
First mentioned in Robley Dunglison's (1798–1869) Practice of Medicine (1842), and clearly known to clinicians at Jefferson Medical College in Philadelphia, George Huntington (1850–1916) assembled observations made initially by his father and grandfather on the familial chorea they had each seen in East Hampton and read his paper to the Meigs and Mason Academy of Medicine, Middleton, Ohio, on 15 February 1872. Later (7 December 1909) he confirmed that: ‘over 50 years ago, in riding with my father on his professional rounds, I saw my first case of “that disorder” which was the way the natives always referred to the dreaded disease…we came upon two women, mother and daughter, both tall, thin, almost cadaverous, both bowing, twisting, grinning…then the Gamaliel-like instruction began; my medical instruction had its inception’. ‘That disorder’ was hereditary, with onset in adult life and with chorea followed by insanity. William Bateson (1861–1926) illustrated the concept of autosomal dominant inheritance with families afflicted by Huntington's disease, and this prompted (Ely) Jelliffe (1866–1945) and (Frederick) Tilney Bateson (1876–1938) later to trace the ancestry to brothers from Essex and Suffolk (UK) who arrived in Boston Bay in 1630. But what is the anatomical and pathological basis for this disorder?

Dr Michell Clarke (1859–1918) describes a ‘form of Chorea, characterised by its appearing first in adult or late adult life…[with a] tendency to affect several members of a family, to be inherited, and to end in insanity…well known, but [with] cases rarely met with in ordinary practice and [with] few opportunities for post-mortem investigation of the morbid changes’. James T, a painter, aged 54 years comes from a family in which one of two siblings, his father and four of five uncles or aunts, two cousins and his paternal grandfather died early with insanity and, where details are known, with chorea. As others have noted, the disease often comes at an earlier age in each generation, although this is by no means always the case. Neither venereal disease, lead-poisoning, fits or apoplecticform attack, nor ‘fright or great mental emotion’ preceded his illness which began with involuntary stamping of the foot 5 years before presentation in September 1895 followed by twitching of the limbs and, more recently, failing memory and agitation. Examination shows generalized chorea, which stops during sleep, without weakness or ataxia and with no reflex abnormalities or altered sensation. He is easily confused by complex instructions, and his memory is defective and inaccurate. His general health and nutrition improve in hospital. George T, his younger brother, is seen at the same time in the Fishponds Bristol Lunatic Asylum where he had been admitted in July 1893 with failing memory having also become ‘irritable and dangerous’. He is demented and deluded and has generalized chorea identical to his brother. He dies in the Asylum, after contracting pneumonia, in November 1895. Dr JV Blanchford (nk) carries out the post-mortem examination 27 h later. The brain weighs 44 oz of which thepons, medulla and cerebellum comprise 6 oz. It appears normal to outward appearance. Careful measurements of the regional grey matter and comparisons made with a case reported by Dr Charles Dana (1819–97) show atrophy of the frontal and temporal lobes but not the motor convolutions or occipital pole. Histological examination of fresh tissue uses the staining method devised by Bevan Lewis ([1847–1929]; used for the first illustrations to appear in Brain at pages 84 and 88 of the issue for July 1878); and the hardened brain, embedded in celloidin, is stained in haemotoxylin and eosin, methylene blue, aniline blue-black, haemotoxylin and picrofuschin, and by Weigert’s method. To varying degrees, the frontal lobe and the motor convolutions show the same features of small, shrunken, pigmented pyramidal cells with obscure nuclei and stunted processes; the vasculature is normal. Overgrowth of branched glia and interstitial cells is apparent also extending into the temporal and occipital lobes. Staining with the Golgi method is capricious (see Brain 2012; 135: 4–8) making for difficulties in assessing the extent of any abnormalities; but nonetheless, it is clear that layers 2 and 3 are selectively affected, the ‘small pyramidal cells showing the most marked changes being shrunken, irregular in shape, their processes stunted with small nodose swellings upon them and disappearance of the little “gemmae” in the affected processes’. Generally, the axons and nerve fibres of white and grey matter are normal, as are the cerebellum and cord. ‘To sum up, the morbid changes consisted in
a widespread but partial degeneration of the cells of the cerebral cortex, especially the cells of the second and third layer, most marked in the frontal lobe and motor convolutions, together with an increased amount of interstitial tissue and number of neuroglia cells’ (Figs 1 and 2).

Dr Michell Clarke has observed a third case presenting with weakness in the legs followed by twitchings; he has generalized chorea, slurred speech and is demented. His father had died after falling from a roof after losing his balance due to choreiform movements. Two of his six siblings have chorea: ‘one is in the workhouse and said to be crazy: her children are mentally defective, the Board-school teachers finding it impossible to teach them’. But the patient’s own daughter, thought within the family to be affected, has diplegia and athetosis consistent with the conclusions of a piece in the Lancet for 21 December 1895 advising that cases of so-called congenital chorea are usually examples of cerebral palsy resulting from perinatal brain injury. Now Dr Michell Clarke reviews the recent literature on Huntington’s disease. (William) Menzies [(1863–1945) Journal of Mental Science 1892; 38: 560–568 and ‘January 1893’ (evidently never published)] has described two families: one with 25 affected members amongst 100 individuals traced; and the other with 13 of the 74 family members. Age at onset is in the second or third decade and disease duration 15–20 years. (Hermann) Oppenheim [(1858–1919) Centralblatt fur innere Medizin 1894; 15 (2): p. 918] has dealt in more detail with the pathology based on cases from two affected families under his care concluding that the disorder is a miliary disseminated encephalitis, cortical and subcortical, followed by atrophy of the cortex. Charles Dana (Journal of Nervous and Mental Disease 1895; 20: 565–583) has described cases in five generations of a single family in which there is grey matter thinning due to small pyramidal cell degeneration, the disease belonging to the group of teratologies ‘being an innate defect in cell structure’. Whereas each of these commentators has noticed occasional vascular changes, considered to be secondary, (P) Kronthal (nk) and (Siegfried) Kalischer [(1862–1956) Virchow’s Archiv 1895; 139: 303–318; abstract in Neurologische Centralblatt 15 May 1895] consider the cortical pathology to result from disease of the vessel walls. For Dr Michell Clarke, ‘there seems . . . no doubt that the cerebral cortex, especially of the motor convolutions, is the seat of the disease; the chief difference of opinion [is] whether the primary change is in the nerve cells themselves or in the supporting tissue. So far as my own sections go they point to a degeneration of the nerve cells, with a concomitant increase of the neuroglia’. In fact, this is not so different from the appearances in ‘ordinary chorea’, on the rare occasions when the pathology can be studied; and the identical character of the ‘spasms’ points to involvement of the same parts of the nervous system in each condition. As to where: ‘the cerebral cortex, especially of the motor convolutions, [is] the seat of the morbid change’; and all forms of chorea are due to disturbance in this region. But is this anatomical localization correct?
This is what Dr (J.A.F.) Pfeiffer (nk) wishes to resolve in his description of two cases, each from Dr Huntington's backyard in Ohio (USA). CS is admitted to the Government Hospital for the Insane on 20 November 1907, aged 66 years. He developed chorea aged 52 years, being still only during sleep. He is depressed, suicidal and irritable; and the mental and physical enfeeblement progress to his death in the hospital on 8 January 1913. At post-mortem, the brain and spinal cord are atrophic. Many stains are applied to the fixed tissues. The frontal cortex, by comparison with the temporal and occipital lobes, is abnormal with cellular degeneration especially in the deep layers; ganglion cells show extensive changes in the Nissl substance with chromatolysis, break-up of the tigroid substance into darkly stained granules, and with the nucleus placed eccentrically and its contours misshapen. There is increase in the glia cells and their fibres, most evident close to degenerating ganglion cells; some are fat laden. Blood vessels, arteries and veins are not normal showing degeneration of their muscular coat and changes to the adventitia and elastica. The cerebellum, medulla, spinal cord and peripheral nerves are relatively uninvolved. But now there is a new emphasis: 'The changes in the corpus striatum are very great. The caudate nucleus appears less affected than the lenticulate nucleus and optic thalamus. The degeneration of the ganglion-cells is striking, and in most of them degeneration is quite advanced...the pronounced increase of the lipoid pigment is the most prominent feature of this degeneration; in fact, in some of the degenerated cells the cytoplasm is entirely filled with fat'. There is hyperplasia of the glia, and the vessel walls are thickened.

Dr Pfeiffer's second case, a former member of the US Marine Corps, is admitted, aged 28 years, with chorea, marked carphology and ideas of persecution for which he is admitted to the Washington Hospital for the Insane dying there 12 years later having deteriorated progressively in his social, mental and physical condition. At post-mortem, the brain and spinal cord appear shrunken. Again, the frontal cortex and pre- and post-central convolutions, more than those of the temporal and occipital lobes, show degeneration of ganglion cells with altered Nissl substance and chromatolysis, eccentric distorted nuclei, increased and morphologically abnormal neuroglia, and with changes in the blood vessels. But in this case too, the most striking abnormalities are in the striatum. The lenticulate nucleus is the most affected with severe changes also in the optic thalamus, and the caudate less involved. There is severe and extensive neuronal degeneration with chromatolysis, darkly stained granules and blunted neurofibrillary processes. The neuroglia are overgrown. Only minor abnormalities are observed in the cerebellum, medulla, spinal cord and peripheral nerves. Taken together, the focus in both cases is on acute degeneration and chronic sclerotic changes of neurons within the optic thalamus, corpus striatum, frontal and pre- and post-central regions; conspicuous increase in neuroglia in the same distribution; and vascular changes mainly in the striatum (Fig. 3). What have others to say on the subject? That the disease is an organic disorder of the brain is agreed; but beyond that nothing much. The concepts of progressive chorea as a meningo-encephalitis and the vascular doctrine seem misplaced. There is consensus that the frontal cortex is always involved, mainly in its deeper layers; and glial hyperplasia is acknowledged.

**Figure 3** (A) Degenerated ganglion cell from the precentral gyrus. Toluidine blue. Zeiss Imm. 1/12 oc. 3. The cell bodies of the surrounding glia elements are filled with yellow pigment, and one of them is seen lying within the cytoplasm of the nerve cell. (B) Distorted pyramidal cell with eccentric nucleus, from the frontal region. Toluidine blue. Zeiss Imm. 1/12 oc. (C) Nerve cell of the third cortical layer, frontal region. Toluidine blue. Zeiss Imm. 1/12 oc. Much shrinkage has occurred. (D) Contiguous degenerated ganglion-cells in paracentral region. Many glia cells are seen in the vicinity of their base. Toluidine blue. Zeiss Imm. 1/12 oc. 3. (E) Pyramidal cell from the anterior central convolution showing fine granular degeneration. Toluidine blue. Zeiss Imm. 1/12 oc. (F) Ganglion cell from paracentral region showing vacuolar degeneration. Toluidine blue. Zeiss Imm. 1/12 oc. (G) Nerve cell from lenticulate nucleus showing extreme fatty degeneration (From Pfeiffer, 1913).
by all commentators. But rather few have noted the involvement of the basal ganglia. Perhaps only (Alois) Alzheimer ([1864–1915] Zeitschrift für die Gesamte Neurologie und Psychiatrie 1911; 4: 356–385] has highlighted this regional involvement. ‘In conclusion, it may be stated that the pathology of chronic degenerative chorea consists not only in a degenerative process in the nervous elements of the cortex, but of the thalamus and corpus striatum’.

Fourteen years later, Dr Adolf Meyer (1866–1950) reports in summary the work of the late Dr Charles Dunlap (nk), chief associate in neuropathology to the Psychiatric Institute of the New York State Hospitals (of which Meyer was director from 1902) and his former pupil from 1899 at the Worcester State Hospital in New York State. Dunlap ‘succumbed to arteriosclerosis of the heart before he could bring to conclusion his study on the corpus striatum in Huntington’s disease’. With help from Dr Bertram Lewin (1896–1971), Dunlap’s studies on 17 brains from definite examples of Huntington’s chorea, 12 other probable cases and a series of vascular lesions of the striatum are now made accessible. It had taken Dr Dunlap some time to devise a method for obtaining in one section a complete reconstructed view of the striatum. This allowed him to conclude that in Huntington’s chorea, the striatum is less than half as large as in controls and with reduction of the cerebral cortex but not the thalamus, brain stem or cerebellum. More specifically, he has observed selective loss of the cells and fibres of the caudate and putamen, extending into the ansa lenticularis, with apparent increased density of neurons in the pallidum resulting from loss of its ground substance. Dunlap considered the red nucleus to be normal; reached no firm conclusions relating to the corpus Luysii; and did not study the substantia nigra. In no case of Huntington’s chorea was the putamen and caudate, the cortex and subcortical white matter, spared. He left drawings that summarized his counts of cell numbers and fibres in different conditions (Figs 4 and 5). Dunlap contrasted the pathology of chorea and athetosis with that in disorders characterized by tremor and spasticity: Huntington’s chorea—reduction of the putamen and caudate without involvement of the pallidum, and no tremor or spasticity; double athetosis and état marbré—possible involvement of the pallidum; Wilson’s disease—tremor and spasticity with involvement of the putamen, caudate and pallidum; and Parkinson’s disease—tremor and spasticity, with a doubtful reduction of cells of the pallidum and atrophy of the ansa. There is overgrowth of astrocytes throughout the striatum. Although not necessarily reduced in number, the cortical neurons are often abnormal. Dunlap warns against neglecting disturbances elsewhere in the nervous system in interpreting symptoms and he ‘remains true to the sound principle of pathology that neither specific symptoms nor nosological entities should be hastily identified with one set of morbid lesions, no matter how conspicuous they may be’.

George Huntington and the pathologist clinicians who studied his disease focused on the clinical and pathological features of...
‘that disorder’. They did not elaborate upon disease mechanisms or possibilities for treatment. But with age at presentation in adults and high penetrance of the autosomal dominant gene maintaining a large number of affected individuals worldwide, these are issues that remain of contemporary importance in clinical neuroscience as papers in the current issue (pages 1165, 1180 and 1197) and the commentary from Sarah Tabrizi, Edward Wild and Ralph Andre make clear.

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