Brain Pathology 9: 251-260(1999)

MINI-SYMPOSIUM: Paraneoplastic Syndromes

The Neuropathology of Paraneoplastic Syndromes

Francesco Scaravilli, Shu F An, Michael Groves and Maria Thom

Department of Neuropathology, Institute of Neurology The National Hospital Queen Square, London, WC1N 3BG UK

The term "paraneoplastic neurological syndromes" encompasses a number of uncommon disorders associated with systemic malignancies. In order to be classified a paraneoplastic neurological syndrome, the malignancies must not invade, compress, or metastasize to the nervous system. They can either focally or diffusely involve the central and peripheral nervous system or the neuromuscular junction.

This paper reviews the neuropathology of the syndrome. It will first describe the clinical presentation and give an account of the systemic tumors most commonly associated with the various types of disorders. Then it will review the general pathological features that consist of an inflammatory process predominantly affecting the gray matter. Finally, it will describe in detail the main clinico-pathological types, including 1) encephalomyelitis, 2) cortical cerebellar degeneration, 3) peripheral neuropathy, 4) opsoclonus-myoclonus and 5) retinopathy. The Lambert-Eaton myasthenic syndrome will be dealt with separately in another paper in this symposium.

Introduction

The incidence of paraneoplastic syndromes varies considerably, depending on the criteria used to define them. Indeed, Croft and Wilkinson (16) identified the syndrome in 66% of 1465 cancer patients with muscle weakness and peripheral neuropathy; this percentage increased after the introduction of quantitative sensory or electrophysiological assessment (50). Moreover, cerebellar dysfunction was reported in 25% of patients with lung cancer (81). However, if only patients with well-defined and disabling paraneoplastic disorders were considered, the incidence decreased steadily (it fell to 0.4% in the same group). Low incidences (0.36 and 0.31%) were also reported by Henson and Urich (38) and Sculier *et al*. (70) among lung cancer and small cell lung cancer patients respectively. In a recent study on lung cancer patients by Van Oosterhout *et al*. (77), the incidence was estimated at 1%. Yet, despite the uncommon occurrence of these syndromes in patients with neoplasms, Lambert-Eaton myasthenic syndrome (LEMS) and paraneoplastic cerebellar degeneration (PCD) are so frequently associated with tumors that, when they occur, investigation for a cancer is mandatory.

When studying paraneoplastic disorders of the nervous system, one should be aware of two main points: first, the correlation between a type of neoplasm and the appearance of the changes in the central and peripheral nervous system is not absolute, and second, in some syndromes, gross and histological abnormalities may be absent. The latter statement is particularly pertinent for LEMS (in which abnormalities can be seen only at ultrastructural level) and for opsoclonus-myoclonus (4, 67).

Paraneoplastic syndromes may become clinically evident before, after, or at the same time as the discovery of the neoplasm. Their outcome is almost invariably ominous, although spontaneous improvement or remission has been reported in patients with Hodgkin's disease, opsoclonus-myoclonus, and neuropathy (29, 66), and some patients with LEMS may respond well to plasmapheresis.

For the purpose of this paper, paraneoplastic syndromes will be classified and described according to their pathological appearances; some forms may coexist in the same patient. The disorder can involve 1) the central nervous system, 2) the peripheral nervous sys-

Corresponding author:
Dr. F Scaravilli, Department of Neuropathology, Institute of Neurology, The National Hospital Queen Square, London WC1N 3BG UK; Tel.: +44 171 829 8731; Fax: +44 171 916 9546; E-mail: F.Scaravilli@ion.ucl.ac.uk

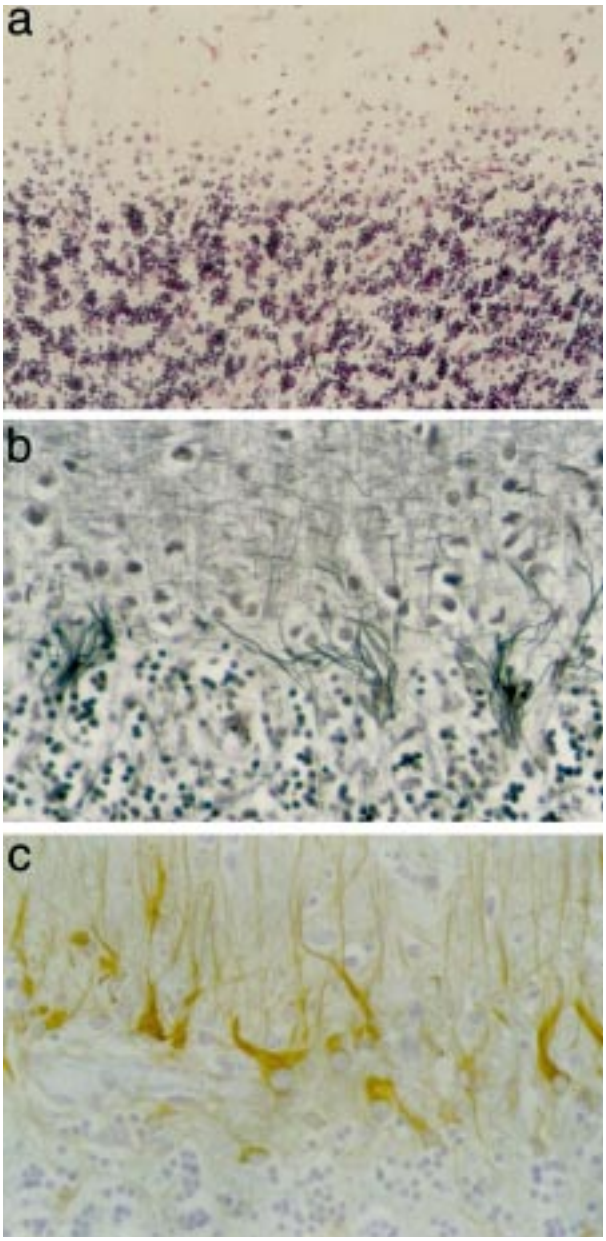

Figure 1. Paraneoplastic Purkinje cells degeneration. **a.** Photomicrograph of the cerebellar cortex in PCD showing complete loss of Purkinje cells. H&E, X 75. **b.** Silver impregnation emphasises the axonal processes of the surviving basket cells. Bielschowsky silver method, X 120 **c.** GFAP immunostaining shows the intense glial proliferation at the level of the Purkinje cell layer. Note the glial processes extending along the molecular layer. X 120

tem, 3) both systems, or 4) the neuromuscular junction (see Table).

Not included in this review are paraneoplastic disorders in which the involvement of the nervous system is

1)	Involving the CNS Paraneoplstic cerebellar degeneration Opsoclonus-myoclonus Retinopathy
2)	Involving the PNS Sensory-motor neuropathy Autonomic neuropathy
3)	Involving both CNS and PNS Paraneoplstic encephalomyelitis/ Sensory neuropathy
4)	Involving the neuromuscular junction Lambert-Eaton myasthenic syndrome (LEMS)

Table 1. Pathological classification of paraneoplastic syndromes.

mediated via changes in a non-neurological organ: for example, the encephalopathy and muscle weakness associated with Cushing's syndrome and Wernicke's encephalopathy secondary to malnutrition related to cancer and opportunistic infections.

Paraneoplastic cerebellar degeneration (PCD)

This disorder was first described in 1919 by Brower (11). Subsequently Brower and Biemond (12) proposed an association between cerebellar changes and neoplasms. In 1982 Henson and Urich (38) reviewed 50 cases; 27 showed a purely degenerative process involving the cerebellar cortex, whereas in a second group of 23 cases these changes were associated with an inflammatory component, either diffuse (18 cases) or localized to the cerebellum (5 cases). Posner (65) estimated that there are fewer than 300 reported cases of PCD, which is considered the commonest paraneoplastic syndrome of the brain (64).

The neurological disorder, which in the majority of the patients precedes the discovery of the neoplasm, usually begins with incoordination in walking. Ataxia of gait, generalized incoordination, dysarthria, and often nystagmus supervene within weeks or months. Although PCD may be associated with any type of malignant tumor, Hammack *et al*. found that those of gynecological origin (mainly from the ovary and breast) were the most numerous (38%). Lung tumors (especially small cell) were the commonest single type (28%), while lymphomas (in particular Hodgkin's type) amounted to 16% (33).

Neuropathology. Macroscopically, the cerebellum appears globally atrophic with widening of the sulci and thinning of the gyri.

The salient histopathological finding is a severe, in some cases total, loss of Purkinje cells (Fig 1a) with preservation of basket cells (Fig 1b). Additional features include axonal swelling of residual Purkinje cells, microglial proliferation, hyperplasia of the Bergmann glia (Fig 1c), thinning of the molecular layer and decrease in the number of granule cells. The appearance of the white matter correlates with the severity of the Purkinje cell loss: it may appear pale with proportional increase of reactive astrocytes. In pure degenerative cases, the deep gray nuclei appear normal. In a number of cases, degeneration may be associated with inflammatory changes, either diffuse to the whole CNS, including the leptomeninges, or circumscribed to the cerebellum. Moreover, some patients with PCD have changes of the cortico-spinal and spino-cerebellar tracts and dorsal columns. All the authors agree that inflammatory changes of the cerebellar cortex occur only rarely.

The cerebellum seems particularly susceptible to cancer. Indeed, in a study of 96 patients with no neurological symptoms and various types of carcinoma, Schmid and Riede (69) found a statistically significant reduction in the number of Purkinje and granule cells, although reduction of the latter was restricted to patients with anaplastic bronchial, ovary, breast, and stomach carcinomas.

Autoantibodies. The CSF and serum of a number of patients with PCD harbor autoantibodies that react with normal nervous tissue. The best categorized antibody, found in patients with gynecological tumors, has been labeled anti-Yo (or Purkinje cell cytoplasmic - PCA-1) and stains the cytoplasm of Purkinje cells. In lung cancer its presence has been documented only once (32). A second autoantibody (anti-Tr) was detected in the serum and CSF of 5 patients with Hodgkin's disease (30).

Paraneoplastic opsoclonus-myoclonus (POM)

As a paraneoplastic syndrome, opsoclonus-myoclonus occurs in association with neuroblastoma in children (64) and with a number of tumors in adults (22). It may occur as the sole neurological symptom, or it may be accompanied by ataxia and myoclonus of the trunk, limbs, head, palate, and diaphragm. Although POM occurs in only 2% of children with neuroblastoma (3), 50% of those with the disorder have neuroblastoma (74). In 50% of the patients, the neoplasm is diagnosed after the appearance of neurological signs. When the tumor is associated with a neurological disorder, the neoplasm tends to be intrathoracic and is less aggressive. In adults with tumor, POM is a less common event, only 20 cases having been reported up to 1991 (64). The commonest tumor is small cell lung cancer.

Neuropathology. In some patients there may be no neuropathological findings. Changes are different from those seen in PCD and range from the complete loss of olivary neurons to the presence of small inflammatory cells in the periaqueductal gray matter. Ridley *et al*. (67) discuss the role of the omnipause nucleus, located in the lower pons, and of the olive in the generation of the disorder. However, the former was intact in both cases they examined, while olivary changes were deemed an unlikely possibility as they are not a frequent finding.

Autoantibodies. As a rule, serum and CSF of children with POM do not contain autoantibodies; notable exceptions are the patients reported by Fisher *et al*. (28) and Dalmau *et al*. (20) in whom anti-Hu antibodies were detected.

The situation in adults is more complex: Luque *et al*. (51) detected Ri-antibodies (or anti neuronal nuclear antibodies type 2 - ANNA-2) in a group of 8 women with breast cancer, most of whom had POM. This antibody stains CNS neuronal nuclei, but not those of dorsal root, sympathetic ganglia, and the myenteric plexus. A similar antibody was found in a single patient with opsoclonus and ataxia and, at post-mortem, severe loss of Purkinje cells and lymphocitic infiltrate in the brain stem (41). Anti-Hu antibodies were reported in a small group of lung cancer patients in whom opsoclonus was part of paraneoplastic encephalomyelitis (40). Finally, other patients with lung cancer either had no detectable antibodies or had atypical antibodies (14).

Paraneoplastic retinopathy

This rare disorder (or cancer associated retinopathy - CAR), is characterized by the following triad of symptoms: severe photosensitivity, scotomatous visual loss and attenuation in caliber of the retinal arteriole (43). Symptoms may begin unilaterally, typically precede the detection of the cancer and progress to painless visual loss. The unusual feature of CAR, associated in 90% of the cases with a small cell lung carcinoma (25), is that the second most common neoplasm is melanoma (54). Boeck *et al*. (7) reviewed 11 patients in the literature with such association. Other associated neoplasms are non-small cell lung carcinoma, breast cancer, uterine sarcoma (26), prostatic cancer (46), and embryonal rhabdomyosarcoma (34).

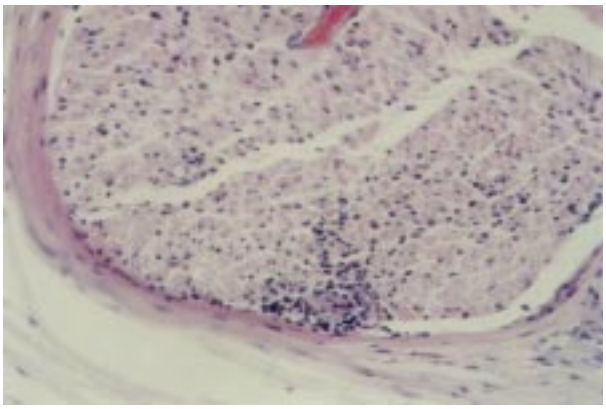

Figure 2. Paraneoplastic peripheral neuropathy. Median nerve showing sub-perineurial lynphocytic infiltration. H&E, X 75

Neuropathology. Changes include diffuse degeneration of photoreceptor cells with relative sparing of cones, almost complete loss of cells of the outer molecular layer, presence of melanin-laden macrophages in the outer retinal layer and the retinal pigment epithelium. The other retinal layers, microvasculature and optic nerves are preserved. In the case of a patient who survived one year after the onset of symptoms, the outer layers appeared to be replaced by glial tissue (64).

Autoantibodies. Most of the cases in which autoantibodies were detected were associated with small cell carcinoma of the lung, ovarian carcinoma (42), or melanoma (7). The best characterized is the so-called anti-CAR antibody that recognizes the photoreceptor protein recoverin (1).

Peripheral neuropathy

Auché (5) is credited as probably the first who described the association between peripheral neuropathy and cancer, followed by Oppenheim (63), Harris (35) and Weber and Hill (80). However, it was Denny-Brown (21) who established the relationship between peripheral neuropathy and carcinoma with his report of 2 cases. The pathology was described by Wyburn-Mason (82). Subsequently Henson and Urich (38) described peripheral neuropathy as the largest, earliest-identified, and best-documented group of paraneoplastic disorders of the nervous system. However, its exact incidence is difficult to establish and largely depends on the criteria applied. Figures vary from 7% in an unsystematic study of patients with carcinoma (36) to 17% and 33% in electrophysiological investigations by Moody (56) and Trojaborg *et al*. (76) respectively. Teräväinen and Larsen (75) quoted an incidence of 48%, whereas Lenman *et al*. (48) produced a figure of 35%. McLeod (52) emphasized the difficulty of establishing the actual frequency of the disorder as its diagnosis depends on a series of factors that include the diligence with which it is sought. The figures he provided vary from 5% for patients with clinical neuropathy, to 12% when quantitative sensory testing is carried out, and up to 30-40% when electrophysiological methods are employed.

From a clinical point of view, paraneoplastic peripheral neuropathies are subdivided into sensory, sensory-motor, and autonomic. The sensory and autonomic forms will be described together with paraneoplastic encephalomyelitis, with which they are frequently associated.

Mixed sensory-motor forms are much more common than pure sensory forms (16) and, in the majority of patients, are associated with lung cancer, although other malignancies (GI tract, breast, uterus, prostate) are sometimes reported (52), including one glioma (53).

The acute form of the neuropathy can present with respiratory paralysis mimicking Guillain-Barré syndrome. The subacute or chronic form is predominantly distal with sensory impairment and reduced reflexes and may either precede the detection of the tumor by up to 5 years or follow it. The remitting and relapsing type may also precede by 2 to 8 years the symptoms related to the tumor, which is found in the lung only in 15% of the patients (17). Remission may follow treatment or the removal of the tumor.

Neuropathology. Axonal degeneration predominates in the majority of the cases (13, 6); segmental demyelination may also be found, and a combination of the two has been described (64), with demyelination leading sometimes to an onion bulb formation (47). A lymphocytic component (Fig 2) may be present around the vessels and it may extend to the dorsal root ganglia. Vincent *et al*. (79) reported microvasculitis in nerves and muscles in 7 patients, all suffering from the sensory-motor form. Ongerboer-de Visser *et al*. (62) detected IgM, C3 and C1q in the inner perineurium and around capillaries. Researchers have also reported a discrete degeneration of dorsal root ganglion cells (18), the posterior columns (18), and anterior horn cells (61), the latter probably due to motor axonopathy.

Paraneoplastic encephalomyelitis/sensory neuropathy

This disorder was first reported by Henson *et al*. (39). However, similar cases had been previously reported by Greenfield (31) and Brain *et al*. (9) who had labeled

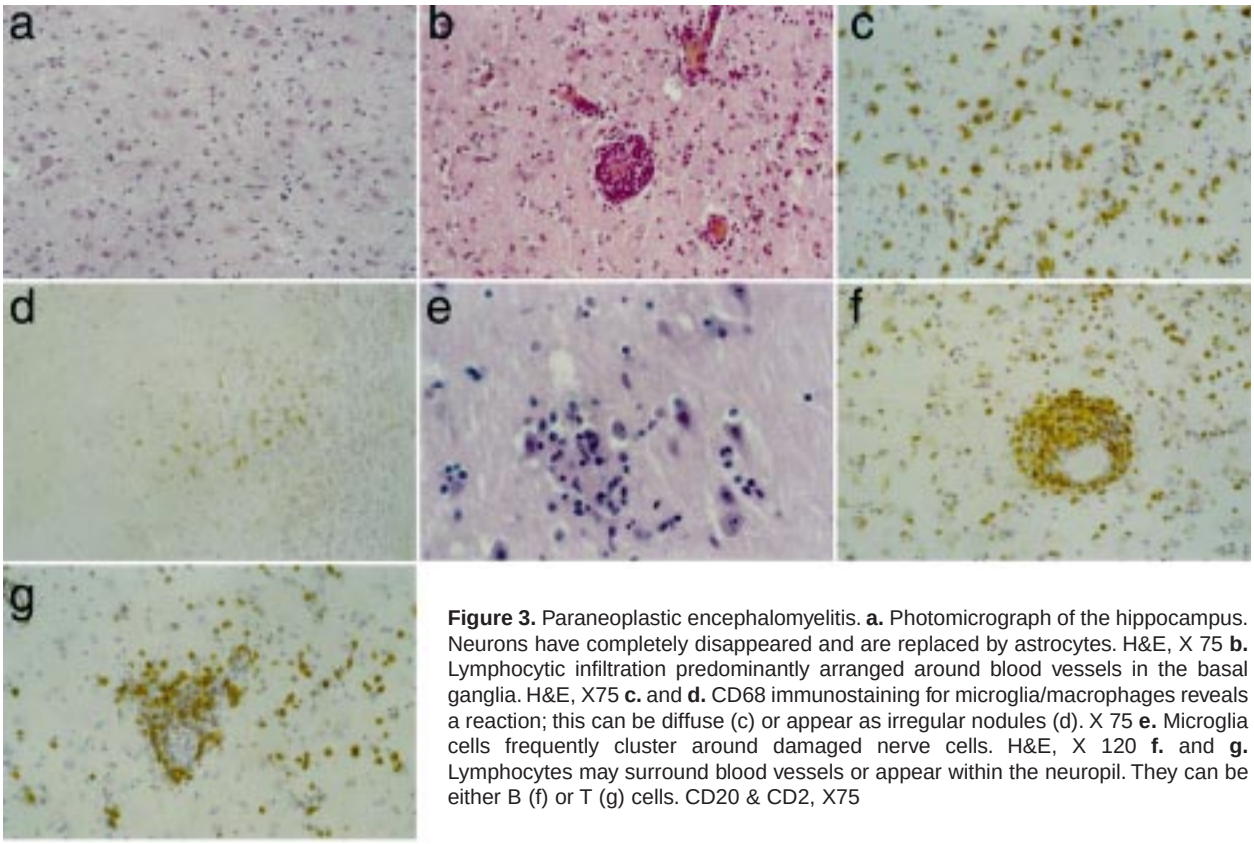

Figure 3. Paraneoplastic encephalomyelitis. **a.** Photomicrograph of the hippocampus. Neurons have completely disappeared and are replaced by astrocytes. H&E, X 75 **b.** Lymphocytic infiltration predominantly arranged around blood vessels in the basal ganglia. H&E, X75 **c.** and **d.** CD68 immunostaining for microglia/macrophages reveals a reaction; this can be diffuse (c) or appear as irregular nodules (d). X 75 **e.** Microglia cells frequently cluster around damaged nerve cells. H&E, X 120 **f.** and **g.** Lymphocytes may surround blood vessels or appear within the neuropil. They can be either B (f) or T (g) cells. CD20 & CD2, X75

them subacute cerebellar degeneration. Russell (68) emphasized the pathological similarities between these cases and viral encephalitides. By 1972 Dorfman and Forno (24) were able to review 20 such cases (increased to 48 and to 69 in two reviews by Henson and Urich [38, 37]). In 75% of the patients, the involvement of the CNS was associated with sensory neuropathy (19). Although this type of paraneoplastic disorder can appear with any form of neoplasm, bronchial carcinoma was detected in 77% of the patients reviewed by Henson and Urich (38); in 42 of them it was of the small cell type. Other types of carcinoma had the following frequency: ovary in 4 patients; breast in 3 (plus 2 additional cases reported by Moossy *et al*. [57]); stomach in 2; uterus in 2; larynx in 1; Hodgkin's lymphoma in 1; and lymphoepithelial thymoma in 1.

Neuropathology. As the distribution of the lesions throughout the CNS and PNS varies enormously, so do the symptoms, although the correlation between severity of nerve cell loss and inflammatory changes on the one hand and symptoms on the other is far from close (25). The following morphological features are shared by all cases examined; the pathological process is a polioencephalomyelitis, although in some cases it can extend to the cerebral and cerebellar white matter (see case 1 of Alajouanine *et al*., [2]). It includes neuronal loss, reactive gliosis (Fig 3a), hyperplasia of the microglia and lymphocytic infiltration (Fig 3b). Microglial cells can be either diffusely distributed (Fig 3c) or arranged to form nodules (Fig 3d) that, in places, can surround severely damaged neurons (neuronophagia)(Fig 3e). The inflammatory reaction consists of both B (Fig 3f) and T (Fig 3g) cells, the latter being of the CD4 helper/inducer type around the vessels, whereas in the parenchymal infiltrate, CD8 cytotoxic predominate over the CD4 helper; natural killer cells are absent.

The distribution of the lesions, which tend to predominate in, or indeed affect only, particular regions of the nervous system, has led to the creation of the following clinico-pathological entities:

Limbic encephalitis. Limbic encephalitis was first described by Brierley *et al*. (10) and reviewed by Corsellis *et al*. (15) who confirmed its frequent association with bronchial carcinoma. Patients manifest hallucinations, abnormal behavior, fits, and loss of recent memory. Pathological changes, which may be detected on MRI scan (23), are found in the hippocampus (Fig

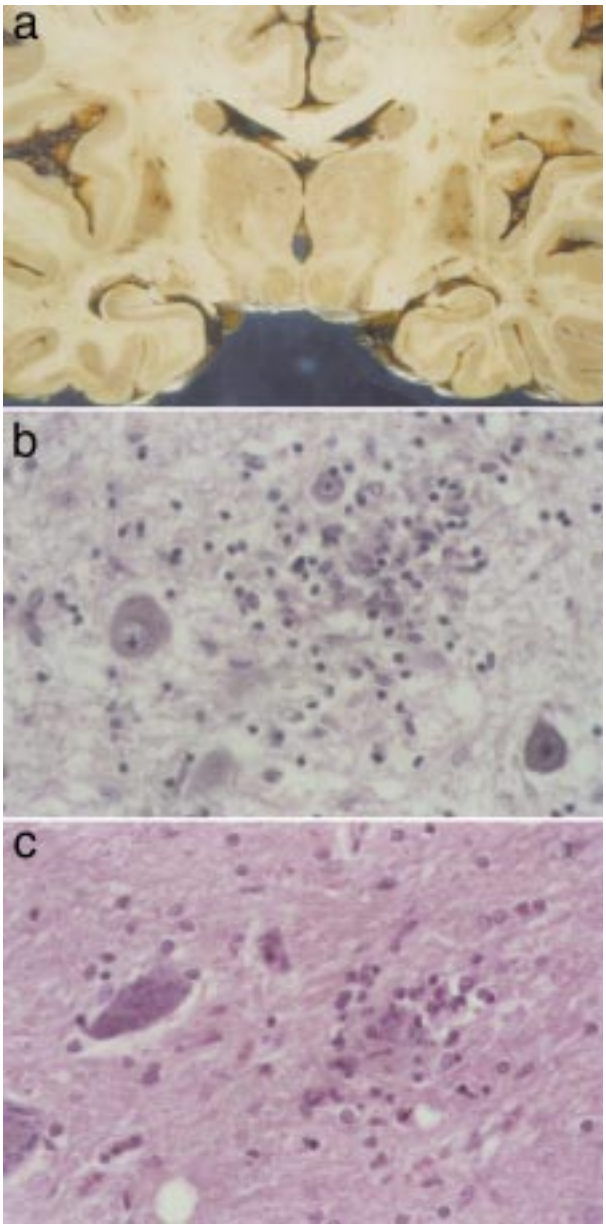

Figure 4. Paraneoplastic encephalomyelitis. **a.** Coronal slice of the brain of a patient with limbic encephalitis. Both hippocampi show thinning of the grey ribbon which appears pink-brown in colour. **b.** Involvement of the vestibular nucleus in a case of brain stem encephalitis. Proliferating microglial cells appear to form an irregular nodule. H&E, X 120 **c.** In the anterior horn of a patient with paraneoplastic myelitis motor neurons disappear; during the acute stager they are replaced by neuronophagic nodules. H&E, X 120

4a), cingulate gyrus, pyriform cortex, frontal orbital surface of the temporal lobe, insula, and amygdala. The pyramidal layer of the hippocampus may show severe neuronal loss and reactive gliosis. The severity of the inflammation varies and may extend to the deep gray nuclei, hypothalamus, and subthalamic nucleus.

Brain stem encephalitis. This subgroup can pose considerable diagnostic problems with other lesions involving the brain stem (vascular disorders, MND, multiple sclerosis, infections, inflammatory disorders, and intrinsic tumors), mainly before the tumor has become manifest. The inflammatory process may involve any of the gray nuclei of the brain stem (Fig 4b). The co-existence of bulbar palsy and evidence of anterior horn cell loss may suggest MND, which, however, is ruled out by the co-existence of sensory disturbances or nystagmus.

Myelitis. Myelitis presents as a poliomyelitis involving both anterior and posterior horns and, in some cases, the Clarke's columns. Changes may be localized to a few segments or may extend to the whole cord. Severe loss of anterior horn cells (Fig 4c) leads to degeneration of anterior roots and to neurogenic muscular atrophy. As myelitis can be only part of a more generalized inflammatory process, it can be associated with degeneration of posterior columns (secondary to ganglioneuritis); cortico-spinal tracts may also be affected.

The existence of a pure form of motor neuron disease (MND) as part of the paraneoplastic process has been debated since Norris and Engel (59) published a series of 130 patients with amyotrophic lateral sclerosis, 10% of whom also suffered from tumors. At the same time Shy and Silverstein (72) concluded that an incidence of 4.5% could not support the association. Among the 11 patients reported by Brain *et al*. (8), three underwent post-mortem examination; of these, two showed additional inflammatory changes and dorsal column pathology. In the third, a carcinoma of the breast was associated with virtually complete loss of motor cells. On the basis of a further study (60), Norris (58) concluded in favor of an association between MND and lung tumors and lymphomas. Evans *et al*. (27) reported a 74-year-old man, still alive at the time of the publication, with motor but no sensory involvement and a renal tumor. Younger *et al*. (83) studied 9 patients with MND and lymphoma. In 8 both upper and lower motor signs were present. No specific autoantibodies are mentioned, but paraproteinaemia was detected in 3 of the 7 in whom it was looked for. Post-mortem examination in 2 cases revealed severe motor neuron loss in the motor cortex, brain stem, and spinal cord with degeneration of the cortico-spinal tracts. No inflammatory changes were mentioned. Verma *et al*. (78) described a 51 year old man with a small cell lung cancer, a pure MND, and loss of anterior horn cells in the cord, associated with decrease in number of Purkinje cells. In this patient high titers of

anti-Hu antibodies were detected. The patient described by Khwaja *et al*. (45), a 67 year old woman with an ovarian carcinoma, also showed a pure motor syndrome; her serum contained PCA-1 (anti-Yo) antibodies. Unfortunately no post-mortem report was included. Finally, the unusual association between a predisposition to cancer of the colon and adult onset MND in 2 brothers should be mentioned (71). No autoantibodies were detected and patient 2 underwent post-mortem examination. Results showed a variable degree of motor cell loss in the brain stem and spinal cord, with preservation of the nuclei of Clarke and Onufrowicz.

Once the cases of paraneoplastic MND associated with myelitis are excluded, the pure degenerative forms are so rare that Henson and Urich (38) concluded that the association is probably fortuitous. Younger *et al*. (83) considered either that lymphoma might cause the neurological disease, perhaps via the paraprotein acting as an antibody, or that both disorders might have a common cause, probably a retrovirus. However, the discovery, in recent years (45, 78), of specific autoantibodies associated with MND suggests that further studies are warranted to clarify this problem.

Ganglioradiculoneuritis and autonomic neuropathy. Ganglioradiculoneuritis may present in isolation or be associated with lesions of CNS. Henson and Urich (38) have classified patients with the latter type of lesion in two groups (38): *a)* presenting as sensory neuropathy, but showing scattered focal inflammatory lesions in the CNS; *b)* presenting as encephalomyelitis, but showing also lesions in the dorsal root ganglia (DRG).

Symptoms include patchy or asymmetric numbness and paraesthesias that may eventually spread to involve all limbs. Burning dysaesthesias and severe aching pain are common. On examination, patients present with sensory ataxia, sensory impairment, and reduced or absent muscle stretch reflexes.

Involvement of the ganglia can be selective or diffuse. In the former event, it can be asymmetrical and affect individual ganglia circumscribed to cervical and lumbar. The degree of severity of the lesion varies and may produce complete destruction of the affected ganglion. Disappearance of ganglion cells is accompanied by comparable increase of nodules of Nageotte, whereas the remaining neurons may show cytoplasmic vacuolation (Fig 5a), chromatolysis, and nuclear shrinkage. Inflammation appears as diffuse lymphocytic infiltration (Fig 5b) or lymphocytic cuffing of the vessels and may extend to the posterior roots. The existence of two separate subgroups of ganglionopathies, inflammatory and non-inflammatory, is questioned by Henson and Urich (38). They argue that the likelihood of finding inflammatory cells depends on the number of ganglia available and the duration of the illness, as the inflammatory process tends to fade and disappear with time.

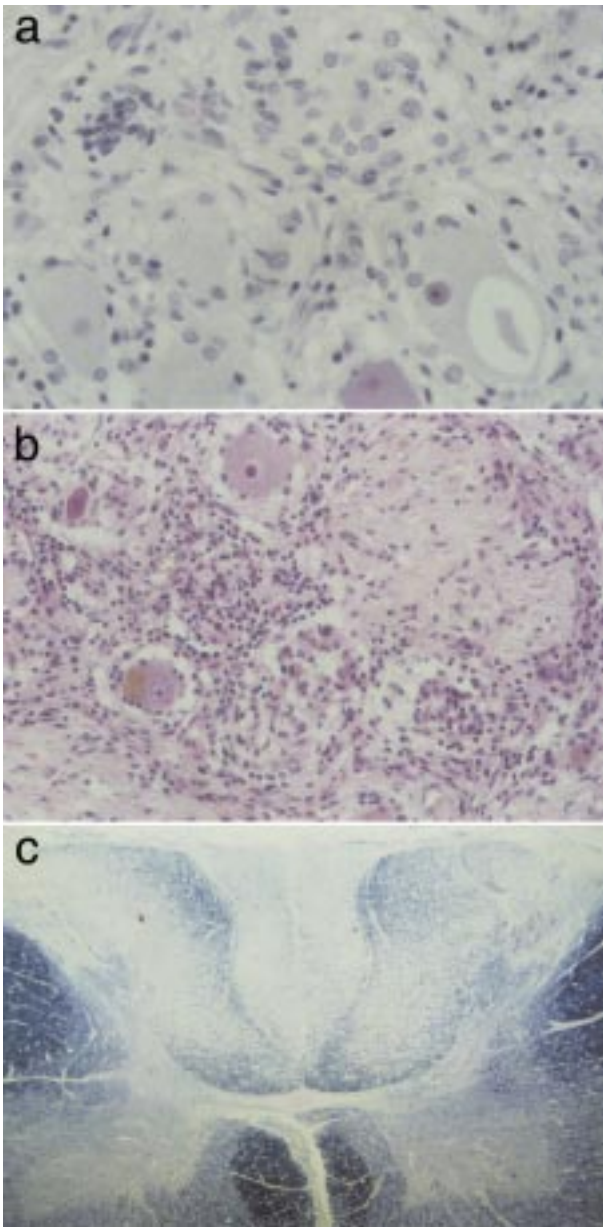

Figure 5. Paraneoplastic ganglioradiculoneuritis. **a.** Dorsal root ganglion. The photomicrograph includes one nodule of Nageotte, one area of proliferation of satellite cells and one vacuolated ganglion cell. H&E, X 120. **b.** Massive lymphocytic infiltration of the same ganglion shown in 5a. Note some ganglion cells with degenerative changes. H&E, X 75. **c.** Degeneration of dorsal columns follows severe dorsal root ganglion cell loss. Luxol fast blue/cresyl violet.

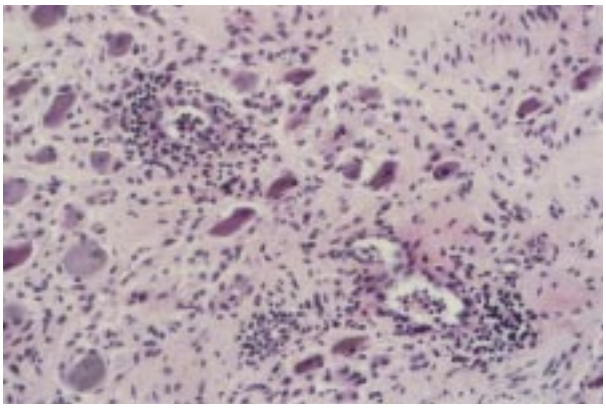

Figure 6. Paraneoplastic encephalomyeloneuritis. Photomicrograph of the superior sympathetic ganglion showing intense lymphocytic infiltration. H&E, X75.

Disappearance of ganglion cells is followed by atrophy of the corresponding posterior roots and by a degree of pallor of the posterior columns proportional to the extent and severity of the neuronal loss (Fig 5c).

Involvement of the autonomic nervous system (Fig 6) has been described, although nerve cell loss in the sympathetic ganglia never reaches the severity of that in sensory ganglia. Neuronal degeneration can be accompanied by lymphocytic infiltration (44). Clinical involvement of the parasympathetic system has been reported (73), whereas Lhermitte *et al*. (49) described inflammatory lesions in the myenteric plexus.

Autoantibodies. The serum and CSF of a large number of patients in these sub-groups have polyclonal antibodies called anti-Hu (also type 1 anti-neuronal nuclear antibodies-ANNA-1) (19, 55). Virtually all patients with this type of disorder and these antibodies have small cell lung carcinoma, while a small number of patients suffer from neuroblastoma, breast, or prostate carcinoma. The characteristic feature of these antibodies is that they stain the nuclei (and more discretely the cytoplasm) of neurons of the CNS and PNS.

References

1. Adamus G, Guy J, Schmied JL, Arendt A and Hargrave PA (1993) Role of anti-recoverin autoantibodies in cancer-associated retinopathy. *Invest Ophthalmol Vis Sci* 34: 2626-33
2. Alajouanine T, Bertrand I and Samson M (1962) Deux observations anatomocliniques de neuropathie cancéreuse. *Rev Neurol* 106: 318-23
3. Altman AJ and Baehner RL (1976) Favorable prognosis for survival in children with coincident opso-myoclonus and neuroblastoma. *Cancer* 37: 846-52
4. Anderson NE, Budde-Steffen C, Rosenblum MK, Graus F, Ford D, Synek BJ and Posner JB (1988) Opsoclonus, myoclonus, ataxia and encephalopathy in adults with cancer: a distinct paraneoplastic syndrome. *Medicine* 67: 100-9
5. Auché M (1890) Des névrites périphériques chez les cancéreux. *Rev Méd* 10: 785-807
6. Barron SA and Heffner RR (1978) Weakness in malignancy: evidence for a remote effect of tumour on distal axons. *Ann Neurol* 4: 268-74
7. Boeck K, Hofman S, Klopfer M, Ian U, Schmidt T, Engst R, Thirkill CE and Ring J (1997) Melanoma-associated paraneoplastic retinopathy: case report and review of the literature. *Brit J Dermatol* 137: 457-60
8. Brain Lord, Croft PB and Wilkinson M (1965) Motor neurone disease as a manifestation of neoplasm (with a note on the course of classical motor neurone disease). *Brain* 88: 479-500
9. Brain WR, Daniel PM and Greenfield JG (1951) Subacute cortical cerebellar degeneration and its relation to carcinoma. *J Neurol Neurosurg Psychiat* 14: 59-75
10. Brierley JB, Corsellis JAN, Hierons R and Nevin S (1960) Subacute encephalitis of later adult life, mainly affecting the limbic area. *Brain* 83: 357-68
11. Brower B (1919) Beitrag zur Kenntis der chronischen diffusen Kleinhirnerkrankngen. *Mendels neurol Zentralblatt* 38: 674-82
12. Brower B and Biemond A (1938) Les affections parenchymateuses du cervelet et leur signification du point de vue de l'anatomie et la physiologie de cet organe. *J Bel Neurol Psychiat* 38: 691-757
13. Brownell B and Hughes JT (1975) Degeneration of muscle in association with carcinoma of the bronchus. *J Neurol Neurosurg Psychiat* 38: 363-70
14. Cher LM, HochbergFH, Teruya J, Nischke M and valenzuela RF (1995) Therapy for paraneoplastic neurologic syndromes in six patients with protein A column immunoadsorption. *Cancer* 75: 1678-83
15. Corsellis JAN, Goldberg GJ and Norton AR (1968) 'Limbic encephalitis' and its association with carcinoma. *Brain* 91: 481-96
16. Croft PB and Wilkinson M (1965) The incidence of carcinomatous neuromyopathy in patients with various types of carcinoma. *Brain* 88: 427-34
17. Croft PB and Wilkinson M (1969) The course and prognosis in some types of carcinomatous neuromyopathy. *Brain* 92: 1-8
18. Crotf CR, Urich H and Wilkinson M (1967) Peripheral neuropayhy of sensorimotor type associated with malignant disease. *Brain* 90: 31-66
19. Dalmau J, Graus F, Rosenblum MK and Posner JB (1992) Anti-Hu-associated paraneoplastic encephalomyelitis/ sensory neuropathy. A clinical study of 71 patients. *Medicine* 71: 59-72
20. Dalmau J, Graus G, Cheung NK, Rosenblum MK and Ho A (1995) Major histocompatibility proteins, anti-Hu antibodies and paraneoplastic encephalomyelitis in neuroblastoma and small cell lung cancer. *Cancer* 75: 99-109

21. Denny-Brown D (1948) Primary sensory neuropathy with muscular changes associated with carcinoma. *J Neurol Neurosurg Psychiat* 11: 73-87

22. Digre KB (1986) Opsoclonus in adults. *Arch Neurol* 43: 1165-75

23. Dirr LY, Elster AD, Donofrio PD and Smith M (1990) Evolution of brain MRI abnormalities in limbic encephalitis. *Neurology* 40: 1304-06

24. Dorfman LJ and Forno LS (1972) Paraneoplsatic encephalomyelitis. *Acta Neurologica Scandinavica* 48: 556-74

25. Dropcho EJ (1998) Neurologic paraneoplastic syndromes. *J Neurol Sci* 153: 264-78

26. Eltabbakh GH, Hoogerland DL and Kay L (1995) Paraneoplastic retinopathy associated with uterine sarcoma. *Gynecol Oncol* 58: 120-23

27. Evans BK, Fagan C, Arnold T, Dropcho EJ and Oh SJ (1990) Paraneoplastic motor neuron disease and renal cell carcinoma: improvement after nephrectomy. *Neurology* 40: 960-62

28. Fisher PG, Wechsler DS and Singer HS (1994) Anti-Hu antibody in a neuroblastoma-associated paraneoplastic syndrome. *Pediatr Neurol* 10: 309-12

29. Graus F and Delattre JY (1995) Immune modulation of paraneoplastic neurologic disorders. *Clin Neurol Neurosurg* 97: 112-16

30. Graus F, Dalmau J, Valldeoriola F, Ferrer I, Rene R, Marin C, Vecht CJ, Arbizu T, Targa C and Moll JW (1997) Immunological characterization of a neuronal antibody (anti-Tr) associated with paraneoplastic cerebellar degeneration and Hodgkin's disease. *J Neuroimmunol* 74: 55-61

31. Greenfield JG (1934) Subacute spinocerebellar degeneration occurring in elderly patients. *Brain* 57: 161-76

32. Hammack J, Kimmel DW, O'Neill BP O'Neill BP and Lennon VA (1990) Paraneoplastic cerebellar degeneration: a clinic comparison of patients with and without Purkinje cell cytoplasmic antibodies. *Mayo Clin Proc* 65: 1423-31

33. Hammack J, Kotanides H, Rosenblum MK and Posner JB (1992) Paraneoplastic cerebellar degeneration: II. Clinical and immunologic findings in 21 patients with Hodgkin's disease. *Neurology* 42: 1938-43

34. Hammerstein W, Jurgens H and Gobel U (1991) Retinal degeneration and embryonal rhabdomyosarcoma of the thorax. *Fortschr Ophthalmol* 88: 463-65

35. Harris W (1926) *Neuritis and Neuralgia*. Oxford Univ press, Oxford, p 38

36. Henson RA (1970) Non-metastatic neurological manifestations of malignant diseases. In *Modern Trends in Neurology*, Williams D ed, Butterworth, London pp 209-25

37. Henson RA and Urich H (1979) Remote effects of malignant disease: certain intracranial disorders. In *Handbook of Clinical Neurology*, Vinken PJ and Bruyn GW eds, North Holland Publishing Co, Amsterdam, vol 38, pp 625-68

38. Henson RA and Urich H (1982) *Cancer and the Nervous System*. Blackwell Scientific, London

39. Henson RA, Russell DS and Wilkinson M (1954) Carcinomatous neuropathy and myopathy. A clinical and pathological study. *Brain* 77: 82-121

40. Hersh B, Dalmau J, Dangond F, Gultekin S, Geller E and Wen PY (1994) Paraneoplastic opsoclonus-myoclonus associated with anti-Hu antibody. *Neurology* 44: 1754-55

41. Hormigo A, Dalmau J, Rosenblum MK, River ME and Posner JB (1994) Immunological and pathological study of an anti-Ri-associated encephalopathy. *Ann Neurol* 36: 896-902

42. Huober J, Holz FG, Schmid H, Nolle B, Bellmann C, Krastel H, Wallwiener D and Bastert G (1997) Paraneoplastic retinopathy in 2 patients with breast carcinoma. *Zentralbl Gynakol* 119: 278-81

43. Jacobson DM, Thirkill CE and Tipping SJ (1990) A clinical triad to diagnose paraneoplsatic retinopathy. *Ann Neurol* 28: 162-67

44. Johnson PC, Roluk LA, Hamilton RH and Laguna JF (1979) Paraneoplastic vasculitis of nerve: a remote effect of cancer. *Ann Neurol* 5: 437-44

45. Khwaja S, Sripathi N, Ahmad BK and Lennon VA (1998) Paraneoplastic motor neuron disease with type 1 Purkinje cell antibody. *Muscle Nerve* 21: 943-45

46. Lafeuillade A, Quilichini R, Chiozza R, Pellegrino P and Thirkill CE (1993) Rétinopathie paranéoplasique (CAR syndrome) révélatrice d'un cancer prostatique. *Presse Méd* 22: 35

47. Lamarche J and Vital C (1987) Carcinomatous neuropathy. An ultrastructural study of 10 cases. *Ann Pathol* 7: 98-105

48. Lenman JAR, Fleming AM, Robertson MAH *et al* (1981) Peripheral nerve function in patients with bronchial carcinoma. Comparison with matched controls and effects of treatment. *J Neurol Neurosurg Psychiat* 44: 54-61

49. Lhermitte F, Gray F, Lyon-Caen O, Pertuiset BF and Bernard P (1980) Paralysie du tube digestif avec lésions des plexus myentériques. Nouveau syndrome paranéoplasique. *Rev Neurol* 136: 825-36

50. Lipton RB, Galer BS, Dutcher JP, Portenoy RK, Berger A, Arezzo JC, Mizruchi M, Wiernik PH and Schaumburg HH (1987) Quantitative sensory testing demonstrates that subclinical sensory neuropathy is prevalent in patients with cancer. *Arch Neurol* 44: 944-6

51. Luque A, Furneaux HM, Ferziger R, Rosenblum MK and Wray S (1991) Anti-Ri: an antibody with paraneoplstic opsoclonus and breast cancer. *Ann Neurol* 29: 241-51

52. McLeod JG (1993) Paraneoplastic neuropathies. In *Periphearl Neuropathy*, Dick PJ and Thomas PK eds, 3rd ed WB Saunders Co, Philadelphia, pp 1583-90

53. Mellgren SI, Mørk S and Nyland H (1978) Malignant glioma and sensorimotor neuropathy. *J Neurol* 48: 1-6

54. Milam AH, Saari JC, Jacobson SG, Lubinski WP, Feun LG and Alexander KR (1993) Autoantibodies against retinal bipolar cells in cutaneous melanoma-associated retinopathy. *Invest Ophthalmol Vis Sci* 34: 91-100

55. Moll JW, Antoine JC, Brashear HR, Delattre J, Drlicek M and Dropcho EJ (1995) Guidelines on the detection of paraneoplastic anti-neuronal-specific antibodies. *Neurology* 45: 1937-41

56. Moody JF (1965) Electrophysiological investigations in the neurological complications of carcinoma. *Brain* 88: 1023-36

57. Moossy J, Todd Troost B and Durkan J (1980) Chronic brainstem-cerebellar encephalitis: a delayed remote effect of breast carcinoma? *Neurology* 30: 430

58. Norris FH jr (1979) Remote effects of cancer on the spinal cord. In *Handbook of Clinical Neurology*, Vinken PJ and Bruyn GW eds, North Holland Publishing Company, Amsterdam, vol 38, pp 669-77

59. Norris FH jr and Engel WK (1965) Carcinomatous amyotrophic lateral sclerosis. In *The Remote Effect of Cancer of the Nervous System*, Lord Brain and Norris HF jr eds, Grune and Stratton, New York, pp 24-34

60. Norris FH jr, McMenemey WH and Barnard RO (1969) Anterior horn pathology in carcinomatous neuromyopathy compared with other forms of motor neuron disease. In *Motor Neuron Disease*, Norris FH jr and Kurland LT eds, Grune and Stratton, New York, pp 100-11

61. Norris FH jr, Rudolph JH and Barney MO (1964) Carcinomatous neuropathy. Rare complication of cancer of the cervix uteri. *Neurology* 14: 202-05

62. Ongerboer de Visser BW, Feltkamp-Wroom TM and Feltkamp CA (1983) Sural nerve immune deposits in polyneuropathy as a remote effect of malignancy. *Ann Neurol* 14: 261-66

63. Oppenheim H (1911) *Textbook of Nervous Diseases.* 5th ed, Edinburgh

64. Posner JB (1991) Paraneoplastic syndromes. *Neurologic Clinics* 9: 919-36

65. Posner JB (1993) Paraneoplastic cerebellar degeneration. *Can J Neurol Sci* 20 (suppl 3): 117-22

66. Posner JB and Dalmau J (1995) Clinical enigmas of paraneoplastic neurologic disorders. *Clin Neurol Neurosurg* 97: 61-70

67. Ridley A, Kennard C, Scholtz CL Büttner-Ennever JA, Summer B and Turnbull A (1987) Omnipause neurons in two cases of opsoclonus associated with oat cell carcinoma of the lung. *Brain* 110: 1699-709

68. Russell DS (1961) Encephalomyelitis and carcinomatous neuropathy. In *The encephalitides*, van Bogaert L, Radermecker J, Hozay J and Lowenthal eds, Elsevier, Amsterdam, pp 131-35

69. Schmid AH and Riede UN (1974) A morphometric study of the cerebellar cortex from patients with carcinoma. *Acta Neuropathol* 28: 343-52

70. Sculier J-P, Feld R, Evans WK, De Boer G, Shepherd FA, Payne DG, Pringle JF, Yeoh JL, Quirt IC, Curtis JE *et al* (1987) Neurologic disorders in patients with small cell lung cancer. *Cancer* 60: 2275-83

71. Shaw PJ, Ince PG, Slade J, Burn J and Cartlidge NEF (1991) Lower motor neuron degeneration and familial predisposition to colonic neoplasia in two adult siblings. *J Neurol Neurosurg Psychiat* 54: 993-96

72. Shy GM and Silverstein I (1965) A study of the effects upon the motor unit by remote malignancy. *Brain* 88: 515-28

73. Sodhi N, Camilleri M, Camoriano JK, Low PA, Fealey RD and Perry MC (1989) Autonomic function and motility in intestinal pseudoobstruction caused by paraneoplastic syndrome. *Dig Dis Sci* 34: 1937-42

74. Telander RL, Smithson WA and Groover RV (1989) Clinical outcome in children with acute cerebellar encephalopathy and neuroblastoma. *J Pediatr Surg* 24: 11-14

75. Teräväinen H and Larsen A (1977) Some features of the neuromuscular complications of pulmonary carcinoma. *Ann Neurol* 2: 495-502

76. Trojaborg W, Frentzen E and Anderson I (1969) Peripheral neuropathy and myopathy associated with carcinoma of the lung. *Brain* 92: 71-82

77. Van Oosterhout AG, Van de Pol M, Ten Velde GPM and Twijnstra A (1996) Neurologic disorders in 203 consecutive patients with small cell lung cancer. *Cancer* 77: 1434-41

78. Verma A, Berger JR, Snodgrass S and Petito C (1996) Motor neuron disease: a paraneoplastic process associated with anti-Hu antibody and small cell lung carcinoma. *Ann Neurol* 40: 112-16

79. Vincent D, Dubas F, Hauw JJ, Godeau P, Lhermitte F, Buge A and Castaigne P (1986) Nerve and muscle microvasculitis in peripheral neuropathy: a remote effect of cancer? *J Neurol Neurosurg Psychiat* 49: 1007-10

80. Weber FP and Hill TR (1933) Complete degeneration of the posterior columns of the spinal cord with chronic polyneuritis in a case of widespread carcinomatous disease. *J Neurol Psychopathol* 14: 57-60

81. Wessel K, Diener HC, Dichgans J and Thron A (1988) Cerebellar dysfucnction in patients with brochogenic carcinoma: clinical and post-urographic findings. *J Neurol* 235: 290-6

82. Wyburn-Mason R (1948) Bronchial carcinoma presenting as a polyneuritis. *Lancet* 1: 203-206

83. Younger DS, Rowland LP, Latov N, Hays AP, Lange DJ, Sherman W, Inghirami G, Pesce MA, Kniowles DM, Powers J, Miller JR, Fetell MR and Lovelace RE (1991) Lymphoma, motor neuron disease and amyotrophic lateral sclerosis. *Ann Neurol* 29: 78-86