

Historical Review

A Brief Prehistory of Huntington's Disease

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In the whole range of medical terminology, there is no such olla podrida as chorea...

–William Osler, *On Chorea*, 1894

Epilepsy, chorea, hysteria ... come to us like so many Sphinxes.

–Jean-Martin Charcot,
Oeuvres completes 1888–1894

Physicians and family members alike have long been curious about the historical origins of Huntington's disease. Despite the fact that families with "hereditary chorea" were described in medical literature for the first time in the 1840s, most authors agree that the genetic abnormality and most likely the panoply of symptoms we know today as Huntington's disease were present centuries earlier in Europe and the Americas, and probably in other parts of the world as well. Twentieth century medical writers have tried to link modern Huntington's disease with the great European dance epidemics of the 14th, 15th, and 16th centuries known as St. Vitus's dance or *danse de St. Guy*. They have cited as possible precedents the descriptions of *chorea Sancti Viti* by the Renaissance physician Paracelsus of Basel, the witch trials of the 17th century in northern Europe and New England, and the accounts of post-rheumatic chorea in children in the late 17th and 18th centuries, written by the English physician Thomas Sydenham and others. They have

noted occasional 18th and early 19th century medical reports of older people with intractable chorea and "idiotism" [1].

But many writers have also noted that none of these descriptions truly evoke the family disorder we know today as Huntington's disease. While chorea is still considered the hallmark of Huntington's, the pre-19th century examples differ considerably from modern Huntington's disease. The episodes of mass dancing were temporary and most likely a response to the trauma of plague epidemics and other catastrophes [2]. Paracelsus was interested mainly in arguing against supernatural notions of disease and establishing a naturalistic understanding of *chorea Sancti Viti*. He did not describe specific cases [3]. As for the famous witch trials of the 17th century, I have seen no convincing evidence that any of the individuals convicted or accused of being witches suffered from symptoms resembling Huntington's although persons with involuntary movements were sometimes believed to be *victims* of witchcraft or demonic possession [4]. The cases of chorea portrayed by Sydenham and others were mostly children who eventually recovered. While some writers on chorea alluded to "hereditary" influences, no one prior to the 19th century, to my knowledge, described families in which several generations were afflicted with similar symptoms, a key point in the post-1800 accounts.

Still, by the early 19th century if not before, some affected families and the communities in which they lived recognized a hereditary illness which they called "St. Vitus's dance" or "the magrums" or "migrims." One of the most convincing early lay reports is an 1806 newspaper article about an East Hampton, Long

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Island woman named Phebe Hedges, whose afflicted son, grandchildren, nieces and nephews were patients of George Huntington's father and grandfather. When the forty-two year old Phebe Hedges walked into the sea and drowned in June of 1806, the local newspaper attributed her death to "her extreme dread of the disorder known as St. Vitus's dance, with which she began to be affected and which her mother now has to a great degree" [5]. As these lines indicate, Phebe Hedges had observed her mother with the disease, probably for many years, perhaps other relatives too, and she knew enough about it to fear for her future. Moreover, as Phebe Hedges was born in 1764 and her mother in 1739, clearly the genetic abnormality was present in this locale for at least a century before the earliest medical accounts of the disease [6].

Why, then, did "hereditary chorea" emerge in medical writing only in the 1840s? Why were the first unambiguous reports in the USA and in Norway, given that affected families clearly were present in many countries around the world? Why did the first case reports attract so little medical attention while George Huntington's report was widely cited within little more than a decade? [7] Since his was not the first description of "hereditary chorea," why do we today know the malady by the name Huntington's disease?

LIFE EXPECTANCY AND "HEREDITARY CHOREA"

One explanation that has been offered for the first medical accounts is a rise in life expectancy. According to this theory, so long as life expectancy remained low, few people across several generations of a family lived long enough to manifest symptoms and therefore the distinctive hereditary element escaped notice. As the English neurologist David L. Stevens wrote in 1972, "the gene that causes the disease was no less common then [pre-1840s] than it is now, but fewer carriers of this gene lived long enough to develop chorea. Consequently, even those who survived long enough to reproduce may often have died before they had themselves manifested the disease that they had transmitted to their offspring, which would tend to conceal the hereditary nature of the condition and would cause the fairly frequent appearance of individuals with chronic incurable chorea, but no apparent family history of the condition" [8].

However low life expectancy at birth to a large extent reflected high infant and child mortality rates. Those who survived beyond childhood and youth had a fairly

good chance of living a long life. Between 1541 and 1871, a woman in England and New England who had a life expectancy at birth of only 35 years might expect to live to about 56 if she survived to the age of 20. If she survived to 30—certainly old enough to have had children—she could expect to live until about 60, far beyond the typical age of onset as reported in the 19th century and today [9].

Still, the question remains whether regional variations in life expectancy may have heightened the visibility of families with chorea in specific settings, especially in the USA and in Norway (which had a comparatively high life expectancy overall in the 19th century, about 49 years in 1846 compared with 39.5 years in the USA in 1850) [10]. It is worth noting that all the towns where families with "hereditary chorea" were first described—Pound Ridge, Bedford, and East Hampton, New York, and the Saatesdaal valley in Norway—were small, isolated, rural communities that tended to have lower mortality than larger towns and cities in the same regions. As Timothy Dwight, president of Yale, noted on an 1811 visit, "East Hampton is uncommonly healthy, as is evident from the number of old people which it contains [11]. Whether this circumstance played a role in instigating the earliest medical descriptions of "hereditary chorea" is unclear.

FROM HUMORAL IMBALANCE TO SPECIFIC DISEASE

A more likely explanation for the early 19th century "discovery" of hereditary chorea was the growing professionalization of physicians—the American Medical Association (AMA) was founded in 1846—and a change in medical thinking about the etiology of disease [12]. In 1800 many physicians still thought in terms of humoral imbalances when treating their patients (although humoral theory had been under attack since the late 17th century). Illnesses were shaped by a myriad of factors both "constitutional" and environmental, and distinctions between physical and mental illness were "tenuous at best" [13]. Although as the historian John Harley Warner notes, there were some well-defined maladies such as small pox and syphilis, diseases generally were regarded as fluid and specific to the individual. They arose not from "discrete causative agents—one invariably producing pneumonia and another typhoid fever—but rather by a variety of destabilizing factors acting singly or more often as an ensemble to unbalance the system" [14]. Therapies aimed to restore the body to its natural bal-

ance, as defined by the life of the individual patient. Behavioral disturbances fell into a few broad categories, such as mania, melancholy, dementia, and “idiotism,” and were treated in similar ways since mental ills were generally thought to arise from physical causes.

By the middle of the 19th century, elite physicians in Europe and the USA had begun to assimilate the idea—associated with the Paris clinical school—that disease was a distinct, lesion-based entity that reenacted itself in every individual sufferer. They thought of “disorders less as systemic imbalances in the body’s natural harmony and more as complexes of discrete signs and symptoms that could be analyzed, separated and measured in isolation.” Specific disease agents produced a specific illness [14]. Categories of mental illness also became more differentiated, with the emergence of psychiatry as a medical specialty in the 1840s and a growing number of institutions for the “insane.” Thus the descriptions of hereditary chorea from the 1840s to 1872 emerged within the context of an epistemological and institutional shift within medicine that highlighted the specificity and somatic basis of disease.

AMERICAN PECULIARITIES AND MEDICAL DISCOVERIES

Two other historical factors may help explain why the earliest accounts appeared in the USA rather than, say, France or Germany, where medical science was far more advanced. First, medicine in the early years of the Republic emphasized regional variations in illnesses and in therapeutics. Medical societies encouraged reports on diseases prevailing in specific localities and medical students often chose to write their theses on the health particularities of their home districts, publishing them in the new medical journals that also proliferated in the 1840s and 1850s [14]. Reflecting this orientation, Charles O. Waters, Charles R. Gorman, Irving W. Lyon, and George Huntington all stressed the boundaries, both geographical and social, within which they observed hereditary chorea [7, 15, 16]. For instance Waters, who is generally credited as the author of the first unambiguous description (in 1841), observed that it was “somewhat common in the southeastern portion of this state” (New York); George Huntington considered that he was describing a “medical curiosity” which existed, “so far as I know, almost exclusively on the east end of Long Island.” The Norwegian public health physician Johann Lund also wrote within a specific geographical context, identify-

ing the locale of the families as the Saetesdaal valley [17].

Second, the great expansion of American medical schools in the 1820s, 1830s and 1840s, most of them unlicensed proprietary operations, produced many young physicians eager to establish their credentials and make themselves known. Between 1790 and 1850, the number of physicians in the USA increased from 5,000 to 40,000 [12]. In this context, it is not surprising that all of the earliest American descriptions of hereditary chorea were written by young men just out of medical school (either Jefferson Medical College in Philadelphia or the Columbia College of Physicians and Surgeons in New York). What is surprising is that none of them, not even George Huntington, described his own patients. Indeed, it is unclear whether Waters, Lyon, or Huntington ever had patients with the disease they described. Rather, they wrote their narratives as reports of a peculiar local medical phenomenon that stirred their curiosity. (Although Lyon was a practicing hospital physician in New York City at the time he published his paper, in 1863, he wrote about families he recalled from childhood, not case reports of his patients at the time) [18]. Their accounts of hereditary chorea derived not from hospital practice or the clinic but from their observations and conversations passing through or growing up in towns where the families lived (and in the case of Huntington, from the observations of his physician father and grandfather as well).

NEUROLOGY, HEREDITY, AND CHOREA

None of these narratives attracted immediate interest. (Besides the fact that he wrote in a language inaccessible to physicians outside Norway, Lund had the misfortune of having the influential *Handbuch der historisch-geographischen Pathologie* [*Handbook of Historical and Geographic Pathology* for 1862–64] interpret his description as “paralysis agitans” or Parkinson’s disease. This error no doubt caused many physicians interested in chorea to overlook it) [17]. George Huntington was more fortunate. His account was accurately summarized in Hirsch and Virchow’s medical *Jahresbericht* (Yearbook) for 1872 [19] and in Hugo von Ziemssen’s *Handbuch der Speciellen Pathologie und Therapie* in 1875 [20], (translated in 1877 as the *Cyclopaedia of the Practice of Medicine*) [21]. The great Italian neuroanatomist Camillo Golgi also mentioned it in an 1874 paper [22, 23]. But there was only sporadic discussion for nearly a decade, especially in the USA. For those physicians who had never

seen a case, the emphasis of all the early writers on how local and unusual this illness was may have made it appear esoteric and irrelevant. Moreover, the hereditary transmission may have seemed unremarkable, for as Charles Rosenberg has noted, “no one *doubted* that disease and deformity could be hereditary” [24]

Yet clinical reports of “chorea of adults,” “chorea associated with mental aberration,” “chorea in the aged,” and soon “hereditary chorea” began to appear with growing frequency in the medical journals of many countries. At first these were mainly in Europe and subsequently in North America but soon also in Argentina (1894), Brazil (1891), Cuba (1890) and Russia (1889). By 1893, according to William Osler, a “copious literature” had gathered around the subject [25]. Some observers considered that the disease was not so rare as had previously been thought [26].

The reasons for this shift are not hard to surmise. Most important was the growing number of mental hospitals and asylums in the USA and in Europe, with rapidly increasing populations of patients. In the 1880s alone, the total population of USA mental hospitals doubled, from 31,973 to 67,754, and nearly doubled again in the following decade [4]. As more families turned to these institutions to care for their members with advanced chorea, many more patients were coming to the attention of a physician.

In addition, the emergence of neurology as a medical specialty, first in Europe in the 1850s and then in the United States in the 1860s and 1870, created a cadre of ambitious younger clinicians specifically interested in diseases of the brain [27]. Differentiating themselves from the more established psychiatrists whom they dismissed as out of date, these young neurologists were drawn to the new laboratory-based medicine. They described many new neurological disorders, such as Freidrich's ataxia in 1863, multiple sclerosis in 1868, and athetosis in 1871. With advances in neurophysiology and neuroanatomy and a growing emphasis within medicine on research, interest in the neuropathology of hereditary chorea grew. A number of early post-mortem studies, including Golgi's in 1874, revealed deterioration in specific brain regions such as the basal ganglia, and more specifically, the striatum. Here was a behavioral disorder whose symptoms could be correlated with distinct lesions in the brain: a neurological disorder *par excellence* although in practice many more patients ended up in the care of a psychiatrist associated with an institution for the “insane.”

Finally, the growing social and scientific focus on heredity starting in the late nineteenth century lent further interest to this disease. Theories of heredity

grew more pessimistic from the 1880s to the early 1900s. Societal as well as medical ills were increasingly ascribed to poor biological heredity and “degeneration” [28]. After 1900, proponents of the new Mendelian genetics such as the English biologist William Bateson became interested in hereditary chorea as a test case for Mendelian theory in humans. Supporters of eugenics also took an interest in families with Huntington's, both to illuminate patterns of human biological inheritance and to further their eugenicist social aims [29].

In response to the growing recognition of what was increasingly known as Huntington's chorea, a new neurological journal called *Neurographs* (New York) devoted an entire “Huntington Number” in 1908 to papers (in English, French, and German) on the disease [30]. From a “medical curiosity,” as George Huntington put it in 1872, hereditary chorea had become a subject of “world-wide interest” and even a focus for research.

A VARIANT OF CHOREA OR SEPARATE DISEASE?

The question of whether hereditary chorea was a distinct disease or another variety of chorea harked back to the earliest medical accounts. However the debate came to a head in the 1880s. In his famous Tuesday lectures (of 1887–88), the eminent French neurologist Jean-Martin Charcot insisted that “Huntington's disease” was “only a variety, an aspect of ordinary chorea.” For Charcot, the clinical similarities with Sydenham's chorea and the fact that some of the symptoms and characteristics of Huntington's were present in other disorders qualified it as a variant within the broader general category of chorea. “In other words, it is ordinary chorea with an exceptional presentation of late onset and chronicity in selected families. The predominant or, in some cases, the exclusive influence of similar hereditary transmission is indeed a remarkable feature. But it does not sufficiently justify our creating a nosographic category” [31].

William Osler (and many others) did not agree. For Osler, “chronic progressive chorea is, I believe, a disease wholly apart from the affection described by Sydenham, having nothing in common but the name” [25]. A year later he noted, with a jab at his French colleagues, that “with the exception of Charcot, and his pupil Huet, all the writers on chronic progressive chorea regard the disease as totally different from chorea minor, a view which seems to me just when we

take into consideration the clinical features, particularly the character of the movements, the progressive course, the heredity, and the anatomical lesions" [32].

In his study of Charcot, Christopher Goetz has pointed out that at the time of these lectures, Charcot had expended considerable energy attempting to differentiate chorea from other movement disorders. He was more attentive, therefore, to the similarities of movement in Huntington's and Sydenham's than to possible differences in their etiology. Moreover, his conviction that most neurological diseases were hereditary may have made the hereditary transmission of Huntington's appear less significant. While he acknowledged that the "similar heredity" of Huntington's chorea—meaning that the symptoms were the same in each generation—was very striking, he did not consider this feature different enough to make the disease an entity of its own [31].

WHY HUNTINGTON'S DISEASE?

In 1887, the name "Huntington's chorea" entered the medical lexicon in Virchow's *Archiv*. But alternatives continued to circulate for over a decade—most commonly hereditary chorea and chronic progressive chorea [33]. Why, then, did these alternatives disappear? Why Huntington's rather than Waters' or Lund's chorea, since both Waters and Lund described the same panoply of symptoms, age of onset, and hereditary transmission? It is tempting to ascribe the eponym to George Huntington's ground-breaking insight into the hereditary pattern of the disease, which was present in none of the other accounts. As he famously wrote, if either of the parents have been affected, one or more offspring almost invariably suffer from the disease if they live to adult age. "But if by any chance these children go through life *without* it, the thread is broken and the grandchildren and great-grandchildren of the original shakers may rest assured that they are free from the disease . . . Unstable and whimsical as the disease may be in *other* respects, in *this* it is firm; it never skips a generation to manifest itself in another; once having yielded its claims, it never regains them" [8]. In other words, only those who actually developed the disease were in danger of passing it on.

This argument, however, did not impress most of George Huntington's contemporaries. Some, like Charcot, felt that insufficient documentation precluded judgment. Others, like the Philadelphia neurologist Wharton Sinkler, thought it "generally the case" but not an unvarying rule. William Osler never mentioned

it. He was more impressed with the frequency than with the pattern of hereditary transmission. On the other hand the timing of Huntington's publication no doubt helped to hasten its prominence, given the growing hospital populations in the 1870s and 1880s and the expanding influence and organization of neurology. There was also the fact that Huntington's description was promptly noted in widely read (and relatively new) European medical publications, before the reports of his predecessors became well known. Finally, the encomium of William Osler—one of the most influential physicians of his time—may have been definitive. Although Osler himself preferred the name chronic progressive chorea to Huntington's chorea, he expressed a view in 1893 that has been widely shared ever since. "In the whole range of descriptive nosology," he wrote, "there is not, to my knowledge, an instance in which a disease has been so accurately and fully delineated in so few words" [25].

It is ironic, actually, that the Huntington name was initially used more often in European and Latin American journals than in those published in the USA, which continued, even into the 1920s, to use hereditary chorea, chronic progressive chorea, and occasionally other alternatives. But gradually Huntington's chorea (later Huntington's disease) won out. The influential *Journal of Nervous and Mental Disease* (New York) consistently used this name while the "Huntington Number" of *Neurographs* reminded USA physicians tempted by more a more descriptive nomenclature that few diseases of such importance were known by an American name [34].

Following the rediscovery of Mendel in 1900, George Huntington's account of the specific inheritance pattern began to be taken seriously as science. The English biologist Reginald Punnett is often credited for confirming the pattern described by Huntington, which conformed to Mendelian dominant inheritance [3]. But in fact it was his colleague William Bateson who first counted cases in pedigrees to demonstrate this point. Eager to test Mendelian inheritance in humans, Bateson began collecting pedigrees of families with "hereditary chorea" in 1906. He continued to do so for the next two years, worrying that the ratios did not demonstrate dominance (half affected and half unaffected). Finally at the end of 1908 he became confident that they did. Unfortunately he announced his findings casually in a November 1908 discussion at the British Royal Society of Medicine (RSM) and then in a textbook, *Mendel's Principles of Heredity*, which he published early the following year [35, 36]. By this time, Punnett had inadvertently preempted him, for in

a February 1908 talk at the RSM, Punnett speculated that “hereditary chorea . . . may eventually turn out” to follow Mendelian dominant inheritance [37]. Thereafter Punnett got the credit that Bateson, in my view, deserves [4].

CONCLUSION

The dramatic epistemological and institutional changes within medicine and science over the course of the 19th century help explain the emergence of hereditary chorea as a distinct clinical entity in the mid-1800s and also the eponym Huntington's chorea. These changes also highlight the irony that in an era when science was rapidly transforming the understanding and diagnosis—if not yet the treatment—of disease, young inexperienced rural practitioners far from the great hospitals and centers of medical research were the authors of a major medical breakthrough. They were authors, not of case reports of patients they had treated in a hospital or asylum but of their neighbors, people they had grown up with, persons they had observed in the community, outside of any clinical setting. They knew local gossip and family secrets in a way hospital physicians usually could not, although most subsequent medical reports of Huntington's were based on patients in clinical settings, a change reflecting the late 19th century growth of hospitals and asylums generally.

This contrast raises an interesting question: did physicians prior to the 19th century come in contact with what was later called hereditary chorea but classify it under broader categories – as a variety of Sydenham's chorea (St. Vitus's dance), a choreic type of “insanity,” as dementia, melancholia, or “nervousness?” Or did doctors rarely see a case, much less several generations of a family, because such individuals did not seek medical care or because physicians and hospitals were simply unavailable? I would suggest that one reason Waters, Lyon, Lund and Huntington were able to describe hereditary chorea was their extended experience in small communities where several generations of affected families happened to live. These early physicians were like ethnographers, transcribing family memory and local knowledge into clinical terms that then became part of the literature of medicine. Even today, the pedigrees that remain the crucial heart of much genetics research depend upon the knowledge of the people whose family memory these pedigrees contain. As the historian Susan Lindee has written, “the stories people tell about their bodies and their families are a critical part of genetic science”

[38]. The genius of these early physicians was to take these stories and make them available to medicine and science in ways that we still benefit from today.

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