This monograph describes the neoplasms, hamartomas, hyperplasias, reactive lesions, and inflammatory pseudotumors arising from or associated with peripheral nerves. Discussed are lesions affecting spinal nerves (intradural and extradural nerve roots and ganglia), peripheral nerves, specialized sensorimotor endings of peripheral nerves, and cranial nerves. Also included are autonomic nerves, their paravertebral and visceral ganglia, and associated neurotransmitter cells of Cajal. Specifically excluded from consideration are lesions of the optic nerve, a central nervous system structure, as well as nontumefactive disorders affecting nerve. Non-neural tumors affecting the substance of nerves, such as metastatic carcinoma, rare examples of melanoma, lymphoma, and direct extensions from surrounding soft tissue neoplasms are also discussed.

Peripheral nerve tumors (PNTs), which account for the large majority of tumors of the peripheral nervous system, are generally classified as soft tissue tumors but differ significantly from other neoplasms in this category. Notable differences include their frequent association with genetic disorders, particularly neurofibromatosis type 1, and the origin of a majority of malignant PNT from a benign precursor lesion, the neurofibroma. PNTs arise from complex tissue with distinctive anatomic compartments. Nerves consist not simply of axons but of specialized ensheathments and compartments. These include: 1) Schwann cells, which ensheathe axons to form “nerve fibers”; 2) accompanying endoneurium consisting of capillaries, fibroblasts, macrophages, and mast cells; 3) perineurium, a specialized barrier layer located at the outer limit of the endoneurium and contributing to a “blood-nerve” barrier; and 4) epineurium, an external layer of fibroadipose tissue. Vascular elements are present in all three layers. Hamartomas, hyperplasias, reactive lesions including true neuromas and inflammatory pseudotumors, and neurofibromas involve several if not all these components simultaneously. Non-neural tumors, with the exception of carcinoma, neurotropic melanoma, and lymphoma, are commonly extrinsic to nerve fascicles and their perineurium, and do not exhibit the endoneurial pattern of spread so characteristic of many primary PNTs.

Primary tumors of peripheral nerve originate from cells of the nerve sheath. Although, in theory, peripheral nerve sheath tumors (PNSTs) may arise from Schwann cells, perineurial cells, fibroblasts, and other cells comprising the nerve sheath, most are derived from Schwann cells. This cell is neuroectodermal in nature, originates in the neural crest, and is unique to peripheral nerve. One characteristic of PNTs is their histologic diversity, a feature in large part attributable to the metaplastic repertoire of neoplastic Schwann cells, which may produce not only a variety of collagens and melanin, but display a remarkable capacity for divergent differentiation toward rhabdomyoblasts, chondroblasts, and various epithelial cell types. Also unique to peripheral nerves are perineurial cells, the tumors of which are uncommon but increasingly encountered. Whereas vascular tumors of the peripheral nerves have been reported, fibroblast-derived neoplasms are not well defined.

The process of diagnosis and classification of tumors of the peripheral nervous system requires correlation with clinical and surgical data, as well as considerable attention to the histologic features. In many instances, an immunohistochemical evaluation is also necessary. Although some authors have concluded that electron microscopy is no longer of diagnostic value, it has played a crucial role in the classification of PNTs and remains useful in recognizing: 1) advanced schwannian differentiation in cellular schwannoma, a lesion that must be distinguished from rare diffusely S-100 protein–positive malignant peripheral nerve sheath tumors (MPNSTs), which often
demonstrate only minor degrees of Schwann cell differentiation; 2) the fully one third of MPNSTs that lack light microscopic or immunohistochemical evidence of nerve sheath differentiation; and 3) occasional perineurial tumors not expressing epithelial membrane antigen immunoreactivity. Most recently, molecular genetics has come to play a role in identifying malignant change in neurofibroma and in distinguishing MPNSTs from other soft tissue tumors, particularly synovial sarcoma.

**HISTORICAL BACKGROUND**

Due to the lessons learned from the application of electron microscopy and immunohistochemistry, we now have unequivocal evidence that the Schwann cell plays the major role in the formation of peripheral nerve neoplasms. An appropriate classification system for PNTs, however, has generated much controversy over the years. Ideal classifications are based on the cell type or composition of a tumor since tumor differentiation reflects its “cell of origin.” Since the mid-19th century, this concept and the controversy surrounding it, propelled by differing views as to the histologic make-up of PNTs, initially involved European pathologists. After World War I, North American views were expressed. Opposing views pitted investigators favoring a Schwann cell origin against those favoring a mesenchymal or fibroblastic derivation. In the absence of general agreement, recourse was also made to a classification based on less specific noncell-oriented criteria. Perineurial cell tumors, both intraneural and extraneural, went unrecognized until recent years when modern methods quickly resolved their nature.

More recently, it has been shown that neural innervation of the gastrointestinal musculature is augmented and aided by the activity of a plexus of cells referred to as interstitial cells of Cajal (ICC) (1). Linked to both enteric nerves and to smooth muscle cells, the plexus is a network of electrically coupled cells functioning as a syncytium (2). ICCs express ionic conductances facilitating the generation and propagation of slow wave, rhythmic activity in gastrointestinal smooth muscles and, in addition, transduce neural inputs (1). Rather than originating from the neural crest, developmental studies have provided convincing evidence of a mesenchymal origin and smooth muscle differentiation (1). ICCs are thought to give rise to the gastrointestinal stromal tumor (GIST) (3,4), a neoplasm that unlike peripheral nerve sheath tumor arises from an electrical impulse-generating cell.

**Early Key Investigators**

**Theodor Schwann** (1810-1882). Born in Neuss, Germany, and medically trained in Bonn, Schwann (fig. 1-1) was the first student of the celebrated microscopist, Johannes Mueller of Berlin, to achieve prominence. He became known for his 1839 joint observation with Matthias Schleiden that cells are the fundamental particles of both plants and animals (5). Key among his many observations was a description of the cellular envelope intimately surrounding peripheral nerve axons, a structure that bears his name.

**Rudolf Virchow** (1821-1902). Berlin based and also a one-time Mueller student who emphasized the importance of microscopy in medicine, Virchow (fig. 1-2) became the most influential pathologist and physician of the 19th century. Guided by observations made earlier by Robert
Remak that cells originated from other cells by cell division (6,7), and through the application of his own concept of the cellular basis of disease (8), Virchow instituted a revolution in medical investigation. This wide-ranging study included peripheral nerve neoplasms which, in keeping with his view regarding soft tissue tumors (9), he concluded were fibroblastic in nature (0). He coined the term neurofibroma.

Frederick von Recklinghausen (1833-1910). Von Recklinghausen (fig. 1-3) completes the triad of German pioneers in peripheral nerve investigation. As Virchow’s favorite disciple, he undertook his 1886 detailed re-examination of patients with multiple peripheral nerve tumors and associated cutaneous pigmented macules (11). The topic had been reported upon by Virchow some 30 years earlier (10). Von Recklinghausen’s work established the disorder as a distinctive syndrome and his name became synonymous with it. This work further promoted the term neurofibroma.

Jose Verocay (1876-1927). A Uruguayan physician of Austrian and Italian ancestry, Verocay (fig. 1-4) received a general education in Italy and medical education, including pathology training, in Prague. During the first decade of the 20th century he described in detail a type of peripheral nerve tumor he regarded as Schwann cell in nature (12). This coincided with findings first reported as early as 1878 and credited to French investigators (13) that peripheral nerve neoplasms were unlikely mesenchymal in nature given their frequent nerve association and cellular fasciculation. Verocay called attention to the presence of distinct bodies with palisaded cells, structures now referred to as “Verocay bodies.” Verocay’s tumor, with its palisaded cell bodies and related processes, was so convincingly indicative of a peripheral nerve tumor distinct from neurofibroma that his report had a significant impact on work in this area. The designation of “neurinoma” which Verocay selected for this tumor was likely based on his
conclusion that the neoplastic Schwann cells contained portions of nerve fibers, an observation in keeping with Schwann’s view that the cells he had described encasing axons actually participated in their formation.

**Pierre Masson (1880-1959).** From Dijon, France, and schooled in biological research before obtaining a medical degree, Masson (fig. 1-5) was an extraordinarily insightful anatomic pathologist. He came to occupy academic Chairs in the field at Strasbourg and later at the University of Montreal in Canada (4). In the latter capacity, assumed in 1927, he acted as a conduit for infusion of French concepts in pathology into North America. A major interest in neuroectodermal neoplasms included the peripheral nerve tumors. Among these was neurinoma, which he concluded was Schwann cell in nature, given the apparent syncytial structure of the neoplastic cells (5). Unconvinced that Schwann cells form axons, he set aside the term “neurinoma” for the cell composition-based designation of “schwannoglioma.” Masson considered neurofibroma and MPNST to also be Schwann cell neoplasms. Schwann cells are neural crest derived (6), and since the neural crest gives rise to the musculature in the head and neck regions, his concept that the majority of nerve sheath neoplasms are Schwann cell derived provided him an explanation for his discovery of examples of MPNST with rhabdomyosarcomatous differentiation (5,7).

**Arthur Purdy Stout (1885-1967).** A key figure in the development of surgical pathology as a specialty, and one of its foremost experts (8), Stout (fig. 1-6), New York City born, was medically trained and pursued a career at Columbia University. His interests were diverse but none captured his attention more than the pathology of the peripheral nervous system. In 1935, a time when the mesenchymal theory of the origin of peripheral nerve tumors prevailed among American neuropathologists (9), Stout published two important papers, both regarding his own and previously reported cases, dealing with Verocay’s neurinoma (20) and MPNST (21).
With respect to neurinoma, Stout thought the term inappropriate because it literally means “nerve fiber tumor,” which it is not, and suggested its replacement with the designation "neurilemoma," his own creation and meaning “nerve sheath tumor,” which it is. The final determination of the tumor’s originating cell he left to future studies. Regarding MPNST, he was convinced that in the past the designation had often been misapplied to spindle cell sarcomas of other derivation. To correct this, he recommended that specific criteria such as origin from a nerve, transformation from neurofibroma, or occurrence in a patient with von Recklinghausen neurofibromatosis be met before making the diagnosis. At this time he still accepted the view that MPNSTs were derived from mesoblastic endoneurium, only rare cases having a neuroectodermal origin (13). Because Stout correlated a defined histology with clinical findings and a routinely benign course, his paper on neurilemomas was a major contribution. Nonetheless, the terminology for this tumor had a drawback. The benefit of a cell-based designation was lost even though 6 years later, on the basis of Murray’s cell culture work (22), he adjusted his view to coincide with Masson. His landmark 1949 fascicle on tumors of the peripheral nervous system (23), which propounded the Schwann cell derivation of all major peripheral nervous system tumors, was instrumental in the general acceptance of that view. Unfortunately, Stout’s characterization of neurilemoma as a consistently benign tumor was not understood by subsequent investigators providing the initial assessments of MPNST (24,25), who referred to the latter as “malignant neurilemoma,” a misuse of the term that sowed confusion among later workers in the field.

Santiago Ramon y Cajal (1852-1934). Santiago Ramon y Cajal (fig. 1-7), Spain’s most illustrious physician, was a founding father of modern neuroscience. His Nobel Prize was in recognition of a life of intense labor, exhaustively studying the microanatomy of the nervous system. Using the modifications of
Camillo Golgi's silver impregnation method and an artist’s facility for fine drawing, he painstakingly recorded his findings. His anatomic studies of nervous tissue were conducted at a series of institutions, lastly at the University of Madrid. Here, he established the prestigious Laboratory of Investigative Biology, a mecca for future leaders in the field. Cajal’s principal achievement was proving that individual nerve cells (neurons) are the basic units of the central nervous system, a novel concept that displaced the reticular theory. Cajal was also the first to describe cells interposed between nerve endings and smooth muscle cells of the gastrointestinal tract, cells now referred to as the interstitial cells of Cajal (ICC). His investigation of these cells, believed by him to be a type of primitive neuron, was solely confined to their description (1,26–28).

**SPECIMEN PRESENTATION, HANDLING, AND ASSESSMENT**

**Specimen Types.** Tissues to be evaluated in cases of PNT vary greatly in size, ranging from fine needle aspiration, to needle biopsy, to open biopsy or a resection specimen. The clinical presentation is usually of a soft tissue mass of uncertain type, or of a lesion clinically or operatively related to peripheral nerve.

**Diagnostic Pitfalls Related to Presentation.** Any suggestion or assurance of a tumor’s origin in nerve must be weighed against imaging and operative findings regarding its location, gross features, and histology. When inconsistencies arise, the clinical reports and gross descriptions should be re-examined. An illustration of the problem, based on the experience of one of the authors, relates to an unusual elongated tumor that partially encircled an arm. Its configuration led to the conclusion of a peripheral nerve origin, but doubt was subsequently raised because most nerves of limbs are longitudinally, not horizontally, disposed. Histologic review showed features inconsistent with a peripheral nerve primary but, rather, compatible with a sweat gland adenoma. Another problematic case was a sclerosing epithelioid fibrosarcoma of the lower extremity that grew as an elongated mass in the calf where, along its length, it was attached to a nerve (fig. 1-8). An erroneous initial assumption that it represented a primary MPNST was made. Yet another example of striking mimicry of a peripheral nerve tumor was provided by an elongated, smooth muscle tumor arising within a limb and involving a neurovascular bundle. The correct diagnosis became apparent on microscopic examination with the finding of an origin in a vessel coursing through the tumor. Histologically similar neoplasms may simulate a PNST. Two lesions in this category are synovial sarcoma of nerve and primitive neuroectodermal tumor (PNET) of soft tissue, which can masquerade as a primary nerve sheath tumor. Synovial
Peripheral Nerve Tumors: Overview

Figure 1-9
AIR-INDUCED TUMOR DISCOLORATION
Gross photo of monophasic synovial sarcoma taken over 3 minutes after sectioning shows beginning pink artifactual discoloration of a usually gray soft tissue tumor.

Sarcomas primary in nerve pose a particular diagnostic challenge (see chapter 2). Their identification is greatly aided by demonstrating the diagnostic translocation t(x;18). The nerve most frequently involved by PNET is the sciatic. Typically, the nerve, irregularly invaded by tumor, is partly or completely surrounded by a soft tissue PNET (see fig. 3-9). Distinguishing a primary soft tissue PNET secondarily involving nerve from a rare MPNST showing PNET differentiation rests upon demonstrating a malignant spindle cell tumor component in the latter.

**Gross Features.** Like other tumors of soft tissue, each of the principal forms of PNT exhibits a distinctive range of gross features. External features of importance in the assessment of PNTs but not evaluable in small specimens include: tumor boundary (circumscription with or without encapsulation versus invasion of adjacent normal tissues) and tumor shape after being freed from surrounding tissue (ovoid, flattened, elongate, cylindrical, fusiform, multinodular, or plexiform). On cut section, color is a key feature in the evaluation of all soft tissue tumors and the one requiring immediate assessment following tumor transection in order to avoid the common artifactual, pink discoloration that occurs after 3 minutes exposure to air (figs. 1-9, 1-10). Other key features include texture, uniformity, tissue homogeneity, and the presence and extent of necrosis.

Before dissection, external specimen examination includes: 1) recording gross features by color photography; 2) measuring in centimeters the specimen's three dimensions; 3) accurately describing gross features, particularly tumor configuration and the presence or absence of a nerve; and 4) if considering malignancy, coating the external surface of the specimen with India ink to permit accurate assessment of resection margins. Having completed these steps, assessment of the specimen interior begins with transection along its long axis by a sharp knife, if possible by a single passage. An exception is made when the tumor is long, cylindrical, and of generally uniform diameter, in which case multiple cross sections are more informative. Generous sections are then submitted for microscopy, at least one for every centimeter of maximal lesion diameter. These should be fully representative of the variations in tumor color and texture. Lastly, sections are taken of proximal, distal, and lateral margins of resection. Additionally, particularly when confronted with a tumor having unusual gross features, a sample in fixative should be set aside for electron microscopy. Although preservation in either glutaraldehyde or Trump fixative is optimal, formalin fixation suffices. In selected cases, setting aside fresh tissue in appropriate media, such as RPMI, facilitates cytogenetic and flow cytometric studies. In addition, a sample can be quick frozen in liquid nitrogen for molecular genetic studies.
REFERENCES


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