The term “paraneoplastic syndromes” refers to symptoms or signs resulting from damage to organs or tissues that are remote from the site of a malignant neoplasm or its metastases. Paraneoplastic syndromes can affect most organs and tissues. Widely known examples include cancer cachexia, hypercalcaemia, Cushings’s syndrome, and Troussaus’s syndrome. Most of these paraneoplastic syndromes occur because the tumor secretes substances that mimic normal hormones or that interfere with circulating proteins. A few paraneoplastic neurologic disorders are caused by similar mechanisms (e.g., carcinoid myopathy and encephalopathy). However, most or all paraneoplastic neurologic disorders are immune-mediated. (We do not consider damage to the nervous system by cancer-induced coagulopathies or opportunistic infections to be paraneoplastic neurologic disorders.) The cancers causing paraneoplastic neurologic disorders are often asymptomatic and sometimes occult; it is the neurologic symptoms that take the patient to the doctor. The combination of an indolent tumor and severe neurologic disability suggests effective antitumor immunity coupled with autoimmune brain degeneration. This review describes paraneoplastic neurologic disorders believed to be immune-mediated and discusses our current understanding of their mechanisms.

Paraneoplastic neurologic disorders can affect any part of the nervous system (Table 1). Some of them affect only a single area (e.g., limbic encephalitis) or a single cell type (e.g., the Purkinje cells of the cerebellum). In other instances, multiple levels of the nervous system are involved (e.g., encephalomyeloradiculitis).

Most symptomatic paraneoplastic syndromes are rare, affecting perhaps 0.01 percent of patients with cancer. Exceptions are the Lambert–Eaton myasthenic syndrome, which affects about 3 percent of patients with small-cell lung cancer; myasthenia gravis, which affects about 15 percent of patients with thymoma; and demyelinating peripheral neuropathy, which affects about 50 percent of patients with the rare osteosclerotic form of plasmacytoma (the polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes [POEMS] syndrome).

Clinical and electrophysiological studies in patients with cancer, particularly small-cell lung cancer, often disclose proximal muscle weakness or delayed conduction along peripheral nerves in asymptomatic patients. Whether these abnormalities are true paraneoplastic neurologic disorders is unknown.

The symptoms and signs of paraneoplastic syndromes are diverse, but certain features are common. The neurologic disorder usually appears before the cancer has been identified. In many instances an initial search for cancer is unrewarding; the tumor is found months or even a few years after the appearance of the neurologic syndrome. Whole-body positron-emission tomography may be the best screening method for locat-
The new england journal of medicine

39

ing the occult cancer. Nonetheless, the neurologic illness usually develops rapidly over days to a few months. Paraneoplastic neurologic disorders are usually severe, often disabling, and sometimes lethal.

LABORATORY FINDINGS
Examination of cerebrospinal fluid reveals a mild pleocytosis (30 to 40 white cells per cubic millimeter), a slightly elevated protein level (50 to 100 mg per deciliter), and an elevated IgG level. Pleocytosis is usually apparent only early in the course of the disease and disappears within several weeks to months. The elevated IgG level may, however, persist. Analysis of cerebrospinal fluid cells in patients with paraneoplastic cerebellar degeneration through fluorescent-activated cell sorting has revealed that the predominant cell type (over 75 percent) is T cells, with a small component (less than 10 percent) of B cells and natural killer cells.

ANTIBODIES
Perhaps most important diagnostically, many patients with paraneoplastic syndromes have antibodies in their serum (and cerebrospinal fluid) that react with both the nervous system and the underlying cancer (Fig. 1 and Table 2). The identification of these antibodies and their target neural antigens has substantially advanced our ability to make an early diagnosis and has led to the concept that paraneoplastic neurologic disorders are immune-mediated.

Although there is considerable overlap, each of these antibodies is associated with a narrow spectrum of clinical syndromes and a restricted subgroup of cancers (Table 2). The antibodies, some of which we named using the first two letters of the surname of the index patient, are highly specific for identifying a patient with neurologic disability who has a paraneoplastic syndrome. These antibodies also suggest the site of the underlying cancer. For example, the presence of anti-Yo antibodies in the serum of a woman with cerebellar symptoms is virtually conclusive evidence that she has paraneoplastic cerebellar degeneration and gynecologic, usually ovarian, cancer (Fig. 1A).

Unfortunately, not all patients with paraneoplastic syndromes have identifiable antibodies in their serum. Whether this is a technical fault in detection or whether some paraneoplastic neurologic disorders are not immune-mediated is not known.

ANTIGENS
In most cases of paraneoplastic syndromes associated with antibodies, the antigen has been identified and the gene coding for the antigen has been cloned and sequenced (Table 2). Some of these antigens are expressed by all tumors of a given histologic type, whether or not the patient mounts an immune response against them. Other tumors rarely express such antigens unless the cancer causes a paraneoplastic neurologic disorder. Failure to find the anti-
gen in the cancer of a patient with paraneoplastic antibodies should prompt a search for a second cancer.22

PATHOPHYSIOLOGICAL FEATURES

THE AUTOIMMUNE MODEL OF PATHOGENESIS

Currently, it is thought that most or all paraneoplastic neurologic disorders are immune-mediated (Fig. 2). The mechanism entails ectopic expression by a tumor of an antigen that normally is expressed exclusively in the nervous system. Some of these so-called onconeural antigens are also expressed in the normal testis, an organ that is, like the brain, an immunologically privileged site. The tumor antigen is identical to the neural antigen,68 but for unknown reasons the immune system identifies it as foreign and mounts an immune attack. The immune attack controls the growth of the cancer and may in a few instances obliterate it (Fig. 3). However, the antibodies and cytotoxic T cells that are specific for the tumor antigen are not sufficient to cause the neurologic disease unless they cross the blood–brain barrier and react with neurons expressing the onconeural antigen (Table 3).

TUMOR IMMUNITY IN PARANEOPLASTIC SYNDROMES

The Tumor

Onconeural antigens are present in the tumor in all patients with antibody-positive paraneoplastic neurologic disorders and in many patients without such disorders. Moreover, the genes for these antigens are not mutated in tumor cells.68,70,71 Thus, paraneoplastic neurologic syndromes cannot be attributed to the infrequency of expression of the relevant tumor antigens or to mutations in the genes encoding these antigens.

The tumor is often occult, and the neurologic disorder typically precedes the diagnosis of the tumor.8,22 For example, patients with the Hu paraneoplastic syndrome typically harbor small-cell lung cancers that are limited to single nodules (53 of 55 patients in one study44), despite the fact that most small-cell lung cancers (over 60 percent) are widely metastatic at diagnosis. In a few instances, unequivocal paraneoplastic syndromes may follow identification and even treatment of the tumor, and may sometimes herald a relapse.

The histologic features of tumors in paraneoplastic neurologic disorders do not differ from those of other tumors, except that the tumors may be heavily infiltrated with inflammatory cells.8,72,73 Many reports suggest that patients with paraneoplastic neurologic disorders have a better prognosis than patients with histologically identical tumors that are not associated with paraneoplastic neurologic disorders.74–77 The improved prognosis is not simply a result of earlier diagnosis of the cancer because the neurologic disease has led to a search for cancer. Patients with low titers of anti-Hu antibodies but without paraneoplastic disorders also have more limited small-cell lung cancer than patients who do not have the antibodies.40,78

The Nervous System

The presence of antigen-specific cytotoxic T cells in paraneoplastic neurologic disorders was clearly documented after a patient with acute paraneoplastic cerebellar degeneration and anti-Yo antibodies was found to have activated T cells in her blood that were able to lyse target cells presenting the Yo (also called cdr2) antigen in vitro.79 Subsequent studies in chronically ill patients with paraneoplastic cerebellar degeneration have used autologous antigen-presenting cells (dendritic cells) to reactivate responses to the cdr2 antigen in memory cytotoxic T cells. Such reactivated responses have been elicited in all patients with paraneoplastic cerebellar degeneration whose T cells were tested for the phenomenon.41,79 These studies have been complemented by reports of a limited V β chain T-cell repertoire in patients with the Hu syndrome (the V β is one of the two chains, V β and V α, of the T-cell receptor).80 Taken together, the evidence indicates that T-cell responses have an important role in paraneoplastic neurologic disorders.

Antibodies in paraneoplastic neurologic disorders react with the portion of the nervous system that is responsible for the clinical symptoms—for example, anti–Purkinje-cell antibodies occur in patients with paraneoplastic cerebellar degeneration.81 In many instances, the reaction is more widespread than the clinical findings. In paraneoplastic neurologic disorders affecting the brain, relatively high titers of the antibody in the cerebrospinal fluid (relative to total IgG) indicate that the antibody is synthesized within the brain, presumably by specific B cells that have crossed the blood–brain barrier.82

One report described the presence of anti-Hu antibodies within neuronal nuclei of the central nervous system in patients who died of their paraneoplastic syndromes.83 Although some believe this
finding to be an artifact, antibodies to double-stranded DNA, the hallmark of systemic lupus erythematosus, have been found within the nuclei of cells in patients with systemic lupus erythematosus.\textsuperscript{84}

\textbf{Antibodies and Cytotoxic T Cells}

The relative roles of humorally mediated immunity (antibodies) and cellular immunity (T cells) in paraneoplastic neurologic disorders are unresolved.\textsuperscript{85} This uncertainty is complicated by the fact that different paraneoplastic neurologic disorders may have different underlying mechanisms. When the target antigens are cell-surface receptors, as in the Lambert–Eaton myasthenic syndrome, myasthenia gravis, and a rare form of paraneoplastic cerebellar degeneration, antibodies appear to have the predominant role.

\textbf{UNRESOLVED ISSUES}

\textbf{Animal Models}

Studies in animals have failed to reproduce paraneoplastic neurologic syndromes, perhaps in part because many of them have focused on antineuronal antibodies, whereas studies in humans have implicated an important cellular component in the immune response in several paraneoplastic neurologic syndromes. In one report, animals immunized with DNA corresponding to the Hu antigen were protected against subsequent inoculation of the tumor,\textsuperscript{86} but the importance of this report, in the face of many similar reports in which protection was induced in animal models of tumors not associated with paraneoplastic neurologic disorders, is uncertain.

\textbf{Protection Against the Tumor}

It is not known whether the antitumor immune response in paraneoplastic neurologic disorders can be harnessed to treat tumors without damaging the nervous system. In the current model of paraneoplastic neurologic disorders (Fig. 2),\textsuperscript{87} apoptosis of tumor cells triggers an antitumor immune response. Indeed, it has been shown that apoptotic tumor cells in paraneoplastic neurologic disorders are a potent means of activating tumor-specific T cells.\textsuperscript{88} Such killer T cells could trigger a feedback loop by inducing apoptosis and hence amplification of the antitumor immune response. These observations suggest that understanding the mechanisms that trigger effective tumor immune responses in patients with paraneoplastic neurologic disorders may have an important role in developing successful approaches to tumor immunotherapy.

\textbf{Variations in Pathological Features}

Another factor complicating our understanding of the neuronal degeneration in paraneoplastic neurologic disorders is the fact that the pathological features of these disorders vary widely. For example, in paraneoplastic cerebellar degeneration, there is total loss of the Purkinje cells of the cerebellum, with little or no pathological change elsewhere in the nervous system and no identifiable inflammatory infiltrates within the cerebellum itself. By contrast, in paraneoplastic encephalomyelitis, there is not only widespread destruction of neurons, including Purkinje cells, but also florid inflammation within the central nervous system and intraneuronal deposits of antibodies.\textsuperscript{83} In some patients with paraneoplastic syndromes, particularly opsoclonus–myoclonus, autopsy may demonstrate an entirely normal brain.
There is no uniform nomenclature for some of the antibodies. In this article, we use the nomenclature developed in our laboratory. Where differences exist, they are indicated in parentheses. VGCC denotes voltage-gated calcium channel, VGKC voltage-gated potassium channel, and MAG myelin-associated glycoprotein.

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Neuronal Reactivity</th>
<th>Protein Antigens</th>
<th>Cloned Genes</th>
<th>Tumor</th>
<th>Paraneoplastic Symptoms</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Hu (ANNA-1)</td>
<td>Nucleus more than cytoplasm (all neurons)</td>
<td>35–40 kD</td>
<td>HuD, HuC, Hel-N1</td>
<td>Small-cell lung cancer, neuroblastoma, prostate cancer</td>
<td>Paraneoplastic encephalomyelitis, paraneoplastic sensory neuronopathy, paraneoplastic cerebellar degeneration, autonomic dysfunction</td>
<td>Graus et al., Szabo et al., Levine et al., Sakai et al.</td>
</tr>
<tr>
<td>Anti-Yo (PCA-1)</td>
<td>Cytoplasm, Purkinje cells</td>
<td>34 and 62 kD</td>
<td>CDR34, CDR62</td>
<td>Ovarian, breast, and lung cancers</td>
<td>Paraneoplastic cerebellar degeneration</td>
<td>Peterson et al., Fathallah-Shaykh et al., Darnell et al.</td>
</tr>
<tr>
<td>Anti-Ri</td>
<td>Nucleus more than cytoplasm (central nervous system neurons)</td>
<td>55 and 80 kD</td>
<td>Nova</td>
<td>Breast, gynecologic, lung, and bladder cancers</td>
<td>Ataxia with or without opsoclonus–myoclonus</td>
<td>Jensen et al., Darnell et al., Luque et al., Buckanovich et al.</td>
</tr>
<tr>
<td>Anti-Tr</td>
<td>Cytoplasm, Purkinje cells</td>
<td>?</td>
<td>—</td>
<td>Hodgkin’s lymphoma</td>
<td>Paraneoplastic cerebellar degeneration</td>
<td>Peltola et al.</td>
</tr>
<tr>
<td>Anti-VGCC</td>
<td>Presynaptic neuromuscular junction</td>
<td>64 kD</td>
<td>P/Q type VGCC, MysB</td>
<td>Small-cell lung cancer</td>
<td>Lambert–Eaton myasthenic syndrome</td>
<td>Carpentier and Delattre</td>
</tr>
<tr>
<td>Antiretinal</td>
<td>Photoreceptors, ganglion cells</td>
<td>23, 65, 145, and 205 kD</td>
<td>Recoverin</td>
<td>Small-cell lung cancer, melanoma, gynecologic cancers</td>
<td>Cancer-associated retinopathy, melanoma-associated retinopathy</td>
<td>Maeda et al., Polans et al., Thirkell et al.</td>
</tr>
<tr>
<td>Anti-amphiphysin</td>
<td>Presynaptic nerve terminals</td>
<td>128 kD</td>
<td>Amphiphysin</td>
<td>Breast cancer, small-cell lung cancer</td>
<td>Stiff-person syndrome, paraneoplastic encephalomyelitis</td>
<td>Saiz et al., De Camilli et al., Folli et al.</td>
</tr>
<tr>
<td>Anti-CRMP5 (Anti-CV2)</td>
<td>Oligodendrocytes, neurons, cytoplasm</td>
<td>66 kD</td>
<td>CRMP5 (POP66)</td>
<td>Small-cell lung cancer, thymoma</td>
<td>Encephalomyelitis, cerebellar degeneration, chorea, sensory neuropathy</td>
<td>Yu et al.</td>
</tr>
<tr>
<td>Anti-PCA-2</td>
<td>Purkinje cytoplasm and other neurons</td>
<td>280 kD</td>
<td>—</td>
<td>Small-cell lung cancer</td>
<td>Encephalomyelitis, cerebellar degeneration, Lambert–Eaton myasthenic syndrome</td>
<td>Bataller et al.</td>
</tr>
<tr>
<td>Anti-Ma1</td>
<td>Neurons (subnucleus)</td>
<td>40 kD</td>
<td>Ma1</td>
<td>Lung cancer, other cancers</td>
<td>Brain-stem encephalitis, cerebellar degeneration</td>
<td>Rosenfeld et al.</td>
</tr>
<tr>
<td>Anti-Ma2</td>
<td>Neurons (subnucleus)</td>
<td>41.5 kD</td>
<td>Ma2</td>
<td>Testicular cancer</td>
<td>Limbic brain-stem encephalitis</td>
<td>Rosenfeld et al.</td>
</tr>
<tr>
<td>ANNA-3</td>
<td>Nuclei, Purkinje cells</td>
<td>170 kD</td>
<td>—</td>
<td>Lung cancer</td>
<td>Sensory neuronopathy, encephalomyelitis</td>
<td>Chan et al.</td>
</tr>
<tr>
<td>Anti-mGluR1</td>
<td>Purkinje cells, olfactory neurons, hippocampus</td>
<td>Metabotropic glutamate receptor</td>
<td>Glu receptor</td>
<td>Hodgkin’s lymphoma</td>
<td>Paraneoplastic cerebellar degeneration</td>
<td>Smitt et al.</td>
</tr>
<tr>
<td>Anti-VGKC</td>
<td>Peripheral nerve</td>
<td>VGKC</td>
<td>Potassium channels</td>
<td>Thymoma, small-cell lung cancer</td>
<td>Neuromyotonia</td>
<td>Vemino and Lennon, Hart et al.</td>
</tr>
<tr>
<td>Anti-MAG</td>
<td>Peripheral nerve</td>
<td>MAG</td>
<td>MAG</td>
<td>Waldenström’s macroglobulinemia</td>
<td>Peripheral neuropathy</td>
<td>Vital</td>
</tr>
</tbody>
</table>
Figure 2. Proposed Pathogenesis of Paraneoplastic Neurologic Disorders.

A tumor not involving the nervous system expresses a neuronal protein that the immune system recognizes as nonself. Apoptotic tumor cells are phagocytized by dendritic cells that migrate to lymph nodes, where they activate antigen-specific CD4+, CD8+, and B cells. The B cells mature into plasma cells that produce antibodies against the tumor antigen. The antibodies or the cytotoxic CD8+ T cells (or both) slow the growth of the tumor, but they also react with portions of the nervous system outside the blood–brain barrier. In the illustration, antibodies are reacting with voltage-gated calcium channels at the neuromuscular junction, causing the Lambert–Eaton myasthenic syndrome. In some instances, plasma cells and cytotoxic T cells cross the blood–brain barrier and attack neurons expressing the antigen they share with the tumor.
even when serial sections are made through the site of the omnipause neurons, which are thought to be responsible for opsoclonus. In the Lambert–Eaton myasthenic syndrome, electron microscopy reveals binding of antibodies against voltage-gated calcium channels at the presynaptic neuromuscular junction, which disrupts the active sites. Thus, although paraneoplastic syndromes involving the nervous system may all be immune-mediated, the site of damage and the exact mechanism may vary from syndrome to syndrome in ways that are not fully understood.

In paraneoplastic neurologic disorders of the central nervous system, where most of the known target antigens are intracellular proteins, animal models have not provided evidence that antibodies have a role in pathogenesis. Documentation of the expression of major-histocompatibility-complex (MHC) class I and MHC class II antigen–presenting molecules in neurons supports the possibility that T cells recognize intracellular antigen presented to them as an MHC–peptide complex and thereby kill neurons. Identification of antigen-specific T cells in the central nervous system would support this hypothesis, as would an animal model in which antigen-specific T cells mediated neuronal degeneration.

Because paraneoplastic syndromes are considered to be immune-mediated, two treatment approaches have been used: removal of the source of the antigen by treatment of the underlying tumor, and suppression of the immune response. For many paraneoplastic syndromes, the first approach is the only effective treatment. In the Lambert–Eaton myasthenic syndrome and myasthenia gravis, plasma exchange or intravenous immune globulin is usually effective in suppressing the immune response. If the disease is mediated by T cells, as is suspected in many central nervous system disorders, such as paraneoplastic cerebellar degeneration with anti-Yo antibodies or encephalomyelitis with anti-Hu antibodies, drugs such as tacrolimus or mycophenolate mofetil may be tried. Because the pathogenesis of many paraneoplastic disorders is unknown and humoral and cell-mediated immunity may both have a role, it may be appropriate to suppress both arms of the immune system.

There are no established protocols for the treatment of most paraneoplastic syndromes, but if the patient’s condition is deteriorating, the physician usually uses a combination of either plasma exchange or intravenous immune globulin and immu-
There is no established protocol for immunosuppressive treatment. Keime-Guibert and colleagues\(^\text{95}\) administered intravenous immune globulin at a dose of 0.5 g per kilogram of body weight per day for five days, intravenous methylprednisolone at 1 g per day for three days, and intravenous cyclophosphamide at 600 mg per square meter of body-surface area for one day on day 4. If there was evidence of improvement or stability, the treatment was repeated three times at three-week intervals. If the patient improved after the third treatment, maintenance treatment with 0.5 g of intravenous immune globulin per kilogram, 1 g of intravenous methylprednisolone, and 600 mg of intravenous cyclophosphamide per square meter was delivered one day monthly for six months.\(^\text{95}\) There is less experience with tacrolimus. We have given tacrolimus at a dose of 0.15 mg per kilogram per day for 14 days, followed by 0.3 mg per kilogram per day for 7 days.\(^\text{41}\) This regimen decreased the number of activated T cells in the spinal fluid but had no substantial effect on the clinical course.

For most paraneoplastic syndromes, immunotherapy is not effective.\(^\text{13,95}\) However, isolated case reports describing responses to various immunotherapeutic interventions encourage physicians to combine immunotherapy with treatment of the cancer in a desperate situation. Since the pathologic features of paraneoplastic neurologic disorders suggest that a destructive immune response is typically present, treatment with immunosuppression should begin as expeditiously as possible.

**Prognosis**

Some disorders, such as the Lambert–Eaton myasthenic syndrome and myasthenia gravis, respond well to immunosuppression and subsequently to treatment of the underlying tumor. The peripheral neuropathy associated with osteosclerotic myeloma generally resolves when the tumor is treated with radiotherapy. A few disorders, such as opsoclonus–myoclonus in adults, may respond to treatment of the underlying tumor, immunosuppression, or both, or they may resolve spontaneously. In many instances, it is not clear whether the paraneoplastic syndrome resolves spontaneously or in response to treatment. Disorders involving the central nervous system, such as encephalomyelitis associated with cancer or paraneoplastic cerebellar degeneration, usually respond poorly to treatment, although they may stabilize when the underlying tumor is treated.

The reason for the different prognoses probably has to do with the underlying pathologic features. The Lambert–Eaton myasthenic syndrome and myasthenia gravis are diseases of the neuromuscular junction, which can recover its function once the causal insult has resolved, because there is no loss of the parent neuron. Disorders such as paraneoplastic cerebellar degeneration are usually associated with neuronal loss, and because they evolve subacutely and treatment is often delayed, the neurons die, making recovery impossible. Some central nervous system disorders, such as opsoclonus–myoclonus, may not involve cellular loss and, in fact, may have no identifiable pathologic features. Thus, patients with these disorders, like those with the Lambert–Eaton myasthenic syndrome, have the potential for recovery.

An important question is whether immunosuppression for treatment of the paraneoplastic syndrome stimulates the growth of the tumor. No evidence of this has been reported. Most reports that describe an absence of response of the paraneoplastic syndrome to immunosuppression do not note an exacerbation of the tumor.

Supported by the Howard Hughes Medical Institute, the Burroughs Wellcome Fund, a grant from the National Cancer Institute (R01 CA85784), and a grant from the National Institute of Neurological Disorders and Stroke (R01 NS34839) (to Dr. Darnell); a grant from the National Center for Research Resources at the National Institutes of Health (GCRC M01-RR00102); and a grant from the National Institute of Neurological Disorders and Stroke (NS 026064) and an Evelyn Frew Clinical Research Professorship from the American Cancer Society (to Dr. Posner).

Editor’s note: Memorial Sloan-Kettering Cancer Center has licensed patents covering methods used to prepare antigens for assays used in the diagnosis of paraneoplastic syndromes; Drs. Darnell and Posner receive a portion of the royalties.


