe nuclei. Rostrally projecting fibers end in various brain regions, such as the corpus striatum, hypothalamus, and cerebral cortex (48).

In one postmortem study, concentrations of serotonin in the choreic corpus striatum from four HD cases were reported as being within the normal range (49).

In a larger unpublished series of cases, Curzon found increases in serotonin concentrations in the HD caudate that were inversely proportional to

the decrease in GAD activity. It would appear that since the terminals for serotonin neurons are in the striatum similar to the dopaminergic neurons, the increased concentrations of serotonin in this region are probably due to the same factors causing dopamine increases.

CSF values of 5-hydroxyindoleacetic acid, the serotonin metabolite, have been reported as normal in choreic subjects, both at steady state and after probenecid loading (38, 39).

Neuropeptides

SUBSTANCE P Substance P (SP) is an undecapeptide that is unevenly distributed in the brain. The highest concentrations are found in the substantia nigra (50, 51).

In Huntington's disease, a significant decrease in the concentration of SP has been found in the medial pallidum and substantia nigra, whereas values in other brain regions were unaffected (52, 53).

ANGIOTENSIN Angiotensin II may possibly be a neurotransmitter in the brain (54). Specific angiotensin II receptor binding has been demonstrated in brain tissue (55). Angiotensin converting enzyme (ACE), a dipeptidyl peptidase which converts the inactive decapeptide angiotensin I to the active octapeptide angiotensin II, is ubiquitous throughout brain tissue, although the highest activities in the rat (56) and in man (57) are present in the corpus striatum.

In postmortem tissue from Huntington's disease cases, a marked depletion in ACE activity has been observed in the corpus striatum (58), and in the substantia nigra (59), suggesting the possibility of involvement of a striatonigral angiotensin-containing pathway and again emphasizing the diversity of neuronal degeneration that may occur in this disorder.

GONADOTROPIN-RELEASING HORMONE There are a number of clinical observations that indicate that there may be a disturbance in either the synthesis or release of this neuropeptide in Huntington's disease. An increased fertility rate has been reported in HD patients (12) and increased libido has been noted among both choreic males and females.

There is evidence which suggests that the release of gonadotropin-releasing hormone (GnRH) is modulated by dopaminergic neurones (60, 61), and since dopamine is increased in choreic brain there is reason to suspect that there may be an alteration in the concentration of this peptide in HD brain. The concentration of GnRH was found to be significantly increased in the median eminence of the female choreic brain but not in that of the male (13) (see Table 2).

MANAGEMENT

The burden of managing a patient with HD usually falls upon the spouse and "at risk" offspring who become both physically and mentally exhausted. The primary physician, therefore, has the whole family to care for and will often need to call on help from consultant neurologists, psychiatrists, genetic counselors, and social workers. Other health-related professionals, such as occupational therapists and dietitians, can ease the burden on the family by keeping the patient occupied and suggesting ways in which meals can be prepared and consumed.

Neuropharmacologic Agents

NEUROLEPTICS In the past, reserpine was useful for reducing abnormal movements. This has been largely replaced by tetrabenazine (Nitoman®), in countries where this drug is available. Tetrabenazine inhibits the reuptake of dopamine in the presynaptic dopaminergic terminals. The tendency is to try to eliminate the movements totally, but unfortunately this usually requires an amount of this drug that will cause depression. Most patients prefer a smaller dose, and I find that a half tablet (12.5 mg), three times a day, will often be satisfactory.

Thioridazine (Mellaril ®) appears to be the most popular phenothiazine agent and haloperidol (Haldol ®) appears to be the butyrophenone that works best for choreics. Most neuroleptic drugs should probably be withheld until the patient becomes a danger to himself by falling or where the patient is aggressive and a danger to others. Again, the dose should be kept as low as possible in order to allow the patient to function and take part in family activities.

INVESTIGATIONAL DRUGS A number of neuropharmacologic agents have been under investigation as a result of the neurochemical findings already discussed. GABA itself does not cross the blood-brain barrier and, therefore, large doses would be required, which unfortunately are dangerous (62). However, a number of GABA-like agents are being developed that might be more successful in crossing the blood-brain barrier and we hope to see these become available for clinical trials. An approach to GABA replacement has been to administer lipid-soluble GABA agonists that might penetrate the CNS. Imidazole-4-acetic acid, a naturally occurring histamine metabolite, will stimulate postsynaptic GABA receptors, but has been shown to be ineffective for chorea (63).

The hope that GABA or GABA agonists will decrease chorea depends on intact GABA receptors in the striatum, and recent studies would appear to indicate that these receptors are decreased in choreic basal ganglia (29).

It is conceivable that these drugs might be effective in the early stages of abnormal movement when GABA receptors are more likely to be intact.

Another method to increase the cerebral concentration of GABA has been directed toward inhibiting GABA-transaminase (GABA-T), the metabolizing enzyme for GABA, with drugs such as sodium valproate and isoniazid. In a double-blind controlled trial, sodium valproate was shown to be ineffective in reducing choreic movements (64). Perry and his coworkers (65) claimed a beneficial response in six out of seven HD subjects taking isoniazid, although this finding could not be confirmed by Paulson et al (66) who used lower doses of this drug, in eleven patients with Huntington's disease. However, it would not be surprising if effective GABA-T inhibitors did not produce a marked improvement in HD since elevation of cerebral GABA concentrations by these agents does not necessarily imply increased amounts of GABA available for release from presynaptic endings because GABA-T is located mostly outside nerve endings in dendrites, cell bodies, and glial cells (67).

If suitable GABA-mimetic drugs do become available they will no doubt require careful regulation of dose since GABA systems are present throughout the CNS and such agents might produce undesirable side effects arising from the potentiation of GABA-mediated functions in regions of the brain other than the corpus striatum and substantia nigra.

Pharmacological studies on central cholinergic mechanisms in Huntington's disease have produced equivocal results. Because of the importance of dopaminergic-cholinergic balance in normal striatal function and the neurochemical pharamcological evidence for dopamine predominance in HD, it might be predicted that drugs which increase or enhance striatal cholinergic neurotransmission would ameliorate choreic movements. Benztropine, a centrally active anticholinergic agent, reportedly exacerbates HD (68). On the other hand, physostigmine has been found by some workers to decrease involuntary movements (69), whereas others have failed to obtain consistent effects (70, 71).

Since choline has been shown to elevate acetylocholine concentration in rat brain (72), choline has been given to HD patients. Mild beneficial effects have been reported by Davis et al (73), whereas Aquilonius & Eckernäs (74) and Growdon & Wurtman (75) failed to find any improvement. Deanol (dimethylaminoethanol) is thought to be converted to acetylcholine intracellularly (72) and favorable results were reported for the effects of this drug in 5 HD patients (76). However, larger clinical trials have shown this drug to be ineffective (77).

The equivocal results obtained with cholinergic agents may be a result of evaluating HD patients at various stages of their disease when cholinergic neurons and their receptors may be in various stages of degeneration. It

appears that many cases of HD in their early stages will have normal choline acetyltransferase activity. Also, the muscarinic cholinergic receptor activities and densities in striatal tissues have been measured by using ^{3}H-propylbenzilyl choline (78) or ^{3}H-quinuclidinyl benzoate (79) and, in each study, an overall reduction of 50% was found. It would appear, therefore, that cholinergic drugs will be of little benefit in Huntington's disease.

Pharmacological investigations on serotonergic function in choreic subjects have produced variable results. 5-Hydroxytryptophan may exacerbate motor dysfunction (80). L-Tryptophan, the immediate precursor of 5-hydroxytryptophan, had no influence on motor activity in HD patients (81, 82). Parachlorophenylalanine, an inhibitor of tryptophan hydroxylase that blocks serotonin synthesis (83), and methysergide, a postsynaptic serotonin receptor antagonist (84), failed to modify movements in HD subjects. It seems unlikely that serotonergic systems have a significant role in the pathophysiology of the extrapyramidal dysfunction in Huntington's disease.

All drug assessments in HD should be following double-blind crossover trials, since a placebo response so often occurs in this disorder. Unfortunately, most of the drug trials for HD, where success has been reported, have not been double-blind. A classical example of this is the reported success with vitamin E that was later evaluated and found to have no value in HD (85).

Considerable progress has been made in characterizing the neurochemistry of Huntington's disease in the last few years. Although the primary defect that causes the neuronal cell death has still not been defined, some of the findings to date may help neuropharmacologists develop agents that might alleviate some of the suffering that patients have with this tragic disease. It is hoped that future molecular genetic studies and investigations for possible defects in cell membranes will provide us with new approaches for the early diagnosis and treatment of HD.

SUMMARY

Huntington's disease (HD), a dominantly inherited disorder of the nervous sytem, is usually manifest about middle age by dance-like movements. The disorder may occur in children, when epilepsy and rigidity may be the predominant signs. Degeneration of neurons occurs throughout the whole brain, but this is most marked in the basal ganglia.

Neurochemical examination of postmortem brain frozen at the time of autopsy has been collected from patients dying with HD and compared with

postmortem brain from psychotic patients and cases without neuropsychiatric disease. A number of alterations in neurotransmitters and their biosynthetic enzymes have been found. There are decreased concentrations of the neuroinhibitory transmitter γ aminobutyric acid and this is associated with increased concentrations of dopamine and serotonin in the basal ganglia. In addition, there is decreased activity of glutamic acid decarboxylase, choline acetyltransferase, angiotensin-converting enzyme, as well as a decreased concentration of the neuropeptide substance P.

Various pharmacologic agents have been tried based on the neurochemical alterations, but nothing has been found to be superior to the various neuroleptics in common use.

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