CHAPTER 36

Paraneoplastic Diseases of Neuro-Ophthalmologic Interest

Daniel M. Jacobson and Howard D. Pomeranz

A number of disorders characterized by visual dysfunction, neurologic dysfunction, or both occur in the setting of known or suspected cancers but do not result from the direct effects of the tumor. These disorders are called *paraneoplastic syndromes* and result from ''remote effects'' of the cancer (1). A paraneoplastic syndrome may develop before or after a cancer declares itself in a primary or disseminated location. The cause and pathogenesis of most paraneoplastic disorders remain unclear, although many are now thought to involve autoimmune mechanisms. Most of these syndromes are defined by their clinical and pathologic features and by the lack of direct damage to the visual apparatus and central nervous system (CNS) by tumor compression or infiltration, common infectious agents, or the toxic side effects of therapy. Some paraneoplastic disorders are associated with specific circulating autoantibodies that serve to identify a particular clinical presentation as being paraneoplastic in nature and to guide the diagnostic evaluation toward certain organs to identify the underlying cancer (2). Paraneoplastic syndromes are much less common than are neurologic or visual disturbances produced by metastatic lesions, metabolic and nutritional complications, or complications of therapy. Thus, in any patient with known or suspected cancer, metastasis and other potentially treatable or reversible complications must be excluded before a paraneoplastic syndrome can be diagnosed. Nevertheless, the overall incidence of remote effects of cancer has been estimated to be as high as 10% (3–5). With inclusion of small-cell lung cancer and ovarian carcinoma, estimates of the incidence of paraneoplastic syndromes are as high as 15%.

Despite the relatively infrequent occurrence of neurologic injury resulting from remote effects of cancer, recognition of paraneoplastic syndromes is important for several reasons. When the syndrome is the initial manifestation of the cancer and is recognized as such, the underlying neoplasm may be diagnosed and treated at an early stage, potentially improving the ultimate prognosis. Recognition of a specific paraneoplastic disorder allows the clinician to target the search for the responsible cancer to certain major organs likely to be associated with that particular remote effect. Although effective treatment for most paraneoplastic disorders does not currently exist, palliative treatment can be offered for

some remote effects, such as the use of adrenocorticotropic hormone (ACTH) to treat the opsoclonus-myoclonus associated with neuroblastoma and the use of plasmapheresis, intravenous immunoglobulin, or immunosuppressive agents to treat the Eaton-Lambert syndrome.

Paraneoplastic syndromes may affect the central nervous system, peripheral nervous system, neuromuscular junction, or the skeletal muscles (1,3,6). In addition, there are a variety of paraneoplastic syndromes that affect the retina and optic nerve and produce progressive visual loss. In this chapter, we discuss several of the paraneoplastic syndromes, emphasizing aspects of neuro-ophthalmologic interest.

PARANEOPLASTIC SYNDROMES AFFECTING THE CENTRAL NERVOUS SYSTEM

PARANEOPLASTIC ENCEPHALOMYELITIS

Henson et al. (7) first used the term *encephalomyelitis with carcinoma* to describe the development of progressive clinical manifestations that implicated injury to multiple levels of the nervous system in a group of patients with various malignancies–most often small-cell lung cancer.

Paraneoplastic encephalomyelitis (PEM) is characterized clinically and pathologically by patchy, multifocal involvement of any or all areas of the cerebral hemispheres, limbic system, cerebellum, brain stem, spinal cord, dorsal root ganglia, and autonomic ganglia. Neuronal loss is accompanied by mononuclear cell infiltration. In most patients with PEM, the neurologic syndrome frequently precedes the discovery of the neoplasm by several months. The most common clinical manifestation of PEM is subacute sensory neuropathy reflecting involvement of dorsal root ganglia (8). Early symptoms are patchy or asymmetric numbness and paresthesias, often involving the face, trunk, or proximal limbs. The symptoms eventually spread to all limbs. Patients can have difficulty walking because of pain and loss of proprioception (9). PEM is not as much a single disease as it is a group of disorders that share a common histopathologic appearance despite differing from each other in clinical manifestations and anatomic sites. The major disorders included under this heading are cerebral (including limbic) encephalitis, brainstem encephalitis, cerebellar encephalitis, and subacute myelitis.

For nosologic purposes, the associated clinical entities of subacute sensory neuronopathy and autonomic neuropathy are discussed in a separate section below under ''Paraneoplastic Peripheral Neuropathies.''

Although the individual paraneoplastic encephalomyelitides are presented as distinct and separate entities in this chapter, there is considerable overlap among them. For example, patients whose main clinical manifestations are those of cerebral encephalitis also may have symptoms and signs of damage to the brainstem (10). In addition, patients with any of these conditions may also have evidence of one or more of the other paraneoplastic syndromes that affect the central and peripheral nervous system. Thus, features of paraneoplastic encephalitis, subacute cerebellar degeneration, and peripheral neuropathy may all be present in the same patient (11–13). Finally, even when clinical symptoms and signs indicate that the primary site of a paraneoplastic process affecting the central nervous system is limited to a specific location, histopathologic abnormalities may also be identified in other locations. Despite clear instances in which multiple syndromes appear to overlap clinically and histopathologically in the same patient, the separation of certain forms of paraneoplastic encephalomyelitis has some merit in the understanding of specific clinical states.

Specific Syndromes

Paraneoplastic Limbic Encephalitis

In the majority of patients with paraneoplastic limbic encephalitis (PLE), the neurologic symptoms are personality changes, irritability, depression, seizures, memory loss, and sometimes dementia (14). MRI findings in paraneoplastic limbic encephalitis usually show increased signals on T2-weighted images in the medial temporal lobes and amygdala and less commonly in the hypothalamus and basal frontal cortex (15,16). Other common manifestations of limbic encephalitis include agitation, anxiety, apathy, paranoia, delusions, hallucinations, inappropriate behavior, and a striking impairment of memory (7,17–20). Patients with this syndrome may therefore be thought to have a psychiatric disorder (21). In these cases, damage is most severe in the hippocampal formation, amygdaloid nucleus, cingulate gyrus, insula, and orbital cortex of the frontal lobe. This pattern has thus been termed ''limbic encephalitis'' (7,17,18).

Bennett et al. (22) reported two patients with testicular cancer who exhibited supranuclear gaze disorders as a manifestation of PEM. In the first patient, a vertical gaze palsy was accompanied by limbic encephalitis, oculogyric crises, ataxia, lid retraction, and the ocular tilt reaction. In the second patient, a left hypertrophic skew deviation was accompanied by a fluctuating, mixed pendular and jerk nystagmus, dysmetria, and dysarthria. Blood from both patients contained the anti-Ta antibody in conjunction with testicular cancer.

Brainstem (Bulbar) Encephalitis

The symptoms of patients with the brainstem or bulbar form of paraneoplastic encephalomyelitis vary considerably. Patients in whom the pons and medulla are the sites of major damage may experience vertigo, loss of hearing, facial numbness, dysphagia, hoarseness, and dysarthria. Ocular symptoms include diplopia, usually horizontal or oblique, and oscillopsia. Neurologic signs in these patients include vestibular nystagmus, downbeat nystagmus, upbeat nystagmus, unilateral or bilateral horizontal gaze paresis, internuclear ophthalmoplegia, skew deviation, abducens nerve paresis, impaired facial sensation, sensorineural hearing loss,

dysarthria, hyperactive or impaired gag reflex, hyperactive jaw jerk, and weakness and atrophy of the tongue and palatal muscles. The symptoms and signs may be diffuse or focal (6,7,12,23–28). Abnormalities in respiration, including periodic hyperventilation, hypoventilation, and apneustic breathing may also develop (10,24,25,28).

Damage to the mesencephalon in patients with paraneoplastic brainstem encephalitis may cause ptosis, conjugate or dysconjugate vertical gaze paresis, diffuse ophthalmoplegia, and abnormal involuntary movements (29–31).

Patients with paraneoplastic brainstem encephalitis may initially be assumed to have metastatic or primary tumor infiltration of the brainstem or carcinomatous leptomeningeal infiltration affecting the cranial nerves. In such patients, the correct diagnosis is often made only at autopsy.

Cerebellar Encephalitis

The symptoms and signs of cerebellar encephalitis include gait and limb ataxia, tremor, dyssynergia, dysmetria, hypotonia, and dysarthria. Ocular motor findings include nystagmus and saccadic intrusions or oscillations. This syndrome is virtually impossible to distinguish clinically from paraneoplastic subacute cerebellar degeneration (see below) except that its onset tends to be more acute. In addition, other forms of paraneoplastic encephalomyelitis may infrequently present initially with evidence of cerebellar dysfunction, usually gait ataxia (1,32). In affected cases, however, pancerebellar findings and clinical evidence of multifocal central and peripheral neurologic involvement eventually develop in the vast majority of affected patients (32).

Subacute Myelitis

Nonnecrotizing paraneoplastic myelitis is an uncommon remote effect of cancer that generally does not occur as a neurologically isolated presentation (6). Affected patients typically demonstrate other clinical manifestations of paraneoplastic encephalomyelitis and peripheral neuropathy (1,32). One clinical presentation correlated with anterior horn cell loss involves progressive weakness, often associated with clinical findings of lower motor neuron dysfunction, including wasting, fasciculations, and impaired muscle stretch reflexes (6,7). The upper extremity and neck muscles are usually affected early from preferential damage to the cervical spinal cord. Respiratory compromise and bulbar paresis may develop if the pathologic process extends into the caudal brainstem cranial nerve nuclei. Although progressive sensory loss rarely occurs from degeneration of the posterior columns, subacute sensory neuronopathy from associated dorsal root ganglia degeneration is more commonly the cause of sensory loss in this setting (6,7). Damage to the descending motor tracts within the spinal cord or the brainstem causes clinical findings of upper motor neuron dysfunction, including hypertonia, hyperactive muscle stretch reflexes, and extensor plantar responses (6). Incontinence of bowel or bladder may develop. These neurologic symptoms and physical findings are generally diffuse and not localized to a specific clinically defined segmental level along the neuraxis. When myelopathic findings are prominent or segmentally localized, MR imaging or some type of myelography is necessary to determine if there is compression or infiltration of the spinal cord by metastatic tumor, infection, or some other structural process.

Another uncommon presentation of nonnecrotizing paraneoplastic myelitis is generalized or segmental rigidity and myoclonus (33–35). Affected patients experience progressive aching and stiffness confined to a single extremity or multiple limbs, followed by rigidity and frequent painful spasms, often precipitated by tactile stimulation or attempted use. Frequent myoclonic jerks of the affected limb occur. The affected muscles are palpably contracted, and electromyography confirms continuous motor activity of these limbs. Widespread damage to all extremities, the abdominal, cervical, and paraspinous muscles gives rise to progressive immobility and neurologic disability. These physical findings correlate with neuronal loss of inhibitory spinal interneurons within the anterior horns of the gray matter (33,34).

Pathology

About 75% of cases of paraneoplastic encephalomyelitis are associated with bronchial carcinomas, primarily small-cell lung cancer; however, a wide spectrum of causative tumors has been reported. These include tumors of the ovary, breast, uterus, stomach, colon, kidney, bladder, prostate, testicles, thymus gland, and larynx as well as Hodgkin's disease and neuroblastoma (1,6). Rare patients with typical clinical features and characteristic neuropathologic findings of paraneoplastic encephalomyelitis have been reported in whom no neoplasm was discovered during life or following careful postmortem examination (36).

In paraneoplastic encephalomyelitis, gross changes in the brain usually are not impressive, although in limbic encephalitis the lesions are occasionally sufficiently extensive to be visible on the surface of the brain and in exposed cut sections. Such changes include thinning of the cortex and discoloration of the hippocampal formation. The characteristic histopathologic changes are inflammatory and consist of prominent perivascular cuffing by lymphocytes and occasionally by plasma cells in the brain and spinal cord parenchyma and to a lesser extent in the overlying meninges. In addition, damage and loss of neurons, neuronophagia, microglial infiltration, and microglial nodule formation in the parenchyma are prominent findings. The process affects gray matter more extensively than white matter. Wallerian degeneration of tracts extending from the regions of neuronal loss also occurs in this setting.

The extent of damage varies from case to case (6,37). Some patients show widespread changes (11), whereas in others the pathologic abnormalities are restricted to a single region (7). In limbic encephalitis, as noted above, the histologic abnormalities are located primarily in mesial temporal lobe structures, including the amygdala, hippocampus, and uncus, as well as in the insula and cingulate gyrus. In brainstem encephalitis, the nuclei of the cranial nerves, the inferior olivary nuclei, the vestibular nuclei, the basis pontis, and the substantia nigra are most commonly affected. When

the cerebellum is the site of the paraneoplastic process, the dentate nuclei are usually most severely affected, resulting in atrophy of the superior cerebellar peduncles. The extent of damage in the cerebellar cortex is variable, but inflammatory changes and loss of neurons usually are not marked. Nonnecrotizing subacute myelitis affects primarily the gray matter and may damage only a portion of the spinal cord (usually the cervical or lumbar segments) or the entire spinal cord. This process damages both the anterior and posterior horns, causing variable degrees of inflammation and neuronal loss. White matter tracts may show Wallerian degeneration from distant lesions in ascending or descending fiber pathways. Loss of neurons in the anterior horns is associated with atrophy of the anterior spinal roots. If the process is severe, there is also neurogenic atrophy in the skeletal muscles supplied by these roots (3). Degeneration of the posterior columns usually occurs secondary to inflammation and neuronal loss affecting the dorsal root ganglia (6).

Diagnostic Evaluations

The protein in the CSF is increased in most cases of paraneoplastic encephalomyelitis, typically in the range of 60–100 mg/dl. A mild lymphocytic pleocytosis, usually between 8–60 cells/mm^3, frequently exists. Oligoclonal bands and elevated immunoglobulin indices and synthesis rates are sometimes detected. The electroencephalogram (EEG) may be abnormal in cases of limbic encephalitis, showing nonspecific slowing or background irregularities, or there may be focal epileptiform discharges that are either unassociated with any behavioral abnormality (21) or that correlate with a clinically evident seizure disorder (38). Cranial CT scanning usually shows no specific abnormality, but it may reveal changes consistent with brain atrophy. In cases of limbic encephalitis, brain MR imaging may show an abnormally high signal intensity in the medial temporal lobes (15,16,39, 40) (Fig. 36.1).

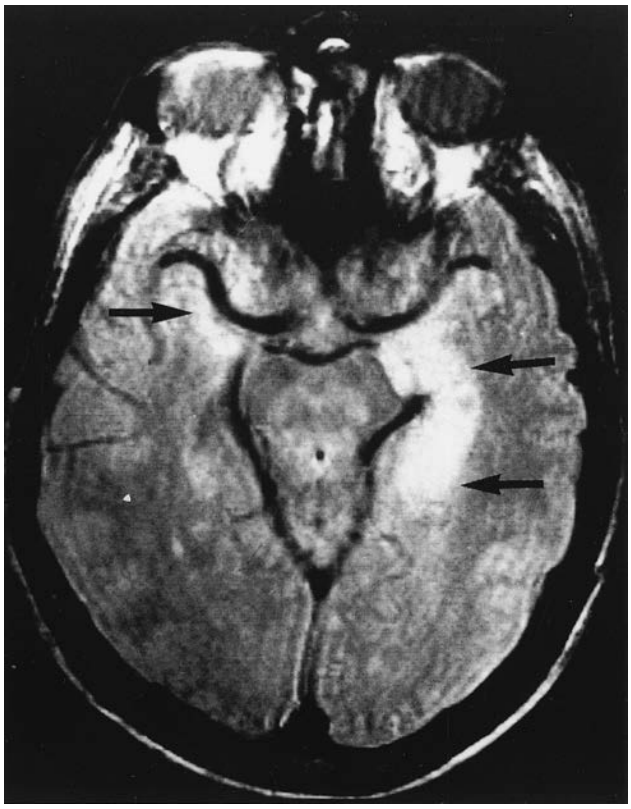

Figure 36.1. Proton density weighted magnetic resonance image from a 56-year-old man who developed seizures, confusion, agitation, and paranoid ideation 2 months before small-cell lung cancer was discovered. Abnormal high signal intensity is seen in the medial aspect of the left temporal lobe (*double arrows*), and to a less dramatic degree, in the right temporal lobe (*single arrow*). (From Kalkman PH, Allan S, and Birchall IWJ. Magnetic resonance imaging of limbic encephalitis. Can Assoc Radiol J 1993; 44:121–124.)

Many patients with paraneoplastic encephalomyelitis have an autoantibody present in high titers in their serum and CSF that reacts with neurons of the central and peripheral nervous system (41). This antibody—often called **anti-Hu** to recognize the first two letters of the last name of the original patient studied by Dr. Jerome Posner and associates at Memorial Sloan-Kettering Cancer Center (42), and also referred to as **antineuronal nuclear antibody type 1** by other investigators to acknowledge its immunohistochemical pattern of reactivity (2,43)—is most commonly identified in patients with paraneoplastic encephalomyelitis associated with small-cell lung cancer (Tables 36.1 and 36.2). However, anti-Hu seropositivity in the setting of paraneoplastic encephalomyelitis also occurs in patients with a variety of other cancers, including neuroblastoma, and occasionally occurs in patients with no identifiable neoplasm (41). The anti-Hu antibody is generally not found in neurologically normal persons or in patients with cancer who have a remote effect other than encephalomyelitis or subacute sensory neuronopathy (4,33). False positive results of anti-Hu testing thus are infrequent (2). Patients with typical encephalomyelitis but without tumor identified either during life or at autopsy have been reported (41). A small proportion of neurologically normal patients with small-cell lung cancer have the anti-Hu antibody, but their titers are generally far lower than those titers found in patients with paraneoplastic encephalomyelitis (44,45). Patients with neurologic complications of primary Sjogren's syndrome who are anti-Hu seropositive have been reported (46). Anti-Hu seropositivity is always present at the time a patient presents with symptoms of paraneoplastic encephalomyelitis, which, as noted above, commonly precedes the identification of the underlying malignancy. Therefore, identification of the anti-Hu antibody in a patient whose clinical presentation is consistent with paraneoplastic encephalomyelitis or who has an unexplained sensory neuronopathy should prompt a careful search for lung cancer or some other malignancy if the initial evaluation is unrevealing. A malignancy is still likely to appear at some later date in those patients with a suspicious neurologic presentation and who have an anti-Hu antibody at high titer but no clinically identified neoplasm.

In a study of survival and outcome in 73 patients with anti-Hu positive paraneoplastic encephalomyelitis, Smitt et al. (47) found that the most frequent signs and symptoms

Table 36.1
Antibodies in Neurologic and Ocular Paraneoplastic Syndromes

Antibody	Size (kd)	Function	Associated Cancer	Syndrome
Antibodies Associated with Paraneoplastic Neurologic or Ocular Syndromes				
Anti-Hu (ANNA-1)	35–40	RNA binding	SCLC, other	Encephalomyelitis, focal encephalitis, cerebellar degeneration, sensory neuropathy, autonomic dysfunction
Anti-Ri (ANNA-2)	53–61, 79–84	RNA binding	Breast, SCLC, gynecologic	Cerebellar ataxia, opsoclonus
Anti-ANNA-3	170	RNA binding	SCLC	Sensory-motor neuropathy, cerebellar ataxia, limbic/brainstem encephalopathy
Anti-Yo (PCA-1)	55–60	DNA binding	Gynecologic, breast	Cerebellar degeneration
Anti-PCA-2	280	DNA binding	SCLC	Limbic/brainstem, encephalitis, cerebellar ataxia
Anti-Tr	Unknown	Unknown	Hodgkin's lymphoma	Cerebellar degeneration
Anti-CV2/CRMP-5	62	Neuronal development	SCLC, other	Encephalomyelitis, cerebellar degeneration, peripheral neuropathy, optic neuritis/retinitis
Anti-Ma	37, 40	Unknown	Germ cell tumors of testis, other cancers	Limbic solidus, brainstem, encephalitis, cerebellar degeneration
Anti-amphiphysin	125	Synaptic vessel endocyte	Breast, SCLC	Stiff-man syndrome, encephalomyelitis
Anti-recoverin	23	Phototransduction	SCLC, gynecologic	Retinopathy
Antibodies Associated with Neurologic Syndromes that Can Occur With or Without Cancer				
Anti-VGCC			SCLC	Lambert-Eaton myasthenic syndrome, cerebellar degeneration
Anti-AchR, anti-titan, anti-MUSK			Thymoma	Myasthenia gravis
Anti-VGKC			Thymoma, others	Neuromyotonia seizures, limbic encephalitis

ANNA, anti-neuronal nuclear antibody; PCA, anti-Purkinje cell cytoplasmic antibody; SCLC, small-cell lung cancer; VGCC, voltage-gated calcium channel; VGKC, voltage-gated potassium channel; AchR, acetylcholine receptor; CRMP, collapsin response mediator protein.
(From Bataller L, Dalmau J. Paraneoplastic neurologic syndromes: approaches to diagnosis and treatment. Semin Neurol 2003;23:215–224.)

at presentation were sensory neuropathy (55%), cerebellar degeneration (22%), limbic encephalitis (15%), and brainstem encephalitis (16%); 23% developed autonomic dysfunction. In 85%, a tumor was detected, which was a lung tumor in 77%. The median delay between onset of symptoms and Hu antibody diagnosis was four months.

Differential Diagnosis

When a patient with neurologic or visual dysfunction has a known primary tumor, intraparenchymal and leptomeningeal metastasis must first be excluded. Opportunistic infections associated with depressed immunity from either the underlying malignancy or from chemotherapy must also be considered when evaluating a patient with cancer who has neuropsychiatric, cranial nerve, or multifocal neurologic deficits. The most common infectious diseases affecting the central nervous system that occur in this setting include encephalitis from *Toxoplasma, Cytomegalovirus*, *Herpes simplex,* or *Herpes zoster;* cerebritis from *Aspergillus, Mucorales,* or *Cytomegalovirus;* abscess formation from *Nocardia* or *Toxoplasma*; meningitis from *Cryptococcus, Candida,* or *Listeria monocytogenes;* and, vasculitis associated with *Herpes zoster, Aspergillus,* or *Mucorales* (48).

Neurologic complications of cancer treatment, including the side effects of chemotherapy and radiation therapy, should also be considered in the differential diagnosis of visual or neurological presentations consistent with the symptoms of paraneoplastic encephalomyelitis already discussed. This topic is discussed in greater detail in Chapter 37, but in this section it is worth emphasizing some of the common offending agents that can injure the eye and nervous system, causing manifestations that mimic those of the remote effects of cancer. These disorders, and the drugs that cause them, include retinopathy from *tamoxifen, cisplatin,* and *interferon alpha;* optic neuropathy from *paclitaxel, cisplatin,* and *vincristine;* encephalopathy from intrathecal or high-dose intravenous *methotrexate, cis-platinum,* and *interferon alpha;* cerebellar dysfunction from *5-fluorouracil* and *cytarabine;* cranial neuropathies from *vincristine;* and sensory neuropathy from *cisplatin* and *paclitaxel* (49,50).

In addition to the direct effects of metastatic disease and the indirect effects related to infectious diseases and side effects of chemotherapy, the differential diagnosis of paraneoplastic disease includes vascular complications of cancer (51). Tumor emboli may produce focal brain infarctions as well as generalized neurologic dysfunction from diffuse or multifocal cerebral ischemia. The alteration in level of consciousness, cranial nerve deficits, cerebellar dysfunction, and weakness that frequently accompanies vertebrobasilar artery thrombosis can mimic the presentation of paraneoplastic encephalomyelitis. Cerebral venous and dural sinus thrombosis and disseminated intravascular coagulation can produce signs of generalized encephalopathy as well as focal neurologic deficits that might be confused with paraneoplastic encephalomyelitis.

The differential diagnosis of paraneoplastic encephalomy-

Table 36.2
Paraneoplastic Disorders and Autoantibodies

Clinical Syndrome	Associated Tumor(s)	Autoantibodies
Multifocal encephalomyelitis/sensory neuronopathy	SCLC	Anti-Hu (ANNA-1)
	SCLC, others	Anti-CV2/CRMP-5
	SCLC, breast	Anti-amphiphysin
	SCLC	Anti-ANNA-3
	Various carcinomas	Anti-Ma
Cerebellar degeneration	Breast, ovarian, others	Anti-Yo (PCA-1)
	SCLC	Anti-Hu
	SCLC, thymoma	Anti-CV2/CRMP-5
	SCLC	Anti-PCA-2
	SCLC	Anti-ANNA-3
	Hodgkin's lymphoma	Anti-Tr
	Hodgkin's lymphoma	Anti-mGluR1
	Breast carcinoma	Anti-Ri (ANNA-2)
	Various carcinomas	Anti-Ma
	Testicular	Anti-Ta/Ma2
Limbic encephalopathy	SCLC	Anti-Hu
	SCLC, thymoma	Anti-CV2/CRMP-5
	SCLC	Anti-PCA-2
	SCLC	Anti-amphiphysin
	SCLC	Anti-ANNA-3
	Testicular, breast	Anti-Ta/Ma-2
Opsoclonus-myoclonus	Breast, ovarian	Anti-Ri
	SCLC, neuroblastoma	Anti-Hu
	SCLC	Anti-amphiphysin
	Testicular	Anti-Ta/Ma2
	Various carcinomas	Anti-Ma
Stiff-man syndrome	Breast, SCLC	Anti-amphiphysin
	Breast	Anti-GAD
Dermatomyositis	Ovarian, lung, pancreas	Unknown
Retinal degeneration	SCLC	Anti-recoverin
	Melanoma	Anti-bipolar cell
Optic neuritis/retinitis	SCLC, others	Anti-CV2/CRMP-5
Neuromyotonia	Thymoma	Anti-VGKC
LEMS	SCLC	Anti-VGCC
Myasthenia	Thymoma	Anti-titin, anti-AchR, anti-MUSK

ANNA, anti-neuronal nuclear antibody; PCA, anti-Purkinje cell cytoplasmic antibody; SCLC, small-cell lung cancer; VGCC, voltage-gated calcium channel; VGKC, voltage-gated potassium channel; AchR, acetylcholine receptor; CRMP, collapsin response mediator protein; GAD, glutamic acid decarboxylase; mGluR1, metatropic glutamate receptor.
(From Dropcho EJ. Remote neurologic manifestations of cancer. Neurol Clin 2002;20:85–122.)

elitis also encompasses a lengthy group of secondary metabolic and nutritional disorders that can cause acute or chronic progressive encephalopathy. These conditions include hypercalcemia, hyponatremia secondary to inappropriate secretion of antidiuretic hormone, hyperosmolality and dehydration, hypoglycemia, hepatic encephalopathy, uremia, pellagra, and deficiencies of folic acid and of vitamins B_1 and B_{12}.

Patients in whom neuropsychiatric symptoms and signs of paraneoplastic encephalitis develop before the discovery of an underlying malignancy initially may be thought to have one of the subacute or chronic dementias, such as Creutzfeldt-Jakob disease, Alzheimer's disease, chronic granulomatous angiitis, tertiary syphilis, and Wernicke-Korsakoff syndrome. Patients with paraneoplastic cerebellar encephalitis may initially be thought to have a variety of conditions, including primary or metastatic tumor in the cerebellum, paraneoplastic subacute cerebellar degeneration, hypothyroidism, drug intoxication, multiple sclerosis, cerebrovascular disease, or late onset hereditary ataxia. Similarly, the clinical features of paraneoplastic brainstem encephalitis may be mimicked by many nonneoplastic disorders, including amyotrophic lateral sclerosis, multiple sclerosis, cerebrovascular disease, Wernicke's encephalopathy, myasthenia gravis, and cerebral Whipple's disease. Paraneoplastic myelitis can cause neurologic deficits that could be confused with the presentations of nonneoplastic inflammatory myelopathy associated with a systemic vasculitis or connective tissue disease or multiple sclerosis, motor neuron disease, subacute combined degeneration of the spinal cord associated with vitamin B_{12} deficiency, or nonneoplastic compression of the spinal cord by, for example, cervical spondylosis.

Pathogenesis: The Anti-Hu Syndrome

Earlier theories of the pathogenesis of paraneoplastic encephalomyelitis speculated that the inflammatory changes were secondary to a primary degenerative process or an occult opportunistic viral infection. Apart from the histopathologic findings in this disorder, the evidence supporting such mechanisms remains sparse. The inflammatory reaction could occur in response to neuronal death that results from a neurotoxin or hormone elaborated by the underlying neoplasm (1,6). More recent investigations have focused on immune mechanisms as the most attractive hypothesis for the cause of paraneoplastic encephalomyelitis (2,433). In general, the immune theory proposes that certain antigens, aberrantly expressed somehow by the cancer, are shared between that tumor and specific neural components of the central and peripheral nervous system or retina. When the immune system somehow recognizes the tumor antigen as foreign, an immune response is directed not only against the tumor, but also against the shared antigen in the nervous system. Both cellular and humoral immune systems are involved in uncertain ways to cause immune-mediated neuronal loss and inflammatory damage (52). A paradoxic benefit of the autoimmune response is that it may limit the rate of growth and dissemination of the tumor against which the response is directed.

The recognition and characterization of the anti-Hu, or antineuronal nuclear type 1, antibody has allowed investigators to explore the neuronal and cancer protein targets of the autoimmune attack. However, the precise role that the autoantibodies assume in neuronal damage and clinical disease development remains undefined. In Western blot analysis, the anti-Hu antibody reacts against protein extracts of neural tissue whose molecular weights range between 35–40 kd (42) (Fig. 36.2). The immunohistochemical reactions of this antibody include staining of the nuclei and, to a lesser degree, the cytoplasm of all neurons of the central nervous system, the dorsal root ganglia, and the autonomic ganglia (Fig. 36.3) (43). Molecular cloning techniques have identified three autoantigens, designated HuD, HuC, and Hel-N1, that belong to a larger family of neuronal RNA binding proteins that anti-Hu antibodies react against (53). The Hu antigen (HuD) is expressed in small-cell lung cancers (54) and, less frequently, in other cancers, including neuroblastomas (41). Serum from anti-Hu positive patients with paraneoplastic encephalomyelitis reacts against small-cell lung cancer in a pattern resembling that reactivity against neurons, supporting the theory that shared antigens are important in the pathogenesis of these paraneoplastic disorders (55). The CSF:serum ratio of anti-Hu antibody activity in patients with paraneoplastic encephalomyelitis is generally greater than 1, suggesting that these autoantibodies are synthesized intrathecally (56). Issues that remain unresolved include identification of those factors that result in the expression of cancer antigens, mechanisms of the aberrant immune response, and determinants of immune-mediated neuronal damage and cell death.

Treatment

There is no specific therapy for any of the paraneoplastic encephalomyelitides. Partial spontaneous improvement of neurologic deficits has been rarely described (57–59). Also, patients have only rarely experienced substantial recovery despite successful treatment of their underlying malignancy (19,26,34,39,60–64). Finally, isolated examples have been reported of patients improving in response to treatment with corticosteroids (65–67) or plasmapheresis (68).

There is no evidence that immunosuppressive treatment in patients with paraneoplastic encephalomyelitis and anti-Hu antibodies is associated with worse tumor outcome (69). Patients with paraneoplastic syndromes associated with antibodies to Ma2 protein, particularly the younger patients with limbic-hypothalamic encephalitis, may have significant neurologic responses to prompt treatment of the tumor and immunomodulation (70).

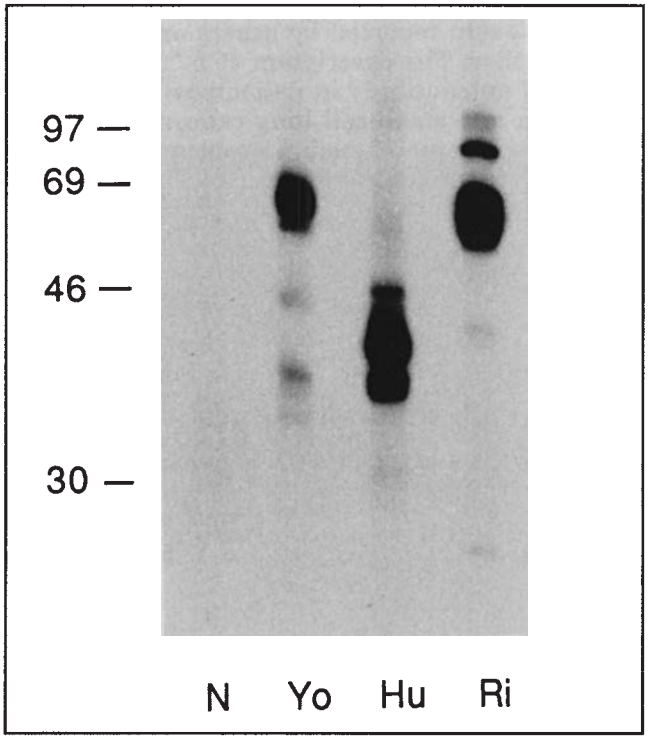

Figure 36.2. Western blot analysis of paraneoplastic antineuronal antibodies performed by incubating human Purkinje cells with serum from a normal patient (lane N), a patient with cerebellar degeneration (lane Yo), a patient with encephalomyelitis/sensory neuropathy (lane Hu), and a patient with opsoclonus-myoclonus-ataxia (lane Ri). Anti-Yo serum reacts with 34- and 62-kd proteins and, to a minor degree, with a 40-kd protein. Anti-Hu serum reacts with 35–40-kd proteins. Anti-Ri serum reacts with 55- and 80-kd proteins. (From Dalmau J, Posner JB. Neurologic paraneoplastic antibodies [anti-Yo, anti-Hu, anti-Ri]: The case for a nomenclature based on antibody and antigen specificity. Neurology 1994;44:2241–2246.)

Prognosis

In most patients who develop paraneoplastic encephalomyelitis, there is a relentless, usually fairly rapid progressive neurologic deterioration over weeks to months, ending in death or prolonged severe disability. Death is usually caused by the neurologic complications of the paraneoplastic pro-

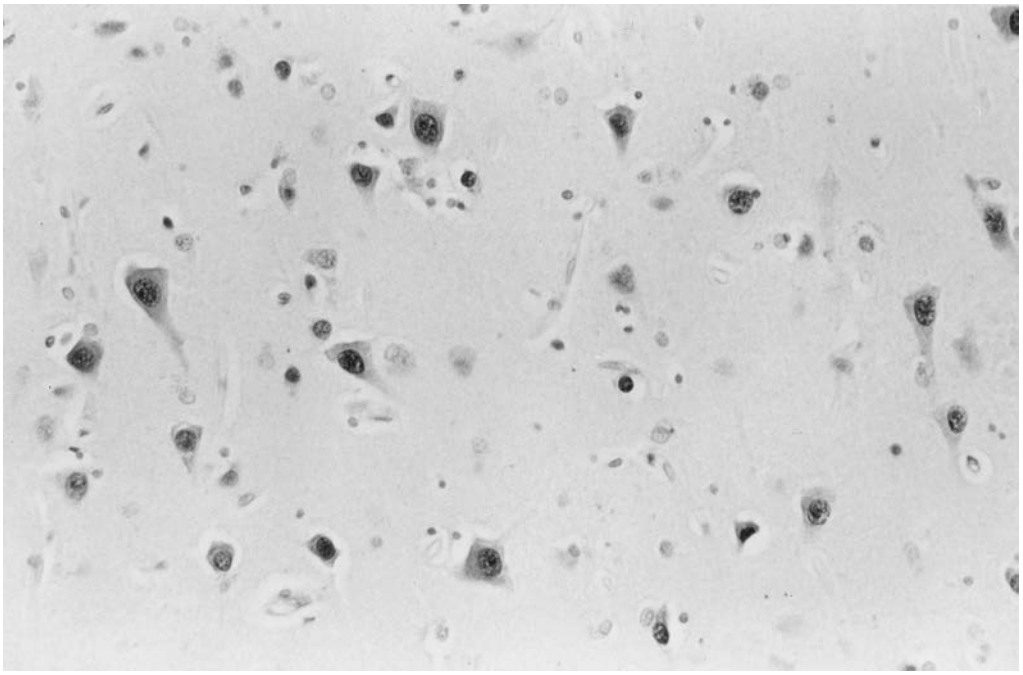

Figure 36.3. Immunohistochemical pattern of reactivity of the anti-Hu/antineuronal nuclear type 1 antibody. Paraffin section of frontal cortex obtained at autopsy from a neurologically normal individual reacted with serum from a patient with paraneoplastic encephalomyelitis and high titer anti-Hu antibodies. Note the predominant reactivity (darker staining) of the anti-Hu antibody with the nuclei of all neurons. Section mildly counterstained with hematoxylin, ×400. (Courtesy of Josep O. Dalmau, M.D, Ph.D.)

cess itself and not by any direct effects of the underlying primary malignancy, which most often is restricted to a single primary location, perhaps with spread to a few regional lymph nodes (41). In fact, some investigators have found that patients with a paraneoplastic syndrome or the anti-Hu antibody have improved cancer survival and less extensive cancer dissemination compared with those patients without remote effects or antibody (4,44,45,71).

SUBACUTE CEREBELLAR DEGENERATION

This is a paraneoplastic syndrome in which the neurologic manifestations are strongly dominated by clinical abnormalities referable to pancerebellar dysfunction, including truncal and limb ataxia. The syndrome is rare compared with paraneoplastic encephalomyelitis. Nevertheless, if one considers all cases of adult, nonfamilial cerebellar degeneration, about 50% will eventually be found to be associated with an underlying malignancy (6).

Clinical Features

Paraneoplastic subacute cerebellar degeneration occurs almost exclusively in adults. The relative proportion of affected women and men is somewhat related to the organ affected by the underlying neoplasm, although women are exclusively affected in that disorder associated with a specific anti-Purkinje cell antibody sometimes referred to as anti-Yo (72,73) (Tables 36.1 and 36.2). Frequently, the condition presents months to a few years before the associated malignancy declares itself (74–76). The earliest manifestation is usually mild gait incoordination, and the typical course is characterized by rapid deterioration over the following few weeks to months involving progressive gait ataxia, truncal instability, symmetric ataxia and dysmetria of all four extremities, dysarthria, and dysphagia. After a few months, the condition stabilizes, leaving the patient with severe and disabling neurologic deficits. Infrequently, the onset may be acute, with rapid deterioration occurring during the following few days to weeks. Conversely, it may be more insidious in onset and may progress more slowly than the typical course.

Oscillopsia, diplopia, vertigo, and nausea are commonly associated manifestations of paraneoplastic subacute cerebellar degeneration. Careful testing of other neurologic functions will occasionally reveal evidence of mild cognitive impairment, hearing loss, upper motor neuron dysfunction, extrapyramidal signs, and peripheral neuropathy (72). Thus, the syndrome may have elements not only of cerebellar degeneration but also cerebral and brainstem encephalomyelitis or peripheral nerve involvement (11,12). In particular, an association between cerebellar degeneration and the Eaton-Lambert syndrome has been noted, most often but not exclusively in patients with small-cell lung cancer (77).

Subacute cerebellar degeneration has most commonly been described in association with carcinomas of the lung and ovary (78), but it may also occur in patients with carcino-

mas of the breast, uterus, fallopian tubes, stomach, colon, prostate, thyroid gland, kidney, and larynx as well as in patients with Hodgkin's disease and non-Hodgkin's lymphoma (1,6,72,73,75,79).

The neuro-ophthalmologic manifestations of paraneoplastic subacute cerebellar degeneration primarily affect the ocular motor system, causing disturbances of fixation, motility, and alignment. Various forms of nystagmus, ocular dysmetria, saccadic pursuit, saccadic intrusions and oscillations, and skew deviation thus occur in a substantial percentage of patients. For example, nearly 50% of the patients with paraneoplastic cerebellar degeneration associated with Hodgkin's disease cases reported by Hammack et al. (79) had downbeat nystagmus, and nearly two thirds had ocular dysmetria.

The syndrome of paraneoplastic subacute cerebellar degeneration can be grouped into certain categories based upon the associated tumor type and cancer-related autoantibody status. Some differences in the general clinical features, course, and prognosis are associated with some of these categories. For example, some patients have a specific type of circulating autoantibody, called **anti-Yo** (after the first two letters of the index patient studied by the investigators at Memorial Sloan-Kettering Cancer Center, New York) or **anti-Purkinje cell cytoplasmic type 1 antibody** (72,73) (Tables 36.1 and 36.2). Seropositive patients are almost always women with ovarian cancer, breast cancer, or some other gynecologic malignancy, whose tumor has generally not spread beyond the affected organ and local lymph nodes. The paraneoplastic presentation usually precedes the recognition of the cancer in these patients. In fact, surgical exploration of the pelvis is strongly recommended by some investigators for seropositive women with an unexplained presentation of cerebellar dysfunction without recognized breast or gynecologic cancer identified by clinical, radiologic, and tumor marker approaches (72,73). The course of neurologic impairment is progressive and debilitating, and it does not respond to treatment of the malignancy.

Another type of paraneoplastic subacute cerebellar degeneration occurs in patients with Hodgkin's disease (79). These patients tend to be younger than non-Hodgkin's disease patients with cerebellar degeneration, and they are most often men. The disorder usually develops after the neoplasm has been established and often when the patient is in remission. Anti-Purkinje cell antibodies are occasionally found, but they demonstrate reactivity characteristics that differ from the anti-Yo antibody. Anti-Tr antibodies and anti-metabotropic glutamate receptor type I (mGluR1) antibodies have been found in some patients with Hodgkin's lymphoma and paraneoplastic subacute cerebellar degeneration. Antibodies against mGluR1 applied to murine cerebellar slices have been shown to reduce basal activity of Purkinje cells, disturb compensatory eye movements, and cause chronic degeneration of Purkinje cells (80). In a study of 28 patients with anti-Tr antibodies (81), a cerebellar syndrome was identified in 27 patients and Hodgkin's lymphoma was diagnosed in 25 patients. Anti-Tr antibodies spontaneously disappeared in 10/10 patients after successful Hodgkin's disease treatment. The clinical features of the neurologic presentation and course do not differ significantly from those of other patients with paraneoplastic cerebellar degeneration except that some of these patients experience spontaneous improvement, either transiently or, in rare cases, permanently.

Pathology

The primary pathologic lesion in the syndrome of paraneoplastic subacute cerebellar degeneration is a *noninflammatory* depopulation of the Purkinje cells in the cerebellar cortex (11,12,74,75,82) (Fig. 36.4). The loss of cells is usually diffuse and severe, but it may occasionally be patchy. Not surprisingly, the loss of this prominent population of neurons is accompanied by gliosis and the formation of microglial shrubbery in the molecular layer, where the dendrites of Purkinje cells normally are located. Loss of Purkinje cell axon projections also produces demyelination and gliosis in the white matter, especially around the dentate nucleus. There may also be some neuronal loss in the granular cell layer. The deep cerebellar nuclei, the peduncles, and the extracerebellar nuclei that have connections to the cerebellum usually remain normal. Occasional cases, particularly those in which there are symptoms of brainstem or spinal cord dysfunction, also have degeneration outside the cerebellum (6,12,32).

Diagnostic Evaluations

In patients with paraneoplastic subacute cerebellar degeneration, the CSF may be normal or may show a mild lymphocytic pleocytosis, increased protein concentration, elevated immunoglobulin indices and synthesis rates, and oligoclonal bands. In advanced cases, cranial CT scanning or brain MR imaging may show enlargement of the fourth ventricle, prominent cerebellar sulci, and enlarged pericerebellar cisterns (Fig. 36.5), but in the early stages, neuroimaging often gives normal results (76). A paraneoplastic antibody workup should be initiated to determine whether anti-Yo or anti-Ri antibodies are present.

Differential Diagnosis

When a person with known or suspected cancer develops cerebellar symptoms and signs, neuroimaging is required to determine if metastases are present within the cerebellum. When such lesions are not identified, one must consider not only paraneoplastic subacute cerebellar degeneration but also paraneoplastic encephalomyelitis, progressive multifocal leukoencephalopathy, meningeal carcinomatosis, or a toxic cerebellar disorder, such as that produced by 5-fluorouracil or cytarabine.

When a subacute cerebellar syndrome evolves in an adult in the absence of a known neoplasm, the possibility of an underlying malignancy must nevertheless be considered, and a careful physical examination, as well as CT scanning of the chest, abdomen, and pelvis in women, should be performed. In this setting, the physician must also consider alternative diagnoses, including alcoholic cerebellar degeneration, multiple sclerosis, hereditary ataxia, vertebrobasilar disease, Creutzfeldt-Jakob disease, hypothyroidism, and

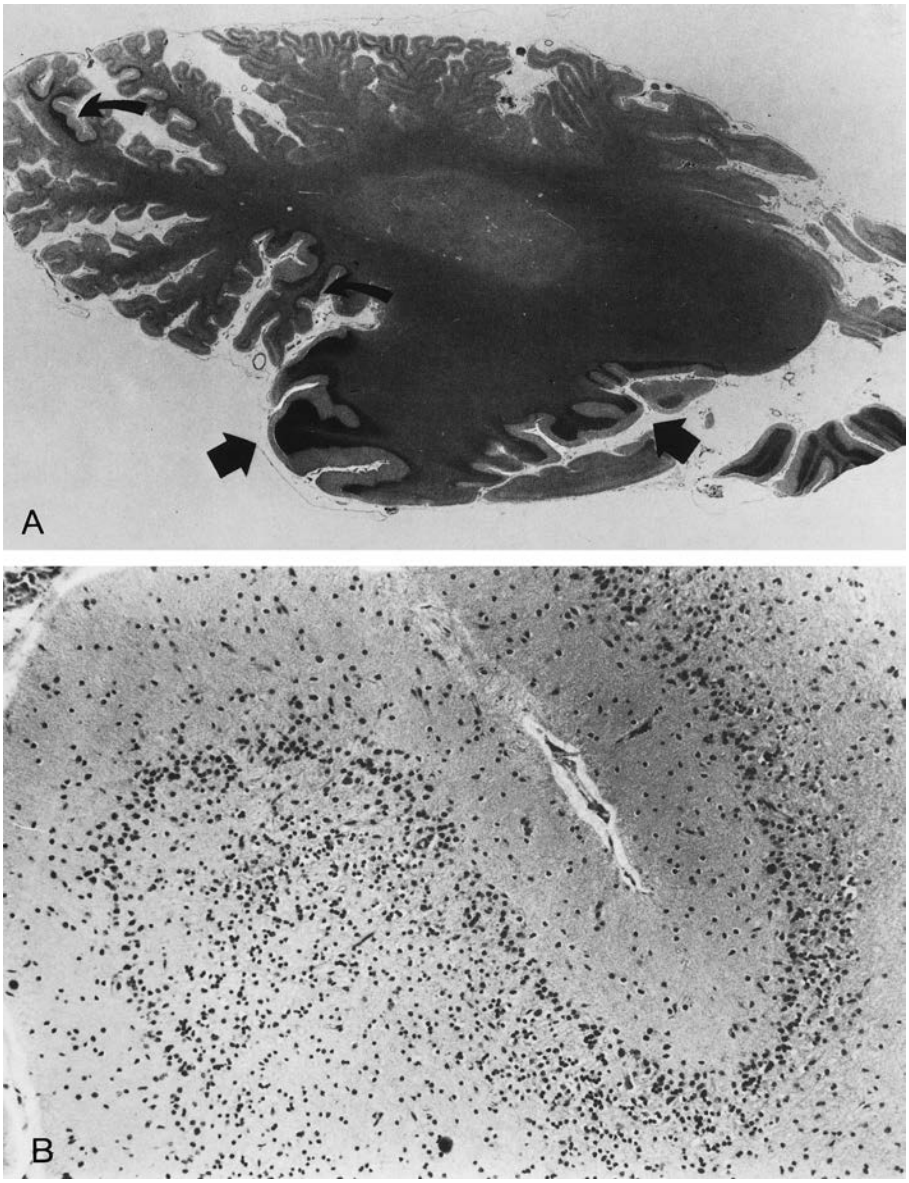

Figure 36.4. Paraneoplastic cerebellar degeneration in a 53-year-old man with a T-cell lymphoma. *A,* Whole mount of one cerebellar hemisphere shows severe cerebellar cortical atrophy, particularly pronounced in superior region. Dorsal and ventral paraflocculus (*arrowheads*) are relatively preserved, as are patchy areas throughout other regions of the hemisphere (*arrows*). *B,* High-power view of affected cerebellar cortex shows profound loss of Purkinje cells and reduction in granular cells. (From Ang LC, Zochodne DW, Ebers GC, et al. Severe cerebellar degeneration in a patient with T-cell lymphoma. Acta Neuropathol 1986;69:171–175.)

toxic effects of such substances as mercury and phenytoin. An acute or subacute pancerebellar syndrome can also occur as a postviral or idiopathic nonparaneoplastic disorder (83).

Pathogenesis

Although all hypotheses concerning the pathogenesis of paraneoplastic subacute cerebellar degeneration are speculative, it is most likely an autoimmune disorder. As already mentioned, antibodies to Purkinje cells may be present in the serum and CSF of patients with subacute cerebellar degeneration associated with a variety of malignancies, including carcinomas of the ovary and breast, small-cell lung cancer, and Hodgkin's disease (84–88) (Fig. 36.6). In addition, the CSF:serum ratio of antibody concentration in seropositive patients is often greater than 1, indicating that these antibodies are produced, or at least concentrated, within the central nervous system (89). In human tissue, the anti-Yo antibody stains the cytoplasm and proximal dendrites of Purkinje cells in a granular pattern (87,90). In immunoblot

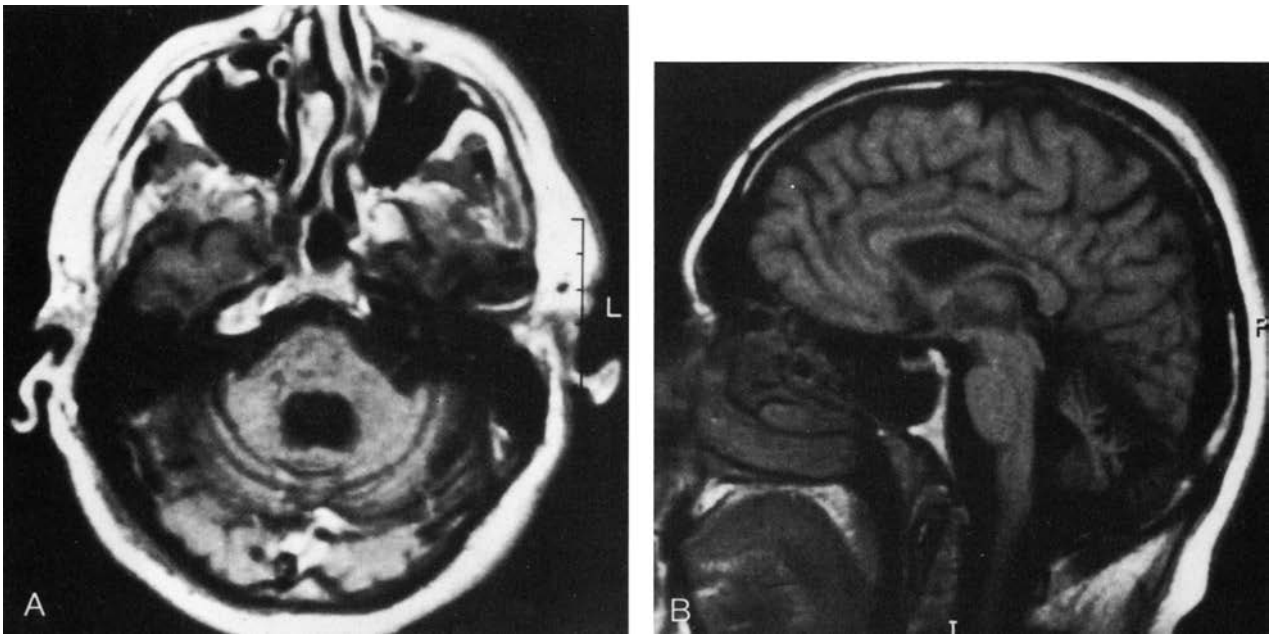

Figure 36.5. T1-weighted magnetic resonance images from a 42-year-old man with Hodgkin's disease and paraneoplastic cerebellar degeneration demonstrating features of cerebellar atrophy. *A*, The axial image shows enlargement of the fourth ventricle and widening of the cerebellar sulci. *B*, The sagittal image shows diffuse atrophy of the cerebellum. (From Hammack J, Kotanides H, Rosenblum MK, et al. Paraneoplastic cerebellar degeneration. II. Clinical and immunologic findings in 21 patients with Hodgkin's disease. Neurology 1992;42:1938–1943.)

preparations using human Purkinje cell proteins, the anti-Yo antibody reacts against antigens whose molecular weights are 62 and 34 kd (42,88) (Fig. 36.2). The cerebellar degeneration related (cdr) protein target of anti-Yo antibodies is localized to the Purkinje cell's cytoplasm where it is associated with membrane-bound and free ribosomes (91) as well as the Golgi apparatus. The function of these proteins is unknown, but it is thought that they may regulate gene transcription by binding to DNA.

Tumors from patients with anti-Yo seropositive cerebellar degeneration express Purkinje cell antigens, suggesting that this disorder, like paraneoplastic encephalomyelitis, results

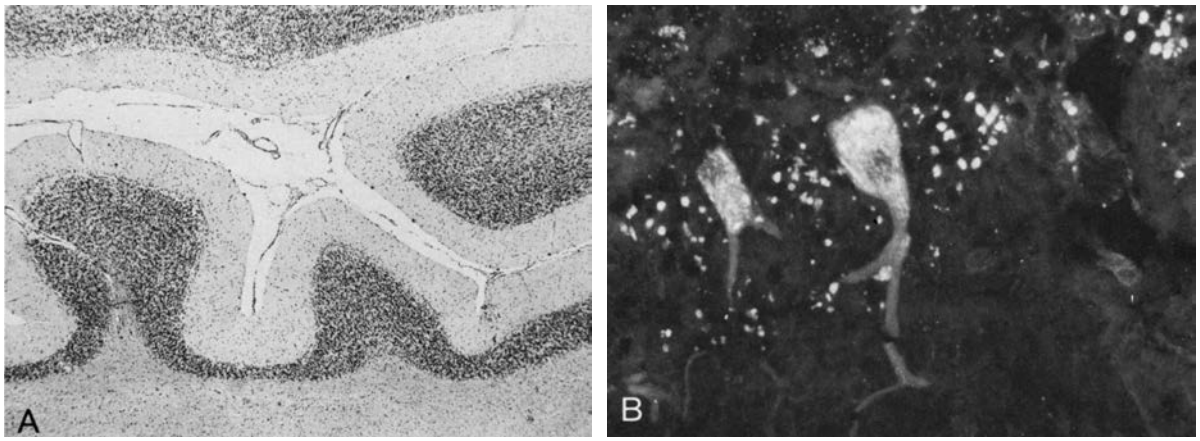

Figure 36.6. Antibodies to cerebellar Purkinje cells in a patient with paraneoplastic cerebellar degeneration and ovarian carcinoma. *A,* Cerebellar cortex shows absence of Purkinje cells and reduction in the number of granular cells. *B,* Section of normal human cerebellum reacted with serum from the patient and stained by the indirect immunofluorescence method shows that Purkinje cells are brightly labeled. Fluorescence is predominantly cytoplasmic. (From Greenlee JE, Brashear HR. Antibodies to cerebellar Purkinje cells in patients with paraneoplastic cerebellar degeneration and ovarian carcinoma. Ann Neurol 1983; 14:609–613.)

from an aberrant autoimmune response associated with shared tumor and central nervous system antigens (92). About 20% of ovarian tumors from patients without paraneoplastic cerebellar degeneration also express Yo antigens (93). Several other anti-Purkinje cell antibodies whose reaction characteristics differ from those of the anti-Yo antibody have been identified (79,94,95).

Finally, non-Purkinje cell antibodies are found in patients with paraneoplastic subacute cerebellar degeneration and anti-Purkinje cell antibodies. For example, autoantibodies to neuronal glutamate receptors are present in the serum of some patients with paraneoplastic cerebellar degeneration and anti-Yo antibodies, suggesting that the remote effect in these patients may occur by excitotoxic mechanisms involving glutamate receptors (96,97). These studies, combined with the lack of evidence supporting any viral or toxic cause, strongly suggest that this paraneoplastic syndrome is autoimmune.

Treatment

The treatment of paraneoplastic subacute cerebellar degeneration is directed at identifying and treating the underlying neoplasm. Unfortunately, most patients do not improve even when the neoplasm is treatable. Nevertheless, in a small number of cases, the neurologic defects stabilize after successful treatment of the cancer (72,76,79,98). Paone and Jeyasingham (99) and Kearsley et al. (100) reported rapid and marked neurologic improvement in their patients after surgical removal of their primary malignancies. Corticosteroids are generally ineffective, but other forms of immunosuppressive treatment have occasionally been shown to be beneficial. For example, intravenous immunoglobulin (101,102) and plasmapheresis (73,103) have produced transient and even sustained improvement in some patients. Widdess-Walsh et al. (104) noted a marked beneficial response to intravenous immunoglobulin (IVIG) and methylprednisolone in a patient with ovarian carcinoma and paraneoplastic subacute cerebellar degeneration. They reviewed the literature and found that good responses were associated with institution of treatment with 2 g/kg IVIG within 1 month of development of symptoms. Finally, isolated patients have experienced improvement after being treated with thiamine (105) or clonazepam (79).

Prognosis

Most patients with paraneoplastic subacute cerebellar degeneration develop progressively severe neurologic deficits that cause debilitating oscillopsia, dysarthria, limb ataxia, and gait unsteadiness, thus limiting their ability to ambulate and perform many other activities of daily living independently. Rarely, the disorder may arrest at an earlier stage so that an affected patient may still be able to ambulate unassisted, although with some ataxia. Eekhof (106) reported spontaneous remission of disease before treatment of adenocarcinoma of the lung in an 83-year-old man. In most patients, however, the syndrome progresses until death results from complications of either the underlying malignancy or the neurologic deficits (e.g., aspiration pneumonia).

Most seropositive patients with known cancer at the time they present with symptoms of cerebellar degeneration have disease limited to the primary organ or regional lymph nodes, or they have metastatic disease of limited volume compared with those patients with cancer unassociated with a paraneoplastic syndrome (73,107). In some patients, the neurologic presentation heralds recurrence or progression of neoplastic disease that was previously treated and controlled (73,100,103,107).

PARANEOPLASTIC SYNDROME OF OPSOCLONUS, MYOCLONUS, AND ATAXIA

Although opsoclonus is discussed in general in Chapter 23, the syndrome of opsoclonus (and ocular flutter), myoclonus, and ataxia is also emphasized here because it can be a remote effect of cancer in patients with neuroblastoma (108–112) or other malignant tumors (113–119).

Clinical Features

Patients with this paraneoplastic disorder typically experience abrupt onset of the cardinal features, often accompanied by vertigo, nausea, vomiting, and, commonly in children, other symptoms that might otherwise suggest the presence of a viral syndrome. Along with the disorder of eye movement, there is almost always truncal and limb ataxia. In addition, most patients show random coarse or fine myoclonic movements of the head, trunk, or limbs. These myoclonic jerks are not generally accompanied by any epileptiform discharges on the EEG, and they are not synchronous with the abnormal eye movements. Even in patients with advanced cancer, the ataxia and myoclonus may be the major cause of disability. Altered mental status, consisting of apathy, lethargy, and confusion in adults, and irritability and confusion in children, frequently occurs along with the other neurologic manifestations (119).

This syndrome is most common in children between the ages of 8 months and 5 years, with a peak incidence at about 18 months of age (120), although it can occur in adults as well. When it occurs in childhood, girls are affected slightly more frequently than boys. In adults, there is no sex predilection. In children, by far the most common malignancy responsible is an occult neuroblastoma. About 2% of childhood neuroblastoma cases present initially with opsoclonus and myoclonus (111); conversely, about 59% of children who develop opsoclonus harbor occult neuroblastomas (120). In adults, carcinomas of the lung, breast, uterus, ovary, fallopian tube, thyroid, thymus, and bladder, as well as lymphomas, sarcomas, and even neuroblastoma may be present (105,111,113,114,117–119,121–129). Exceptional examples of this syndrome occurring with intracranial neoplasms were reported by Keane and Devereaux (116) in a patient with a hemispheric glioblastoma multiforme and by Boghen et al. (130) in a patient with a craniopharyngioma. In adults, about 20% of patients presenting with opsoclonus have occult malignancies (123).

Pathology

The pathologic abnormalities in patients with the paraneoplastic opsoclonus-myoclonus-ataxia syndrome vary.

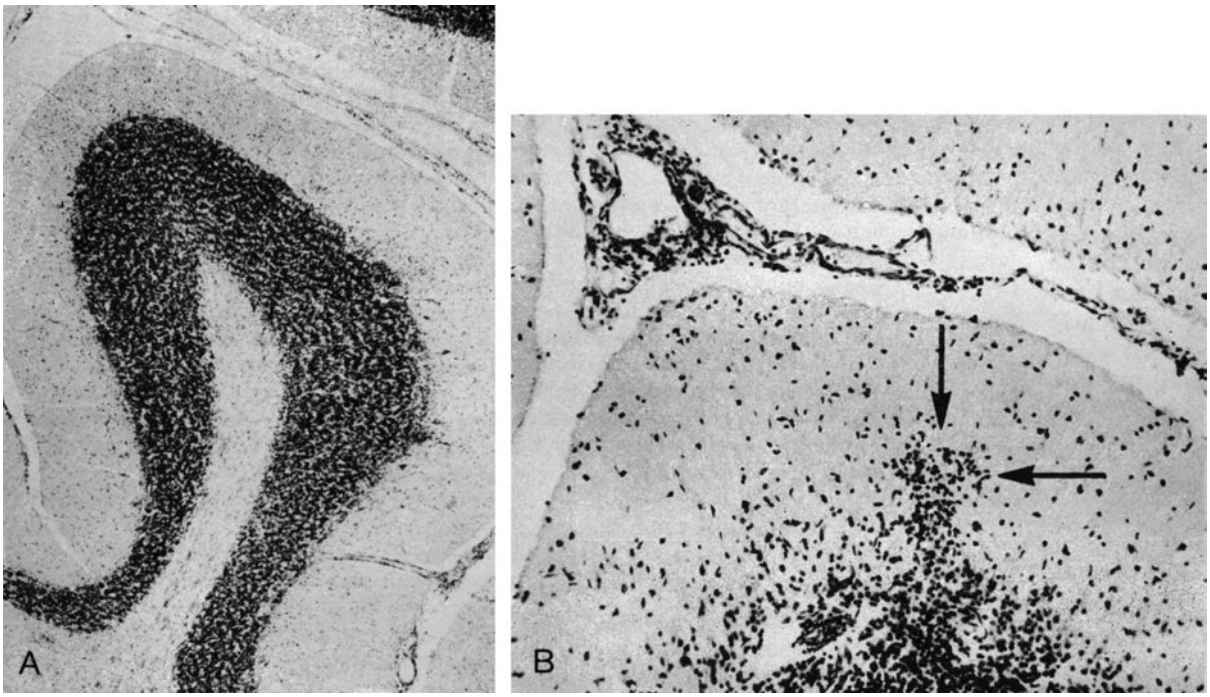

Figure 36.7. Histopathologic appearance of the cerebellum in a 58-year-old woman with opsoclonus and signs of cerebellar disease in association with carcinoma of the breast. *A,* Cerebellar folia show severe loss of Purkinje cells. *B,* High-power view shows a focus of gliosis in the molecular layer (*arrows*) and infiltration of the meninges by nonneoplastic mononuclear cells. (From Ellenberger C Jr, Netsky MG. Anatomic basis and diagnostic value of opsoclonus. Arch Ophthalmol 1970;83:307–310.)

Some cases have shown a patchy decrease in the number of Purkinje cells in the cerebellum with demyelination and gliosis around or in the dentate nucleus (113–115,131) (Fig. 36.7). Other neuropathologic changes in the cerebellum and elsewhere in the central nervous system include perivascular lymphocytic cuffing, microglial infiltration, and astrocytic gliosis (129,132). One of the patients reported by Ridley et al. (133) had, in addition to loss of Purkinje cells, complete loss of neurons of the inferior olivary nuclei and scattered perivascular and parenchymal lymphocytic infiltrates within the midbrain, pons, and periaqueductal gray matter. In other cases, however, the cerebellum and brainstem are both grossly and microscopically normal (116,130,133).

Diagnostic Evaluations

Except for those exceptionally rare patients with an intracranial neoplasm, most patients with the paraneoplastic opsoclonus-myoclonus-ataxia syndrome have normal neuroimaging studies of the CNS. Nevertheless, the patient reported in the Case Records of the Massachusetts General Hospital (134) showed an abnormal T2-weighted signal in the midbrain tectum on MR imaging, and another adult patient reported by Hersh et al. (132) had abnormal hypersignal intensity in the brainstem. The CSF is usually normal in this syndrome but may show a mildly increased concentration of protein and lymphocytic pleocytosis in both children and adults (112,120,123,129,133,135).

Antineuronal autoantibodies may be found in some patients with paraneoplastic opsoclonus and may help to direct the search for an occult malignancy. The anti-Hu antibody has occasionally been identified in adults and children with neuroblastomas and other neoplasms (71,132,136) (Tables 36.1 and 36.2). Anti-Yo and other anti-Purkinje cell antibodies may be found in women with paraneoplastic opsoclonus and cerebellar degeneration associated with cancer of the breast or gynecologic organs (73,123,134,137) and, rarely, in some patients with other neoplasms (138). In addition, a third antineuronal antibody, called anti-Ri by the investigators at Memorial Sloan-Kettering Cancer Center to acknowledge the first two letters of the last name of their index case, which is called ''antineuronal nuclear antibody type 2'' by other investigators (2,43) (Tables 36.1 and 36.2), is sometimes found in the serum and CSF of adult patients with paraneoplastic opsoclonus and ataxia. Like the anti-Hu antibody, the anti-Ri antibody reacts with the nuclei of all neurons of the central nervous system, including Purkinje cells (Fig. 36.8). Unlike the anti-Hu antibody, however, the anti-Ri antibody does not react against neurons of the peripheral nervous system, such as the dorsal root and sympathetic ganglia (139). The anti-Ri antibody is further distinguished by its unique reactions with antigens whose molecular weights are about 55 and 80 kd in Western blot analysis using neuronal extracts (42,135) (Fig. 36.2). Two closely related ''Nova'' protein antigens reacting with anti-Ri antibodies have been cloned (140–141). The Nova proteins share sequence homology with a group of nuclear RNA-

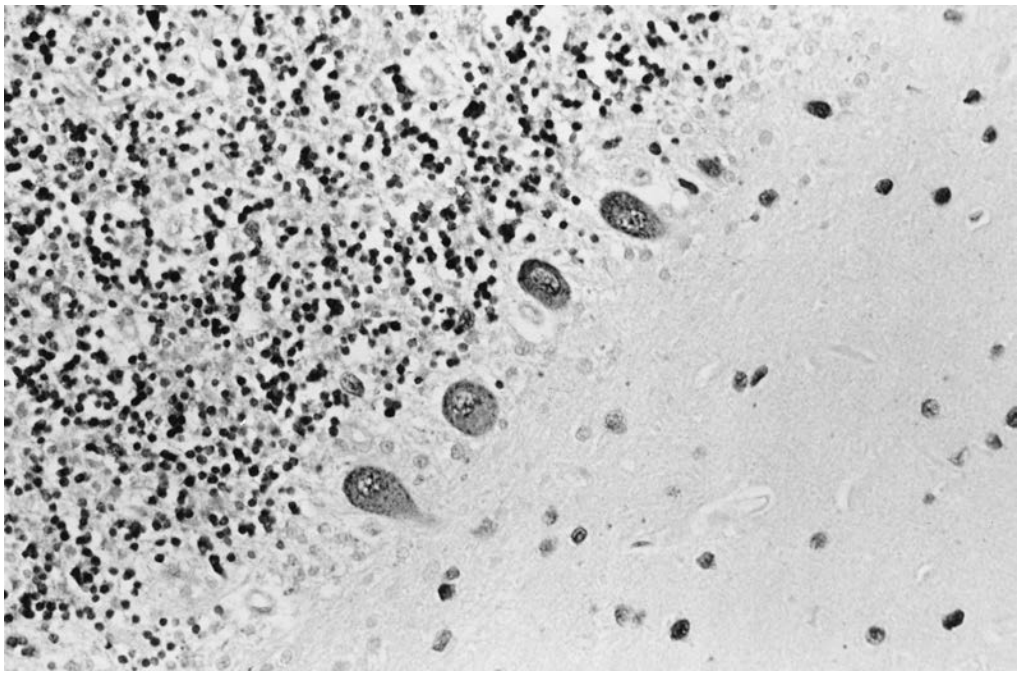

Figure 36.8. Immunoreactivity of the anti-Ri/antineuronal nuclear type 2 antibody. Paraffin section of cerebellum obtained at autopsy from a neurologically normal individual reacted with serum from a patient with paraneoplastic opsoclonus and ataxia associated with high titer of anti-Ri antibodies. Note that the anti-Ri antibodies predominantly react with the nuclei of all neurons (dark staining of the larger Purkinje cells and small neurons of the granular and molecular layers). There is less intense diffuse reactivity with the cytoplasm of neurons, better demonstrated in the Purkinje cells. Section mildly counterstained with hematoxylin, ×400. (Courtesy of Josep O. Dalmau, M.D., Ph.D.)

binding proteins believed to be involved in the regulation of mRNA splicing. Most anti-Ri seropositive patients, whether or not they have the opsoclonus-myoclonus-ataxia syndrome, have breast cancer (135); but rare examples of anti-Ri seropositive patients with other malignancies have been reported (135,142), as have examples of patients with the opsoclonus-myoclonus-ataxia syndrome but without cancer, patients with neither cancer nor neurologic dysfunction (143–145), and patients with neurologic remote effects of cancer but without opsoclonus (31). Despite these rare exceptions, anti-Ri antibodies are generally not found in normal persons, patients with breast cancer who do not have paraneoplastic syndromes, or patients with nonparaneoplastic opsoclonus (142).

Because of the well-established association between occult cancer and the opsoclonus-myoclonus-ataxia syndrome, any child or adult with this presentation must undergo careful and complete clinical and radiologic evaluations to identify an underlying neoplasm. As already mentioned, this association is particularly strong in children harboring occult neuroblastomas. Children with neuroblastomas that present with opsoclonus commonly do not have a palpable tumor, elevated concentrations of urinary catecholamines, or masses detected with plain radiographs of the chest or abdomen (112,120,146,147). Therefore, children with opsoclonus should undergo CT scanning or MR imaging of the neck, chest, and abdomen unless the results of clinical examination and plain radiographs suggest a more specific region. Radioactive metaiodobenzylguanidine scanning may be a more sensitive test than CT scanning for the early detection and localization of an occult neuroblastoma in children presenting with opsoclonus (148). Normal results of screening tests (e.g., urine catecholamines) or plain radiographs do not exclude the presence of a neuroblastoma.

Differential Diagnosis

The qualities of abnormal eye movement that clinically define opsoclonus are so characteristic that they should not usually cause the examining clinician to generate an expanded differential diagnosis, although opsoclonus may at times be confused with other forms of saccadic oscillations, such as square-wave jerks and macrosaccadic oscillations, nystagmus, or the corrective saccades associated with saccadic dysmetria. In addition, rare persons who are otherwise normal and who have no evidence of underlying neurologic disease can voluntarily generate abnormal eye movements with characteristics similar to, but not identical with, those of opsoclonus and ocular flutter (149).

The syndrome of opsoclonus-myoclonus-ataxia can occur in the setting of other paraneoplastic CNS disorders, including encephalomyelitis and subacute cerebellar degeneration. In the setting of a known malignancy, this syndrome can be caused by posterior fossa metastases that directly injure the brainstem or cerebellum or that indirectly produce obstruc-

tive hydrocephalus, by a coagulopathy or a bleeding diathesis that cause an ischemic or hemorrhagic stroke affecting the brainstem or cerebellum, by radiation injury to the neural or vascular structures in the posterior fossa, or by the toxic effects of certain chemotherapeutic agents, such as 5-fluorouracil or cytarabine. In children, additional nonparaneoplastic causes of opsoclonus include viral encephalitis and a transient benign disorder observed in otherwise healthy neonates (119,123,150), whereas nonparaneoplastic causes of opsoclonus in adults include viral encephalitis, cerebrovascular disorders, demyelinating disease, and toxins (119,123,150).

Pathogenesis

The pathophysiology of the paraneoplastic opsoclonus-myoclonus-ataxia syndrome is unclear, but most investigators believe that it is an autoimmune disorder. Supporting this hypothesis are investigations demonstrating antineuronal antibodies in the serum and CSF of patients with the condition. The higher concentrations of antibody in the CSF compared with the serum in many affected patients suggest that local intrathecal production of these antibodies is important in the development of this remote effect (135). Antineuronal immunoglobulins from seropositive patients are found in the brainstem and cerebellum during postmortem examinations (132,145); Hu-antigens are present in neuroblastomas and other neoplasms from anti-Hu seropositive patients with paraneoplastic opsoclonus (71,132,136); and anti-Ri antibodies obtained from seropositive women with paraneoplastic opsoclonus react against the underlying tumor tissue obtained from surgical pathology specimens (135). These studies suggest that autoantibodies produced in response to the expression of certain specific tumor antigens may cross-react against various central nervous system antigens, such as a biochemically characterized Ri-associated antigen, called Nova, that is a protein detected in the human brain and expressed in the developing ventral brainstem of mice (151–152). How the interaction between autoantibodies and CNS neuronal antigens leads to the syndrome of opsoclonus-myoclonus-ataxia remains undefined. The beneficial response of some patients when treated with immunosuppressant medication (e.g., corticosteroids) or immunomodulating agents (e.g., intravenous immunoglobulin) also indirectly supports an autoimmune mechanism of disease development.

Additional evidence in favor of an autoimmune pathogenesis of the paraneoplastic opsoclonus-myoclonus-ataxia syndrome is the finding of alterations of cell-mediated immunity in patients with this condition. Herishanu et al. (122) performed immunologic studies in a patient with adenocarcinoma of the breast who developed the opsoclonus-myoclonus-ataxia syndrome and demonstrated decreased function of suppressor T-cells and hyperactivity of helper T-cells despite a normal suppressor:helper ratio. The immunologic abnormalities (as well as the clinical syndrome) improved when the patient was treated with systemic corticosteroids. Helper/inducer T-cells were predominantly found in the perivascular inflammatory infiltrate of the region of the paramedian pontine reticular formation, whereas suppressor/cytotoxic T-cells were mainly found in the interstitium of a patient who had anti-Ri-associated opsoclonus (145). Natural killer cells and compliment reactivity were also present in this patient (145).

Causes other than an autoimmune response may be responsible for at least some cases of the paraneoplastic opsoclonus-myoclonus-ataxia syndrome. The improvement that followed administration of thiamine in a patient reported by Nausieda et al. (105) suggests that, at least in that patient, nutritional deficiencies that may be attributable to metabolic activity of the tumor may have been responsible for the syndrome. Pranzatelli et al. (434) found significantly lower CSF levels of 5-hydroxyindoleacetic acid, the major oxidative metabolite of serotonin, in some, but not all, children with opsoclonus-myoclonus compared with controls, suggesting that biochemical alterations may be important in the pathogenesis of opsoclonus in some affected patients. Because of the confounding interaction of age, these investigators were not able to determine whether differences existed between those children with neuroblastomas and those without malignancies.

Treatment

Opsoclonus, myoclonus, and ataxia frequently persist after resection of the underlying neoplasm. Nevertheless, Caviness et al. (127) reported a 53-year-old woman who developed opsoclonus and myoclonus around the time she was discovered to have adenocarcinoma of the breast. After bilateral radical mastectomies, the opsoclonus and myoclonus resolved and did not return during the next 7 years of follow-up. Other investigators have also reported resolution of the paraneoplastic opsoclonus-myoclonus-ataxia syndrome after resection of the underlying neoplasm (see below).

In circumstances when a tumor thought responsible through distant effects for the opsoclonus-myoclonus-ataxia syndrome is not amenable to cure or radical resection, the use of ACTH (112,120), systemic corticosteroids (112,120,122, 134), and clonazepam (118,126,127,129) may provide at least transient improvement in the symptoms and signs of the paraneoplastic process. As noted above, Nausieda et al. (105) reported that the administration of thiamine reversed the opsoclonus in a 52-year-old man with anaplastic bronchogenic carcinoma. Although plasmapheresis has not been proven beneficial in patients with the paraneoplastic opsoclonus-myoclonus-ataxia syndrome, other forms of immunomodulating treatments, including intravenous immunoglobulin (136) and immunoadsorption (138) may induce partial remission. Rarely, treatment of the underlying malignancy in adults who have tumors other than neuroblastomas may provide partial improvement (125,129).

Prognosis

The ultimate prognosis in patients with the opsoclonus-myoclonus-ataxia syndrome is related to eradication of the underlying tumor. When the tumor can be treated successfully, the paraneoplastic syndrome may resolve, and even radical excision of an incurable malignancy may be associ-

ated with transient improvement or at least stabilization of the neurologic dysfunction (100,120). The best prognosis is in children with neuroblastoma, in whom the opsoclonus-myoclonus syndrome seems to indicate a localized, curable tumor (110,120,147,152,153). Nevertheless, many patients, particularly children with neuroblastoma, have residual neurologic deficits, especially intellectual impairment, behavioral disorders, and motor dysfunction (120,147,153). In addition, many investigators emphasize that the neuroblastoma-associated neurologic disorder in children tends to be chronic and characterized by remissions induced by corticosteroids or ACTH and by relapses frequently associated with withdrawal of medication, febrile illnesses, and immunizations (112,147,153).

The prognosis is far less favorable in adults with the paraneoplastic opsoclonus-myoclonus-ataxia syndrome. Adults whose tumors cannot be cured tend to have progression or recurrence of neurologic symptoms and signs, and they eventually succumb to the effects of either the primary cancer or neurologic dysfunction. Relapse of symptoms and signs in those patients whose neurologic disorder initially responded to treatment of the underlying tumor often signifies local recurrence of tumor or metastatic dissemination (100,129).

NECROTIZING MYELOPATHY

Necrotizing myelopathy is the rarest of the central nervous system remote effects of cancer. Indeed, its existence as a distinct paraneoplastic syndrome was unknown for many years until several pathologically verified cases associated with systemic malignancies were reported (6).

Clinical Features

Although necrotizing myelopathy may be the initial manifestation of an occult neoplasm, it more often develops after a cancer has established itself. It may also occur in patients previously treated for cancer who have no clinical or pathologic evidence of malignancy (154).

A variety of malignancies can be associated with necrotizing myelopathy, including Hodgkin's disease, lymphoma, acute leukemia, and cancers of the lung, breast, ovary, stomach, prostate, thyroid, and kidney (6,154–158). Affected patients experience acute or, less often, subacute onset of asymmetric flaccid paresis of the lower extremities, ascending sensory loss, and bowel and bladder dysfunction. The course is typically rapid, with progression of deficits occurring over days to weeks, and ultimately culminating in paraplegia and a segmental sensory level, or the clinical characteristics of a Brown-Sequard syndrome (157). Paraplegia, bulbar paresis, and respiratory failure frequently occur when the pathologic process extends rostrally into the cervical spinal cord and brainstem (158).

Pathology

Two general patterns of pathologic abnormalities are observed during postmortem examination of patients with necrotizing myelopathy (6). Most investigations have revealed massive necrosis of both gray and white matter within the thoracic spinal cord, with gradual tapering of the process both rostrally and caudally. In these cases, the rostral extension of the necrosis may reach the lower brainstem. In other cases, patchy multifocal regions of necrosis affecting different levels of the spinal cord are present. The necrosis in some cases preferentially affects the white matter. In this setting, it is often with associated spongiform degeneration and demyelination. Wallerian degeneration of the affected ascending and descending tracts can also occur. Inflammatory changes are generally minimal and are probably caused by the necrotic process itself. Vessels are generally not affected by inflammation, necrosis, or thrombosis. A case of necrotizing myelopathy described by Lester et al. (156), in which a 66-year-old man with Hodgkin's disease was found to have typical pathologic changes along with fibrinoid necrosis of vessel walls and vasculitis, is a notable exception.

Diagnostic Evaluations

The CSF is usually unremarkable in patients with necrotizing myelopathy, but it may show xanthochromia, a few red blood cells, a mild lymphocytic pleocytosis, and an increased concentration of protein. An increased concentration of myelin basic protein was present in the CSF of the patient described by Kuroda et al. (158).

Early reports described normal-appearing spinal cords using myelography in patients with necrotizing myelopathy. In the case described by Kuroda et al. (158), however, the entire cervical cord showed diffuse hypointensity on T1-weighted MR imaging.

Differential Diagnosis

In a patient with known or suspected cancer who develops an acute myelopathic syndrome, intradural or extradural compression, intramedullary infiltration by metastatic disease, or an opportunistic infection, must be emergently excluded using MR imaging, intrathecally enhanced CT scanning, examination of the CSF, or a combination of these modalities. An acute necrotic myelopathy may rarely occur following intrathecal administration of either methotrexate or cytarabine (159). Late-delayed radiation-induced injury to the spinal cord usually occurs 1–4 years after exposure and causes a subacute myelopathy that progresses over several weeks to months or, in some cases, years. An acute myelopathy can occur as part of the syndrome of paraneoplastic encephalomyelitis, as discussed earlier.

Cerebrovascular complications referable to the spinal cord, as seen with a hypercoagulopathy-associated infarct or epidural hematoma causing compression, can present as an acute myelopathy. Finally, cancer patients are predisposed to nutritional deficiencies (e.g., vitamin B_{12}) that can cause myelopathies, but the onset and course of these disorders are generally more insidious than paraneoplastic necrotizing myelopathy.

Pathogenesis

The pathogenesis of paraneoplastic necrotizing myelopathy is unknown. The longitudinal distribution of damage

along the spinal neuraxis does not respect vascular territories supplying the spinal cord. Because of this observation and because of the absence of vessel occlusion in most cases, a hypercoagulopathy or cerebrovascular mechanism is unlikely. The intense vasculitis present in the case described by Lester et al. (156) suggests that a primary inflammation may be important for development of this unusual syndrome in some patients. Support for an immunologic mechanism comes from the report of Kuroda et al. (158), who found increased proportions of activated helper T-cells in the CSF, and reduced proportions of suppressor-inducer T-cells in the peripheral blood of their patient at the time of onset of symptoms.

Treatment and Prognosis

There is no treatment for paraneoplastic necrotizing myelopathy. Affected patients experience rapid progression of neurologic impairment and general deterioration, often dying within weeks following the onset of symptoms from complications related to respiratory failure or sepsis.

PARANEOPLASTIC PERIPHERAL NEUROPATHIES

The most common cause of peripheral neuropathy in a patient with cancer is compression of a nerve trunk by a mass of tumor cells. Less commonly, neuropathies result from infiltration by tumor cells of the epineurium of spinal or cranial nerve roots or peripheral nerves. Peripheral nerves can also be injured by the toxic effects of certain chemotherapeutic agents and radiation treatment. In addition, some patients with malignancies develop a progressive peripheral neuropathy that is unassociated with evidence of metastatic tumor or the effects of cancer treatment and is therefore thought to be a remote effect of the primary lesion, an association first recognized and described in detail by Denny-Brown (161).

Paraneoplastic peripheral neuropathies usually occur in patients with known malignancies, but, like the paraneoplastic syndromes that affect the central nervous system, they are occasionally the initial manifestation of the malignancy. Several types of paraneoplastic peripheral neuropathies have been described (3,6,162), including a pure sensory neuropathy, a pure motor neuropathy, sensorimotor neuropathies, and autonomic neuropathies.

SUBACUTE SENSORY NEURONOPATHY

A pure sensory neuronopathy can occur as a neurologically isolated remote effect of cancer (161,163), but it more often develops in the setting of a more extensive paraneoplastic encephalomyelitis (6,7,41). Isolated paraneoplastic subacute sensory neuronopathy is most often associated with small-cell lung cancer, but it also occurs in patients with multiple myeloma, Hodgkin's disease, diffuse large cell lymphoma, other cancers of the lung, and carcinomas of the breast, ovary, and gastrointestinal tract (8,164).

Paraneoplastic sensory neuronopathy often becomes symptomatic before the discovery that a systemic cancer is present (8,164). In a typical case, the patient experiences tingling and spontaneous pain in the limbs along with a progressive sensory ataxia that eventually renders arm and leg movements very clumsy. These disturbances begin distally, but they gradually spread proximally over a period of several weeks to months. Symptoms often begin in the arms and are frequently asymmetric at the onset. Neurologic examination shows distal loss of sensitivity to all primary modalities, although proprioception and vibration sense are affected much more dramatically than pain and light touch sense. Loss of positional sense is usually very severe and causes sensory ataxia of all extremities. Muscle stretch reflexes are reduced or absent. A form of sensory neuronopathy with acute onset and rapid progression of deficits was described by Vallat et al. (165).

Some patients with subacute sensory neuronopathy have evidence of autonomic dysfunction, particularly orthostatic hypotension (8,41). In fact, in some patients, symptoms related to pandysautonomia or selective dysfunction of the circulatory system, gastrointestinal tract, bladder, or sudomotor system may be more disabling than symptoms referable to sensory loss (166–172). Some of these patients have tonic pupils (8,164,167–169,173–175; see below).

In patients with subacute sensory neuronopathy, the CSF frequently contains an increased concentration of protein that ranges from 50–200 mg/dl (8,164). The CSF cell count is usually normal and there may be a mild lymphocytic pleocytosis. Anti-Hu antineuronal antibodies are frequently present in the serum of affected patients, especially in those whose underlying malignancy is small-cell cancer of the lung (41,56,176). In a series reported by Molinuevo (177), the specificity of the anti-Hu antibodies for paraneoplastic sensory neuronopathy was 99.8% and sensitivity was 82%. Electrophysiologic studies show markedly diminished or absent sensory nerve action potentials, normal motor nerve conductions, and no electromyographic abnormalities (8,164,178). Some abnormalities of motor conduction and muscle activity can be seen in severely or chronically affected patients.

The neuropathologic findings in patients with paraneoplastic subacute sensory neuronopathy consist of degeneration and inflammation of the dorsal root ganglia with secondary degeneration of the posterior roots and the dorsal columns of the spinal cord (164,179). In some acute cases, perivascular endoneurial inflammation is present (165). Sural nerve biopsies show loss of both myelin and axons, fibrosis, and occasional mononuclear inflammatory infiltrates around epineural vessels (8,164). In patients with autonomic dysfunction, additional pathologic changes, including interstitial and perivascular lymphocytic infiltration, loss of neurons, and loss of myelinated fibers, may be observed in the paravertebral autonomic ganglia (169). The myenteric plexus is infiltrated with mononuclear cells and shows neuronal loss and degeneration in those patients with selective gastrointestinal failure causing intestinal pseudo-obstruction (167,171,172).

SUBACUTE MOTOR NEUROPATHY

Patients with subacute motor neuropathy usually have an underlying systemic lymphoma that has been diagnosed by the time symptoms of the neuropathy occur. This syndrome has rarely been described in patients with other malignancies (180). Affected patients have no significant sensory symptoms or signs. Instead, they develop painless progressive weakness that may be proximal or distal, symmetric or asymmetric, usually affecting the legs more than the arms (181). The weakness is associated with findings of lower motor neuron dysfunction, including fasciculations, reduction in muscle stretch reflexes, and eventual atrophy of affected muscles. The bulbar and respiratory muscles are often spared, but when they are affected the damage is usually not severe. Unlike other forms of paraneoplastic peripheral neuropathies, subacute motor neuropathy usually stabilizes or may even improve spontaneously after months or even years, independent of the course of the underlying neoplasm.

The pathologic findings in paraneoplastic subacute motor neuropathy consist of loss of anterior horn neurons, sometimes accompanied by variable degrees of inflammatory infiltrates; patchy demyelination of the spinal white matter tracts; partial degeneration of the posterior columns; secondary degeneration of ventral spinal roots; patchy demyelination of spinal roots and of cervical and lumbar plexuses; and neurogenic atrophy of skeletal muscle (181,182). Because these features are similar to those seen in patients with poliomyelitis, it has been suggested that paraneoplastic subacute motor neuropathy may be caused by an opportunistic virus (182). Direct evidence supporting a viral mechanism, however, is lacking.

CHRONIC PROGRESSIVE SENSORIMOTOR NEUROPATHY

This paraneoplastic peripheral neuropathy is actually a heterogeneous group of conditions whose common clinical feature includes a relentless course of progressive loss of motor and sensory function over many months or even years. The clinical manifestations are nonspecific but reflect injury of peripheral motor and sensory nerves. They include progressive weakness, loss of muscle stretch reflexes, muscle atrophy, and progressive loss of sensation that is symmetric in the extremities but worse in the lower than in the upper limbs, and worse distally than proximally. Cranial nerve dysfunction is extremely uncommon. The clinical, electrophysiologic, and pathologic features usually reflect an underlying axonal-loss neuropathy but may in any one individual patient fulfill features of an *axonal neuropathy, demyelinating neuropathy,* or of *mononeuritis multiplex* associated with vasculitis of the vasa nervorum (6,162). Many of these neuropathies are thought to result from nutritional deficiencies or the cachectic state induced by the neoplasm (183).

Paraneoplastic sensorimotor peripheral neuropathies not infrequently develop in patients with carcinomas in a variety of locations (6,184,185), i.e., in patients with lymphomas (186–188) and in patients with plasma cell dyscrasias, particularly multiple myeloma (189–192). In most cases, this form of neuropathy develops in patients whose malignancies are well established and often is a terminal manifestation of the disease (185).

There are no studies that can be used to diagnose with certainty the chronic progressive form of paraneoplastic sensorimotor neuropathy. Many affected patients have increased protein in the CSF, but the cell count and other constituents are otherwise normal. Because an axonal-loss neuropathy is the most frequently encountered form of the chronic progressive sensorimotor neuropathies in cancer patients, nerve conduction studies usually disclose reduced sensory and motor amplitudes but with normal or only mildly reduced velocities. The electromyogram usually shows evidence of denervation, particularly in the muscles of the lower extremities.

When a chronic progressive sensorimotor peripheral neuropathy develops in a patient with a known malignancy who has not received any neurotoxic chemotherapy, there is usually little reason to look for causes other than the neoplasm. On the other hand, when the neuropathy develops before a cancer declares itself at a primary or metastatic site, it is necessary to include in the differential diagnosis the many toxic, metabolic, nutritional, hereditary, and inflammatory neuropathies.

Some patients have an unusual multisystem disorder that includes **p**eripheral neuropathy, **o**rganomegaly, **e**ndocrinopathy, **m**onoclonal gammopathy, and **s**kin changes, called the *POEMS syndrome* (193,194). The peripheral neuropathy is generally a chronic progressive sensorimotor variety, associated with a mild elevation of CSF protein content. Electrophysiologic studies and nerve biopsy reveal evidence of axonal degeneration alone or mixed axon degeneration and demyelination. The liver, spleen, and lymphatic system are the most commonly affected organs in this syndrome. Endocrine dysfunction includes diabetes, hypogonadism associated with impotence and gynecomastia in men, amenorrhea in women, and hypothyroidism. The plasma cell dyscrasias associated with the POEMS syndrome include immunoglobulin G (IgG) or IgA monoclonal gammopathies, usually associated with lambda light chains. Most affected patients have solitary or multiple bone lesions, usually in the spine, pelvis, and ribs. The bone lesions are usually sclerotic or mixed sclerotic-lytic. Pure lytic bone lesions and significant bone marrow infiltration by plasma cells, typical findings in multiple myeloma, rarely occur in patients with the POEMS syndrome. Skin manifestations include hyperpigmentation, thickening, and hypertrichosis.

From 37–73% of patients with the POEMS syndrome have swollen optic discs (193–195). Such patients generally have normal visual acuity and full peripheral fields (195,196). The intracranial pressure in some of these patients is elevated when a lumbar puncture is performed, indicating that the disc swelling is probably papilledema. In other patients in whom the intracranial pressure is normal, the pathogenesis of the disc swelling is unclear. It may be caused by infiltration of the optic nerve or its sheath by an inflammatory process, or it may result from a localized increase in capillary permeability. Some patients with the POEMS syndrome have prominent stare and upper eyelid retraction, suggesting thyroid eye disease (197).

ACUTE OR SUBACUTE SENSORIMOTOR NEUROPATHY

In this group of peripheral neuropathies, the clinical syndrome is similar to that of the Guillain-Barré syndrome. Patients develop acute or subacute weakness and numbness of the extremities associated with a variable increase in CSF protein concentration. A mild lymphocytic pleocytosis may also be present. Nerve conduction velocities are characteristically slow in most cases, reflecting the presence of segmental demyelination. The electromyogram usually does not reveal extensive denervation, at least early in the course of the disorder, since axons tend to be spared during the acute process. The pathologic findings in this condition are demyelination of the peripheral nerves and spinal nerve roots, variable degrees of axonal loss, and sparse lymphocytic infiltration in some cases.

Most patients who develop the acute or subacute forms of paraneoplastic sensorimotor neuropathy have a systemic lymphoma (198–201) or one of the plasma cell dyscrasias, particularly multiple myeloma (190). An acute or subacute sensorimotor neuropathy may also occur in patients with carcinomas and leukemias (201,435), most notably of the lung and breast (185,202).

Some patients with the acute and subacute forms of paraneoplastic sensorimotor neuropathy have a rapidly progressive course that ends in death within several weeks to months (185,198,199,202). In other patients, the disorder appears to be self-limited, with variable degrees of remission, including complete recovery in some cases (199,201). Finally, some patients who present with what appears to be a typical acute or subacute sensorimotor neuropathy of the Guillain-Barré type appear to recover, only to relapse later. In some reported cases of this syndrome, there have been as many as four relapses spread over several years. The relapsing/remitting form of sensorimotor neuropathy occurs more frequently with lymphomas (particularly Hodgkin's disease) (185, 199,201) than with carcinomas (185,202) or plasma cell dyscrasias (190).

As is the case with the other paraneoplastic peripheral neuropathies, the association between the acute and subacute sensorimotor neuropathies and an underlying malignancy usually poses no diagnostic problem when the primary malignancy is already known at the time symptoms and signs of the neuropathy develop. When an acute or subacute sensorimotor neuropathy develops in a patient in whom no malignancy is suspected, the differential diagnosis includes the Guillain-Barré syndrome, chronic immune demyelinating polyneuropathy, diphtheritic neuropathy, acute poliomyelitis, tick-borne paralysis, hypo- or hyperkalemic periodic paralysis, myasthenia gravis, botulism, porphyria, and drug intoxication (e.g., with isoniazid or nitrofurantoin).

Because the acute and subacute forms of paraneoplastic peripheral neuropathy are most often associated with lymphoproliferative malignancies, it has been speculated that the pathogenesis is related to a disorder of the immune system. There is no direct evidence, however, that this is the case.

CARCINOMATOUS NEUROMYOPATHY

Historically, the term *carcinomatous neuromyopathy* was once used to describe all remote effects of cancer affecting the peripheral nervous system that caused weakness (29,203). As the identification of specific paraneoplastic disorders affecting the peripheral nerves, neuromuscular junction, and skeletal muscles became better characterized, this term became obsolete. Still, there exists a group of patients who experience subacute onset of weakness, usually affecting the proximal muscles of the legs more so than the arms who have depressed or absent muscle stretch reflexes and other findings of a peripheral neuropathy and whose physical findings and diagnostic studies do not fulfill criteria for inclusion into one of the peripheral nerve disorders discussed above. Some investigators believed that this condition occurs from the effects of malnutrition and the cachectic state associated with cancer (183,204), but there is electrophysiologic and pathologic evidence that this disorder is a neuropathy caused by damage to intramuscular distal axons (205,206).

Carcinomatous neuromyopathy usually occurs in patients with carcinomas. It can develop either before the malignancy declares itself or after the diagnosis of cancer has become well established.

EATON-LAMBERT SYNDROME: A PARANEOPLASTIC DISORDER OF THE NEUROMUSCULAR JUNCTION

A disorder resembling myasthenia gravis, occurring in patients with bronchogenic carcinoma, was first described by Anderson et al. in 1953 (440). During the next decade, Eaton, Lambert, Rooke, and their associates at the Mayo Clinic studied the clinical and physiologic characteristics of this disorder in 30 patients (207–211). These investigators concluded that it was associated with failure of neuromuscular junction transmission but was distinct from myasthenia gravis.

CLINICAL FEATURES

This myasthenic syndrome, also called the Eaton-Lambert syndrome, is more common in men than in women when associated with malignancies (212). Almost all of those affected are adults, but children with the disorder have been described (213,214). About 60% of patients have a malignant neoplasm, almost always small-cell lung cancer, but this syndrome has also been described in patients with carcinoma of the breast, prostate, stomach, pancreas, kidney, and rectum; in patients with lymphoma and other lymphoproliferative diseases; and in patients with lung cancers other than the small-cell variety. As is the case with most of the other paraneoplastic syndromes described in this chapter, symptoms and signs of the Eaton-Lambert syndrome frequently develop before there is any clinical evidence of a malignancy.

Patients with the Eaton-Lambert syndrome typically pres-

ent with generalized weakness and easy fatigability of the proximal muscles of the limbs, especially of the hips, shoulders and thighs. Affected individuals often have difficulty arising from chairs, climbing stairs, and using their arms above the head. Decreased energy and stamina are common complaints. In some patients, strength can be demonstrably improved following a brief period of exercise, but it then deteriorates with further sustained activity. Muscle stretch reflexes are reduced or absent but can be enhanced in some patients following brief contraction of the appropriate muscle (215,216). The phenomenon of *improvement* in muscle strength after voluntary muscle contraction is termed *facilitation.* It can be demonstrated electromyographically and is the reverse of the progressive weakness and decremental response shown by affected muscles in patients with myasthenia gravis. When present, facilitation serves to distinguish patients with the Eaton-Lambert syndrome from those with myasthenia gravis. Some patients experience aching, stiffness, and paresthesias of their affected limbs. As is the case with myasthenia gravis, neuromuscular transmission worsens and weakness increases when patients with this disorder are subjected to increasing external or internal temperature. Eaton-Lambert syndrome may first show up as prolonged weakness or respiratory insufficiency after surgery in which neuromuscular blocking agents were given.

Unlike myasthenia gravis, in which ocular and bulbar signs are common, such manifestations are quite uncommon in patients with the Eaton-Lambert syndrome. Nevertheless, ptosis and both clinical and subclinical disorders of eye movement may occur in this syndrome (217–221). O'Neill et al. (212) noted ptosis in about 50% of their patients, and about half of the patients in this series complained of intermittent double vision, although significant ophthalmoparesis was not observed in any of them. Cruciger et al. (222) examined five patients with the Eaton-Lambert syndrome, all of whom complained of intermittent ptosis and three of whom complained of intermittent diplopia. Three of the patients were noted to have ptosis at the time of examination. In addition, two of three patients whose eye movements were measured before and after exercise had saccadic velocities that were normal before exercise but increased up to 40% after exercise. Thus, the extraocular muscles, like the peripheral muscles, may show the phenomenon of facilitation. Dell'Osso et al. (223) examined saccades in five patients with the Eaton-Lambert syndrome. All of the patients made saccades that were similar to those made by patients with myasthenia gravis in that the saccades were often hypometric or multiple and closely spaced. Two patients demonstrated both saccadic facilitation and positive testing with edrophonium chloride (Tensilon); however, all of the patients had slow or normal saccadic velocities, rather than the superfast velocities often found in patients with myasthenia gravis (see Chapter 21).

In addition to muscle weakness and depressed muscle stretch reflexes, patients with Eaton-Lambert syndrome often have symptoms of autonomic dysfunction, including blurred vision, dry mouth, constipation, difficulty with urination, impotence, and, infrequently, orthostatic light-headedness. Evaluation of autonomic function in affected patients reveals evidence of both parasympathetic and sympathetic dysautonomia (224–226). Some patients with Eaton-Lambert syndrome have large, poorly reactive pupils that constrict in response to topically applied dilute cholinergic agonists (212,224,227). However, in the absence of light-near dissociation and segmental paresis of the iris sphincter, such pupils should not be confused with true tonic pupils (224).

Diagnostic Evaluation

Transient improvement of upper eyelid strength in response to intravenously administered edrophonium chloride occasionally occurs in patients with the Eaton-Lambert syndrome who have ptosis, although such a response is generally more characteristic of myasthenia gravis. Electromyographic studies show a low-amplitude compound muscle action potential that declines at low rates of stimulation, augments greatly at high rates of stimulation and, as noted above, shows marked facilitation after exercise (208, 211,216) (Fig. 36.9). Single-fiber electromyography reveals increased jitter and blocking that improve as muscle units fire at increasingly higher rates (216,228,229).

Serum antibodies directed against the P/Q- or N-type voltage-gated calcium channel of the nerve terminal are present in 28–75% of patients with the Eaton-Lambert syndrome who have small-cell lung cancer (230–232). The clinical usefulness of these antibodies remains to be defined, since they are also present in many patients with the Eaton-Lambert syndrome unassociated with cancer, in some patients with other systemic autoimmune disorders (e.g., systemic lupus erythematosus), and in patients with small-cell lung cancer who do not have the Eaton-Lambert syndrome (230–232).

There are no clinical features that differentiate patients with the Eaton-Lambert syndrome associated with cancer from those without an underlying malignancy. However, one should be particularly suspicious that a patient with the Eaton-Lambert syndrome has an occult malignancy if the

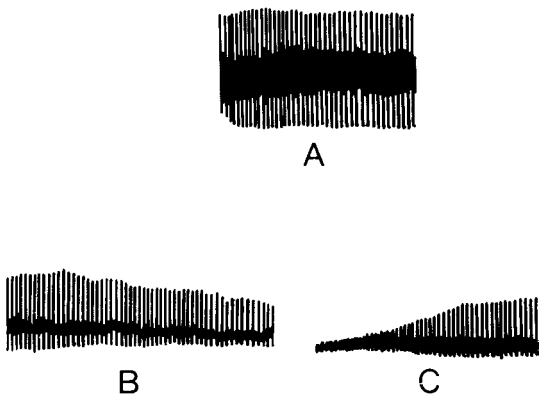

Figure 36.9. Electromyograms in a normal person (*A*), a patient with myasthenia gravis (*B*), and a patient with the Eaton-Lambert myasthenic syndrome (*C*). Note the facilitation response in the myasthenic syndrome as opposed to the decremental response in myasthenia gravis during repetitive nerve stimulation.

patient also has other symptoms or findings of some other paraneoplastic syndrome, such as a peripheral neuropathy. In addition, some immunologic differences exist that may help to distinguish patients with the Eaton-Lambert syndrome as a remote effect of cancer from similarly affected patients without cancer. Robb et al. (233) found that patients with the Eaton-Lambert syndrome associated with cancer had significantly reduced numbers of OKT8 + T-lymphocytes, whereas normal control subjects, patients with cancer but without the Eaton-Lambert syndrome, and patients with Eaton-Lambert syndrome without an associated neoplasm had normal numbers of these cells. In addition, in one patient, a 72-year-old woman, the reduction in this population of T-cells antedated clinical detection of her tumor by 5 months. The prevalence of organ-specific autoantibodies, such as antithyroglobulin, antiparietal cell, and antiskeletal muscle antibodies, is higher in patients with the Eaton-Lambert syndrome who do not have a malignancy compared with control patients (234). Nonorgan-specific autoantibodies, such as antinuclear, antismooth muscle, and antimitochondrial antibodies, are also found more frequently in patients with the Eaton-Lambert syndrome who have cancer compared with patients who do not have cancer (235). The prevalence of anti-voltage-gated calcium channel antibody seropositivity is higher in patients with the Eaton-Lambert syndrome associated with neoplasms compared with those patients who have no malignancy (230).

Differential Diagnosis

Paraneoplastic peripheral and autonomic neuropathies can cause weakness, impairment of muscle stretch reflexes, and dysautonomia, the typical triad of abnormalities that occur in patients with the Eaton-Lambert syndrome. Results of electrophysiologic studies will identify in most patients the characteristic defect of neuromuscular transmission that is present in this disorder and will distinguish this defect from the postsynaptic disturbance that occurs in myasthenia gravis. Other disorders affecting the peripheral and autonomic nervous systems that could cause diagnostic confusion with the Eaton-Lambert syndrome include botulism, diabetes mellitus, chronic alcohol toxicity, Sjogren's syndrome, amyloidosis, and the acute and chronic inflammatory demyelinating polyradiculoneuropathies.

Finally, primary muscle disorders (e.g., inclusion body myositis) and carcinomatous neuromyopathy can superficially resemble the course and progression of the proximal limb weakness and sparing of bulbar muscles that occurs in patients with the Eaton-Lambert syndrome.

Pathogenesis

The weakness in patients with the Eaton-Lambert syndrome results from impaired release of acetylcholine from the presynaptic nerve terminals (236,237), rather than from defective reception of acetylcholine by the postsynaptic membrane as occurs in myasthenia gravis. Acetylcholine synthesis and mobilization are unimpaired, and the amount of depolarization produced by single quanta is normal in patients with the Eaton-Lambert syndrome. The impaired release of acetylcholine results in end-plate potentials that are too small to trigger muscle action potentials. At low rates of stimulation, the number of quanta released and the amplitude of end-plate potentials decline, whereas at rates of stimulation above 10 Hz there is increasing release and increasingly large end-plate potentials. In this setting, an increase in the concentration of calcium at the neuromuscular junction or the addition of guanidine augments the release of acetylcholine (236,238). Electron microscopic studies of neuromuscular junctions in mice treated with IgG from patients with the Eaton-Lambert syndrome demonstrate depletion of the active zone, the site of synaptic vessel exocytosis, and both depletion and aggregation of active zone particles in the presynaptic membrane (239,240). The postsynaptic region in patients with the Eaton-Lambert syndrome appears overdeveloped, with highly complex clefts and folds (241–243).

The Eaton-Lambert syndrome appears to be an autoimmune disorder. The target is apparently a component of the presynaptic nerve terminal involved in the calcium-dependent release of acetylcholine from the active zone. An extract of small-cell lung cancer from a patient with this syndrome reproduced characteristic electrophysiologic abnormalities from in vitro nerve-muscle preparations (244). In addition, several investigators reported that the defect in neuromuscular transmission can be passively transferred to mice by injection of IgG from patients with the Eaton-Lambert syndrome (239,240,245,246). Serum autoantibodies that bind voltage-gated calcium channels expressed by small-cell lung cancer cell lines are found in many patients with the Eaton-Lambert syndrome (230,247). The neuromuscular antigen against which these antibodies react has been cloned and found to be homologous to a beta subunit of the voltage-gated calcium channel (248). It therefore seems likely that the Eaton-Lambert syndrome is caused by an antibody-mediated autoimmune response that downregulates the voltage-gated calcium channel and thereby impairs the calcium-dependent release of acetylcholine from the presynaptic active zone. The production of serum antibodies against muscle voltage-gated calcium channels may be an aberrant autoimmune response against an antigen expressed by the cancer, similar to the autoimmunity that appears important in the pathogenesis of many of the other remote effects that have already been discussed in this chapter.

Treatment and Prognosis

Treatment of the underlying cancer may significantly improve the status of some patients with the Eaton-Lambert syndrome (249–251). For the many others who remain symptomatic after aggressive treatment of their malignancy, agents that enhance neuromuscular transmission are frequently helpful. Anticholinesterase medications, such as pyridostigmine (Mestinon), are not as effective in patients with the myasthenic syndrome as they are for patients with myasthenia gravis, but they are often used as first-line agents because they are well tolerated. Also, these drugs are useful in supplementing the therapeutic effect of other treatments (215,216). Guanidine hydrochloride improves neuromuscu-

lar transmission by raising presynaptic calcium levels, but it is not frequently used because of its high frequency of serious adverse effects, which include bone marrow suppression and hepatic and renal toxicity (215,216). Aminopyridines are drugs that enhance the release of acetylcholine by blocking potassium channels, thus prolonging the action potential and activation of voltage-gated calcium channels at the nerve terminal; 3,4-diaminopyridine is effective and well tolerated, and it is currently the aminopyridine of choice for patients with the Eaton-Lambert syndrome (252).

Some patients remain symptomatic despite treatment of the cancer and the use of drugs that enhance neuromuscular transmission. In this setting, immunosuppressive therapy using prednisone or azathioprine, or immunomodulating therapy using plasmapheresis or intravenous immunoglobulin, are beneficial (215,216,253). Unfortunately, both forms of therapy have major disadvantages. Immunosuppressive therapy has the disadvantage of delayed action, whereas immunomodulating treatments have the disadvantage of providing only temporary responses. Despite the many drugs that can be used to treat patients with the Eaton-Lambert syndrome, most patients with this disorder eventually become severely debilitated from weakness before their eventual death from their underlying cancer (212).

PARANEOPLASTIC DISORDERS OF VOLUNTARY MUSCLE

Several paraneoplastic disorders are characterized by primary damage to voluntary muscle, including polymyositis, dermatomyositis, acute necrotizing myopathy, cachectic myopathy, and endocrine myopathies. Ocular signs and symptoms can occur in each of these syndromes and can even be the presenting manifestation of the condition.

POLYMYOSITIS AND DERMATOMYOSITIS

Polymyositis is an inflammatory myopathy that affects striated skeletal muscle and, less commonly, cardiac muscle. The diagnosis of polymyositis is based on the presence of at least two of the following (254–255):

1. Proximal muscle weakness.
2. Elevated serum levels of muscle-associated enzymes such as creatine kinase, aldolase, and lactic dehydrogenase.
3. An active myopathic pattern on electromyography.
4. Inflammatory changes, often associated with necrosis, degeneration, and regeneration of muscle fibers, in a muscle biopsy specimen.

When a characteristic rash is present in a patient with polymyositis, a diagnosis of dermatomyositis is made. The rash, called a heliotrope rash, is typically a violaceous and sometimes edematous eruption that affects the upper eyelids more prominently than the lower eyelids. In addition, patients with dermatomyositis may have a flat red rash on the malar region, anterior chest, and extensor surfaces over large joints. Violaceous papules and scaly plaques, called Gottron's papules, characteristically appear over joints, most commonly the knuckles. Nonspecific nail bed changes develop, including periungual telangiectasias and cuticular irregularity and thickening (256). Both the rash and weakness of dermatomyositis usually evolve subacutely and appear simultaneously. The rash may, however, be an isolated phenomenon that develops shortly before the weakness occurs. The weakness that occurs in both polymyositis and dermatomyositis primarily affects the proximal limb muscles, although there may also be involvement of the neck flexors and the pharyngeal musculature.

The muscles innervated by cranial nerves are usually not affected and, therefore, ophthalmoplegia and ptosis almost never occur in either polymyositis or dermatomyositis, although some unique exceptions have been reported. (257–260).

Ophthalmologic abnormalities may occur in patients with dermatomyositis. The most common abnormality is a retinopathy that is characterized by diffuse cotton wool spots (soft exudates) and both deep and superficial intraretinal hemorrhages (261–267). Postinflammatory optic atrophy, choroidal infarction, uveitis, secondary glaucoma, scleritis, and episcleritis can also occur (268,269).

From 7–34% of adult patients with dermatomyositis or polymyositis also have an underlying malignancy (255, 270–275). The wide variation in the reported frequency of this association is due, in part, to differences in population biases and methodologies among the many studies that have investigated this issue (276). Although Lakhanpal et al. (273) suggested that the association between malignant tumors and dermatomyositis or polymyositis may be fortuitous and not significantly higher than that which would be expected in the normal population, the bulk of epidemiologic evidence supports a relationship between the inflammatory disorder (especially dermatomyositis) and the underlying cancer (275–279).

The range of tumors that occurs in association with dermatomyositis and polymyositis is extensive. Most are carcinomas, with the most common being carcinomas of the breast, ovary, endometrium, or cervix in women, and carcinoma of the lung, prostate, bladder, or gastrointestinal tract in men (270,271,280). Hodgkin's disease, non-Hodgkin's lymphomas, leukemias, and multiple myeloma also occur with a higher frequency in patients with polymyositis and dermatomyositis than in the normal population (279). Although other types and sites of malignancies have been sporadically reported in patients with dermatomyositis or polymyositis, the number of reports is too small to determine whether or not there is a true association between these other malignancies and the inflammatory myopathies.

In most series, cancer-associated dermatomyositis or polymyositis occurs slightly more often in women than in men, with the highest incidence occurring in adults over 50 years of age (270,271,274,279–281). Although children with malignancies and dermatomyositis or polymyositis have been described, the number of cases is extremely small.

When a malignancy is present in a patient with dermato-

myositis or polymyositis, the tumor is usually identified within the first two years following the diagnosis of the inflammatory myopathy, although longer intervals have been described (280). Nevertheless, some investigators (271,276,279) suggest that if a malignancy is not present or is discovered within a year or two from the time that the diagnosis of dermatomyositis or polymyositis is made, then the patient has the same risk of developing a malignancy as does an otherwise healthy person of the same age and sex.

Some clinical and laboratory features may suggest that a patient with dermatomyositis or polymyositis has an underlying malignancy. Patients with paraneoplastic myositis, for example, tend to be older than patients without an associated malignancy (271,272), although this phenomenon may simply reflect the age-dependent frequency of cancer in the general population. On the other hand, it is clear that patients with dermatomyositis or polymyositis who have evidence of a connective tissue disease or interstitial pulmonary fibrosis are unlikely to have an associated malignancy (278), whereas patients who have a normal concentration of creatine kinase in the serum at the time of diagnosis of dermatomyositis have an increased risk of malignancy (436). Antinuclear antibody seropositivity is more common in patients with dermatomyositis without cancer than in patients with paraneoplastic dermatomyositis (437). Antibodies to Jo-1, an extractable nuclear antigen that is highly specific to polymyositis and dermatomyositis, is not generally found in affected patients who have associated cancers (283).

Since some investigators question whether or not there is a true relationship between malignancy and dermatomyositis or polymyositis (273) and since studies affirming a relationship between cancer and these inflammatory myopathies describe a wide variety of types and sites of associated malignancies, the physician faced with an adult patient who has either dermatomyositis or polymyositis must decide to what extent that patient should undergo an evaluation for an occult neoplasm. Many investigators advocate performing a complete physical examination, including a rectal examination in all patients, pelvic and breast examinations in women, and routine hematologic and serum biochemical studies as the initial approach to such patients and to then obtain further investigations only if indicated by the results of the initial evaluation (273,276). Some investigators also suggest obtaining a chest x-ray in all patients, mammography in women, and an assay for prostate-specific antigen in men; however, most do not recommend additional or exhaustive non-goal-directed investigations for an occult malignancy (277,278,281,282). In patients with dysphagia, it is important to exclude carcinoma of the esophagus or gastroesophageal junction before attributing the symptoms to the myositis (281,282,284). Additional concern that a patient might be harboring an occult malignancy seems prudent if the patient is elderly, does not respond initially to standard treatment, or experiences an unexplained flare-up of disease during treatment.

Polymyositis and dermatomyositis are probably autoimmune diseases (285,436). The rash and selective damage to the heart, lungs, and peripheral joints are also manifestations of other autoimmune disorders, and abundant evidence has accumulated that supports the role of both humoral and cellular immune-mediated mechanisms of muscle injury, although the relative contributions of each differ in dermatomyositis and polymyositis (277,281,282). A variety of myositis-specific autoantibodies, of which anti-Jo-1 is the most common, are found in the serum of about 33% of affected patients. These antibodies target certain cytoplasmic proteins and ribonucleic acids involved in protein synthesis (286). Their pathogenetic role is uncertain, however, since the specific in vivo muscle target antigens and factors that initiate self-sensitization are unknown (277). Other evidence that supports an autoimmune basis for dermatomyositis and polymyositis includes the development of disease in some patients following a viral illness or vaccination, the favorable response of most patients to immunosuppressant therapies, and the production of a similar disease in animals using injections of muscle antigens and adjuvant.

The standard initial therapy for patients with paraneoplastic dermatomyositis and polymyositis is treatment with systemic corticosteroids. This therapy results in resolution of the skin rash and reduction in weakness in most patients, although the ultimate prognosis is related to the success or failure of treating the underlying neoplasm. Other forms of treatment, including cytotoxic agents such as azathioprine or methotrexate (277,282), plasmapheresis (287), total body irradiation (288,289), and intravenous immunoglobulin (290,291) have also been used with variable success.

ACUTE NECROTIZING MYOPATHY

Acute necrotizing myopathy is a rare and, often times, rapidly fatal noninflammatory disorder that occurs in association with various carcinomas (57,292–296). Affected patients experience rapidly progressive proximal weakness associated with painful and tender muscles and, in many cases, difficulty swallowing and breathing. Elevated serum creatine kinase and urine myoglobin concentrations are present. Muscle necrosis without an inflammatory component characterizes the major pathologic findings. The features that differentiate acute necrotizing myopathy from polymyositis include the rapid course, presence of myoglobinuria, lack of response to corticosteroid treatment, and absence of inflammation on muscle biopsy in the former condition. The pathogenesis of acute necrotizing myopathy is unknown. There is no treatment for the progressive necrotic process. Death occurs in most patients within several weeks to months following the onset from complications related to inability to swallow or respiratory failure.

CACHECTIC MYOPATHY

This condition is characterized by severe, diffuse muscle wasting and loss of subcutaneous fat, with relative preservation of strength in the affected muscles. Myoedema may be present, and the muscle stretch reflexes may be depressed. In its extreme form, this disorder is progressive and severely debilitating to the point that respiration is impaired. Neither the extraocular muscles nor the muscles that serve eyelid function are generally affected. The combination of proximal weakness and loss of muscle stretch reflexes can cause diag-

nostic confusion with carcinomatous neuromyopathy, although patients generally appear well nourished in the latter condition.

Cachectic myopathy occurs most often as a paraneoplastic process in patients with a variety of carcinomas and lymphomas. It also occurs in patients with other chronic debilitating diseases, such as tuberculosis.

Histologic studies performed on affected muscles in patients with cachectic myopathy reveal extensive deposition of lipofuscin (297), with two patterns of atrophy of muscle fibers. In the first type, single atrophic fibers or groups of fibers are randomly distributed throughout the affected muscle, with fast twitch fibers being more severely affected. In the second type of atrophy, all fibers served by a specific motor unit are atrophic (3).

The pathogenesis of the muscle wasting in cachectic myopathy is unknown. It does not result from disuse or starvation. Instead, it may result from a combination of high-energy consumption by the tumor and a metabolic derangement of muscle. Interestingly, carcinoma in rats is associated with muscle wasting that is at least partially mediated by elevated intracellular protease activity (298). A similar phenomenon might occur in humans.

There is no specific treatment for paraneoplastic cachectic myopathy. Dietary supplements may slow the process, but they rarely reverse it. The prognosis is poor unless the underlying tumor can be cured.

ENDOCRINE MYOPATHIES

Skeletal muscle is an important endocrine target organ that may be damaged in certain metabolic disorders that occur in association with cancer (299). A steroid myopathy may develop in patients with ACTH-secreting tumors or tumors of the adrenal cortex, and thyrotoxic myopathy can occur in patients with thyroid gland carcinoma or small-cell lung cancer. In both of these conditions, the extraocular muscles may be affected.

A particularly important, although rare, myopathy occurs in patients with carcinoid tumors (300–302). The myopathy is characterized by severe proximal muscle weakness. Administration of cyproheptadine, an antagonist of both serotonin and histamine, improves muscle strength, suggesting that increased levels of serotonin may be responsible for this myopathy (303,304). Neither the eyelids nor the extraocular muscles are affected in carcinoid myopathy.

PARANEOPLASTIC RIGIDITY, THE STIFF-MAN SYNDROME, AND NEUROMYOTONIA

In the setting of a known or suspected neoplasm, a patient may experience progressive rigidity of the trunk and limbs from one of three paraneoplastic disorders: *encephalomyelitis* with predominant spinal cord involvement, an unusual syndrome called the *stiff-man syndrome,* and *neuromyotonia* (305). Progressive rigidity in the setting of encephalomyelitis is discussed above. In this section, we discuss the paraneoplastic stiff-man syndrome and paraneoplastic neuromyotonia.

STIFF-MAN SYNDROME

Stiff-man syndrome is a disorder characterized by progressive symmetric stiffness and spasms affecting the muscles of the trunk, abdomen, and proximal extremities that produces an awkward posture and gait appearance from whence the name of the disorder was derived (306–308). The facial and bulbar muscles are usually spared in this condition. Early symptoms include muscle aching and tightness. Later, intermittent intense painful spasms of affected muscles, lasting minutes at a time, are typically precipitated by various stimuli, such as sudden loud noises or passive stretching of an affected limb. Physical findings include an awkward appearing and cautious gait from lumbar hyperlordosis and fear of painful spasms, and tight hard paravertebral and abdominal muscles. Motor, sensory, cranial nerve, cerebellar, and muscle stretch reflex functions are generally otherwise normal apart from hyperreflexia.

Symptoms are abolished during sleep. Electromyographic findings include continuous motor unit activity when the patient is trying to relax the tested muscle. The presence of continuous motor unit activity, absence of other peripheral or central nervous system physical findings, and partial relief of symptoms using agents that either reduce central catecholamine activity (e.g., clonidine) or enhance central gamma-aminobutyric acid activity (e.g., diazepam or baclofen) all suggest that the stiff-man syndrome results from a brainstem or spinal cord imbalance of these two neurotransmitter systems (308). The frequent association of insulin-dependent diabetes and other organ-specific autoimmune disorders in patients with stiff-man syndrome further suggests that this disorder may have an immune-mediated basis. In fact, many patients with stiff-man syndrome have circulating autoantibodies to gamma-aminobutyric acid neuron terminals, pancreatic beta cells, and other organs using in vitro assay systems (309,310). The antigen these autoantibodies target appears to be a component of glutamic acid decarboxylase, the rate-limiting enzyme in the production of gamma-aminobutyric acid within neurons.

There is an apparent relationship between stiff-man syndrome and cancer, particularly small-cell lung cancer, adenocarcinoma of the breast, and Hodgkin's disease (310–312); however, it is unclear from the available reports whether the progressive rigidity and spasms that these patients have are due to a true stiff-man syndrome, as defined by Lorish et al. (308), or paraneoplastic encephalomyelitis. In fact, the 71-year-old man described by Bateman et al. (35), who experienced progressive asymmetric stiffness and spasms of the extremities 6 months before small-cell lung cancer was discovered, ultimately had postmortem findings of the spinal cord that were typical of paraneoplastic encephalomyelitis.

Considerable clinical and electrophysiologic overlap exists between paraneoplastic subacute myelitis causing rigidity and the stiff-man syndrome, suggesting that the two con-

ditions might share common pathogenetic mechanisms. Common features of both conditions include the presence of progressive hypertonia, stimulus-evoked and spontaneous painful spasms of affected muscles, and electromyographic evidence of continuous involuntary motor unit activity. Some clinical differences between stiff-man syndrome and subacute myelitis can be used to differentiate these two disorders. The rigidity of stiff-man syndrome begins insidiously, progresses slowly over months to years, predominantly involves the lumbar, abdominal, and proximal limb muscles, is distributed symmetrically, and tends to plateau and stabilize after a period of progression. In contrast, the rigidity associated with paraneoplastic myelitis begins more abruptly, progresses faster over a period of days to weeks, generally affects the extremities, is distributed asymmetrically and segmentally, and continues relentlessly. In addition, the neurologic findings in stiff-man syndrome are usually limited to the motor system, whereas the central nervous system injury that occurs with paraneoplastic myelitis frequently affects the cranial nerves, reflex pathways, and sensory tracts.

NEUROMYOTONIA

Acquired neuromyotonia, also called *Isaacs' syndrome*, the *syndrome of continuous muscle fiber activity*, or *pseudomyotonia*, is a disorder of unknown cause that produces continuous muscle activity and delayed relaxation following active contraction (313,314). The continuous motor unit activity is caused by peripheral nerve hyperexcitability and thus persists during sleep, may or may not be eliminated by peripheral nerve block, and is abolished by curare. Neuromyotonia can develop in association with clinical or electrophysiologic evidence of a peripheral neuropathy or as a neurologically isolated syndrome. Affected patients typically experience progressive stiffness and twitching of muscles, cramping and increased stiffness with use of the extremities, and, during ambulation, difficulty relaxing the muscles following use, difficulty ambulating, and excessive perspiration. Abnormal physical findings include continuous myokymia and fasciculations of affected muscles, hypertonia, a stiff awkward-appearing gait with extended extremities, reduced muscle stretch reflexes, and prolonged contraction of muscles following exercise (pseudomyotonia). Weakness and wasting of muscle bulk are generally not present in neuromyotonia. In contrast to the stiff-man syndrome (see above), the distal and proximal limb muscles, the facial muscles, the bulbar muscles, and the extraocular muscles can be affected. Also in contrast to stiff-man syndrome, the motor findings of neuromyotonia persist during sleep. Electrophysiologic abnormalities in this condition include continuous motor unit discharges (e.g., fasciculations and myokymia) and muscle fiber discharges (e.g., high-frequency repetitive discharges), as well as afterdischarges following direct compound muscle action potential or in response to voluntary contraction or percussion.

Intrathoracic malignancies, most notably lung cancers and thymomas, are occasionally found in some adults with acquired neuromyotonia (315–322). Acquired neuromyotonia developed before the discovery of an IgM plasmacytoma in the patient reported by Zifko et al. (323). At autopsy, this patient did not have evidence of peripheral neuropathy, spinal cord abnormality, or immunoglobulin deposition within skeletal muscle.

A syndrome consisting of neuromyotonia, symptoms of cholinergic hyperactivity (e.g., hyperhidrosis and toxic encephalopathy), acetylcholine receptor antibody seropositivity, and benign or malignant thymus tumors has been described. Some affected patients have no evidence of myasthenia gravis (318,320[Case 1]), whereas others have clinical or electrophysiologic abnormalities consistent with dysfunction of the neuromuscular junction (319,320[Case 2],322). It is suggested that paraneoplastic acquired neuromyotonia is caused by an autoimmune-mediated paradoxic facilitation of cholinergic neuromuscular transmission. It is important to determine whether or not a patient with thymoma-associated neuromyotonia has clinical or electrophysiologic evidence of myasthenia gravis since the use of anticholinesterase agents in this setting can cause deterioration of motor function (320[Case 2]).

An autoimmune pathogenesis of paraneoplastic acquired neuromyotonia is further supported by the temporary improvement of symptoms following plasmapheresis, by the identification in some patients of circulating antibodies against voltage-gated potassium channels, and by the observation that mice injected with IgG from some affected patients show enhanced release of acetylcholine at motor endplates and increased resistance of neuromuscular transmission to tubocurarine (314,324,325). This evidence suggests that at least some cases of paraneoplastic acquired neuromyotonia are caused by the production of autoantibodies that interfere with the ion channels that regulate nerve membrane excitability.

Phenytoin and carbamazepine are often effective in reducing the symptoms of neuromyotonia. Plasmapheresis has been used to provide temporary improvement in motor function in particularly severely affected patients. The overall prognosis of paraneoplastic neuromyotonia is related to the prognosis of the underlying malignancy, although some patients experience improvement of symptoms coincident with treatment of their neoplasm (315,318[Case 1],321).

PARANEOPLASTIC SYNDROMES INVOLVING THE EYES AND OPTIC NERVES

Three main paraneoplastic conditions can produce visual symptoms and signs from specific damage to ocular structures. These are the paraneoplastic retinopathies, paraneoplastic optic neuropathy, and paraneoplastic tonic pupils.

PARANEOPLASTIC RETINOPATHIES

Visual loss from retinal degeneration as a remote effect of systemic cancer was first described in 1976 by Sawyer et al. (326) who reported three patients who initially com-

plained of episodic blurring and dimming of vision, photopsias, and nyctalopia, and who subsequently experienced slowly progressive, bilateral visual loss initially characterized by constriction of the visual fields, paracentral scotomas, and eventual loss of central vision. The appearance of the fundi in these patients was initially unremarkable; however, with time, the retinal arteries became markedly narrowed. In one of the patients, an electroretinogram (ERG) was flat. All three patients eventually died from small-cell lung cancer. At autopsy, the eyes of all three patients showed total degeneration of the retinal photoreceptors with preservation of the inner layers of the retina. Sawyer et al. (326) postulated that the degeneration of photoreceptors that occurred in these patients was cause by the distant effects of their neoplasms and emphasized that in two of the three patients, the neoplasm was not known to be present at the time visual symptoms began.

Since this initial report of patients with what is now called *cancer-associated retinopathy* (CAR), numerous additional patients have been described, and numerous scientific investigations have been performed, expanding the clinical spectrum of cancer-associated retinal degenerations and clarifying their pathogenesis. It is now clear that paraneoplastic disorders causing visual loss through retinal dysfunction encompass many distinct conditions that can be differentiated from each other in life by their unique clinical characteristics, electrophysiologic abnormalities and, occasionally, by their immunologic profile (327,328). The term *paraneoplastic retinopathy* is most appropriate to use when referring to these disorders in general. When possible, a more specific diagnostic term should be applied to the visual demise of an individual patient who has retinal dysfunction as a remote effect of cancer (Table 36.3). In the following section, we discuss the various individual paraneoplastic retinopathy syndromes now recognized as distinct entities.

Cancer-Associated Retinopathy

Cancer-associated retinopathy (CAR) is the most frequently encountered primary visual paraneoplastic disorder. Patients with this condition develop symptoms and physical findings referable to both cone and rod dysfunction in the absence of other neurologic symptoms usually harbor small-cell lung cancer and often have circulating autoantibodies against certain retinal proteins (329[Case 1],330–340). Clinical manifestations of cone dysfunction include photosensitivity and prolonged glare following light exposure, loss of visual acuity and color discrimination, and central scotomas. Clinical manifestations of rod dysfunction include night blindness and prolonged adaptation to a dark environment, and peripheral or ring scotomas.

Table 36.3
Classification of the Paraneoplastic Retinopathies

Cancer-associated retinopathy (CAR)
Cancer-associated cone dysfunction
Melanoma-associated retinopathy (MAR)
Diffuse uveal melanocytic proliferation (DUMP)
Uveomeningitic syndromes

Most patients with CAR experience progressive symptoms of cone and rod dysfunction, often preceded by or associated with transient dimming of vision, bright or colorful photopsias, or bizarre entoptic symptoms. One of our patients described seeing flame-like flickers of light in his peripheral field, large white amoeba-shaped objects obstructing his central field of vision, and illusions that he likened to raindrops striking a foggy automobile windshield. Most patients will admit to photosensitivity if specifically questioned. They often note that their vision is better at twilight or if they wear dark sunglasses. Symptoms are often experienced in both eyes at the onset. When the onset is reported as only affecting one eye, similar symptoms occur in the fellow eye within a period of days or weeks.

As with many of the other paraneoplastic syndromes discussed above, symptoms of photoreceptor dysfunction usually begin several months before or around the time of discovery of the underlying malignancy. The majority of patients with CAR have small-cell carcinoma of the lung, although the disorder can occur in patients with other lung neoplasms (332[Case 2],341,342); cancers of the cervix (330), uterus (343), thymus (344,345), and breast (346); and in patients with metastatic carcinoma of unknown origin (347[Case 1]). An exceptional patient described by Matsui et al. (347) developed CAR five years after the discovery of prostate, bladder, and laryngeal cancer. Retinopathy has been described in a 24-year-old patient with Hodgkin's lymphoma who had serum antibodies that reacted with a 65-kd photoreceptor protein (348).

Typical physical findings in patients with CAR include bilateral reduced visual acuity, impaired color discrimination, and a pattern of visual field loss that includes central scotomas, ring scotomas, both, or more extensive peripheral loss with retained islands of vision (Fig. 36.10). The posterior pole often appears normal when a patient is evaluated shortly after he or she has begun to experience visual symptoms. However, within weeks to months, the fundi show a variety of abnormalities, including arteriolar narrowing, retinal pigment epithelial thinning and mottling, and pallor of the optic discs (Fig. 36.11). Other abnormal ocular abnormalities that may develop in patients with CAR are cells in the vitreous and anterior chamber, sheathing of retinal arterioles, periphlebitis, and nonspecific changes in the appearance of the retinal pigment epithelium.

The cone and rod-mediated ERG responses are generally nonrecordable or significantly attenuated by the time an affected patient seeks medical care and is evaluated by a physician who suspects that the presenting symptoms and physical findings are referable to retinal dysfunction. The CSF may show a mild lymphocytic pleocytosis and an increased concentration of protein. These abnormalities, however, are nonspecific.

As one would predict based on the clinical and ERG abnormalities in patients with CAR, pathologic studies reveal degeneration of photoreceptors in all affected patients (326,330,331,338–340). The most conspicuous abnormality is marked loss of cones and rods with virtually complete degeneration and loss of the cells of the outer nuclear layer (cell bodies of the photoreceptors) (Figs. 36.12 and 36.13).

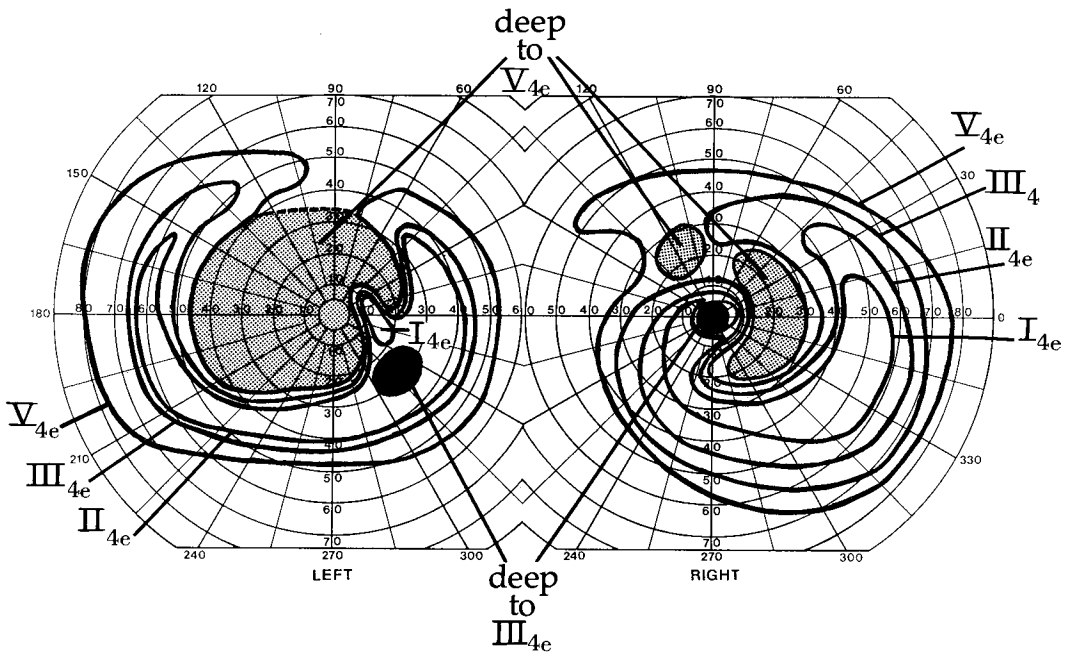

Figure 36.10. Kinetic perimetry in a 65-year-old woman with a several-month history of progressive loss of vision in both eyes, photosensitivity, and improved vision when wearing dark sunglasses. She had abnormal visual acuity and color vision in both eyes, mild narrowing of the retinal vessels, and asymmetric visual field abnormalities that included central scotomas, ring scotomas, and more extensive midperipheral loss. Electroretinography confirmed cone and rod dysfunction. An anterior neck mass that she had discovered around this same period of time was biopsied and found to be an invasive follicular adenocarcinoma of the thyroid. Her serum contained an antibody that reacted against a 68-kd human retinal protein but not against the 23-kd cancer-associated retinopathy (CAR) antigen.

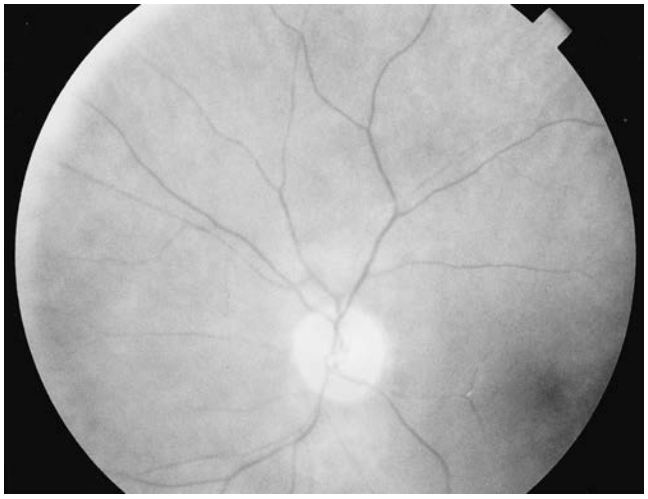

Figure 36.11. Posterior pole of the left eye of a 67-year-old man with cancer-associated retinopathy (CAR) showing narrowing of some retinal arterioles and mild optic disc pallor. He presented with episodic dimming of vision followed by gradual loss of sight, as well as photosensitivity and glare when exposed to bright light. He had loss of visual acuity, color vision, and peripheral field in both eyes. Electroretinography showed markedly attenuated photopic and scotopic amplitudes. Small-cell lung cancer was found during evaluation of his visual symptoms. His serum contained autoantibodies that reacted against the 23-kd CAR antigen and another retinal protein whose molecular weight was 48 kd.

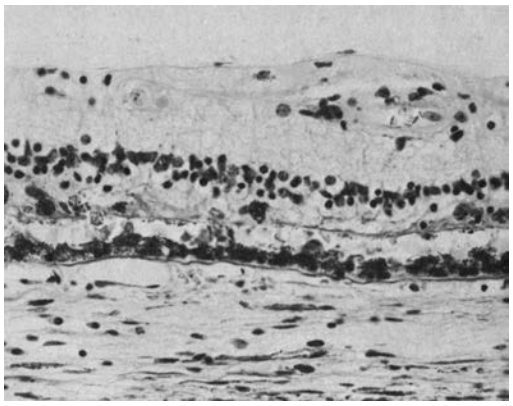

Figure 36.12. Ocular histopathology in paraneoplastic photoreceptor degeneration (cancer-associated retinopathy, CAR). The peripheral retina from a patient with progressive loss of central and side vision that occurred three months before systemic symptoms resulted in the detection of a metastatic small-cell tumor thought to have originated in the lung. There is complete degeneration of photoreceptor cells and their nuclei. Pigmented macrophages are seen in the outer plexiform layer. (From Sawyer RA, Selhorst JB, Zimmerman LE, et al. Blindness caused by photoreceptor degeneration as a remote effect of cancer. Am J Ophthalmol 1976; 81:606–613.)

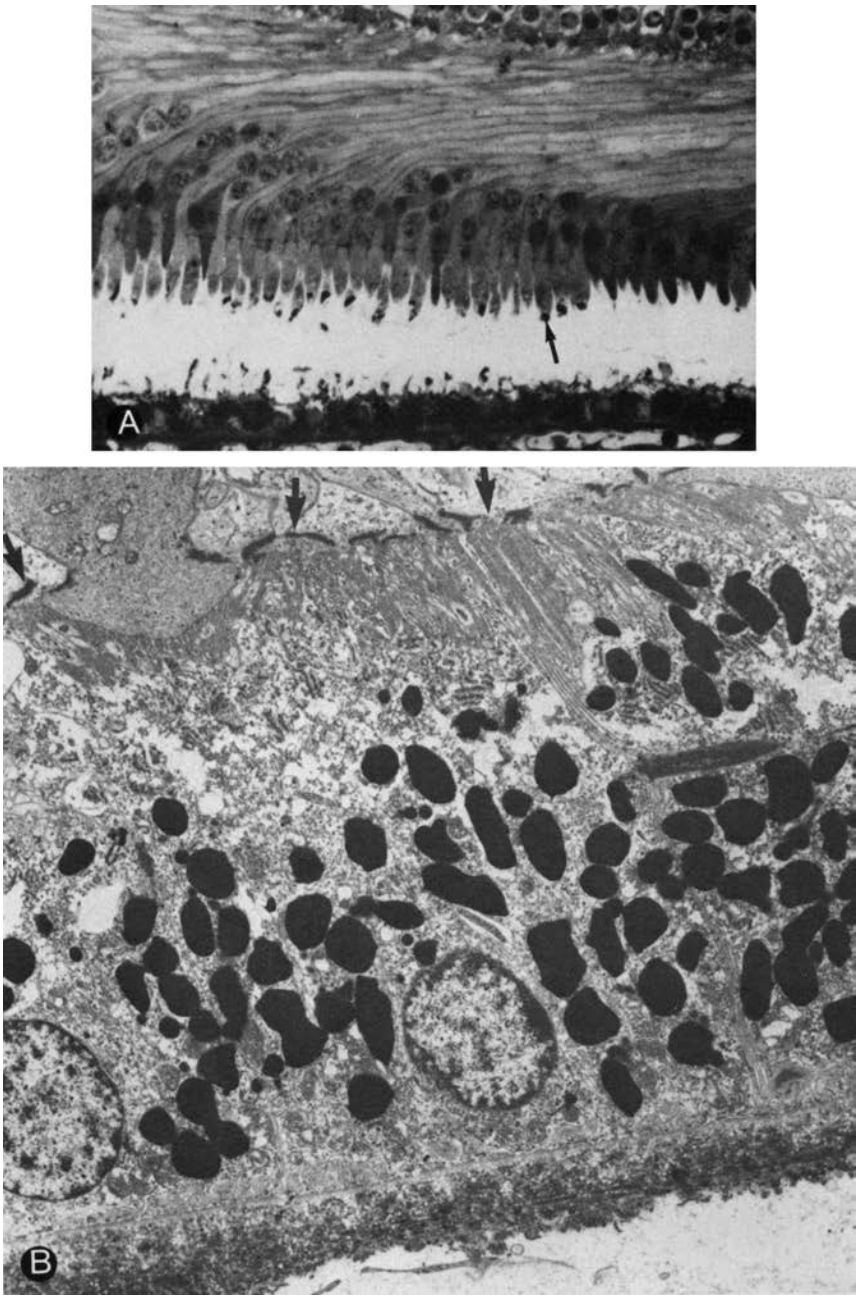

Figure 36.13. Ultrastructural appearance of paraneoplastic photoreceptor degeneration in a 66-year-old man with oat cell carcinoma of the lung. *A,* Light micrograph shows marked photoreceptor cell loss from parafoveal retina. Cone cells (*pale staining*) show remnants of outer segments (*arrow*), whereas rod cells (*dark stain*) show complete loss of outer segments. *B,* Electron micrograph of same region shows complete loss of photoreceptor cells with external limiting membrane (*arrows*) in close apposition to the retinal pigment epithelium. (From Buchanan TAS, Gardiner TA, Archer DB. An ultrastructural study of retinal photoreceptor degeneration associated with bronchial carcinoma. Am J Ophthalmol 1984;97:277–287.)

Any remaining photoreceptors, especially those around the fovea, show severe disintegration of the inner and outer segments. Scattered melanophages are seen in the outer retinal layers. The inner retinal layers, including the ganglion cells, are preserved. Inflammation, vascular changes in the retina and choriocapillaris, and optic nerve degeneration and demyelination are conspicuously absent in this condition.

Like so many of the other paraneoplastic disorders discussed above, CAR appears to be an autoimmune process. Circulating antibodies to human retinal photoreceptors were identified in the serum of the patient reported by Keltner et al. (330). In three additional patients later examined by Thirkill et al. (332), serum reacted in high titers against saline-solubilized extracts of normal human, rat, and bovine retina as well as pooled bovine and human choroid, but there was no reaction using lens or iris extracts as the test antigen. Only low background readings were produced by serum from normal persons and patients with cancer but without loss of vision. Selective immunostaining of the outer retina using serum from patients with CAR adds further support for the autoimmune nature of this disorder (Fig. 36.14) (338). Kornguth and colleagues (329,349,350) found antibodies against retinal ganglion cells in two patients with visual paraneoplastic disorders and small-cell lung cancer, one of whom

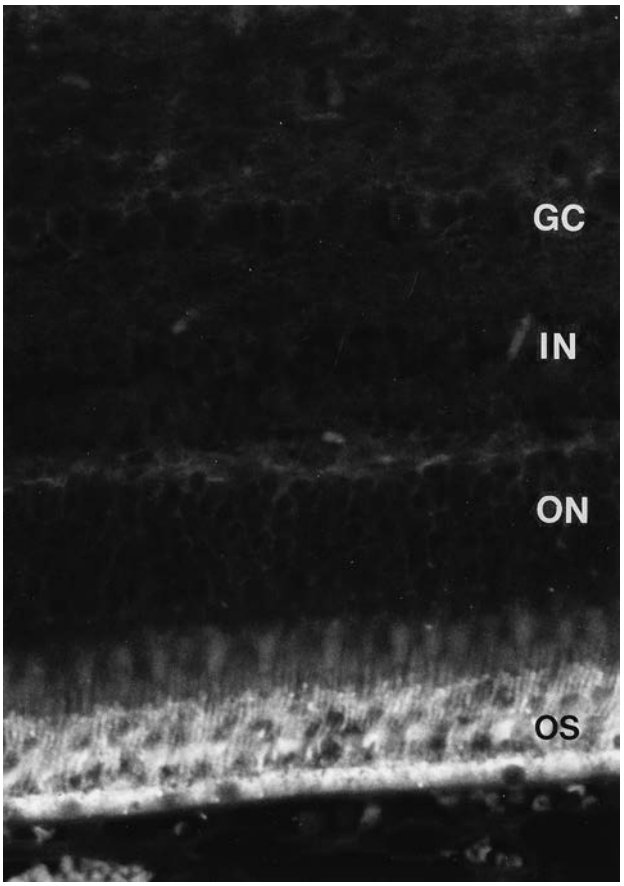

Figure 36.14. Immunoreactivity of the cancer-associated retinopathy (CAR) antibody, using serum from a patient with small-cell lung cancer and rapid loss of vision in both eyes, reacting on rhesus monkey retina. Strong immunofluorescent staining is seen in the outer segments (OS) of the photoreceptors, but not in the outer nuclear layer (ON), inner nuclear layer (IN), or ganglion cell layer (GC). (Courtesy of Charles E Thirkill, Ph.D.)

had clinical and electrophysiologic abnormalities consistent with photoreceptor degeneration and another who had clinical and pathologic evidence of an optic neuropathy (351). In these patients, the antibodies recognized four protein antigens in extracts of both retina and small-cell lung cancer. These antigens have molecular weights of 205,000, 145,000, 65,000, and 20,000–24,000 daltons. These molecular weights are similar to those of the proteins in the neurofilament triplet of neural cells, and it has therefore been hypothesized that the neural antigens are released in response to rapid growth or necrosis of the tumor and that they then trigger the production of antibodies against similar or cross-reacting antigens contained on neuronal cell surfaces (349,350). However, antineurofilament antibodies are found in some normal subjects and in patients without cancer who have other retinal degenerations, such as retinitis pigmentosa and age-related macular degeneration (328). Even if this hypothesis is correct, it does not appear to explain the finding of pure **photoreceptor degeneration** rather than degeneration of ganglion cells in the eyes of patients with this paraneoplastic syndrome.

Using immunoblot analysis, an antibody to the 23-kd protein, the so-called CAR antigen, is found in the serum of most (352), but not all (338), patients with CAR . Antibody has also been recovered from aqueous humor (353). The gene encoding the CAR antigen has been isolated using anti-CAR serum (354), and subsequent nucleotide sequence analysis demonstrates extensive homology of this protein with recoverin, a calcium-dependent retinal protein that modulates photoreceptor guanylyl cyclase activity (438). Other investigators have confirmed that recoverin is the autoantigen against which serum from affected patients reacts (339,355). Thirkill et al. (356) demonstrated that cultured small-cell lung cancer cell lines express an antigen completely homologous with the 23-kd CAR antigen and suggested that cross reactivity between cancer and retina proteins is responsible for initiating the immune-mediated subsequent cascade of events that ultimately leads to photoreceptor degeneration. Polans et al. (357) demonstrated that recoverin was, in fact, expressed by small-cell lung cancer in a patient with CAR who had circulating anti-recoverin antibodies. These studies strongly implicate an autoimmune mechanism initiated by the expression of recoverin in a subset of patients with CAR who have small-cell lung cancer and perhaps other tumors. The immune response against tumor-associated recoverin may also generate an immunologic response against photoreceptor-associated recoverin, which in turn may cause immune-mediated photoreceptor degeneration.

McGinnis et al. (358,359) proposed a hypothesis for CAR as a single mutational event, such as a deletion or translocation, that inactivates a copy of the p53 tumor suppressor gene, which turns on the synthesis of a recoverin protein with the cell line becoming cancerous because of the loss of the tumor's suppressor activity of the p53 protein.

Ohguro and Nakazawa (360) propose that retina specific recoverin is aberrantly expressed in cancerous tissues and recognized by immunocytes leading to production of an antibody against recoverin. The circulating antibody reaches the retina and penetrates photoreceptor cells where it specifically binds and blocks recoverin function, resulting in enhancement of rhodopsin phosphorylation by G-protein-coupled protein kinases, which, in turn, induces caspase dependent apoptosis in photoreceptor cells. Shiraga and Adamus (361) found that anti-recoverin antibody internalized by retinal cells induced apoptosis through the mitochondrial pathway involving caspases 9 and 3. Maeda et al. (362) demonstrated that co-injection of caspase inhibitors with anti-recoverin antibody inhibited rhodopsin phosphorylation.

Some patients with CAR produce antibodies against other proteins (363–365), including enolase (366), although the significance of these other reactions is less clear than that associated with the CAR antigen. Ohguro et al. (367) found antibodies against heat shock cognate protein 70 (hsc 70) in sera from patients with CAR. Hsc 70 belongs to a family of proteins synthesized in response to a variety of cellular stresses and plays an important role as a chaperon, assisting in (*a*) translocation of proteins into organelles, (*b*) correct

folding and rearrangement of proteins, (*c*) dissolution of protein aggregates, and (*d*) protein degradation. The fact that not all antibodies associated with CAR recognize the same antigens suggests that this disorder is not a single entity but rather a group of autoimmune conditions whose pathogenesis results in photoreceptor degeneration. Over 20 antigens have been described in the CAR syndrome. These antigens are found in retinal rods, cones, and ganglion cells, and in the optic nerve.

CAR should be considered in any adult patient who develops progressive visual loss suggestive of retinal dysfunction in the setting of a malignancy, particularly small-cell lung cancer. In addition, patients who begin to develop progressive loss of visual function in a pattern consistent with retinal dysfunction (e.g., preservation of visual acuity with constriction of the visual field or development of paracentral or ring scotomas; development of unexplained photosensitivity or nyctalopia; progressive narrowing of retinal arteries), unexplained loss of cone function (e.g., loss of visual acuity; color vision; central scotomas), or unusual unexplained photopsias or other entoptic symptoms should undergo electroretinography to determine if a diffuse process of retinal photoreceptors is present. If the ERG is abnormal and if there is no family history of retinitis pigmentosa or similar disease, such patients should undergo a complete systemic evaluation with particular attention to the lungs, breasts, and pelvic organs.

There is no effective therapy for this paraneoplastic photoreceptor degeneration. Most patients lose virtually all vision, and this may occur months or even years before they succumb to the effects of their malignancy. Some patients treated with corticosteroids will show modest improvement of visual function, although this improvement is rarely sustained. Plasmapheresis reduced the titers of circulating complement-fixing antiretinal antibodies in a patient reported by Thirkill et al. (335) with CAR and small-cell lung cancer, but it did not produce any visual improvement. Guy and Aptsiauri (368) demonstrated improvement in visual acuity in two of three patients with CAR treated with intravenous immunoglobulin.

Cancer-Associated Cone Dysfunction

In contrast to the marked impairment of both cone and rod function that characterizes the clinical and electrophysiologic presentation of a patient with CAR, some patients experience symptoms and findings that reflect injury only to the cone system. Cogan et al. (369) described a 72-year-old woman who developed sudden photosensitivity and subacute loss of vision. She noted that her vision was better when wearing dark sunglasses. In addition to impaired visual acuity, she also had an absolute loss of color perception, central scotomas, and attenuated retinal vessels. The ERG showed suppression of cone responses. She had no other neurologic symptoms. MR imaging gave normal results, but examination of the CSF revealed a mild lymphocytic pleocytosis. The patient's visual symptoms and findings did not respond to a brief trial of corticosteroids. Evaluation of a bloody vaginal discharge a few months after the onset of her visual symptoms revealed small-cell endometrial cancer. She died 2 months later from widespread intraabdominal spread of the tumor. Postmortem examination of the retina revealed a diffuse loss of cones, most marked in the macula and associated with infiltration of the remaining layers of the retina by pigmented macrophages. Similar cases have been reported (370–372). Circulating antibodies against retinal proteins, including the CAR antigen and a protein whose molecular weight is 50 kd, were demonstrated in the patient reported by Jacobson and Thirkill (372).

Although rare, a visual remote effect of cancer should be considered when evaluating an adult with an unexplained acquired cone dysfunction syndrome, especially in the absence of a positive family history for a similar disorder or in the setting of a known or suspected malignancy.

Melanoma-Associated Retinopathy

A specific retinopathy caused by the remote effect of cutaneous malignant melanoma can be clinically distinguished from the two paraneoplastic retinopathy syndromes discussed above, because the symptoms and findings in this retinopathy reflect dysfunction of rods. Patients with this melanoma-associated retinopathy (MAR) experience sudden shimmering, flickering, or pulsating continuous or intermittent photopsias, difficulty seeing in the dark, and occasionally floaters or photosensitivity (373–384). Symptoms may develop in both eyes at the same time, or they may begin monocularly, only to be followed by similar symptoms in the fellow eye within a period of a few weeks to months.

Unlike the marked impairment of visual acuity, color vision, and central visual field that typifies the cone dysfunction of most patients with CAR, patients with MAR often retain near normal visual acuity, color vision, and central visual field. In some patients, however, loss of visual acuity occurs, and mild abnormalities along the red-green axis, blue-yellow axis, or both can be demonstrated using sensitive measures of color vision (e.g., the Farnsworth-Munsell 100-hue or D-15 panel tests). The visual field may be entirely normal, or it can show a generalized depression, peripheral constriction, or contain midperipheral or paracentral scotomas. Central scotomas, commonly found in patients with CAR, are unusual in patients with MAR. The posterior pole may appear completely normal, although narrowing of retinal vessels, nonspecific changes of the retinal pigment epithelium, and pallor of the optic discs are often noted in patients with symptoms that have been present for several months. Infrequently noted ophthalmologic findings include vitreous inflammation, round and oval-shaped white lesions at the level of the outer retina or retinal pigment epithelium, diffuse retinal pigment epithelium loss of pigment, small atrophic lesions involving the retina, choroid and retinal pigment epithelium, and retinal phlebitis (385–387). Cerebrospinal constituents were normal in both patients evaluated by Weinstein et al. (383). Vitiligo was documented in a patient described by Borkowski et al. (387). Unilateral MAR has also been reported (388).

Many other differences between CAR and MAR exist.

Men are more frequently affected in MAR compared with the more evenly distributed gender involvement in CAR. In contrast to the relentless loss of visual function that occurs in patients with CAR, patients with MAR often do not develop significant progression of retinal dysfunction despite persistence of night blindness and photopsias, although exceptions occur (383,385,386). In contrast to patients with CAR whose symptoms often occur before the underlying neoplasm is recognized, most patients with MAR already have an established diagnosis of cutaneous malignant melanoma for a few months to as long as several years at the time they develop night blindness and photopsias. Metastatic disease is often discovered within several months before or after the onset of visual symptoms, although this association may simply reflect the unpredictable nature of disseminated melanoma or the fact that once a patient is diagnosed as having MAR, he or she may undergo a more intensive search for metastatic disease than might be performed as part of a routine oncologic follow-up.

Kelter et al. (389) reviewed the clinical and immunological findings of 62 patients with MAR. Age at onset of visual symptoms ranged from 30–78 years (average 57.5 years). Visual acuity of 20/60 or better was initially present in 82% of patients in their review. Fundus examination was normal in 44%, optic disc pallor was present in 23%, and retinal vessel attenuation was present in 30%. Vitreous cells were present in 30%. The latency from diagnosis of melanoma to recognition of MAR syndrome averaged 3.6 years.

Jacobsen and Adamus (390) reported a 51-year-old woman with progressive visual glare for 1 year who had normal visual acuity and color vision, paracentral scotomas, and a normal-appearing retina. ERG revealed no responses of the right eye and attenuated responses in the left eye, especially under scotopic conditions. Anti-bipolar antibodies were detected. Subsequent evaluation revealed colon adenocarcinoma. After tumor resection and chemotherapy, no evidence of anti-bipolar antibodies was found and ERG responses were markedly improved.

The ERG in MAR reveals a characteristic set of abnormalities that includes a markedly reduced or absent dark-adapted B-wave with preservation of the A-wave, resulting in a response dominated by a negative-appearing waveform (376,377,379,380,382). The light-adapted B-wave response may be normal or show a reduced amplitude or delayed implicit time but usually not to the same abnormal degree as that response obtained under scotopic conditions. Defects in the function of cone ''ON''-center bipolar cells and blue-sensitive cones occur in some patients (377,380,385,439), and there is even some evidence that the damage is restricted to those cells that are part of the magnocellular pathway (391,392). Finally, oscillatory potential amplitudes are reduced. This pattern of ERG abnormalities is similar to that observed in some forms of congenital stationary night blindness and is consistent with failure of neural transmission from rods, and some cones, to the inner retina.

Patients with MAR have circulating IgG autoantibodies that show specific immunofluorescent staining of some, but not all, human rod bipolar cells (Fig. 36.15) (380,383,389, 393,394). Although it has not been proven that these antibodies directly cause retinal dysfunction, the immunologic and electrophysiologic abnormalities in patients with MAR suggest that the disease is caused by the production of antibodies against melanoma that cross-react with retinal bipolar cells, a process that somehow interferes with neural retina transmission from the photoreceptors through the inner retina. The antigen against which these antibodies react is unknown, although some evidence suggests that the bipolar cell antigen is a lipid, not a protein (328). Gittinger and Smith (395) performed histopathologic studies on both eyes of a 59-year-old man who had visual loss due to MAR and who died of metastatic cutaneous melanoma. They reported a marked reduction in the density of bipolar neurons in the inner nuclear layer, transsynaptic atrophy of ganglion cells, and normal outer nuclear layer photoreceptor cells (Fig. 36.16).

No specific therapy for MAR exists. Corticosteroids do not appear to improve symptoms or reverse the ERG abnormalities. Similarly, treatment of the primary tumor or of metastatic disease does not alter the progression of visual symptoms. The overall prognosis is related to the behavior of the malignancy. Keltner et al. (389) reported that seven patients had improvement of vision with treatment, especially with intravenous immunoglobulin and cytoreductive surgery.

A visual remote effect of cancer should be considered in any patient with a cutaneous malignant melanoma who develops sudden or subacute night blindness, unexplained photopsias, or peripheral visual field loss. An ERG will indicate if such symptoms are caused by rod dysfunction, the characteristic abnormality associated with MAR. Although similar abnormalities can also be observed in patients with congenital stationary night blindness, juvenile retinoschisis, vincristine toxicity, and central retinal artery or vein occlusion, these disorders should be distinguished by a complete personal and family history and ophthalmologic examination. Conversely, a careful dermatologic examination is indicated in a patient with clinical and electroretinographic abnormalities suspicious for MAR but who does not have an established diagnosis of cutaneous malignant melanoma. If no malignancy is identified, and no alternative explanation for the symptoms exists, then periodic surveillance is warranted. A patient with established melanoma who develops MAR should be evaluated frequently for evidence of disseminated disease.

Diffuse Uveal Melanocytic Proliferation

Diffuse uveal melanocytic proliferation (DUMP) differs from the paraneoplastic retinopathies described above because cellular *infiltration,* not degeneration, is responsible for the symptoms and findings that characterize this syndrome. Bilateral proliferation and infiltration throughout the uveal tract by benign melanocytes occurs in this unusual visual remote effect of cancer. Initial reports suggested that this condition was the result of either infiltration of the choroid by malignant ocular melanoma or choroidal metastases from cutaneous malignant melanoma (396–400), but subse-

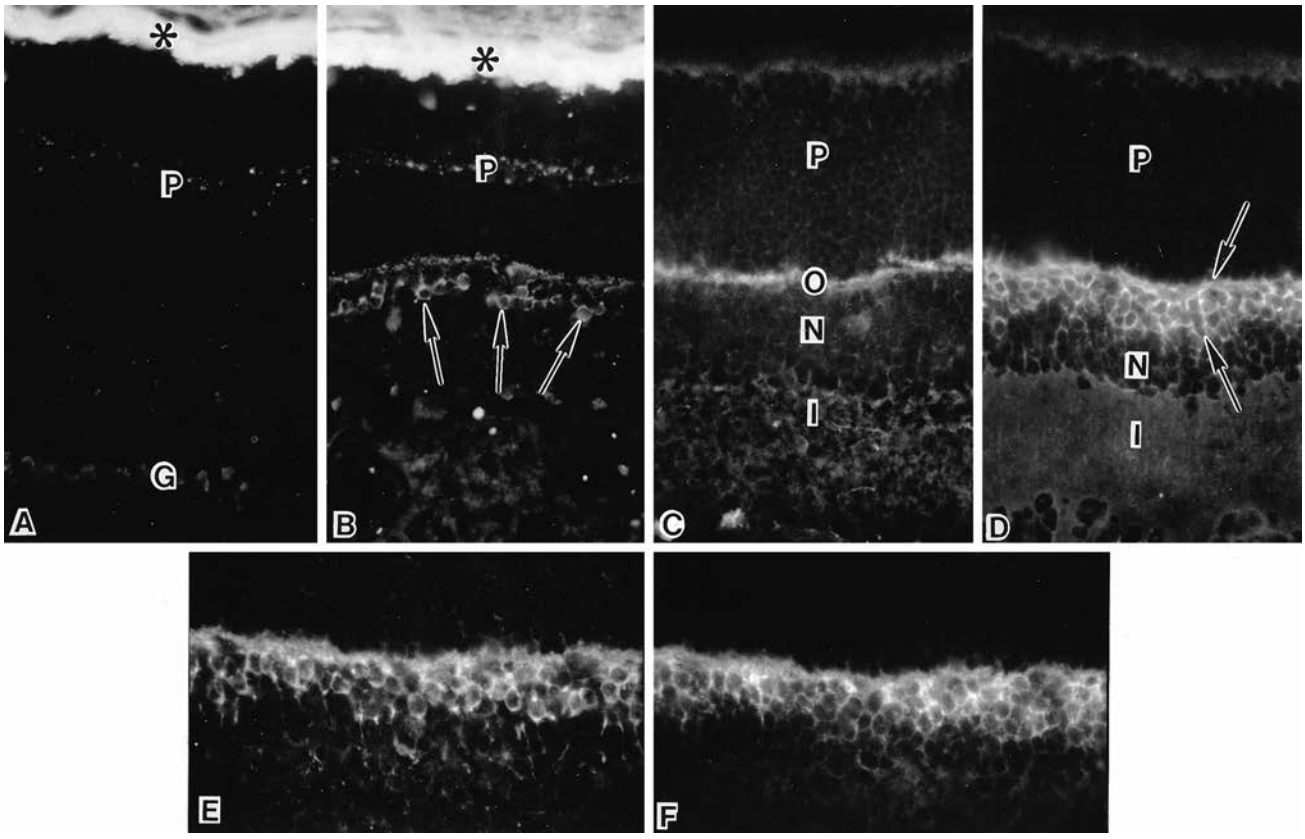

Figure 36.15. Immunohistochemical reactions in the melanoma-associated retinopathy (MAR) syndrome, using cryosections of unfixed retinas processed for immunofluorescence with secondary antihuman immunoglobulin (IgG) labeled with fluorescein isothiocyanate (FITC). *A* and *B,* Sections of normal human retina. Asterisks, autofluorescent lipofuscin granules in the retinal pigment epithelium; P, photoreceptors containing scattered lipofuscin granules, ×300. *A,* A section processed with serum from a normal subject, showing absence of specific immunolabeling; G, indicates weakly autofluorescent ganglion cells. *B*, A section processed with serum from a patient with MAR, demonstrating specific labeling of a population of bipolar cells (*arrows*). *C–F,* Sections of normal rat retina processed for immunofluorescence using secondary antihuman IgG labeled with FITC. P indicates photoreceptor layer, N indicates inner nuclear layer, and I indicates inner plexiform layer. *C*, A section processed with serum from a normal subject, showing absence of specific labeling. The bright line in the outer plexiform layer (O) was found in sections of rat retina treated with FITC-labeled secondary antibody alone, ×300. *D,* A section processed with serum from a patient with MAR showing specific labeling of a population of bipolar cells (*between arrows*). The remainder of cells in the inner portion of the inner nuclear layer (N) are unlabeled, ×300. *E* and *F,* Double labeling of a single section of rat retina processed using serum from a patient with MAR followed by FITC-labeled anti-human IgG and photographed with a FITC-filter (*E*), and processed using an antibody prepared in mouse against protein kinase C (a marker for rod bipolar cells) followed by rhodamine-labeled anti-mouse IgG and photographed with a rhodamine-filter (×450) *F*. The same population of bipolar cells is labeled with both markers. (Courtesy of Ann H Milam, Ph.D.)

quent histopathologic observations indicate that the infiltrate is composed of more benign-appearing melanocytes (401–403).

DUMP occurs equally often in women and men and is associated with a number of seemingly unrelated carcinomas, especially ovarian cancer in women (398,401, 404–406) and a variety of lung malignancies in men (399, 401,403,407–409). Other patients with DUMP may have cancer of the cervix (405), uterus (400), colon and rectum (401,410), gallbladder (402), and retroperitoneal space (396). In some cases, there may be evidence of metastases from a primary tumor whose location cannot be determined (397,401,411). Visual loss precedes identification of the underlying malignancy in about one-half to two-thirds of cases by a few months to a few years. In those patients with established cancer, symptoms referable to DUMP occur from 1 month to as long as 6 years after the malignancy is diagnosed, although they most often develop within the first year.

Patients with DUMP experience slow, painless, progressive, bilateral (but often asymmetric) loss of vision over several months. The visual loss is primarily caused by outer retinal damage from subretinal infiltration and exudative retinal detachment caused by the melanocytic proliferation, but it can also result from the secondary development of cataracts, iridocyclitis, and glaucoma. Gass et al. (405) summarized five major signs that characterize this disorder:

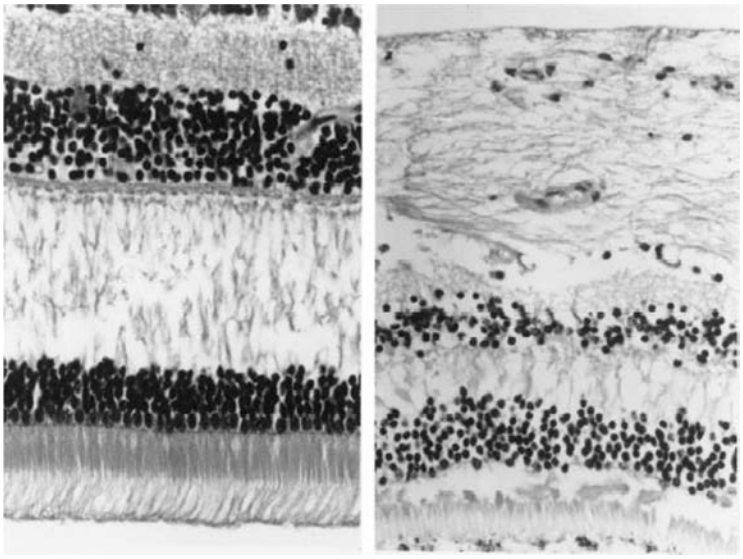

Figure 36.16. Photomicrographs of normal retina from near the fovea (*left*) and of a corresponding area of the retina with cutaneous melanoma-associated paraneoplastic retinopathy (*right*). The photoreceptors are preserved in the eye with melanoma-associated paraneoplastic retinopathy, but the bipolar and ganglion cell layers are reduced (hematoxylin and eosin, ×40). (From Gittinger JW, Smith TW. Cutaneous melanoma-associated paraneoplastic retinopathy: Histopathological observations. Am J Ophthalmol 1999;127:612–614.)

1. Multiple round or oval red spots or patches at the level of the retinal pigment epithelium scattered throughout the posterior pole (an early finding).
2. Multifocal hyperfluorescence during fluorescein angiography corresponding to these lesions (Fig. 36.17).
3. Multiple slightly elevated pigmented and nonpigmented uveal melanocytic tumors and diffuse thickening of the uveal tract (an early or late finding).
4. Exudative retinal detachment (a late finding).
5. Rapidly progressive cataract formation.

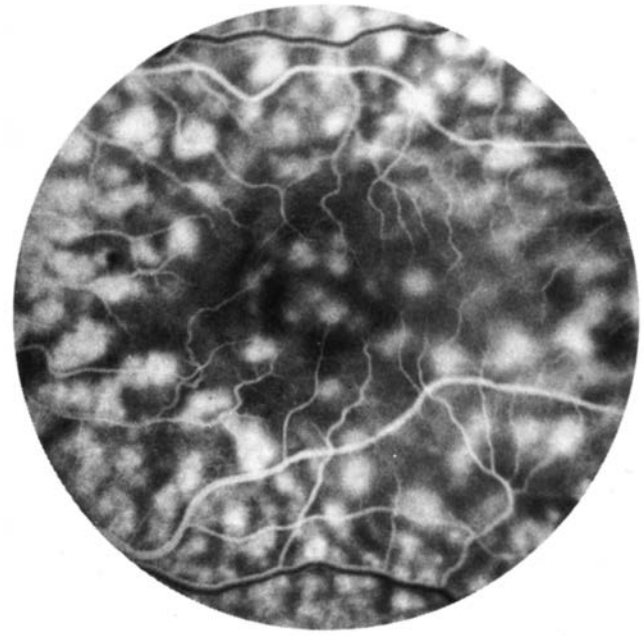

Figure 36.17. The DUMP syndrome. Fluorescein angiography from a 66-year-old woman with carcinoma of the uterus who experienced loss of vision in both eyes during a 2-month period of time, showing multiple early hyperfuorescent lesions in the posterior pole of her left eye that corresponded with orange spots seen ophthalmoscopically. (From Gass JDM. Stereoscopic Atlas of Macular Diseases. Diagnosis and Treatment. Ed 3, Vol 1. St. Louis, CV Mosby, 1987:189.)

Systemic findings, apart from those associated with the underlying malignancy, generally do not occur, although some patients develop hyperpigmented lesions of the oral mucosa, penis, and skin (409,410).

Chahud et al. (412) reviewed 20 cases of DUMP. The average patient age was 63 years (range 34–89 years). There were 13 women and 7 men. In approximately 50% of the cases, visual symptoms preceded those of the associated tumor, which frequently was a poorly differentiated carcinoma. The most common types of tumors were ovarian carcinomas and uterine tumors in females and pulmonary tumors in men. All five inciting tumors whose histopathology was reviewed expressed neuron-specific enolase.

Orbital echography in patients with DUMP may reveal evidence of acquired hyperopia, diffuse choroidal thickening, or discrete subretinal masses. Electroretinography shows nonspecific reduction of amplitudes, often affecting the scotopic responses more than the photopic responses, at least in early cases.

The differential diagnosis of DUMP includes inflammatory and neoplastic disorders that infiltrate the choroid and uveal tract, including the uveal effusion syndrome, benign reactive lymphocytic hyperplasia, lymphoma, leukemia, metastatic carcinomas, multifocal choroiditis, acute posterior multifocal placoid pigment epitheliopathy, sympathetic uveitis, sarcoidosis, posterior scleritis, Harada's disease, and rhegmatogenous retinal detachment. The multifocal pigmentary changes of the outer retina observed in patients with DUMP may also be confused with metastatic melanoma, subretinal hematomas, choroidal nevi, and hypertrophy of the retinal pigment epithelium (405).

The pathologic spectrum of DUMP varies considerably

from case to case. Macroscopically, the entire uveal tract, including the iris, ciliary body, and choroid, appear diffusely thickened. Retinal detachment is commonly seen. The infiltrating cells are usually small and spindle-shaped, but they are occasionally more rounded or epithelioid, and they have homogeneous dark-staining, benign-looking nuclei (399,401–403,405,406,411). These cells stain positive with S-100, indicating their epithelial origin, and they contain pigment granules of various density. Mitotic figures are rare. More malignant-appearing epithelioid cells suggesting malignant melanocytic transformation are rarely observed (404,409). Areas of necrosis are often present, usually associated with melanophages. The retinal pigment epithelium and photoreceptors show degeneration. The choriocapillaris is not affected in this condition.

The pathogenesis of DUMP is unknown. Some investigators speculate that the presence of a systemic neoplasm leads to uveal melanocytic infiltration or transformation through elaboration of tumor-associated trophic hormones or by some other oncogenic stimulation factor that initiated the growth of the underlying malignancy (401,403,413). Such a mechanism, however, cannot account for the melanocytic proliferation that occurs in some ocular structures normally devoid of melanocytes (e.g., the posterior corneal surface). Gass et al. (405) hypothesized that patients with DUMP have bilateral diffuse congenital uveal melanocytic nevi that are clinically silent until their cancer develops and causes proliferation and melanin production through some hormonal influence. This hypothesis does not explain how or why cataract formation, retinal detachment, and photoreceptor degeneration occur in this syndrome. These extra-melanocytic manifestations might be caused by local toxic or immune-mediated reactions that develop in response to the uveal proliferation (411).

No effective treatment exists to halt the progressive bilateral loss of vision that occurs in patients with DUMP. Neither treatment of the underlying malignancy nor the use of corticosteroids improves vision. The overall prognosis is related to the systemic malignancy. There is one case of a patient with DUMP retaining useful vision in one eye four years after undergoing ocular irradiation and drainage of subretinal fluid (414).

Uveomeningitic Syndromes

Rudge (415) described a 49-year-old woman who lost vision in both eyes and was found to have bilateral macular edema associated with mild anterior uveitis. She was treated with systemic and topical corticosteroids, but over the next 7 days her vision continued to worsen, as she developed bilateral optic disc swelling associated with large central scotomas. Lumbar puncture revealed a normal opening pressure. The CSF contained 200 lymphocytes/mm^3, a mildly increased concentration of protein, and no malignant cells. A palpable breast mass discovered at this time was removed one month later and found to be a primary carcinoma. After surgery, the patient experienced a dramatic improvement in visual acuity from 20/80 to 20/20 in both eyes within 1 month. Within 5 months both the swelling of the optic discs and the edema of the macula had subsided in each eye. A repeat examination of the CSF 8 months after the onset of symptoms was normal.

Gass (416) reported a 71-year-old woman who experienced severe visual loss associated with floaters and nyctalopia, as well as headaches, cutaneous vitiligo, and abnormal hearing during a 2-week period. A cutaneous melanoma had been removed from the sole of her foot 3 years earlier. Abnormal findings in both eyes included visual acuity of light perception, unreactive pupils, cells within the anterior chamber and vitreous, keratic precipitates, multiple patches of yellow-white retinal depigmentation, narrowed retinal arterioles, and optic disc swelling. She also had cutaneous vitiligo and poliosis of her head and limbs, inguinal adenopathy, hearing loss, and mild confusion. An ERG was extinguished in both eyes. The CSF contained 130 lymphocytes/mm^3 and had an increased protein concentration. Biopsy of an inguinal node showed metastatic melanoma. She was thought to have suffered an acute autoimmune reaction against the melanocytes of the uveal tract, meninges, skin, and ear. Her visual acuity improved after she received 80 mg prednisone daily for several days. A few weeks later, visual acuity was 20/70 in both eyes. When the prednisone was discontinued 1 month later, the vision deteriorated within several weeks to counting fingers in each eye. Prednisone was restarted, and the visual acuity promptly recovered again. The patient maintained good vision while receiving prednisone for the next 15 months until she died from metastatic melanoma. Although this patient had melanoma and evidence of retinal dysfunction, several of her clinical features differed from those observed in patients with typical MAR, including the associated systemic abnormalities, meningeal reaction, visual response to corticosteroids, optic disc swelling, and depigmentation of the retinal pigment epithelium. The abnormal ERG responses, however, suggest that the visual loss of this patient was caused, in part, by damage to the outer retinal neural elements.

Antoine et al. (417) described a 61-year-old woman who developed visual loss in both eyes and was found to have bilateral posterior uveitis and a severe vitreous reaction. Breast carcinoma had been diagnosed and treated 6 years earlier, and the patient was in complete remission at the time of her visual presentation. The vision in her right eye responded to topically applied corticosteroid treatment but deteriorated every time the dose was tapered. Fluorescein angiography performed 14 months after the onset of her visual loss revealed staining of retinal blood vessel walls and of the optic discs on both sides. One month later, she developed further loss of vision in her right eye, dysarthria, nystagmus, ataxia, abolished muscle stretch reflexes, and orthostatic hypotension with evidence of dysautonomia. Electrophysiologic studies confirmed a peripheral neuropathy. Cerebrospinal fluid contained 40 white cells/mm^3 and no malignant cells. Metastatic carcinoma was discovered about 1 year later. She died from complications associated with DIC. At autopsy, her cerebellum showed severe loss of Purkinje cells. A few perivascular lymphocytic cuffs were observed in the cerebral white matter, spinal cord, and sensory ganglia. The optic nerves were normal. Permission to examine the retina

was not granted. It would seem that this patient developed posterior uveitis and a vitreous reaction several months before she developed paraneoplastic encephalomyelitis and a sensory neuropathy. In view of this report and the others described above, it seems reasonable to consider the possibility of an underlying malignancy in any patient who develops an uveomeningitic syndrome.

PARANEOPLASTIC OPTIC NEUROPATHY

Paraneoplastic optic neuropathy results in a subacute, progressive, bilateral loss of vision, usually without accompanying pain. The optic disc is edematous or normal in appearance. The optic chiasm can also be involved. Associated findings include cranial nerve palsies, polyneuropathy, vertical or down-beating nystagmus, and cerebellar signs. Direct compression or infiltration of the optic nerves and ischemic optic neuropathy must be ruled out. Paraneoplastic optic neuropathy is very rare. As of 2002, only 18 cases of paraneoplastic optic neuropathy had been reported. Neuropathologic findings reveal nonspecific vascular infiltration of the optic nerve by lymphocytes as well as axonal loss or demyelination of the optic nerve (Fig. 36.18).

Paraneoplastic optic neuropathy can also be associated with a subacute cerebellar syndrome (418). Most of these patients have a serum antibody specific for a recently defined 62-kd neuronal antigen named *collapsing response-mediator protein-5* (CRMP-5). CRMP-5 is expressed in adult central and peripheral neurons, including synapses. The CRMP family of proteins is thought to mediate growth guidance cues during neurogenesis. The CRMP-5 antibody was found to be present in serum as frequently as anti-Yo and less frequently than anti-Hu. In all, 116 patients whose sera contained CRMP-5 antibodies were found to have chorea (11%), cranial neuropathy (17%, including 10% loss of olfaction or taste and 7% optic neuropathy), peripheral neuropathy (47%), autonomic neuropathy (31%), cerebellar ataxia (26%), subacute dementia (25%), and neuromuscular junction disorders (12%). Spinal fluid was inflammatory in 86%, and CRMP-5 antibodies in 37% equaled or exceeded serum titers. Lung carcinoma (mostly small-cell) was found in 77% of patients, and thymoma was found in 6%. Basal ganglia abnormalities were evident by MRI imaging and at autopsy in a subset of patients with chorea and CRMP-5 antibodies (419).

Cross et al. (420) described the characteristics of 16 patients with CRMP-5-associated combined optic neuritis and retinitis in greater detail. All were smokers. Their ages ranged from 52 to 74 years at presentation; 11 had small-cell lung carcinoma; vision loss was subacute and painless in 15 patients and was bilateral within weeks or months. Some patients reported blurred or dimmed vision; others reported spots or flashes, dazzling vision, or tunnel vision. Visual acuities ranged from 20/20 to 20/400. Visual field abnormalities included enlarged blind spots, arcuate and altitudinal defects, paracentral scotomas, peripheral constriction

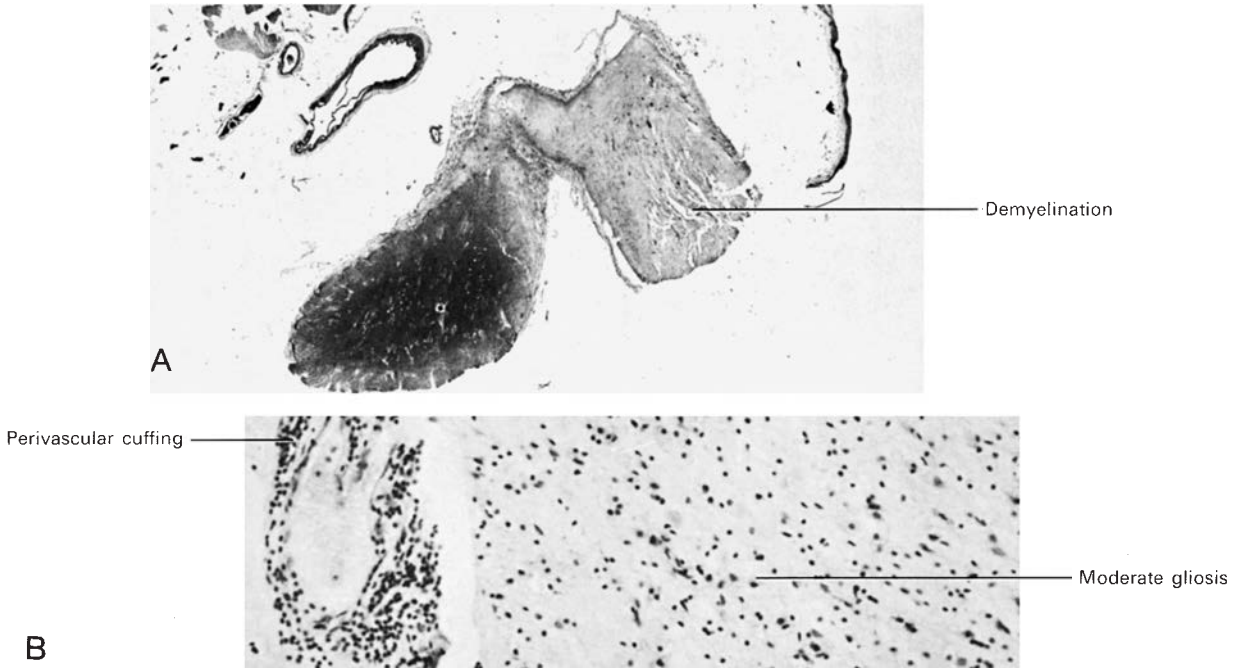

Figure 36.18. Paraneoplastic optic neuropathy in a 61-year-old woman with carcinoma of the breast who rapidly lost vision in the right eye and was thought to have central nervous system metastasis. *A,* The right optic nerve is totally demyelinated. The demyelination extends into the optic chiasm and affects the portion of the left optic nerve as it enters the chiasm. *B,* There is severe perivascular infiltration by lymphocytes, similar to that seen in multiple sclerosis. Moderate gliosis is present, indicating that the lesion is old. (From Lindenberg R, Walsh FB, Sacks JG. Neuropathology of Vision: An Atlas. Philadelphia: Lea & Febiger, 1973:253.)

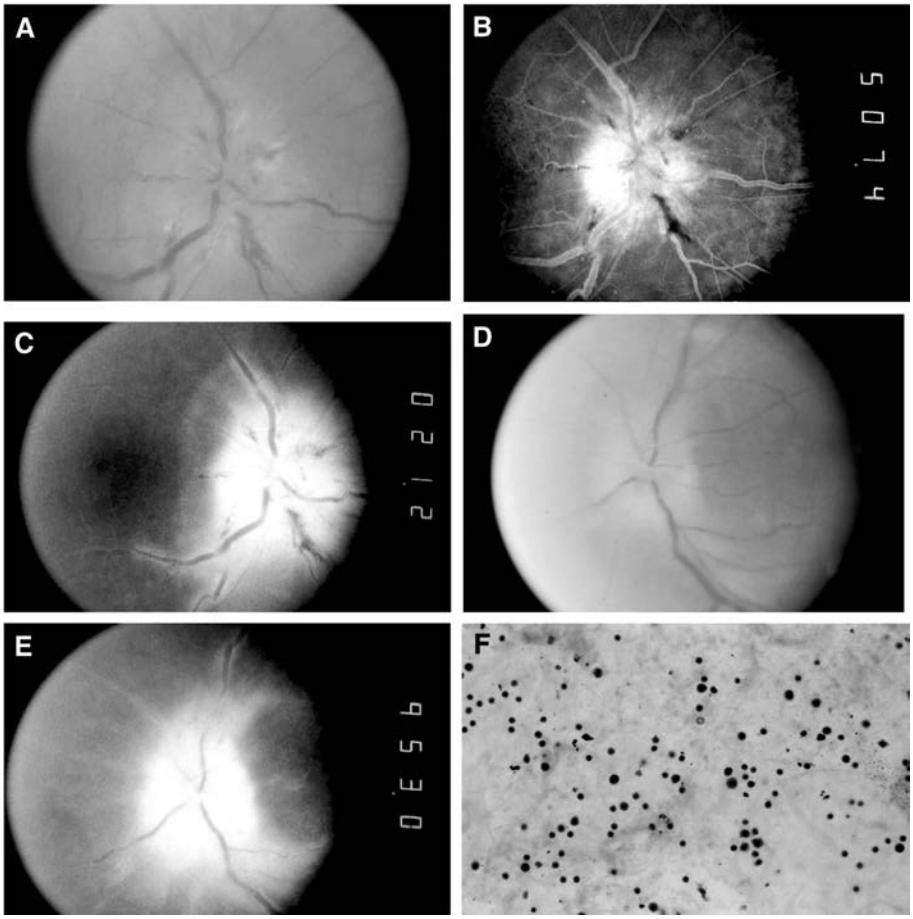

Figure 36.19. Optic disc photographs, fluorescein images, and vitreous biopsy. *A,* Right eye shows severe acute optic disc swelling with tortuous vessels, cotton wool spots, and nerve fiber layer hemorrhages. *B* and *C,* Late arterial fluorescein image shows dye leakage on disc surface (*B*), and late phase shows dye persistence at the disc and perivenous fluorescence, indicating vascular incompetence (*C*). *D* and *E,* Left eye shows chronic disc swelling, optic atrophy with dye leakage (*D*), and vascular incompetence remote from the disc (*E*). *F,* Pleomorphic cellularity consistent with reactive lymphocytosis in right eye vitreous (hematoxylin and eosin, ×400). (From Cross SA, Salomao DR, Parisi JE, et al. Paraneoplastic autoimmune optic neuritis with retinitis defined by CRMP-5-IgG. Ann Neurol 2003;54:38–50.)

and generalized depression. Chronic or subacute optic disc swelling was noted in all but one patient. Nerve fiber layer hemorrhages were common. Fluorescein angiography revealed hyperfluorescence of the optic disc and leakage (Fig. 36.19). Full-field ERG abnormalities included prolongation of the scotopic combined rod-cone (maximal) response, the photopic-cone response, and the photopic 30-Hz flicker response. The presence of cells in the posterior vitreous was noted in 9 of the 16 patients. No patients had pars planitis. These vitreous cells were found to be $CD4^+$ reactive lymphocytes. All patients had other neurological signs or symptoms at some point in their illness. These included mental status changes, cranial neuropathy, motor and sensory problems, and autonomic abnormalities. Cerebrospinal fluid contained lymphocytes, elevated protein, multiple oligoclonal immunoglobulin bands, and CRMP-5 antibody. No patients had recoverin antibodies.

Acute or subacute vision loss with optic disc swelling and vitreous cells can occur in other types of disease states in addition to paraneoplastic optic neuropathy. These include vasculitis, infectious or postinfectious inflammatory disorder such as bacterial or viral infections, infiltrative etiologies such as sarcoid and lymphoma, and demyelinating disease such as multiple sclerosis or Devic's disease. A diverse group of patients without malignancy who produce antibodies that are reactive with optic nerve and/or retina have also been described. This syndrome has been called autoimmune-related retinopathy and optic neuropathy syndrome by Keltner (421). Many of these patients also have one or more systemic autoimmune diseases. These patients may be more responsive to treatment with steroids or other immunomodulators.

Adult patients with unexplained subacute painless vision loss, optic disc swelling, and cells in the posterior vitreous (with or without subacute cerebellar ataxia) should have a complete neurological examination and evaluation of the serum and cerebrospinal fluid for CRMP-5 antibodies and other antibody markers of paraneoplastic disease (420). If CRMP-5 antibody is found, a work-up for lung cancer should be initiated.

Treatment of the specific cancer in patients with paraneoplastic optic neuropathy with chemotherapy and/or radiation therapy resulted in significant visual improvement (422–424). Some improvement in vision has also been demonstrated with steroids (65,425,426).

TONIC PUPILS

Tonic pupils develop as a remote effect of cancer in the following three settings: (*a*) in patients with autonomic neu-

ropathy, with or without other clinical or electrophysiologic evidence of sensory neuropathy (8); (*b*) in patients with the Eaton-Lambert syndrome as a component of the dysautonomia that frequently accompanies that disorder (212,226,227) (see above); and (*c*) in one reported case of a child with neuroblastoma and paraneoplastic opsoclonus-ocular flutter and myoclonus (136,427).

Most cases of paraneoplastic tonic pupils are bilateral and are found during evaluation of a peripheral neuropathy that has preceded the diagnosis of an underlying malignancy. Baumann (173) described a patient with a severe sensory neuropathy who had bilaterally dilated, unreactive pupils. Small-cell lung cancer was detected 7 months later. At autopsy, there was severe degeneration of dorsal root ganglion cells and posterior columns. The ciliary ganglia were not studied. Similar cases were subsequently reported (164, 167,178,428,429).

Maitland et al. (174) described two patients with tonic pupils in the setting of malignancy. The first patient developed bilateral tonic pupils (Fig. 36.20), first in his left eye and later in the right eye over a 6-month period, associated with evidence of a subacute progressive sensory neuropathy. Eight months after his visual and sensory symptoms began, he was found to have an adenocarcinoma of the colon. The second patient also had bilateral tonic pupils in the setting of orthostatic hypotension and other evidence of autonomic dysfunction. She was eventually found to harbor small-cell lung cancer. A tonic pupil was also present in a patient with stage IIA Hodgkin's disease who developed severe orthostatic hypotension, dry mouth, constipation, and urinary retention (168). During treatment of the Hodgkin's disease, the patient's orthostatic hypotension improved slightly, bowel and bladder function became normal, and her mouth began to feel less dry. The tonic pupil remained.

Bell (175) described a 51-year-old man who developed a unilateral tonic pupil during an exacerbation of chronic relapsing polyneuropathy. The subsequent finding of metastasis from a prostate carcinoma suggested that both the polyneuropathy and the tonic pupil were paraneoplastic processes. The patient died from bronchopneumonia. At autopsy, no tumor was found in the central or peripheral nervous system. There was, however, a severe primary peripheral polyneuropathy characterized by marked axonal and myelin loss affecting the sural, radial, and tibial nerves. This process was associated with marked, secondary ascending degeneration of neurons within the dorsal ganglia, tracts of the dorsal columns, and cell bodies of the nucleus cuneatus and nucleus gracilis in the medulla. There was also secondary chromatolysis and loss of anterior horn cells.

In some cases of paraneoplastic autonomic neuropathy,

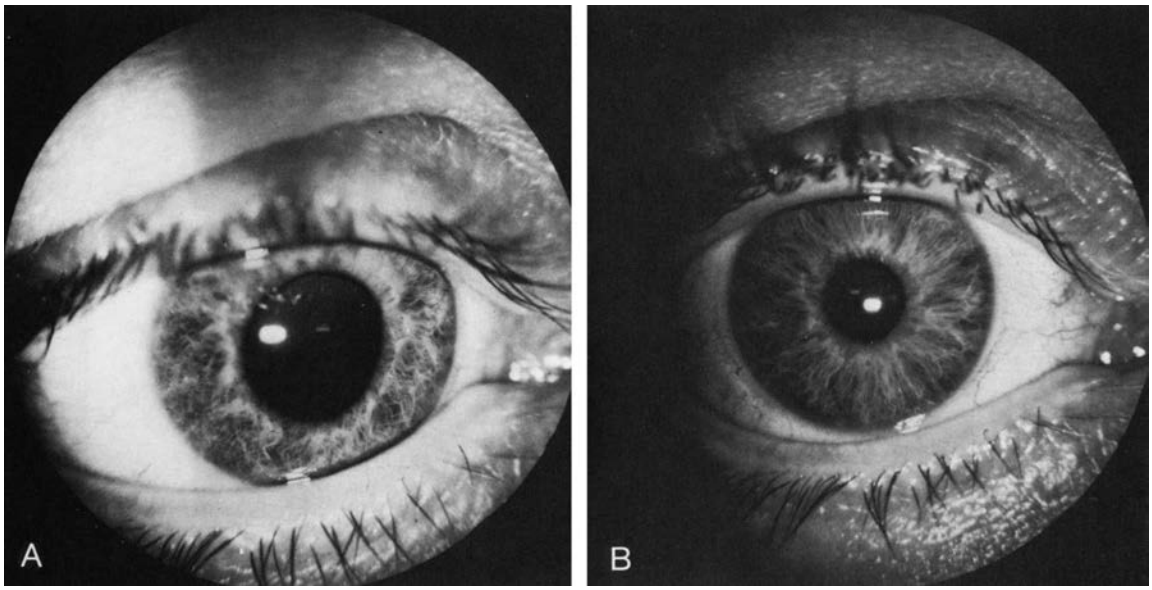

Figure 36.20. Paraneoplastic tonic pupils in a 32-year-old man with distortion of smell and taste, anorexia, nausea, and vomiting after meals. He also had a dysesthetic sensation over the left posterior scalp and complained of blurred vision in both eyes. Neurologic examination revealed left hemiparesis, diminished position, vibration, pain sensation on the left side, and left-sided dysmetria. Deep tendon reflexes were exaggerated in the right arm and leg, but they were absent at the left knee and ankle. There was anisocoria with the right pupil smaller than the left. The right pupil was normally reactive, and the left pupil was poorly reactive to light and near stimuli. Electroneuromyography showed absent sensory nerve action potentials but normal distal motor latencies and conduction velocities. A sural nerve biopsy showed mild, nonspecific axon loss and myelin disruption. Over the next 4 weeks, the right pupil became dilated, irregular, and nonreactive to light or near stimuli, whereas the left pupil became smaller and showed light-near dissociation. *A,* The right pupil is large and irregular at rest. *B,* After instillation of dilute (0.125%) pilocarpine, the pupil shows marked constriction. Eight months after symptoms began, the patient complained of abdominal pain and was found to have a malignant polyp of the colon. (From Maitland CG, Scherokman BJ, Schiffman J, et al. Paraneoplastic tonic pupils. J Clin Neuroophthalmol 1985;5:99–104.)

an autoimmune mechanism is likely, with the reaction being directed against autonomic ganglion cells. Bell and coworkers (430–432) demonstrated that small-cell carcinomas of the lung regularly exhibit antigenic determinants that are also expressed in neurons of parasympathetic myenteric plexuses. Lennon et al. (170) identified circulating antibodies that reacted against neurons of the myenteric plexus in some patients with small-cell lung cancer who had intestinal pseudo-obstruction, including one patient (Case 3) who also had dilated pupils. Although antibodies against cells within the ciliary ganglion have not been identified in any patients with this syndrome, it is likely that they are present. Regardless of the precise pathophysiology, the occurrence of bilateral tonic pupils in a patient with other evidence of autonomic dysfunction, sensory neuropathy, or unexplained central nervous system symptoms may be the first sign of an underlying systemic malignancy.

REFERENCES

1. Posner JB. Paraneoplastic syndromes. In: Neurologic Complications of Cancer. Philadelphia: FA Davis, 1995:353–385.
2. Dropcho EJ. Autoimmune central nervous system paraneoplastic disorders: Mechanisms, diagnosis, and therapeutic options. Ann Neurol 1995;37(Suppl 1): S102–S113.
3. Spence AM, Sumi SM, Ruff R. Paraneoplastic syndromes that involve the nervous system. Curr Probl Cancer 1983;8:4–43.
4. de la Monte SM, Hutchins GM, Moore GW. Paraneoplastic syndromes and constitutional symptoms in prediction of metastatic behavior of small-cell carcinoma of the lung. Am J Med 1984;77:851–857.
5. Elrington GM, Murray NMF, Spiro SG, et al. Neurological paraneoplastic syndromes in patients with small-cell lung cancer. A prospective survey of 150 patients. J Neurol Neurosurg Psychiatr 1991;54:764–767.
6. Henson RA, Urich H. Cancer and the Nervous System. Oxford, UK: Blackwell Scientific, 1982.
7. Henson RA, Hoffman HL, Urich H. Encephalomyelitis with carcinoma. Brain 1965;88:449–464.
8. Chalk CH, Windebank AJ, Kimmel DW, et al. The distinctive clinical features of paraneoplastic sensory neuropathy. Can J Neurol Sci 1992;19:346–351.
9. Dropcho EJ. Remote neurologic manifestations of cancer. Neurol Clin 2002;20: 85–122.
10. Case Records of the Massachusetts General Hospital (Case 30-1985). N Engl J Med 1985;313:249–257.
11. Vick N, Schulman S, Dan P. Carcinomatous cerebellar degeneration, encephalomyelitis, and sensory neuropathy (radiculitis). Neurology 1969;19:425–441.
12. Halperin JJ, Richardson EP Jr, Ellis J, et al. Paraneoplastic encephalomyelitis and neuropathy: Report of a case. Arch Neurol 1981;38:773–775.
13. Prockop LD, Buchdolt SL. Fatal nonmetastatic neurological complications of pulmonary carcinoma. J Fla Med Assoc 1985;72:345–349.
14. Gultekin SH, Rosenfeld MR, Voltz R, et al. Paraneoplastic limbic encephalitis: Neurological symptoms, immunological findings and tumour association in 50 patients. Brain 2000;123:1481–1494.
15. Dirr LY, Elster AD, Donofrio PD, et al. Evolution of brain MRI abnormalities in limbic encephalitis. Neurology 1990;40:1304–1306.
16. Kodama T, Numaguchi Y, Gellad FE, et al. Magnetic resonance imaging of limbic encephalitis. Neuroradiology 1991;33:520–523.
17. Brierly JB, Corsellis JAN, Hierons R, et al. Subacute encephalitis of later adult life mainly affecting the limbic areas. Brain 1960;83:357–368.
18. Corsellis JAN, Goldberg GJ, Norton AR. Limbic encephalitis and its association with carcinoma. Brain 1968;91:481–496.
19. Brennan LV, Craddock PR. Limbic encephalopathy as a nonmetastatic complication of oat cell lung cancer: Its reversal after treatment of the primary lung lesion. Am J Med 1983;75:518–520.
20. Bakheit AMO, Kennedy PGE, Behan PO. Paraneoplastic limbic encephalitis: Clinico-pathological correlations. J Neurol Neurosurg Psychiatr 1990;53: 1084–1088.
21. Newman NJ, Bell IR, McKee AC. Paraneoplastic limbic encephalitis: Neuropsychiatric presentation. Biol Psychiatry 1990;27:529–542.
22. Bennett JL, Galetta SL, Frohman LP, et al. Neuro-ophthalmologic manifestations of a paraneoplastic syndrome and testicular carcinoma. Neurology 1999;52: 864–867.
23. Verhaart WJC. Grey matter degeneration of the central nervous system in carcinosis. Acta Neuropathol 1961;1:107–112.
24. Waxman SG, Sabin TD, Embree LJ. Subacute brainstem encephalitis. J Neurol Neurosurg Psychiatr 1974;37:811–816.
25. Dietl HW, Pulst St-M, Engelhardt P, et al. Paraneoplastic brainstem encephalitis with acute dystonia and central hypoventilation. J Neurol 1982;227:229–238.
26. Lowe BA, Mershon C, Mangalik A. Paraneoplastic neurological syndrome in transitional cell carcinoma of the bladder. J Urol 1992;147:462–464.
27. Gulya AJ. Neurologic paraneoplastic syndromes with neurotologic manifestations. Laryngoscope 1993;103:754–761.
28. Ball JA, Warner T, Reid P, et al. Central alveolar hypoventilation associated with paraneoplastic brain-stem encephalitis and anti-Hu antibodies. J Neurol 1994;241:561–566.
29. Henson RA, Russell DS, Wilkinson M. Carcinomatous neuromyopathy and myopathy: A clinical and pathological study. Brain 1954;77:82–121.
30. Golbe LI, Miller DC, Duvoisin RC. Paraneoplastic degeneration of the substantia nigra with dystonia and Parkinsonism. Mov Dis 1989;4:147–152.
31. Escudero D, Barnadas A, Codina M, et al. Anti-Ri-associated paraneoplastic neurologic disorder without opsoclonus in a patient with breast cancer. Neurology 1993;43:1605–1606.
32. Dalmau J, Furneaux HM, Cordon-Cardo C, et al. The expression of the Hu (paraneoplastic encephalomyelitis/sensory neuropathy) antigen in human normal and tumor tissues. Am J Pathol 1992;141:881–886.
33. Campbell AMG, Garland H. Subacute myoclonic spinal myoclonus. J Neurol Neurosurg Psychiatr 1956;19:268–274.
34. Roobol TH, Kazzaz BA, Vecht Ch J. Segmental rigidity and spinal myoclonus as a paraneoplastic syndrome. J Neurol Neurosurg Psychiatr 1987;50:628–631.
35. Bateman DE, Weller RO, Kennedy P. Stiffman syndrome: A rare paraneoplastic disorder. J Neurol Neurosurg Psychiatr 1990;53:695–696.
36. Daniel SE, Love S, Scaravilli F, et al. Encephalomyeloneuropathy in the absence of a detectable neoplasm: Clinical and postmortem findings in three cases. Acta Neuropathol 1985;66:311–317.
37. Reddy RV, Vakili ST. Midbrain encephalitis as a remote effect of a malignant neoplasm. Arch Neurol 1981;38:781–782.
38. Ahern GL, O'Conner M, Dalmau J, et al. Paraneoplastic temporal lobe epilepsy with testicular neoplasm and atypical amnesia. Neurology 1994;44:1270–1274.
39. Kalkman PH, Allan S, Birchall IWJ. Magnetic resonance imaging of limbic encephalitis. Can Assoc Radiol J 1993;44:121–124.
40. Tsukamoto T, Mochizuki R, Mochizuki H, et al. Paraneoplastic cerebellar degeneration and limbic encephalitis in a patient with adenocarcinoma of the colon. J Neurol Neurosurg Psychiatr 1993;56:713–716.
41. Dalmau J, Graus F, Rosenblum MK, et al. Anti-Hu-associated paraneoplastic encephalomyelitis/sensory neuropathy: A clinical study of 71 patients. Medicine 1992;71:59–72.
42. Dalmau J, Posner JB. Neurologic paraneoplastic antibodies (anti-Yo; anti-Hu; anti-Ri): The case for a nomenclature based on antibody and antigen specificity. Neurology 1994;44:2241–2246.
43. Lennon VA. Paraneoplastic autoantibodies: The case for a descriptive generic nomenclature. Neurology 1994;44:2236–2240.
44. Dalmau J, Furneaux HM, Gralla RJ, et al. Detections of the anti-Hu antibody in the serum of patients with small-cell lung cancer: A quantitative Western blot anaylsis. Ann Neurol 1990;27:544–552.
45. Mason WP, Verschuuren J, Graus F, et al. Anti-Hu antibodies in patients with small-cell lung cancer but no paraneoplastic disorder. Ann Neurol 1995;38: 341–342.
46. Moll JW, Markusse HM, Pijnenburg JJ, et al. Antineuronal antibodies in patients with neurological complications of primary Sjogren's syndrome. Neurology 1993;43:2574–2581.
47. Smitt PS, Grefkens J, de Leeuw B, et al. Survival and outcome in 73 anti-Hu positive patients with paraneoplastic encephalomyelitis/sensory neuropathy. J Neurol 2002;249:745–753.
48. Pruitt AA. Central nervous system infections in cancer patients. Neurol Clin 1991;9:867–888.
49. Imperia PS, Lazarus HM, Lass JH. Ocular complications of systemic cancer chemotherapy. Surv Ophthalmol 1989;34:209–230.
50. Posner JB. Side effects of chemotherapy. In Neurologic Complications of Cancer. Philadelphia: FA Davis, 1995:282–310.
51. Graus F, Rogers LR, Posner JB. Cerebrovascular complications in patients with cancer. Medicine 1985;64:16–35.
52. Jean WC, Dalmau J, Ho A, et al. Analysis of the IgG subclass distributions and inflammatory infiltrates in patients with anti-Hu-associated paraneoplastic encephalomyelitis. Neurology 1994;44:140–147.
53. Liu J, Dalmau J, Szabo A, et al. Paraneoplastic encephalomyelitis antigens bind to the AU-rich elements of mRNA. Neurology 1995;45:544–550.
54. Manley GT, Smitt PS, Dalmau J, et al. Hu antigens: Reactivity with Hu antibodies, tumor expression, and major immungenic sites. Ann Neurol 1995;38: 102–110.
55. Kiers L, Altermatt HJ, Lennon VA. Paraneoplastic anti-neuronal nuclear IgG autoantibodies (type I) localize antigen in small-cell lung cancer. Mayo Clin Proc 1991;66:1209–1216.
56. Vega F, Graus F, Chen QM, et al. Intrathecal synthesis of the anti-Hu antibody in patients with paraneoplastic encephalomyelitis or sensory neuropathy: Clinical-immunologic correlation. Neurology 1994;44:2145–2147.
57. Pillay PK, Estes ML. Acute necrotizing myopathy in association with carcinoma of the tongue. Ann Acad Med 1993;22(Suppl 3):516–517.

58. Boghen D, Sebag M, Michaud J. Paraneoplastic optic neuritis and encephalomyelitis: Report of a case. Arch Neurol 1988;45:353–356.
59. Furman JMR, Eidelman BH, Fromm GH. Spontaneous remission of paraneoplastic ocular flutter and saccadic intrusions. Neurology 1988;38:499–501.
60. Burton GV, Bullard DE, Walther PJ, et al. Paraneoplastic limbic encephalopathy with testicular carcinoma: A reversible neurologic syndrome. Cancer 1988;62: 2248–2251.
61. Amir J, Galbraith RC. Paraneoplastic limbic encephalopathy as a nonmetastatic complication of small-cell lung cancer. South Med J 1992;85:1013–1014.
62. Batson OA, Fantle DM, Stewart JA. Paraneoplastic encephalomyelitis: Dramatic response to chemotherapy alone. Cancer 1992;69:1291–1293.
63. Kaniecki R, Morris JC. Reversible paraneoplastic limbic encephalitis. Neurology 1993;43:2415–2418.
64. Cunningham JD, Burt ME. Limbic encephalitis secondary to malignant thymoma. Ann Thorac Surg 1994;58:250–251.
65. Waterston JA, Gilligan BS. Paraneoplastic optic neuritis and external ophthalmoplegia. Aust NZ J Med 1986;16:703–704.
66. Oh SJ, Dropcho EJ. Steroid-responsive paraneoplastic encephaloneuropathy. Neurology 1990;40(Suppl 1):246.
67. Oh SJ, Dropcho EJ, Claussen GC. Anti-Hu-associated paraneoplastic sensory neuronopathy responding to early aggressive immunotherapy: Report of two cases and review of the literature. Muscle Nerve 1997;20:1576–1582.
68. Jaeckle KA, Rogers L, Wong M. Autoimmune paraneoplastic limbic encephalitis. Neurology 1988;38(Suppl 1):390.
69. Keime-Guibert F, Graus F, Broet P, et al. Clinical outcome of patients with anti-Hu-associated encephalomyelitis after treatment of the tumor. Neurology 1999; 53:1719–1723.
70. Rosenfeld MR, Eichen JG, Wade DF, et al. Molecular and clinical diversity in paraneoplastic immunity to Ma proteins. Ann Neurol 2001;50:339–348.
71. Dalmau J, Graus F, Cheung NV, et al. Major histocompatibility proteins, anti-Hu antibodies, and paraneoplastic encephalomyelitis in neuroblastoma and small-cell lung cancer. Cancer 1995;75:99–109.
72. Hammack JE, Kimmel DW, O'Neill BP, et al. Paraneoplastic cerebellar degeneration: A clinical comparison of patients with and without Purkinje cell cytoplasmic antibodies. Mayo Clin Proc 1990;65:1423–1431.
73. Peterson K, Rosenblum MK, Kotanides H, et al. Paraneoplastic cerebellar degeneration. I. A clinical analysis of 55 anti-Yo antibody-positive patients. Neurology 1992;42:1931–1937.
74. Brain WR, Daniel PM, Greenfield JG. Subacute cortical cerebellar degeneration and its relation to carcinoma. J Neurol Neurosurg Psychiatr 1951;14:59–75.
75. Brain WR, Wilkinson M. Sub-acute cerebellar degeneration associated with neoplasms. Brain 1965;88:465–478.
76. Greenberg HS. Paraneoplastic cerebellar degeneration: A clinical and CT study. J Neuro-Oncol 1984;2:377–382.
77. Clouston PD, Saper CB, Arbizu T, et al. Paraneoplastic cerebellar degeneration. III. Cerebellar degeneration, cancer and the Lambert-Eaton myasthenic syndrome. Neurology 1992;42:1944–1950.
78. Steven MM, Mackay IR, Carnegie PR, et al. Cerebellar cortical degeneration with ovarian carcinoma. Postgrad Med J 1982;58:47–51.
79. Hammack JE, Kotanides H, Rosenblum MK, et al. Paraneoplastic cerebellar degeneration. II. Clinical and immunologic findings in 21 patients with Hodgkin's disease. Neurology 1992;42:1938–1943.
80. Coesmans M, Sillevis Smitt PA, Linden DJ, et al. Mechanisms underlying cerebellar motor deficits due to mGluR1-autoantibodies. Ann Neurol 2003;53: 325–336.
81. Bernal F, Shams'ili S, Rojas I, et al. Anti-Tr antibodies as a markers of paraneoplastic cerebellar degeneration and Hodgkin's disease. Neurology 2003;60: 230–234.
82. Ang LC, Zochodne DW, Ebers GC, et al. Severe cerebellar degeneration in a patient with T-cell lymphoma. Acta Neuropathol 1986;69:171–175.
83. Ropper AH. Seronegative non-neoplastic acute cerebellar degeneration. Neurology 1993;43:1602–1605.
84. Trotter JL, Hendin BA, Osterland CK. Cerebellar degeneration with Hodgkin's disease: An immunological study. Arch Neurol 1976;33:660–661.
85. Greenlee JE, Brashear HR. Antibodies to cerebellar Purkinje cells in patients with paraneoplastic cerebellar degeneration and ovarian carcinoma. Ann Neurol 1983;14:609–613.
86. Jaeckle KA, Houghton AM, Nielsen SL, et al. Demonstration of serum anti-Purkinje antibody in paraneoplastic cerebellar degeneration and preliminary antigenic characterization. Ann Neurol 1983;14:111.
87. Jaeckle KA, Graus F, Houghton A, et al. Autoimmune response of patients with paraneoplastic cerebellar degeneration to a Purkinje cell cytoplasmic protein antigen. Ann Neurol 1985;18:592–600.
88. Cunningham J, Graus F, Anderson N, et al. Partial characterization of the Purkinje cell antigens in paraneoplastic cerebellar degeneration. Neurology 1986; 36:1163–1168.
89. Furneaux HF, Reich L, Posner JB. Autoantibody synthesis in the central nervous system of patients with paraneoplastic syndromes. Neurology 1990;40: 1085–1091.
90. Smith JL, Finley JC, Lennon VA. Autoantibodies in paraneoplastic cerebellar degeneration bind to cytoplasmic antigens of Purkinje cells in humans, rats, and mice and are of multiple immunoglobulin classes. J Neuroimmunol 1988;18: 37–48.
91. Hida C, Tsukamoto T, Awano H, Yamamoto T. Ultrastructural localization of anti-Purkinje cell antibody-binding sites in paraneoplastic cerebellar degeneration. Arch Neurol 1994;51:555–558.
92. Furneaux HF, Rosenblum MK, Dalmau J, et al. Selective expression of Purkinje-cell antigens in tumor tissue from patients with paraneoplastic cerebellar degeneration. N Engl J Med 1990;322:1844–1851.
93. Liu S, Mezrich J, Berk J, et al. Expression of Purkinje cell antigens in ovarian tumor and presence of anti-Purkinje cell antibodies in the serum of patients without paraneoplastic cerebellar degeneration. Neurology 1995;45(Suppl 4): A228–A229.
94. Tsukamoto T, Yamamoto H, Iwasaki Y, et al. Antineural autoantibodies in patients with paraneoplastic cerebellar degeneration. Arch Neurol 1989;46: 1225–1229.
95. Nemni R, Camerlingo M, Fazio R, et al. Serum antibodies to Purkinje cells and dorsal root ganglia neurons in sensory neuropathy with malignancy. Ann Neurol 1993;34:848–854.
96. Gahring LC, Twyman RE, Greenlee JE, et al. Autoantibodies to neuronal glutamate receptors in patients with paraneoplastic neurodegenerative syndrome enhance receptor activation. Molecular Medicine 1995;1:245–253.
97. Greenlee JE, Gahring LC, Rogers SW. Antibodies to glutamate receptor subunit proteins in sera from patients with paraneoplastic cerebellar degeneration and type I (''anti-Yo'') antibody response. Ann Neurol 1995;38:283.
98. Mintz BJ, Sirota DK. A case report of neurologic improvement following treatment of paraneoplastic cerebellar degeneration. Mt Sinai J Med 1993;60: 163–164.
99. Paone JF, Jeyasingham K. Remission of cerebellar dysfunction after pneumonectomy for bronchogenic carcinoma. N Engl J Med 1980;302:156.
100. Kearsley JH, Johnson P, Halmagyi M. Paraneoplastic cerebellar disease: Remission with excision of the primary tumor. Arch Neurol 1985;42:1208–1210.
101. Counsell CE, McLeod M, Grant R. Reversal of subacute paraneoplastic cerebellar syndrome with intravenous immunoglobulin. Neurology 1994;44: 1184–1185.
102. Felician O, Renard JL, Vega F, et al. Paraneoplastic cerebellar degeneration with anti-Yo antibody in a man. Neurology 1995;45:1226–1227.
103. Cocconi G, Ceci G, Juvarra G, et al. Successful treatment of subacute cerebellar degeneration in ovarian carcinoma with plasmapheresis: A case report. Cancer 1985;56:2318–2320.
104. Widdess-Walsh P, Tavee JO, Schuele S, et al. Response to intravenous immunoglobulin in anti-Yo associated paraneoplastic cerebellar degeneration: Case report and review of the literature. J Neurooncol 2003;63:187–190.
105. Nausieda PA, Tanner CM, Weiner WJ. Opsoclonic cerebellopathy: A paraneoplastic syndrome responsive to thiamine. Arch Neurol 1981;38:780–781.
106. Eekhof JLA. Remission of a paraneoplastic cerebellar syndrome. Clin Neurol Neurosurg 1985;87:133–134.
107. Hetzel DJ, Stanhope CR, O'Neill BP, et al. Gynecologic cancer in patients with subacute cerebellar degeneration predicted by anti-Purkinje cell antibodies and limited metastatic volume. Mayo Clin Proc 1990;65:1558–1563.
108. Solomon GE, Chutorian AM. Opsoclonus and occult neuroblastoma. N Engl J Med 1968;279:475–477.
109. Bray PF, Ziter FA, Lahey ME, et al. The coincidence of neuroblastoma and acute cerebellar encephalopathy. J Pediatr 1969;75:983–990.
110. Musarella MA, Chan HSL, DeBoer G, et al. Ocular involvement in neuroblastoma: Prognostic implications. Ophthalmology 1984;91:936–940.
111. Kaye JA, Warhol MJ, Kretschmar C, et al. Neuroblastoma in adults: Three case reports and a review of the literature. Cancer 1986;58:1149–1157.
112. Mitchell WG, Snodgrass SR. Opsoclonus-ataxia due to childhood neural crest tumors: A chronic neurologic syndrome. J Child Neurol 1990;5:153–158.
113. Ross AT, Zeman W. Opsoclonus, occult carcinoma, and chemical pathology in dentate nuclei. Arch Neurol 1967;17:546–551.
114. Ellenberger C, Campa JF, Netsky MG. Opsoclonus and parenchymatous degeneration of the cerebellum. Neurology 1968;18:1041–1046.
115. Ellenberger C, Netsky MG. Anatomic basis and diagnostic value of opsoclonus. Arch Ophthalmol 1970;83:307–310.
116. Keane JR, Devereaux MW. Opsoclonus associated with intracranial tumor. Arch Ophthalmol 1974;92:443–445.
117. Bellur SN. Opsoclonus: Its clinical value. Neurology 1975;25:502–507.
118. Dropcho E, Payne R. Paraneoplastic opsoclonus-myoclonus: Association with medullary thyroid carcinoma and review of the literature. Arch Neurol 1986; 43:410–415.
119. Pranzatelli MR. The neurobiology of the opsoclonus-myoclonus syndrome. Clin Neuropharmacol 1992;15:186–228.
120. Boltshauser E, Deonna T, Hirt HR. Myoclonic encephalopathy of infants or ''dancing eyes syndrome.'' Helv Paediatr Acta 1979;34:119–133.
121. Kilgo GR, Schwartze GM. Opsoclonus: Update on clinical and pathologic associations. J Clin Neuroophthalmol 1984;4:109–113.
122. Herishanu Y, Apte R, Kuperman O. Immunological abnormalities in opsoclonus cerebellopathy. Neuroophthalmology 1985;5:271–276.
123. Digre KB. Opsoclonus in adults: Report of three cases and review of the literature. Arch Neurol 1986;43:1165–1175.

124. Schwartz M, Sharf B, Zidan J. Opsoclonus as a presenting symptom in thymic carcinoma. J Neurol Neurosurg Psychiatr 1990;53:534.
125. Kay CL, Davies-Jones GAB, Singal R, et al. Paraneoplastic opsoclonus-myoclonus in Hodgkin's disease. J Neurol Neurosurg Psychiatr 1993;56:831–832.
126. Scholz J, Vieregge P, Ruff C. Paraneoplastic opsoclonus-myoclonus syndrome in metastatic ovarian carcinoma. J Neurol Neurosurg Psychiatr 1994;57:763–764.
127. Caviness JN, Forsyth PA, Layton DD, et al. The movement disorder of adult opsoclonus. Mov Dis 1995;10:22–27.
128. Mitoma H, Orimo S, Sodeyama N, et al. Paraneoplastic opsoclonus-myoclonus syndrome and neurofibrosarcoma. Eur Neurol 1996;36:322.
129. Anderson NE, Budde-Steffen C, Rosenblum MK, et al. Opsoclonus, myoclonus, ataxia, and encephalopathy in adults with cancer: A distinct paraneoplastic syndrome. Medicine 1988;67:100–109.
130. Boghen D, Michaud J, Ouaknine G. Darting eyes in a tremulous woman. Presented at the 18th Frank B. Walsh Society Meeting. Seattle, Feb 21–22, 1986.
131. Giordana MT, Soffietti R, Schiffer D. Paraneoplastic opsoclonus: A neuropathologic study of two cases. Clin Neuropathol 1989;8:295–300.
132. Hersh B, Dalmau J, Dangond F, et al. Paraneoplastic opsoclonus-myoclonus associated with anti-Hu antibody. Neurology 1994;44:1754–1755.
133. Ridley A, Kennard C, Scholtz CL, et al. Omnipause neurons in two cases of opsoclonus associated with oat cell carcinoma of the lung. Brain 1987;110: 1699–1709.
134. Case Records of the Massachusetts General Hospital (Case 9-1988). N Engl J Med 1988;318:563–570.
135. Luque FA, Furneaux HM, Ferziger R, et al. Anti-Ri: An antibody associated with paraneoplastic opsoclonus and breast cancer. Ann Neurol 1991;29:241–251.
136. Fisher PG, Wechsler DS, Singer HS. Anti-Hu antibody in a neuroblastoma-associated paraneoplastic syndrome. Pediatr Neurol 1994;10:309–312.
137. Greenlee JE, Brashear R, Rodnitzky RL, et al. Fall in antineuronal antibody titers and improvement of neurologic deficit following tumor removal in paraneoplastic cerebellar degeneration. Neurology 1986;36(Suppl 1):334.
138. Nitschke M, Hochberg F, Dropcho E. Improvement of paraneoplastic opsoclonus-myoclonus after protein A column therapy. N Engl J Med 1995;332:192.
139. Lennon VA. The case for a descriptive generic nomenclature: Carification of immunostaining criteria for PCA-1, ANNA-1, and ANNA-2 autoantibodies. Neurology 1994;44:2412–2415.
140. Buckanovich RJ, Yang YY, Darnell RB. The onconeural antigen Nova-1 is a neuron-specific RNA-binding protein, the activity of which is inhibited by paraneoplastic antibodies. J Neurosci 1996;16:1114–11122.
141. Yang YY, Yin GL, Darnell RB. The neuronal RNA-binding protein Nova-2 is implicated as the autoantigen targeted in POMA patients with dementia. Proc Natl Acad Sci USA 1998;95:13254–13259.
142. Gennaula CP, Eidelman BH. Anti-Ri paraneoplastic syndrome in association with primary lung carcinoma. Neurology 1995;45:1417.
143. Dropcho EJ, Kline KB, Riser J. Antineuronal (anti-Ri) antibodies in a patient with steroid-responsive opsoclonus-myoclonus. Neurology 1993;43:207–211.
144. Casado JL, Gil-Peralta A, Graus F, et al. Anti-Ri antibodies associated with opsoclonus and progressive encephalomyelitis with rigidity. Neurology 1994; 44:1521–1522.
145. Hormigo A, Dalmau JM, Rosenblum MK, et al. Immunological and pathological study of anti-Ri-associated encephalopathy. Ann Neurol 1994;36:896–902.
146. Farrelly C, Daneman A, Chan HSL, et al. Occult neuroblastoma presenting with opsoclonus: Utility of computed tomography. AJR 1984;142:807–810.
147. Koh PS, Raffensperger JG, Berry S, et al. Long-term outcome in children with opsoclonus-myoclonus and ataxia and coincident neuroblastoma. J Pediatr 1994; 125:712–716.
148. Parisi MT, Hattner RS, Matthay KK, et al. Optimized diagnostic strategy for neuroblastoma in opsoclonus-myoclonus. J Nucl Med 1993;34:1922–1926.
149. Yee RD, Spiegel PH, Yamada T, et al. Voluntary saccadic oscillations resembling ocular flutter and opsoclonus. J Neuroophthalmol 1994;14:95–101.
150. Borodic GE, Miller DC, Bienfang DC. Opsoclonus: Three cases and literature review. In Smith JL, Katz RS, eds. Neuro-Ophthalmology Enters the Nineties. Hialeah, FL: Dutton Press, 1988:213–232.
151. Buckanovich RJ, Posner JB, Darnell RB. Nova, the paraneoplastic Ri antigen, is homologous to an RNA-binding protein and is specifically expressed in the developing motor system. Neuron 1993;11:657–672.
152. Altman AJ, Baehner RL. Favorable prognosis for survival in children with coincident opso-myoclonus and neuroblastoma. Cancer 1976;37:846–852.
153. Telander RL, Smithson WA, Groover RV. Clinical outcome in children with acute cerebellar encephalopathy and neuroblastoma. J Pediatr Surg 1989;24: 11–14.
154. Ojeda VJ. Necrotizing myelopathy associated with malignancy: A clinicopathologic study of two cases and literature review. Cancer 1984;53:1115–1123.
155. Mancall EL, Rosales RK. Necrotizing myelopathy associated with visceral carcinoma. Brain 1964;87:639–656.
156. Lester EP, Feld E, Kinzie JJ, et al. Necrotizing myelopathy complicating Hodgkin's disease. Arch Neurol 1979;36:583–585.
157. Handforth A, Nag S, Sharp D, et al. Paraneoplastic subacute necrotic myelopathy. Can J Neurol Sci 1983;10:204–207.
158. Kuroda Y, Miyahara M, Sakemi T, et al. Autopsy report of acute necrotizing opticomyelopathy associated with thyroid cancer. J Neurol Sci 1993;120:29–32.
159. Grisold W, Lutz D, Wolf D. Necrotizing myelopathy associated with acute lymphoblastic leukemia: Case report and review of the literature. Acta Neuropathol 1980;49:231–235.
160. Sack GH. Levin J, Bell WR. Trousseau's syndrome and other manifestations of chronic disseminated coagulopathy in patients with neoplasms: Clinical, pathophysiologic, and therapeutic features. Medicine 1977;56:1–37.
161. Denny-Brown D. Primary sensory neuropathy with muscular changes associated with carcinoma. J Neurol Neurosurg Psychiatr 1948;11:73–87.
162. Graus F, Rene R. Paraneoplastic neuropathies. Eur Neurol 1993;33:279–286.
163. Wyburn-Mason R. Bronchial carcinoma presenting as polyneuritis. Lancet 1948; 1:203–206.
164. Horwich MS, Cho L, Porro RS, et al. Subacute sensory neuropathy: A remote effect of carcinoma. Ann Neurol 1977;2:393–396.
165. Vallat JM, Leboutet MJ, Hugon J, et al. Acute pure sensory paraneoplastic neuropathy with perivascular endoneurial inflammation: Ultrastructural study of capillary walls. Neurology 1986;36:1395–1399.
166. Lhermitte F, Gray F, Lyon-Caen O, et al. Paralysis of digestive tract with lesions of myenteric plexus: A new paraneoplastic syndrome. Rev Neurol 1980;136: 825–836.
167. Schuffler MD, Baird HW, Fleming CR, et al. Intestinal pseudo-obstruction as the presenting manifestation of small-cell carcinoma of the lung. Ann Intern Med 1983;98:129–134.
168. Van Lieshout JJ, Wieling W, Van Montfrans GA, et al. Acute dysautonomia associated with Hodgkin's disease. J Neurol Neurosurg Psychiatr 1986;49: 830–832.
169. Veilleux M, Bernier JP, Lamarche JB. Paraneoplastic encephalomyelitis and subacute dysautonomia due to an occult atypical carcinoid tumour of the lung. Can J Neurol Sci 1990;17:324–328.
170. Lennon VA, Sas DF, Busk MF, et al. Enteric neuronal autoantibodies in pseudo-obstruction with small-cell lung carcinoma. Gastroenterology 1991;100: 137–142.
171. Gerl A, Storck M, Muller-Hocker J, et al. Paraneoplastic chronic intestinal pseudo-obstruction as a rare complication of bronchial carcinoid. Gut 1992;33: 1000–1003.
172. Condom E, Vidal A, Rota R, et al. Paraneoplastic intestinal pseudo-obstruction associated with high titers of Hu autoantibodies. Virchows Archiv A Pathol Anat 1993;423:507–511.
173. Baumann G. Sensory polyneuropathy in bronchial carcinoma. Schweiz Arch Neurol Neurochir Psychiatr 1968;101:1–10.
174. Maitland CG, Scherokman BJ, Schiffman J, et al. Paraneoplastic tonic pupils. J Clin Neuroophthalmol 1985;5:99–104.
175. Bell TAG. Adie's tonic pupil in a patient with carcinomatous neuromyopathy. Arch Ophthalmol 1986;104:331–332.
176. Graus F, Elkon KB, Cordon-Cardo C, et al. Sensory neuropathy and small-cell lung cancer: Antineuronal antibody that reacts with the tumor. Am J Med 1986; 80:45–52.
177. Molinuevo JL, Graus F, Serrano C, et al. Utility of anti-Hu antibodies in the diagnosis of paraneoplastic sensory neuopathy. Ann Neurol 1998;44:976–980.
178. Donofrio PD, Alessi AG, Albers JW, et al. Electrodiagnostic evolution of carcinomatous sensory neuropathy. Muscle Nerve 1989;12:508–513.
179. Croft PB, Henson RA, Urich H, et al. Sensory neuropathy with bronchial carcinoma: A study of four cases showing serological abnormalities. Brain 1965;88: 501–514.
180. Stoll DB, Lublin F, Brodovsky H, et al. Association of subacute motor neuropathy with thymoma. Cancer 1984;54:770–772.
181. Schold SC, Cho E-S, Somasundaram M, et al. Subacute motor neuropathy: A remote effect of lymphoma. Ann Neurol 1979;5:271–287.
182. Walton JN, Tomlinson BE, Pearce GW. Subacute ''poliomyelitis'' and Hodgkin's disease. J Neurol Sci 1968;6:435–445.
183. Hawley RJ, Cohen MH, Saini N, et al. The carcinomatous neuromyopathy of oat cell lung cancer. Ann Neurol 1980;7:65–72.
184. Fisher CM, Williams HW, Wing ES. Combined encephalopathy and neuropathy with carcinoma. J Neuropathol Exp Neurol 1961;20:535–547.
185. Croft PB, Urich H, Wilkinson M. Peripheral neuropathy of sensori-motor type associated with malignant disease. Brain 1967;90:31–66.
186. Rowland LP, Schneck S. Neuromuscular disorders associated with malignant neoplastic disease. J Chron Dis 1963;16:777–795.
187. Currie S, Henson RA, Morgan HG. The incidence of non-metastatic neurological syndromes of obscure origin in the reticuloses. Brain 1970;93:629–640.
188. Walsh JC. Neuropathy associated with lymphoma. J Neurol Neurosurg Psychiatr 1971;34:42–50.
189. Victor M, Banker BQ, Adams RD. The neuropathy of multiple myeloma. J Neurol Neurosurg Psychiatr 1958;21:73–88.
190. Kelly JJ, Kyle RA, Miles JM, et al. The spectrum of peripheral neuropathy in myeloma. Neurology 1981;31:24–31.
191. Camacho J, Arnalich F, Anciones B, et al. The spectrum of neurological manifestations in myeloma. J Med 1985;16:597–611.
192. McLeod JG, Pollard JD. Peripheral neuropathy associated with paraproteinemia. In Matthews WB, ed. Handbook of Clinical Neurology, Vol 7. New York: Elsevier, 1987:429–444.

193. Miralles GD, O'Fallon JR, Talley NJ. Plasma-cell dyscrasia with polyneuropathy: The spectrum of POEMS syndrome. N Engl J Med 1992;327:1919–1923.
194. Soubrier MJ, Dubost J, Sauvezie BJM, French Study Group on POEMS Syndrome. Am J Med 1994;97:543–553.
195. Bolling JP, Brazis PW. Optic disk swelling with peripheral neuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS syndrome). Am J Ophthalmol 1990;109:503–510.
196. Brazis PW, Liesegang TJ, Bolling JP. When do optic disc edema and peripheral neuropathy constitute poetry? Surv Ophthalmol 1990;35:219–225.
197. Gheradi RK, Chouaib S, Malapert D, et al. Early weight loss and high serum tumor necrosis factor-alpha levels in polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes syndrome. Ann Neurol 1994;35:501–505.
198. Klingon GH. The Guillain-Barré syndrome associated with cancer. Cancer 1965; 18:157–163.
199. Lisak RP, Mitchell M, Zweiman B, et al. Guillain-Barré syndrome and Hodgkin's disease: Three cases with immunological studies. Ann Neurol 1977;1: 72–78.
200. Julien J, Vital C, Aupy G, et al. Guillain-Barré syndrome and Hodgkin's disease. J Neurol Sci 1980;45:23–27.
201. Sumi SM, Farrell DF, Knauss TA. Lymphoma and leukemia presenting with steroid-responsive neuropathy. Arch Neurol 1983;40:577–582.
202. Peterson K, Forsyth PA, Posner JB. Paraneoplastic sensorimotor neuropathy associated with breast cancer. J Neurooncol 1994;21:159–170.
203. Croft PB, Wilkinson M. The incidence of carcinomatous neuromyopathy in patients with various types of carcinoma. Brain 1965;88:427–434.
204. Hildebrand J, Coers C. The neuromuscular function in patients with malignant tumours. Electromyographic and histological study. Brain 1967;90:67–82.
205. Campbell MJ, Paty DW. Carcinomatous neuromyopathy. 1. Electrophysiological studies: An electrophysiological and immunological study of patients with carcinoma of the lung. J Neurol Neurosurg Psychiatr 1974;37:131–141.
206. Barron SA, Heffner RR. Weakness in malignancy: Evidence for a remote effect of tumor on distal axons. Ann Neurol 1978;4:268–274.
207. Lambert EH, Eaton LM, Rooke ED. Defect of neuromuscular conduction associated with malignant neoplasms. Am J Physiol 1956;187:612–613.
208. Lambert EH, Rooke ED, Eaton LM, et al. Myasthenic syndrome occasionally associated with bronchial neoplasm: Neurophysiologic studies. In Viets HR, ed. Myasthenia Gravis: The 2nd International Symposium Proceedings. Springfield, IL: Charles C Thomas, 1961:362–410.
209. Lambert EH, Rooke ED. Myasthenic state and lung cancer. In Brain WR, Norris FH, eds. The Remote Effects of Cancer on the Nervous System. New York: Grune & Stratton, 1965:67–80.
210. Lambert EH, Okihiro M, Rooke ED. Clinical physiology of the neuromuscular junction. In Paul WM, Daniel EE, Kay CM, et al., eds. Muscle. New York: Pergamon Press, 1965:487.
211. Eaton LM, Lambert EH. Electromyography and electric stimulation of nerves in diseases of motor unit: Observations on myasthenic syndrome associated with malignant tumors. JAMA 1957;163:1117–1124.
212. O'Neill JH, Murray MF, Newsom-Davis J. The Lambert-Eaton myasthenic syndrome: A review of 50 cases. Brain 1988;111:577–596.
213. Shapira Y, Cividalli G, Szabo G, et al. A myasthenic syndrome in childhood leukemia. Dev Med Child Neurol 1974;16:668–671.
214. Chelmicka-Schorr E, Bernstein LP, Surbrugg EG, et al. Eaton-Lambert syndrome in a 9-year-old girl. Arch Neurol 1979;36:572–574.
215. McEvoy KM. Diagnosis and treatment of Lambert-Eaton myasthenic syndrome. Neurol Clin NA 1994;12:387–399.
216. Sanders DB. Lambert-Eaton myasthenic syndrome: Clinical diagnosis, immune-mediated mechanisms, and update on therapies. Ann Neurol 1995;37(Suppl 1): S63–S73.
217. Hedges TR Jr. Ophthalmoplegia of myasthenia and bronchial neoplasm. Arch Ophthalmol 1963;70:333–334.
218. Elmqvist D, Lambert EH. Detailed analysis of neuromuscular transmission in a patient with the myasthenic syndrome sometimes associated with bronchogenic carcinoma. Mayo Clin Proc 1968;43:689–713.
219. Oh SJ. The Eaton-Lambert syndrome in ocular myasthenia gravis. Arch Neurol 1974;31:183–186.
220. Black JT. Neuromuscular disorders that affect the eye. Int Ophthalmol Clin 1978;18:83–121.
221. Rousseaux M, Leys D, Dubois F, et al. Bilateral external ophthalmoplegia revealing an Eaton-Lambert syndrome. Neuroophthalmology 1985;5:207–210.
222. Cruciger MP, Brown B, Denys EH, et al. Clinical and subclinical oculomotor findings in the Eaton-Lambert syndrome. J Clin Neuroophthalmol 1983;3: 19–22.
223. Dell'Osso LF, Ayyar DR, Daroff RB, et al. Edrophonium test in Eaton-Lambert syndrome: Quantitative oculography. Neurology 1983;33:1157–1163.
224. Rubenstein AE, Horowitz SH, Bender AN. Cholinergic dysautonomia and Eaton-Lambert syndrome. Neurology 1979;29:720–723.
225. Khurana RK, Koshi CL, Mayer RF. Autonomic dysfunction in Lambert-Eaton myasthenic syndrome. J Neurol Sci 1988;85:77–86.
226. Clark CV, Newsom-Davis J, Sanders MD. Ocular autonomic nerve function in Lambert-Eaton myasthenic syndrome. Eye 1990;4:473–481.
227. Beallo A. Bilateral tonic pupils, ptosis, and myasthenic syndrome associated with oat cell carcinoma of the lung. Trans Pac Coast Otol Ophthalmol Soc 1965; 1:98–102.
228. Schwartz MS, Stalberg E. Myasthenic syndrome studied with single fiber electromyography. Arch Neurol 1975;32:815–817.
229. Schwartz MS, Stalberg E. Myasthenia gravis with features of the myasthenic syndrome. Neurology 1975;25:80–84.
230. Lennon VA, Lambert EH. Autoantibodies bind solubilized calcium channel-w-conotoxin complexes from small-cell lung carcinoma: A diagnostic aid for Lambert-Eaton myasthenic syndrome. Mayo Clin Proc 1989;64:1498–1504.
231. Leys K, Lang B, Johnston I, et al. Calcium channel autoantibodies in the Lambert-Eaton myasthenic syndrome. Ann Neurol 1991;29:307–314.
232. Pelucchi A, Ciceri E, Clementi F, et al. Calcium channel autoantibodies in myasthenic syndrome and small-cell lung cancer. Am Rev Respir Dis 1993;147: 1229–1232.
233. Robb SA, Bowley TJ, Willcox HNA, et al. Circulating T-cell subsets in the Lambert-Eaton myasthenic syndrome. J Neurol Neurosurg Psychiatr 1985;48: 501–505.
234. Lennon VA, Lambert EH, Whittingham S, et al. Autoimmunity in the Lambert-Eaton myasthenic syndrome. Muscle Nerve 1982;5:S21–S25.
235. Lennon VA. Serological diagnosis of myasthenia gravis and the Lambert-Eaton myasthenic syndrome. In Lisak RP, ed. Handbook of Myasthenia Gravis and Myasthenic Syndromes. New York: Dekker, 1994:149–164.
236. Lambert EH, Elmqvist D. Quantal components of end-plate potentials in the myasthenic syndrome. Ann NY Acad Sci 1971;183:183–199.
237. Cull-Candy SG, Miledi R, Trautmann A, et al. On the release of transmitter at normal, myasthenia gravis and myasthenic syndrome affected human end-plates. J Physiol 1980;299:621–638.
238. Lambert EH. Defects of neuromuscular transmission in syndromes other than myasthenia gravis. Ann NY Acad Sci 1966;135:367–384.
239. Fukunaga H, Engel AC, Lang B, et al. Passive transfer of Lambert-Eaton myasthenic syndrome with IgG from man to mouse depletes the presynaptic membrane active zones. Proc Natl Acad Sci USA 1983;80:7636–7640.
240. Fukuoka T, Engel AG, Lang B, et al. Lambert-Eaton myasthenic syndrome. I. Early morphological effects of IgG on the presynaptic membrane active zones. Ann Neurol 1987;22:193–199.
241. Fukuhara N, Takamori M, Gutman L, et al. Eaton-Lambert syndrome: Ultrastructural study of the motor end-plates. Arch Neurol 1972;27:67–78.
242. Engel AG, Santa T. Motor endplate fine structure: Quantitative analysis in disorders of neuromuscular transmission and prostigmine-induced alterations. In Desmedt JT, ed. New Developments in Electromyography and Clinical Neurophysiology. Basel, Germany: Karger, 1973:196–228.
243. Lindstrom JM, Lambert EH. Content of acetylcholine receptor and antibodies bound to receptor in myasthenia gravis, experimental autoimmune myasthenia gravis, and Eaton-Lambert syndrome. Neurology 1978;28:130–138.
244. Ishikawa K, Engelhardt JK, Frijisana T, et al. A neuromuscular block produced by a cancer tissue extract derived from a patient with myasthenic syndrome. Neurology 1977;27:140–143.
245. Lang B, Newsom-Davis J, Wray D, et al. Autoimmune aetiology for myasthenic (Eaton-Lambert) syndrome. Lancet 1981;2:224–226.
246. Prior C, Lang B, Wray D, et al. Action of Lambert-Eaton myasthenic syndrome IgG at mouse motor nerve terminals. Ann Neurol 1985;17:587–592.
247. Lennon VA, Kryzer TJ, Griesmann GE, et al. Calcium-channel antibodies in the Lambert-Eaton syndrome and other paraneoplastic syndromes. N Engl J Med 1995;332:1467–1474.
248. Rosenfeld MR, Wong E, Dalmau J, et al. Cloning and characterization of a Lambert-Eaton myasthenic syndrome antigen. Ann Neurol 1993;33:113–120.
249. Clamon GH, Evans WK, Shepard FA, et al. Myasthenic syndrome and small-cell cancer of the lung: Variable response to antineoplastic therapy. Arch Intern Med 1984;144:999–1000.
250. Chalk CH, Murray NMF, Newsom-Davis J, et al. Response of the Lambert-Eaton myasthenic syndrome to treatment of associated small-cell lung carcinoma. Neurology 1990;40:1552–1556.
251. Blumenfeld AM, Recht LD, Chad DA, et al. Coexistence of Lambert-Eaton myasthenic syndrome and subacute cerebellar degeneration: Differential effects of treatment. Neurology 1991;41:1682–1685.
252. McEvoy KM, Windebank AJ, Daube JR, et al. 3,4-Diaminopyridine in the treatment of Lambert-Eaton myasthenic syndrome. N Engl J Med 1989;321: 1567–1571.
253. Newsom-Davis J, Murray NMF. Plasma exchange and immunosuppressive drug treatment in the Lambert-Eaton myasthenic syndrome. Neurology 1984;34: 480–485.
254. Bohan A, Peter JB. Polymyositis and dermatomyositis. N Engl J Med 1975; 292:344–347; 403–407.
255. Bohan A, Peter JB, Bowman RL, et al. A computer-assisted analysis of 153 patients with polymyositis and dermatomyositis. Medicine 1977;56:255–286.
256. Richardson JB, Callan JP. Dermatomyositis and malignancy. Med Clin NA 1989; 73:1211–1220.
257. Susac JO, Garcia-Mullin R, Glaser JS. Ophthalmoplegia in dermatomyositis. Neurology 1973;23:305–310.
258. Klein BR, Hedges TR III, Dayal Y, et al. Orbital myositis and giant cell myocarditis. Neurology 1989;39:988–990.

259. Kattah JC, Zimmerman LE, Kolsky MP, et al. Bilateral orbital involvement in fatal giant cell polymyositis. Ophthalmology 1990;97:520–525.
260. Harris GJ, Murphy ML, Schmidt EW, et al. Orbital myositis as a paraneoplastic sydnrome. Arch Ophthalmol 1994;112:380–386.
261. Bruce GM. Retinitis and dermatomyositis. Trans Am Ophthalmol Soc 1938;36: 282–297.
262. Lisman JV. Dermatomyositis with retinopathy. Arch Ophthalmol 1947;37: 155–159.
263. Munro S. Fundus appearance in a case of acute dermatomyositis. Br J Ophthalmol 1959;43:548–558.
264. Klien BA. Comments on cotton-wool lesion of the retina. Am J Ophthalmol 1965;59:17–23.
265. Liebman S, Cook C. Retinopathy with dermatomyositis. Arch Ophthalmol 1965; 74:704–705.
266. Harrison SM, Frenkel M, Grossman B, et al. Retinopathy in childhood dermatomyositis. Am J Ophthalmol 1973;76:786–790.
267. Cohen BH, Sedwick LA, Burde RM. Retinopathy of dermatomyositis. J Clin Neuroophthalmol 1985;5:177–179.
268. Hollenhorst RW, Henderson JW. The ocular manifestations of the diffuse collagen disease. Am J Med Sci 1951;221:211–222.
269. Tuovinen E, Raudasoja R. Poikilodermatomyositis with retinal hemorrhages and secondary glaucoma. Acta Ophthalmol 1965;43:669–672.
270. Benbassat J, Gefel D, Larholt K, et al. Prognostic factors in polymyositis/dermatomyositis: A computer-assisted analysis of 92 cases. Arthritis Rheum 1985;28: 249–255.
271. Manchul LA, Jin A, Pritchard KI, et al. The frequency of malignant neoplasms in patients with polymyositis-dermatomyositis: A controlled study. Arch Intern Med 1985;145:1835–1839.
272. Hochberg MC, Feldman D, Stevens MB. Adult onset polymyositis/dermatomyositis: An analysis of clinical and laboratory features and survival in 76 patients with a review of the literature. Semin Arthritis Rheum 1986;15:168–178.
273. Lakhanpal S, Bunch TW, Ilstrup DM, et al. Polymyositis-dermatomyositis and malignant lesions: Does an association exist? Mayo Clin Proc 1986;61:645–653.
274. Bonnetblanc JM, Bernard P, Fayol J. Dermatomyositis and malignancy: A multicenter cooperative study. Dermatologica 1990;180:212–216.
275. Zantos D, Zhang Y, Felson D. The overall and temporal association of cancer with polymyositis and dermatomyositis. J Rheumatol 1994;21:1855–1859.
276. Masi AT, Hochberg MC. Temporal association of polymyositis-dermatomyositis with malignancy: Methodologic and clinical considerations. Mt Sinai J Med 1988;55:471–478.
277. Dalakas MC. Polymyositis, dermatomyositis, and inclusion-body myositis. New Engl J Med 1991;325:1487–1498.
278. Callan JP. Relationship of cancer to inflammatory muscle diseases. Rheumatol Clin NA 1994;20:943–953.
279. Chow WH, Gridley G, Mellemkjaer L, et al. Cancer risk following polymyositis and dermatomyositis: A nationwide cohort study in Denmark. Cancer Causes Control 1995;6:9–13.
280. Barnes BE. Dermatomyositis and malignancy: A review of the literature. Ann Intern Med 1976;84:68–76.
281. Mastaglia FL, Ojeda VJ. Inflammatory myopathies: Part 1. Ann Neurol 1985; 17:215–227.
282. Mastaglia FL, Ojeda VJ. Inflammatory myopathies: Part 2. Ann Neurol 1985; 17:317–323.
283. Hochberg MC, Feldman D, Stevens MB, et al. Antibody to Jo-1 in polymyositis/dermatomyositis: Association with interstitial pulmonary disease. J Rheumatol 1984;11:663–665.
284. Karp SJ. Acute dermatomyositis associated with squamous cell carcinoma of the oesophagus. J Roy Soc Med 1985;78:770–771.
285. Whitaker JN. Inflammatory myopathy: A review of etiologic and pathogenetic factors. Muscle Nerve 1982;5:573–592.
286. Miller FW. Myositis-specific autoantibodies: Touchstones for understanding the inflammatory myopathies. JAMA 1993;270:1846–1849.
287. Dau PC. Plasmapheresis in idiopathic inflammatory myopathy: Experience with 35 patients. Arch Neurol 1981;38:544–552.
288. Engel WK, Lichter AS, Galdi AP. Polymyositis: Remarkable response to total body irradiation. Lancet 1981;1:658.
289. Hubbard WN, Walport MJ, Halnan KE, et al. Remission from polymyositis after total body irradiation. Br Med J 1982;284:1915–1916.
290. Jann S, Beretta S, Moggio M, et al. High-dose intravenous human innumoglobulin in polymyositis resistant to treatment. J Neurol Neurosurg Psychiatr 1992; 55:60–62.
291. Esteve E, Cambie MP, Serpier H, et al. Paraneoplastic dermatomyositis: Efficacy of intravenous gammaglobulin. Brit J Dermatol 1994;131:917–918.
292. Smith B. Skeletal muscle necrosis associated with carcinoma. J Pathol 1969; 97:207–210.
293. Urich H, Wilkinson M. Necrosis of muscles with carcinoma: Myositis or myopathy. J Neurol Neurosurg Psychiatr 1970;33:398–407.
294. Brownell B, Hughes JT. Degeneration of muscle in association with carcinoma of the bronchus. J Neurol Neurosurg Psychiatr 1975;38:363–370.
295. Yutani C, Matsuda Y, Murao S, et al. Necrotizing myopathy as a remote effect of gastric cancer accompanied with Hashimoto's thyroiditis. Acta Pathol Jpn 1978;28:165–174.
296. Vobkamper M, Korf B, Franke F, et al. Paraneoplastic necrotizing myopathy: A rare disorder to be differentiated from polymyositis. J Neurol 1989;236: 489–492.
297. Marin OSM, Denny-Brown D. Changes in skeletal muscles associated wih cachexia. Am J Pathol 1962;41:23–39.
298. Mayer M, Rosen F. Interaction of glucocorticoids and androgens with skeletal muscle. Metabolism 1977;26:937–962.
299. Henson RA. Neuromuscular disorders associated with malignant disease. In Walton J, ed. Disorders of Voluntary Muscle. Ed 4. Edinburgh, UK: Churchill Livingstone, 1981:712–724.
300. Berry EM, Maunder C, Wilson M. Carcinoid myopathy and treatment with cyproheptadine (periactin). Gut 1974;15:34–38.
301. Swash M, Fox KP, Davidson AR. Carcinoid myopathy: Serotonin-induced muscle weakness in man? Arch Neurol 1975;32:572–574.
302. Lederman RJ, Bukowski RM, Nickerson P. Carcinoid myopathy. Cleve Clin J Med 1987;54:299–303.
303. Parker JM, Mendell JR. Proximal myopathy induced by 5-HT-imipramine simulates Duchenne dystrophy. Nature 1974;247:103–104.
304. Patten BM, Oliver KL, Engel WK. Serotonin-induced muscle weakness. Arch Neurol 1974;31:347–349.
305. Thompson PD. Stiff muscles. J Neurol Neurosurg Psychiatr 1993;56:121–124.
306. Moersch FP, Woltman HW. Progressive fluctuating muscular rigidity and spasm (''stiff-man'' syndrome): Report of a case and some observations in 13 other cases. Mayo Clin Proc 1956;31:421–427.
307. Gordon EE, Januszko DM, Kaufman L. A critical survey of stiff-man syndrome. Am J Med 1967;42:582–599.
308. Lorish TR, Thorsteinsson G, Howard FM. Stiff-man syndrome updated. Mayo Clin Proc 1989;64:629–636.
309. Solimena M, Folli F, Aparisi R, et al. Autoantibodies to GABA-ergic neurons and pancreatic beta cells in stiff-man syndrome. N Engl J Med 1990;322: 1555–1560.
310. Grimaldi LME, Marino G, Braghi S, et al. Heterogeneity of autoantibodies in stiff-man syndrome. Ann Neurol 1993;34:57–64.
311. Ferrari P, Federico M, Grimaldi LME, et al. Stiff-man syndrome in a patient with Hodgkin's disease: An unusual paraneoplastic syndrome. Haematoligca 1990;75:570–572.
312. Folli F, Solimena M, Cofiell R, et al. Autoantibodies to a 128-kd synaptic protein in three women with the stiff-man syndrome and breast cancer. N Engl J Med 1993;328:546–551.
313. Isaacs H. A syndrome of continuous muscle-fibre activity. J Neurol Neurosurg Psychiatr 1961;24:319–325.
314. Newsom-Davis J, Mills KR. Immunological associations of acquired neuromyotonia (Isaacs' syndrome): Report of five cases and literature review. Brain 1993; 116:453–469.
315. Waerness E. Neuromyotonia and bronchial carcinoma. Electromyogr Clin Neurophysiol 1974;14:527–535.
316. Walsh JC. Neuromyotonia: An unusual presentation of intrathoracic malignancy. J Neurol Neurosurg Psychiatr 1976;39:1086–1091.
317. Partanen VSJ, Soinenen H, Saksa M, et al. Electromyographic and nerve conduction findings in a patient with neuromyotonia, normocalcemic tetany and small-cell lung cancer. Acta Neurol Scand 1980;61:216–226.
318. Hallbach M, Homberg V, Freund H-J. Neuromuscular, autonomic and central cholinergic hyperactivity associated with thymoma and acetylcholine receptor-binding antibody. J Neurol 1987;234:433–436.
319. Piccolo G, Martino G, Moglia A, et al. Autoimmune myastenia gravis with thymoma following the spontaneous remission of stiff-man syndrome. Ital J Neurol Sci 1990;11:177–180.
320. Garcia-Merino A, Cabello A, Mora JS, et al. Continuous muscle fiber activity, peripheral neuropathy, and thymoma. Ann Neurol 1991;29:215–218.
321. Smith CH, Hamilton SR, Orcutt JC, et al. Ocular myasthenia with malignant myoclonus. Presented at the 24th Annual Frank B Walsh Society Meeting. Los Angeles, CA: Feb 18–19, 1992.
322. Perini M, Ghezzi A, Basso PF, et al. Association of neuromyotonia with peripheral neuropathy, myasthenia gravis and thymoma: A case report. Ital J Neurol Sci 1994;15:307–310.
323. Zifko U, Drlicek M, Machacek E, et al. Syndrome of continuous muscle fiber activity and plasmacytoma with IgM paraproteinemia. Neurology 1994;44: 560–561.
324. Hart IK, Vincent A, Leys K, et al. Serum autoantibodies bind to voltage-gated potassium channels in acquired neuromyotonia. Ann Neurol 1994;36:325.
325. Shillito P, Molenaar PC, Vincent A, et al. Acquired neuromyotonia: Evidence for autoantibodies directed against K+ channels of peripheral nerves. Ann Neurol 1995;38:714–722.
326. Sawyer RA, Selhorst JB, Zimmerman LE, et al. Blindness caused by photoreceptor degeneration as a remote effect of cancer. Am J Ophthalmol 1976;81: 606–613.
327. Thirkill CE. Cancer-associated retinopathy: The CAR syndrome. Neuroophthalmol 1994;14:297–323.
328. Milam AH. Clinical Aspects: Paraneoplastic Retinopathy. In Djamgoz MBA,

Archer SN, Vallerga S, eds. Neurobiology and Clinical Aspects of the Outer Retina. London: Chapman and Hall, 1995:461–471.
329. Kornguth SE, Klein R, Appen R, et al. Occurrence of anti-retinal ganglion cell antibodies in patients with small-cell carcinoma of the lung. Cancer 1982;50: 1289–1293.
330. Keltner JL, Roth AM, Chang S. Photoreceptor degeneration: Possible autoimmune disorder. Arch Ophthalmol 1983;101:564–569.
331. Buchanan TAS, Gardiner TA, Archer DB. An ultrastructural study of retinal photoreceptor degeneration associated with bronchial carcinoma. Am J Ophthalmol 1984;97:277–287.
332. Thirkill CE, Roth AM, Keltner JL. Cancer-associated retinopathy. Arch Ophthalmol 1987;105:372–375.
333. Van Der Pol BAE, Planten JTh. A non-metastatic remote effect of lung carcinoma. Doc Ophthalmol 1987;67:89–94.
334. Vargas Nunez JA, Bonilla Velasco F, Casas Fernandez-Tejerina J, et al. Degeneracion retiniana paraneoplastica. Medicina Clinica 1987;88:431.
335. Thirkill CE, FitzGerald P, Sergott RC, et al. Cancer-associated retinopathy (CAR syndrome) with antibodies reacting with retinal, optic-nerve, and cancer cells. N Engl J Med 1989;321:1589–1594.
336. Jacobson DM, Thirkill CE, Tipping SJ. A clinical triad to diagnose paraneoplastic retinopathy. Ann Neurol 1990;28:162–167.
337. Keltner JL, Thirkill CE, Tyler NK, et al. Management and monitoring of cancer-associated retinopathy. Arch Ophthalmol 1992;110:48–53.
338. Rizzo JF, Gittinger JW. Selective immunohistochemical staining in the paraneoplastic retinopathy syndrome. Ophthalmology 1992;99:1286–1295.
339. Adamus G, Guy J, Schmied JL, et al. Role of anti-recoverin autoantibodies in cancer-associated retinopathy. Invest Ophthalmol Vis Sci 1993;34:2626–2633.
340. Ohnishi Y, Ohara S, Sakamoto T, et al. Cancer-associated retinopathy with retinal phlebitis. Br J Ophthalmol 1993;77:795–798.
341. Gehrs K, Tiedeman J. Hemeralopia in an older adult. Surv Ophthalmol 1992; 37:185–189.
342. Oohira A, Takamaki Y, Nagahara K, et al. A case of paraneoplastic retinopathy. Jpn J Ophthalmol 1993;37:28–31.
343. Crofts JW, Bachynski BN, Odel JG. Visual paraneoplastic syndrome associated with undifferentiated endometrial carcinoma. Can J Ophthalmol 1988;23: 128–132.
344. Yamada G, Ohguro H, Aketa K, et al. Invasive thymoma with paraneoplastic retinopathy. Hum Pathol 2003;34:717–719.
345. Katsuta H, Okada M, Nakauchi T, et al. Cancer-associated retinopathy associated with invasive thymoma. Am J Ophthalmol 2002;134:383–389.
346. Klingele TG, Burde RM, Rappazzo JA, et al. Paraneoplastic retinopathy. J Clin Neuroophthalmol 1984;4:239–245.
347. Matsui Y, Mehta MC, Katsumi O, et al. Electrophysiological findings in paraneoplastic retinopathy. Graefe's Arch Clin Exp Ophthalmol 1992;230:324–328.
348. To KW, Thirkill CE, Jakobiec FA, et al. Lymphoma-associated retinopathy. Ophthalmology 2002;109:2149–2153.
349. Grunwald GB, Klein R, Simmonds MA, et al. Autoimmune basis for visual paraneoplastic syndrome in patients with small-cell lung carcinoma. Lancet 1985;1:658–661.
350. Kornguth SE, Kalinke T, Grunwald GB, et al. Anti-neurofilament antibodies in the sera of patients with small-cell carcinoma of the lung and with visual paraneoplastic syndrome. Cancer Res 1986;46:2588–2595.
351. Grunwald GB, Kornguth SE, Towfighi J, et al. Autoimmune basis for visual paraneoplastic syndrome in patients with small-cell lung carcinoma. Retinal immune deposits and ablation of retinal ganglion cells. Cancer 1987;60: 780–786.
352. Thirkill CE, Keltner JL, Tyler NK, et al. Antibody reactions with retina and cancer-associated antigens in 10 patients with cancer-associated retinopathy. Arch Ophthalmol 1993;111:931–937.
353. Ohguro H, Maruyama I, Nakazawa M, Oohira A. Antirecoverin antibody in the aqueous humor of a patient with cancer-associated retinopathy. Am J Ophthalmol 2002;134:605–607.
354. Thirkill CE, Tait RC, Tyler NK, et al. The cancer-associated retinopathy antigen is a recoverin-like protein. Invest Ophthalmol Vis Sci 1992;33:2768–2772.
355. Polans AS, Burton MD, Haley T, et al. Recoverin, but not visnin, is an autoantigen in the human retina identified with a cancer-associated retinopathy. Invest Ophthalmol Vis Sci 1993;34:81–90.
356. Thirkill CE, Tait RC, Tyler NK, et al. Intraperitoneal cultivation of small-cell carcinoma induces expression of the retinal cancer-associated retinopathy antigen. Arch Ophthalmol 1993;111:974–978.
357. Polans AS, Witkowska D, Haley TL, et al. Recoverin, a photoreceptor-specific calcium-binding protein, is expressed by the tumor of a patient with cancer-associated retinopathy. Proc Natl Acad Sci 1995;92:9176–9180.
358. McGinnis JF, Austin B, Klisak I, et al. Chromosomal assignment of the human gene for the cancer-associated retinopathy protein (recoverin) to chromosome 17p13.1. J Neurosci Res 1995;40:165–168.
359. McGinnis JF, Lerious V, Pazik J, Elliott RW. Chromosomal assignment of the recoverin gene and cancer-associated retinopathy. Mamm Genome 1993;4: 43–45.
360. Ohguro H, Nakazawa M. Pathological roles of recoverin in cancer-associated retinopathy. Adv Exp Med Biol 2002;514:709–724.
361. Shiraga S, Adamus G. Mechanism of CAR syndrome: anti-recoverin antibodies are the inducers of retinal cell apoptotic death via the caspase-9 and caspase-3-dependent pathway. J Neuroimmunol 2002;132:72–82.
362. Maeda T, Maeda A, Maruyama I, et al. Mechanisms of photoreceptor cell death in cancer-associated retinopathy. Invest Ophthalmol Vis Sci 2001;42:705–712.
363. Peek R, Dijkstra BG, Meek B, et al. Autoantibodies to photoreceptor proteins and outer plexiform layer in patients with cancer-associated retinopathy. Clin Exp Immunol 2002;128:498–503.
364. Murphy MA, Thirkill CE, Hart WM. Paraneoplastic retinopathy: A novel autoantibody reaction associated with small-cell lung cancer. J Neuroophthalmol 1997; 17:77–83.
365. Eichen JG, Dalmau J, Demopoulos A, et al. The photoreceptor cell-specific nuclear receptor is an autoantigen of paraneoplastic retinopathy. J Neuroophthalmol 2001;21:168–172.
366. Aptsiauri N, Guy J, Flannery J, et al. Immunocytochemical localization of anti-enolase reactivity in cancer associated retinopathy (CAR). Invest Ophthalmol Vis Sci 1995;36:S1039.
367. Ohguro H, Ogawa K, Nakagawa T. Recoverin and hsc70 are found as autoantigens in patients with cancer-associated retinopathy. Invest Ophthalmol Vis Sci 1999;40:82–89.
368. Guy J, Aptsiauri N. Treatment of paraneoplastic visual loss with intravenous immunoglobulin. Arch Ophthalmol 1999;117:471–477.
369. Cogan DG, Kuwabara T, Currie J, et al. Paraneoplastische Retinopathie unter dem klinischen Bild einer Zapfendystrophie mit Achromatopsie. Klin Mbl Augenheilk 1990;197:156–158.
370. Campo E, Brunier MN, Merino MJ. Small-cell carcinoma of the endometrium with associated ocular paraneoplastic syndrome. Cancer 1992;69:2283–2288.
371. Rios RJ, Odel JG, Camac A, et al. A 45 year old female with Guillain-Barré and optic neuritis. Presented at the 26th Annual Frank B Walsh Society Annual Meeting. Chicago, IL, April 9–10, 1994.
372. Jacobson DM, Thirkill CE. Paraneoplastic cone dysfunction: An unusual visual remote effect of cancer. Arch Ophthalmol 1995;113:1580–1582.
373. Ripps H, Carr RE, Siegel IM, et al. Functional abnormalities in vincristine-induced night blindness. Invest Ophthalmol Vis Sci 1984;25:787–794.
374. DuBois LG, Sadun AA, Lawton TB. Inner retinal layer loss in complicated migraine. Arch Ophthalmol 1988;106:1035–1037.
375. Dubois LG, Sadun AA. Response to MacKay CJ. Retinitis pigmentosa misdiagnosed as complicated migraine. Arch Ophthalmol 1991;109:175.
376. Berson EL, Lessell S. Paraneoplastic night blindness with malignant melanoma. Am J Ophthalmol 1988;106:307–311.
377. Alexander KR, Fishman GA, Peachey NS, et al. 'On' response defect in paraneoplastic night blindness with cutaneous malignant melanoma. Invest Ophthalmol Vis Sci 1992;33:477–490.
378. Pollock S, Kuwashima L, Kelman S, et al. Melanoma-associated retinopathy (MAR). Presented at the 18th Annual North American Neuro-ophthalmology Society Meeting. San Diego, CA, Feb 23–27, 1992.
379. Andreasson S, Ponjavic V, Ehinger B. Full-field electroretinogram in a patient with cutaneous melanoma-associated retinopathy. Acta Ophthalmol 1993;71: 487–490.
380. Milam AH, Saari JC, Jacobson SG, et al. Autoantibodies against retinal bipolar cells in cutaneous melanoma-associated retinopathy. Invest Ophthalmol Vis Sci 1993;34:91–100.
381. Rush JA. Paraneoplastic retinopathy in malignant melanoma. Am J Ophthalmol 1993;115:390–391.
382. Kim RY, Retsas S, Fitzke FW, et al. Cutaneous melanoma-associated retinopathy. Ophthalmology 1994;101:1837–1843.
383. Weinstein JM, Kelman SE, Bresnick GH, et al. Paraneoplastic retinopathy associated with antiretinal bipolar cell antibodies in cutaneous malignant melanoma. Ophthalmology 1994;101:1236–1243.
384. Singh AD, Milam AH, Shields CL, et al. Melanoma-associated retinopathy. Am J Ophthalmol 1995;119:369–370.
385. Kellner U, Bornfeld N, Foerster MH. Severe course of cutaneous melanoma associated retinopathy (MAR). Invest Ophthalmol Vis Sci 1994;35:2117.
386. Remulla JFC, Pineda R, Gaudio A, et al. Cutaneous melanoma-associated retinopathy with retinal periphlebitis. Arch Ophthalmol 1995;113:854–855.
387. Borkowski LM, Grover S, Fishman GA, Jampol LM. Retinal findings in melanoma-associated retinopathy. Am J Ophthalmol 2001;132:273–275.
388. Janaky M, Palffy A, Kolozsvari L, et al. Unilateral manifestation of melanoma-associated retinopathy. Arch Ophthalmol 2002;120:866–867.
389. Keltner JL, Thirkill CE, Yop PT. Clinical and immunologic characteristics of melanoma-associated retinopathy syndrome: 11 new cases and a review of 51 previously published cases. J Neuroophthalmol 2001;21:173–187.
390. Jacobson DM, Adamus G. Retinal anti-bipolar cell antibodies in a patient with paraneoplastic retinopathy and colon carcinoma. Am J Ophthalmol 2001;131: 806–808.
391. Wolf JE, Arden GB. Selective magnocellular damage in melanoma-associated retinopathy: Comparison with congenital stationary nightblindness. Vision Res 1996;36:2369–2379.
392. Wolf JE, Arden GB, Plant GT. Selective damage to either the ''M'' or ''P'' cell pathway in human retinal disease: Implications for visual processing. Eur J Ophthalmol 1996;6:208–214.

393. Milam AH, Saari JC. Autoantibodies against retinal rod bipolar cells in melanoma-associated retinopathy. Invest Ophthalmol Vis Sci 1994;35:2116.
394. Boeck K, Hofmann S, Klopfer M, et al. Melanoma-associated paraneoplastic retinopathy: Case report and review of the literature. Br J Dermatol 1997;137: 457–460.
395. Gittinger JW, Smith TW. Cutaneous melanoma-associated paraneoplastic retinopathy: Histopathologic observations. Am J Ophthalmol 1999;127:612–614.
396. Machemer R. Zur Pathogenese des flachenhaften malignen Melanoms. Klin Monatsbl Augenheikd 1966;148:641–652.
397. Prusiner PE, Butler A, Yavitz EQ, et al. Metastatic adenocarcinoma presenting as bilateral blindness. Ann Ophthalmol 1983;15:653–656.
398. Mullaney J, Mooney D, O'Connor M, et al. Bilateral ovarian carcinoma with bilateral uveal melanoma. Br J Ophthalmol 1984;68:261–267.
399. Prause JU, Jensen OA, Eisgart F, et al. Bilateral diffuse malignant melanoma of the uvea associated with large cell carcinoma, giant cell type, of the lung: Case report of a newly described syndrome. Ophthalmologica 1984;189:221–228.
400. Tsukahara S, Wakui K, Ohzeki S. Simultaneous bilateral primary diffuse malignant uveal melanoma: Case report with pathological examination. Br J Ophthalmol 1986;70:33–38.
401. Barr CC, Zimmerman LE, Curtin VT, et al. Bilateral diffuse melanocytic uveal tumors associated with systemic malignant neoplasms: A recently recognized syndrome. Arch Ophthalmol 1982;100:249–255.
402. de Wolff-Rouendaal D. Bilateral diffuse benign melanocytic tumours of the uveal tract. A clinicopathological study. Int Ophthalmol 1985;7:149–160.
403. Filipic M, Ambler JS. Bilateral diffuse melanocytic uveal tumours associated with systemic malignant neoplasm. Aust NZ J Ophthalmol 1986;14:293–299.
404. Margo CE, Pavan PR, Gendelman D, et al. Bilateral melanocytic uveal tumors associated with systemic non-ocular malignancy. Malignant melanomas or benign paraneoplastic syndrome? Retina 1987;7:137–141.
405. Gass JDM, Gieser RG, Wilkinson CP, et al. Bilateral diffuse uveal melanocytic proliferation in patients with ocult carcinoma. Arch Ophthalmol 1990;108: 527–533.
406. Leys AM, Dierick HG, Sciot RM. Early lesions of bilateral diffuse melanocytic proliferation. Arch Ophthalmol 1991;109:1590–1594.
407. Ryll DL, Campbell RJ, Robertson DM, et al. Pseudometastatic lesions of the choroid. Ophthalmology 1980;87:1181–1186.
408. Lafaut BA, Bourgoignie KB, Sallet G, et al. Proliferation bilaterale diffuse des melanocytes uveaux. A propos d'un cas particulier. J Fr Ophtalmol 1994;17: 208–213.
409. Mooy CM, de Jong PTVM, Strous C. Proliferative activity in bilateral paraneoplastic melanocytic proliferation and bilateral uveal melanoma. Br J Ophthalmol 1994;78:483–484.
410. Gass JDM, Glatzer RJ. Acquired pigmentation simulating Peutz-Jeghers syndrome: Initial manifestation of diffuse uveal melanocytic proliferation. Br J Ophthalmol 1991;75:693–695.
411. Borruat FX, Othenin-Girard P, Uffer S, et al. Natural history of diffuse uveal melanocytic proliferation: Case report. Ophthalmology 1992;99:1698–1704.
412. Chahud F, Young RH, Remulla JF, et al. Bilateral diffuse uveal melanocytic proliferation associated with extraocular cancers. Am J Surg Pathol 2001;25: 212–218.
413. Rohrbach JM, Roggendorf W, Thanos S, et al. Simultaneous bilateral diffuse melanocytic uveal hyperplasia. Am J Ophthalmol 1990;110:49–56.
414. Ritland JS, Eide N, Taujo J. Bilateral diffuse uveal melanocytic proliferation and uterine cancer: A case report. Acta Ophthalmol Scand 2000;78:366–368.
415. Rudge P. Optic neuritis as a complication of carcinoma of the breast. Proc R Soc Med 1973;66:1106–1107.
416. Gass JDM. Acute Vogt-Koyanagi-Harada-like syndrome ocurring in a patient with metastatic cutaneous melanoma. In Saari KM, ed. Uveitis Update. Proceedings of the International Symposium on Uveitis–Hanasaari, Espoo, Finland, May 16–19, 1994. Elsevier Science Publishers, 1994:407–408.
417. Antoine JC, Honnorat J, Vocanson C, et al. Posterior uveitis, paraneoplastic encephalomyelitis and auto-antibodies reacting with developmental protein of brain and retina. J Neurol Sci 1993;117:215–223.
418. Yu Z, Kryzer TJ, Griesmann GE, et al. CRMP-5 neuronal autoantibody: marker of lung cancer and thymoma-related autoimmunity. Ann Neurol 2001;49: 146–154.
419. Vernino S, Tuite P, Adler CH, et al. Paraneoplastic chorea associated with CRMP-5 neuronal antibody and lung carcinoma. Ann Neurol 2002;51:625–630.
420. Cross SA, Salomao DR, Parisi JE, et al. Paraneoplastic autoimmune optic neuritis and retinitis defined by CRMP-5-IgG. Ann Neurol 2003;54:38–50.
421. Keltner JL, Thirkill CE, Huynh PM. Autoimmune-related retinopathy and optic neuropathy (ARRON) syndrome. J Neuroophthalmol (Abstr) 2002;22:160–161.
422. Luiz JF, Lee AG, Keltner JL, et al. Paraneoplastic optic neuropathy and autoantibody production in small-cell carcinoma of the lung. J Neuroophthalmol 1998; 18:178–182.
423. Lambercht ER, van der Loos TL, van der Eerden AH. Retrobulbar optic neuritis as the first sign of glucagonoma syndrome. Int Ophthalmol 1987;11:13–15.
424. Blumenthal D, Schochet S, Gutmann L, et al. Small-cell carcinoma of the lung presenting with paraneoplastic peripheral nerve microvasculitis and optic neuropathy. Muscle Nerve 1998;21:1358–1359.
425. Hoh ST, The M, Chew SJ. Paraneoplastic optic neuropathy in nasopharyngeal carcinoma—report of a case. Singapore Med J 1991;32:170–173.
426. Coppeto JR, Monteiro MLR, Cannarozzi DB. Optic neuropathy associated with chronic lymphomatous meningitis. J Clin Neuroophthalmol 1988;8:39–45.
427. West CE, Repka MX. Tonic pupils associated with neuroblastoma. J Pediatr Ophthalmol Strabismus 1992;29:382–383.
428. Inoue Y, Motegi T, Yuasa T, et al. Subacute sensory neuropathy manifested by tonic pupils associated with small-cell carcinoma of the lung. Clin Neurol (Jpn) 1989;29:1302–1305.
429. Nemoto H, Fujioka T, Okada S, et al. A case of carcinomatous autonomic and sensory neuropathy. Clin Neurol (Jpn) 1992;32:543–546.
430. Bell CE, Seetharam S, McDaniel RC. Endodermally derived and neural crest-derived differentiation antigens expressed by a human lung tumor. J Immunol 1976;116:1236–1243.
431. Bell CE, Seetharam S. Expression of endodermally derived and neural crest-derived differentiation antigens by human lung and colon tumors. Cancer 1979; 44:13–18.
432. Bell CE, Seetharam S. Identification of the Schwann cell as a peripheral nervous system cell possessing a differentiation antigen expressed by a human lung tumor. J Immunol 1977;118:826–831.
433. Posner JB. The anti-Hu syndrome: A model paraneoplastic disorder. Recent Results Cancer Res 1994;135:77–90.
434. Pranzatelli MR, Huang Y, Tate E, et al. Cerebrospinal fluid 5-hydroxyindoleacetic acid and homovanillic acid in the pediatric opsoclonus-myoclonus syndrome. Ann Neurol 1995;37:189–197.
435. Vital C, Bonnaud C, Arne L, et al. Polyradiculo-névrite au course d'un leucémie lymphoide chronique. Acta Neuropathol 1975;32:169–172.
436. Fudman EJ, Schnitzer TJ. Dermatomyositis without creatine kinase elevation: A poor prognostic sign. Am J Med 1986;80:329–332.
437. Nishika M, Sato A. Low incidence of antinuclear antibodies in dermatomyositis with malignancy. Ann Rheum Dis 1990;49:422.
438. Gray-Keller MP, Polans AS, Palczewski K, et al. The effect of recoverin-like calcium-binding proteins on the photoresponse of retinal rods. Neuron 1993;10: 523–531.
439. MacKay CJ, Gouras P, Yamamoto S. S-cone and rod ERGs reduced in paraneoplastic retinal degeneration. Invest Ophthalmol Vis Sci 1992;33:1074.
440. Anderson HJ, Churchill-Davidson HD, Richardson AT. Bronchial neoplasm with myasthenia. Lancet 1953;2:1291–1293.