Sensory radicular neuropathy associated with muscle wasting in two cases. By A.M.G. Campbell and the late H.L. Hoffman (From the Bristol Royal Hospital, Bristol, and the Royal United Hospital, Bath). Brain 1964: 87; 67–74.

First, Drs Campbell and Hoffman briefly rehearse clinical and pathological accounts of conditions manifesting as hereditary perforating ulcer of the foot since the disorder was first described in the mid-19th century French literature as *acropathie ulcéro-mutilante*. Little was known of the pathological substrate for this condition until Dr Derek Denny-Brown correlated primary degeneration in the dorsal root ganglia with secondary involvement of the posterior roots, peripheral nerves and posterior columns of the spinal cord in one such case—designating the condition as ‘hereditary sensory radicular neuropathy’ (Denny-Brown D. Hereditary sensory radicular neuropathy *Journal of Neurology Neurosurgery and Psychiatry* 1951: 14; 237–252). This report was based on one of 10 affected individuals from a family first reported 30 years earlier (Hicks EP. Hereditary perforating ulcer of the foot. *Lancet* 1922; i; 319–321), in whom the cardinal features were ‘perforating ulcers of the feet, shooting pains about the body and deafness, with clinical signs of dissociated sensory loss and areflexia in the feet’. In the following year, England and Denny-Brown described a pedigree in which 57 individuals amongst 303 family members had peroneal muscular atrophy, but two also showed trophic lesions of the feet for which each subsequently required leg amputation (England AC and Denny-Brown D. Severe sensory changes and trophic disorder in peroneal muscular atrophy: Charcot-Marie-Tooth Type. *Archives of Neurology* 1952: 67; 1–22). Denny-Brown distinguished these examples of peroneal muscular atrophy from his earlier description of hereditary sensory radicular neuropathy, but Campbell and Hoffman seemed not so sure; and the purpose of their report was to clarify the nosology of this group of disorders and to nail the pathological substrate. They describe two families and one sporadic case.

Family X, with nine definite and three partially affected individuals in four generations, showed a rather uniform phenotype confined to the lower limbs and manifesting as hyperkeratosis on the soles of the feet, starting in early adult life, that later ulcerated, enlarged, became infected and proved destructive of the metatarsals and pedal anatomy (see Figs 1 and 2). And yet, the patients remained ambulant, not noticing (in three instances) that one had a nail impaled through the foot, another a gramophone needle driven deep into the sole and a third was carrying around a large glass marble trapped in the shoe, since the lesions were painless and associated with dissociated sensory loss—pain and (usually but not invariably) temperature being preferentially affected below the knees compared to touch. Although bed rest and surgical debridement sometimes allowed the ulcers to heal, one patient had required amputation of a chronically ulcerated leg, observers being astonished that this man had been able to walk on such a deformed limb. Only one patient had lost the tendon reflexes and that individual was the only person also to show involvement of the upper limbs.

Family Y included three definite and two possible affected individuals. Case 2 suffered ulcerated feet for 40 years, always wore surgical boots and later had several toes amputated. Confined to bed for several years in his late 70s, he found the appearance of his left little toe so unpleasant that he himself cut it off, without discomfort, but gangrene supervened, the leg was amputated (this time by surgeons) and he died post-operatively, aged 81. Case 7 lost his hallux to ‘frost-bite’ during the Second World War and was noted to have areflexia with dissociated sensory loss when first assessed in 1953; but he remained fully ambulant over the next 8 years and, when seen in 1961, had normal tendon reflexes and a history of one foot ulcer that had healed in a few weeks. Case 5, the older brother of case 7, presented when he discovered that a missing shoe-horn was wedged in the shoes he had been wearing for several days. Campbell and Hoffman point out that, despite having drunk Guinness since he was a small child and with a later preference for whisky, Case 5 nonetheless won the 1953 President’s Cup and Club Championship of the Bath Bowling Club. But despite admission to this sporting Hall of Fame, by 1956 he suffered infected foot ulceration and required serial amputation of several toes. Progressive weakness and wasting of the hands (see Fig. 3) with areflexia and
loss both of cutaneous and proprioceptive sensation in all four limbs, together with enthusiastic maintenance of his former dietary habits, led to deterioration in personal care and Case 5 died from pneumonia in 1961.

In Patient Z, excision of a plantar wart led to ulceration on the sole of that foot and the demonstration of pain and temperature loss, with preserved proprioception, in the legs. The clawed and ulcerated toes of both feet were removed in stages over the next 2 years. His feet remained numb and paraesthetic with blue discolouration. Later, painless cuts and burns developed in his hands and these were seen to be wasted, weak and clumsy. Most of the tendon reflexes were preserved. Electrophysiological studies favoured a neuropathy but sural nerve biopsy was considered to be normal.

Dr Ronald Norman was able to examine material obtained at a limited post-mortem in Case 6 from Family X. The cord showed loss of myelinated fibres in the gracile tract, especially in the lumbar region; Lissaeur's tract but not Fleschig's posterior root zone was involved. Myelin pallor was apparent in outer parts of the anterolateral white matter and there was axonal loss with astrogliosis in the posterior roots. The anterior horn cells and ventral roots were normal. The one posterior tibial nerve that was sampled showed severe nerve fibre depletion. Biopsy of a digital nerve taken 6 months before death in Case 5 from Family Y, examined by Professor William Blackwood, had shown severe loss of myelin and nerve fibres with reactive changes in Schwann cells and fibrous tissue. At autopsy, there was demyelination in the posterior columns, especially the gracile tract (see Fig. 4). Dr Marion Smith demonstrated active nerve fibre degeneration in the middle laminated fibres of the posterior columns, extending to the posterior roots and sensory nerve fibres. Neurons were replaced by spindle-shaped nuclei; many of the survivors were

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**Fig. 2** Extensive ulceration and deformity of the feet of Case 6 from the X. family.

**Fig. 3** Wasting of hands of Case 5 from the Y. family.

**Fig. 4** Demyelination in the posterior columns of Case Y.5. Loyez. x 12. (The appearance in the cord of Case X.6 was very similar).
chromatolytic with increased perineuronal satellite cells (see Fig. 5). Apart from patchy loss at C8, the anterior horn cells and their connections were normal. The tibial nerve showed demyelination and globular deposits of myelin. The changes of neurogenic atrophy were apparent in one quadriceps muscle.

So, does this small series illuminate the nature of ‘(hereditary) perforating ulcer of the foot’? Having set out their stall around the dilemma of overlap or absolute difference between cases having foot mutilation with or without features of peroneal muscular atrophy, Campbell and Hoffman approach the discussion of their own examples by parading the relevant literature in more detail. Thus, to the cases of Denny-Brown (1951) and England and Denny-Brown (1952), are added those of Barraquer-Ferre` and Barraquer-Bordas (Barraquer-Ferre` L, Barraquer-Bordas L. Posterior ganglio-radicular semeiology in Charcot-Marie-Tooth amyotrophy; trophic disorders, fulgurant pains, sensory disorders. *Acta Neurologica Belgica* 1953: 53; 55–70) and van Bogaert (van Bogaert L. Familial ulcers, mutilating lesions of the extremities and acro-osteolysis. *British Medical Journal* 1957: 17; 367–371) who reported individuals with foot mutilation in pedigrees having peroneal muscular atrophy and hereditary ataxia, respectively. Conversely, examples from Riley (Riley HA. Syringomyelia or Myleodysplasia. *Journal of Nervous and Mental Disease* 1930: 72; 1–27) and Passouant *et al.* (Passouant P, Vallat G, Temple J. Familial ulceromutilating acropathy; associated manifestations *Revue Neurologique* 1951: 84; 248–252) of hereditary ulceration of the feet accompanied by muscle wasting—formulated by Thévenard (Thévenard A. Familial ulceromutilating acropathy *Acta Neurologica Belgica* 1953: 53; 1–24) as ‘la forme paréto-amyotrophique d’acropathie ulcéro-mutilante’—make the opposite point concerning transitional cases. A more complex phenotype had been reported by Reimann and colleagues (Reimann HA, McKechnie WG, Stanisavljevic S. Hereditary sensory radicular neuropathy and other defects in a large family: reinvestigation after 20 years and report of a necropsy. *American Journal of Medicine* 1958: 25; 573–579) in which hereditary ulceration of the feet was associated in two cases with cleft lip and palate, menigocoele and subsequent wasting and weakness of the extremities, and histological evidence for involvement of the anterior horn cells and ventral roots in another. Lamely, in our opinion, Campbell and Hoffman do no more by way of conclusion than to note similarities between these accounts in the literature and Case 5 from their Family Y, leaving open the issue of coincidental alcoholic neuropathy, but preferring the interpretation that these are all transitional cases linking hereditary sensory neuropathy with peroneal muscular atrophy and drawing attention to their more thorough histological examination. Thus, they lump rather than split these disorders—a clinical formulation that needed the genotype–phenotype analyses to which Henry Houlden and colleagues from the UK now make a further important contribution.

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