Regrettting the difficulties in understanding what exactly is meant by the term cerebellar atrophy, based on the many accounts of that topic in the literature that fail to achieve a detailed and accurate clinical description with detailed pathological examination—and paying lip service to the work of (Giovanni) Mingazzini (1859–1929), (Gordon) Holmes (1876–1965) and (La Salle) Archambault (1879–1940)—Harry L. Parker (nk) and (James Watson) Kernohan (1896–1981) aim to clarify the condition first reported by (Augusto) Murri (1841–1932) as ‘cerebellar degeneration due to intestinal intoxication’ and most comprehensively described by (Pierre) Marie (1853–1940), (Charles) Foix (1882–1927) and (Théophile) Alajouanine (1890–1980: Revue neurologique 1922; 38: 849–85 and 1082–111). The literature contains 11 reasonably well described examples of ‘primitive parenchymatous atrophy of the cerebellum of cortical localization’. Nothing in the family or past history suggests a cause for the insidious but progressive disturbance of balance with incoordination of the limbs and dysarthria but less marked nystagmus. At autopsy, the cerebellum is invariably atrophic with widened sulci and shrivelled folia affecting especially the superior and anterior portions of the midline structures. Histologically, the conspicuous finding is the near complete ‘wiping out’ of Purkinje cells and the plexus above and below considered by (Santiago Ramon y) Cajal (1852–1934) to be retrograde collateral fibres. Surrounding basket cells are preserved as are the climbing, mossy and T-shaped fibres. There is proliferation of neuroglia but rather little alteration in myelin. Now, Drs Parker and Kernohan hedge their bets favouring direct viral intoxication and...
described in sheep from the north of England in which Purkinje cells are destroyed and the disease is transmissible. They speculate that some examples result from alcoholism; others are due to premature senescence of Purkinje cells; and there is ‘a group of cases in which clues as to the essential cause are lacking and the aetiology is unknown’. As for the associated ovarian tumour present in their own case of parenchymatous cortical cerebellar atrophy: ‘in considering the diagnosis in their own case of parenchymatous cortical cerebellar atrophy: ‘in considering the diagnosis… the patient had… a pelvic tumour of uncertain nature… with regard to the influence of the carcinoma on the disease, one can only assume that… it constituted a terminal event… the cachexia and weakness resulting from it exaggerated the general functional impairment and helplessness… the carcinoma had no causal connection, although it made the diagnosis more difficult’.

In the next volume of Brain, J.G. (Joseph Godwin) Greenfield (1884–1958), writing on subacute spino-cerebellar degeneration, considers that ‘it seems unlikely that so unusual a pathological picture could have been missed in the past, the occurrence of two cases in one hospital within 2 years of one another makes it likely that this variant of spino-cerebellar degeneration is not a mere sport, and that other cases of this type will crop up from time to time’. The first of these, E.H. aged 66 years, is admitted under the care of Dr (Sir Charles) C.P. Symonds (1890–1978) in June 1931 with dysarthria, abnormal eye movements, head tremor, incoordination of the limbs, unsteadiness and extensor plantar responses; her manner is facile and ‘with a somewhat childish euphoria’. There is no other relevant history ‘apart from a small tumour in the left breast which had been removed in July 1930’. The CSF contains 30 lymphocytes per cubic millilitre with an increase in globulins and Lange curve showing changes in the higher dilutions (0000112122). His condition deteriorates and F.L. remains unable to move, incontinent due to mental deterioration, and bed-bound within 2 months of developing pain in the legs, weight loss and breathlessness. He is wasted and weak with absent lower limb tendon reflexes and severe ataxia. His CSF contains 120 cells per cubic millilitre with an increase in globulins and Lange curve showing changes in the higher dilutions (0000112122). His condition deteriorates and F.L. remains unable to move, incontinent due to mental deterioration, and communicating only with grunts and groans; the only material change is the development of bilateral extensor plantar responses prior to his death after being ill for only 7 months. At autopsy, there is well-established degeneration of the dorsal spino-cerebellar pathways with more recent changes in the ventral spino-cerebellar and pyramidal tracts and dorsal columns (Fig. 3). The cerebellum shows almost complete loss of Purkinje cells but with preserved granule cells and cortical nerve fibres (Figs 4 and 5). Degeneration is also seen in the dentate nuclei, the nuclei of Luys and the strio-Luysian fibres, both fillets, and the superior cerebellar peduncles and posterior longitudinal bundles. The affected parts are characterized by intense perivascular lymphocytic infiltration (Fig. 6). But there is one other finding: ‘examination of the chest showed a large mass of glands lying in front of and behind the trachea at its bifurcation and extending upwards to the root of the neck… the left lung was extensively invaded by white cancerous growth, a small nodule of which projected through the mucosa of the main bronchus… the tumour proved histologically to be a bronchial carcinoma composed of masses of elongated darkly staining cells… numerous mitoses gave evidence of rapid growth’. 
Greenfield distinguishes these cases of ‘subacute cerebellar degeneration’ from those of ‘parenchymatous cortical cerebellar atrophy’ on the basis of the intense limb pains, more rapid course and associated mental deterioration. Anatomically, they share conspicuous loss of cerebellar Purkinje cells but differ with respect to the degeneration of the spinal tracts conveying kinaesthetic information, and involvement of the pyramidal tracts and nuclei of Luys. Distinctions can be made with the histology of cases classified as olivo-ponto-cerebellar degeneration not least because the pons and olives are unaffected and by the much more obvious long tract involvement. In life, the inflammatory changes in affected tissue and the CSF abnormalities suggested the diagnosis of disseminated sclerosis to the extent that autopsy was performed in the first case merely in order to examine an example of that condition presenting at the age of 66 years; and disseminated sclerosis was also considered in Case 2 but rejected on the basis that the concentration of protein in the CSF was excessive. Pausing only to reject the possibility that this form of cerebellar degeneration is due to latent syphilis, and the theory suggested by Parker and Kernohan of a link to ‘Louping ill’, Dr Greenfield reminds readers that inflammation does not necessarily imply infection, being also seen as a reaction to infarction. But of the carcinoma of the bronchus there is not even a mention in discussing the aetiology: taken together, ‘we can do no more than place [these cases] among the system diseases of unknown aetiology’.

It took another 30 years for the full realization to dawn that these were cases of subacute cerebellar degeneration in which the carcinoma of the ovary, bronchus or breast, noted but otherwise ignored by the authors, was in fact causal; and for the clues provided by the perivascular lymphocytic infiltration and evidence from examination of the CSF for synthesis of antibody within the CNS, to gain credence. Gradually, the tentative views of Richmond Prehn in his contribution to the volume on The Remote Effects of Cancer on the Nervous System suggesting that ‘the profusion of antigenic types found in cancers…of man…may cause an occasional immunological cross-reaction between elements of the nervous system and the tumor’ gathered...
momentum. Now ‘parenchymatous cortical cerebellar atrophy (chronic atrophy of Purkinje’s cells)’ and ‘subacute spino-cerebellar degeneration’ have graduated from the realms of a ‘system disease of unknown aetiology’ to one of the fertile crop of well-characterized neuroimmunological diseases of the nervous system. Forty-eight years later, Dr Richmond Prehn (still publishing and attending the University of Washington) recalls nothing of the conference held at the University of Rochester in 1964. But he recognizes that memory can play tricks for someone now is his 90th year: ‘even at a much earlier time I once did the same experiment twice without realizing it!’ He considers that his 1964 remarks must have been only the wildest speculation. Others would disagree. In the citation given when Dr Prehn received the 1977 Rous–Whipple Award of the American Association of Pathologists, Dr George Martin wrote: ‘When Richmond T Prehn graduated from the Long Island College of Medicine in 1947, most respectable tumour biologists did not consider immunology to be particularly relevant to their discipline. By 1957, the situation had changed drastically, largely due to Prehn’s use of a very well-controlled inbred mouse system to demonstrate specific cancer antigens (Prehn and Main: Journal of the National Cancer Institute 1957;18: 769–78). This seminal work, and subsequent elaboration by Prehn and co-workers and by other groups, catalyzed an explosion of research in tumour immunology, resulting in the development of a virtual dogma of immunosurveillance as the critical homeostatic mechanism for the elimination of incipient neoplasms’. Commenting on his demonstration that immunity to cancer does actually occur, Dr Prehn now recalls: ‘Before then it was widely believed that such was an impossibility; immunity against the self—how absurd!’ And with respect to his contributions to the conference on Remote Effects of Cancer on the Nervous System: ‘only after 1964 did a framed sign appear on my office wall: “A prayer: O Lord, teach me to keep my big mouth shut until I know what I am talking about”. Unless I am misinformed, my remarks made in 1964 would probably be speculative even today’. Dr Prehn is wrong and does himself a disservice. The story of how these disorders came to be recognized as remote effects of cancer and their immunological mechanisms elucidated is told in the current issue by Josep Dalmau and Francesc Graus in their review of Paraneoplastic syndromes by Robert Darnell and Jerome Posner (page 1650).

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Figure 6 Thoracic segment of cord. Haematoxylin, van Giesen. To show an ‘inflammatory’ nodule and perivascular infiltration. (From Greenfield, 1934).