# S-100 Protein in Soft-Tissue Tumors Derived From Schwann Cells and Melanocytes

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**In soft tissues outside the central nervous system, S-100 protein is found normally only in Schwann cells. Using the peroxidase–antiperoxidase immunohistochemical method S-100 was also found in tumors derived from Schwann cells and melanocytes, including neurofibromas, neurilemomas, granular cell myoblastomas, cutaneous nevi, and malignant melanomas. S-100 was not detected in malignant Schwannomas, neuroblastomas, oat cell carcinomas, medullary carcinomas of the thyroid, paragangliomas, or meningiomas. S-100 was also absent from neoplasms of soft tissues not usually considered to arise from cells of neural crest origin. S-100 appears to be a useful marker for identifying neoplasms derived from Schwann cells and melanocytes. (Am J Pathol 1982, 106:261–268)**

S-100 PROTEIN (S-100) can be isolated from mammalian central nervous systems (CNS).[1,2] Its biologic function however, remains unknown. Within the CNS, S-100 is found in astrocytes and oligodendrocytes,[3–5] but it has also been detected in neurons.[6–8] Outside of the CNS, S-100 can be demonstrated in Schwann cells of the peripheral nervous system, including satellite cells surrounding neuronal perikarya in dorsal root and autonomic ganglia.[9] In human and rat peripheral nervous systems, S-100 is found neither in neuronal perikarya nor in axons.[9] Examination of soft tissues and viscera outside of the CNS using the peroxidase–antiperoxidase technique of Sternberger and an antiserum againt S-100 revealed S-100 only in Schwann cells; no other cell type was stained.[9] In addition to human glial tumors, S-100 has been identified in accoustic neurinomas, malignant melanomas, a clone of neoplastic rat Schwann cells, and chemically induced tumors of the rat nervous system.[10–15] S-100 has also been found in granular cell "myoblastomas" from various locations, supporting the currently prevailing impression that these tumors are Schwann cell neoplasms.[16]

In routine practice of surgical pathology it is often difficult to determine the cell of origin of tumors arising in soft tissues. Neoplasms derived from fibroblasts, smooth muscle cells, and Schwann cells may have similar histologic features. Similarly, malignant melanoma is frequently confused with malignant lymphoma, sarcoma, and carcinoma when an undifferentiated neoplasm is found in a lymph node or other site remote from an identifiable primary tumor. Electron microscopy has been useful in identifying ultrastructural characteristics of the various cell types comprising these tumors. But ultrastructural characteristics are not always sufficient to identify the cell types in an undifferentiated neoplasm. By permitting detection of cell-specific antigens, immunohistochemistry adds a new dimension to the identification of cells not recognizable by morphologic features alone. It also has the advantage of being applicable to routine paraffin-embedded histologic sections.[17] Using a well-characterized antiserum, which in soft tissues outside of the CNS reacts only with Schwann cells,[9] we examined several tumors selected from the surgical pathology files at the University of Chicago. The object of this study was to determine whether S-100 is expressed in all neoplasms generally thought to arise from Schwann cells and to look for the presence of S-100 in neoplasms considered to arise from other cell types.

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Table 1—Tumors Studied

| Histologic diagnosis | No. containing S-100 | No. without S-100 |
|---|---|---|
| Dermal neurofibroma | 10 | 0 |
| Neural nevus | 1 | 0 |
| Plexiform neurofibroma | 6 | 0 |
| Traumatic neuroma | 1 | 0 |
| Schwannoma | 6 | 0 |
| Granular-cell myoblastoma | 14 | 0 |
| Cutaneous nevus | 3 | 0 |
| Metastatic malignant melanoma | 8 | 2* |
| Malignant Schwannoma | 0 | 4† |
| Neuroblastoma | 0 | 4 |
| Oat cell carcinoma of lung | 0 | 4 |
| Medullary carcinoma of thyroid | 0 | 4 |
| Meningioma | 0 | 6 |
| Otic paraganglioma | 0 | 4 |
| Glomus tumor of finger | 0 | 1 |
| Leiomyoma | 0 | 3 |
| Leiomyosarcoma | 0 | 5 |
| Fibrosarcoma | 0 | 3 |
| Fibrous histiocytoma (1 malignant) | 0 | 4 |
| Dermatofibrosarcoma | 0 | 1 |
| Rhabdomyosarcoma | 0 | 2 |
| Malignant lymphoma | 0 | 3 |

* One spindle cell variant contained S-100 in scattered multinucleated giant cells but not in most of the spindle cells.

† The plexiform neurofibromas and normal nerve fascicles were stained, while the surrounding spindle cell sarcomas in the same sections remained unstained.

## Materials and Methods

Blocks of paraffin-embedded tissues selected for this study included (Table 1) a traumatic neuroma, plexiform neurofibromas, cutaneous neurofibromas, Schwannomas, malignant Schwannomas from patients with neurofibromatosis, granular cell myoblastomas (reported elsewhere),[16] intradermal nevi, metastatic malignant melanomas, malignant lymphomas, meningiomas, small-cell (oat cell) carcinomas of lung, medullary carcinomas of thyroid, neuroblastomas, paragangliomas of the ear, a glomus tumor of the finger, leiomyomas, leiomyosarcomas, an epithelioid leiomyosarcoma, fibrous histiocytomas, malignant fibrous histiocytomas, fibrosarcomas, a dermatofibrosarcoma, and rhabdomyosarcomas.

Seven-$\mu$-thick sections cut from these blocks were deparaffinized and stained with the use of antiserum to S-100 in the peroxidase-antiperoxidase technique of Sternberger as previously described.[9,16] The antiserum was a generous gift of Dr. Blake Moore.[1,2] All tissue sections selected for this study contained normal nerve fibers, which served as internal positive controls. Internal negative controls could be found in adjacent nonneoplastic tissue. In addition, all tissue samples were stained with the use of the antiserum to S-100 that had been absorbed with S-100 until it no longer reacted with normal brain and serum from a rabbit that had been injected with complete Freund's adjuvant alone.

## Results

All Schwannomas were intensely stained by the antiserum to S-100. Almost every cell in the densely cellular (Antoni A) tissue contained S-100, but S-100 was also present in cells in the loosely arranged (Antoni B) tissue (Figure 1). The cells infiltrating the

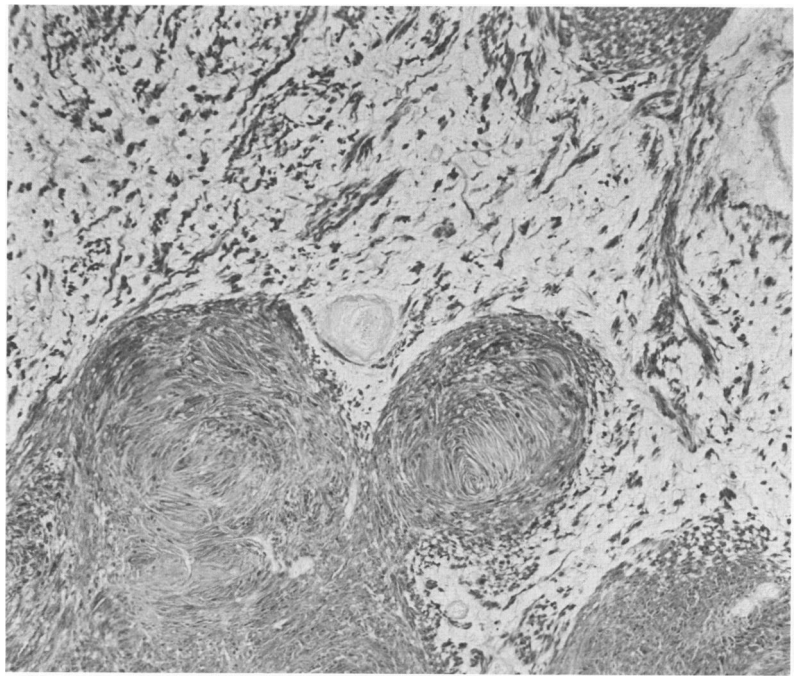

**Figure 1**—Accoustic neurilemoma. The elements containing S-100 are visualized by dark reaction product. The reaction product is present in nuclei and cytoplasm of tumor cells in Antoni A and B areas. Since no other stain has been used, the rest of the tissue is barely visible as poorly focused shadows. This is also the case with unstained areas of the sections shown in Figures 2B and C, 3B, 4B, 5, and 6B. (S-100 immunoperoxidase without counterstain, × 100)

edematous nerve fascicles in the plexiform neurofibromas were heavily stained by this antiserum. The perineurial sheaths and the epineurial connective tissue, as well as the axons entrapped within the infiltrate, were not stained (Figure 2). The Schwann cells in a traumatic neuroma were stained, while the axons and connective tissue elements remained unstained. The cells of the cutaneous neurofibromas contained S-100. The only elements stained in the adjacent skin and subcutaneous tissues were Schwann cells of nerves (Figure 3). Spindle cell sarcomas arising in the region of plexiform neurofibromas in large nerve trunks from 4 patients with neurofibromatosis were not stained, although the adjacent neurofibromas were stained as in Figure 2.

All of the tumor cells of the dermal nevi were intensely stained by the antiserum to S-100. In the surrounding skin the only other elements that were stained were Schwann cells of nerve fibers (Figure 4). When diaminobenzidine is used as the chromogen in the peroxidase-antiperoxidase technique, the fine brown precipitate indicating the presence of S-100 is obscured by the melanin granules in pigmented cells; and it is therefore difficult to be certain whether or not normal melanocytes also contain S-100. Many tumor cells of malignant melanomas infiltrating tissues remote from their cutaneous origins were also heavily stained (Figure 5). However, in one melanoma composed of spindle-shaped cells with occasional multinucleated tumor giant cells, only the giant cells were stained. Another metastatic tumor in lymph nodes, which was thought to have originated within a lentigo malignans, remained unstained.

In histologic sections of neuroblastomas, medullary carcinomas of thyroid, oat cell carcinomas of lung, meningiomas, paragangliomas, a glomus tumor, malignant lymphomas, leiomyomas, leiomyosarcomas, fibrosarcomas, fibrous histiocytomas, malignant fibrous histiocytomas, a dermatofibrosarcoma, and rhabdomyosarcomas, only Schwann cells associated with normal nervous tissue adjacent to the neoplasms were stained (Figure 6).

## Discussion

Neurilemomas are frequently referred to as Shwannomas because of the similarities of the cells constituting these tumors to normal Schwann cells. They have continuous basal laminas, long thin cytoplasmic processes, and intracytoplasmic microfilaments.[18] But because of the absence of a morphologic association between the neurilemoma cells and axons, the identification of the Schwann cell as the progenitor of these tumors has been open to question;

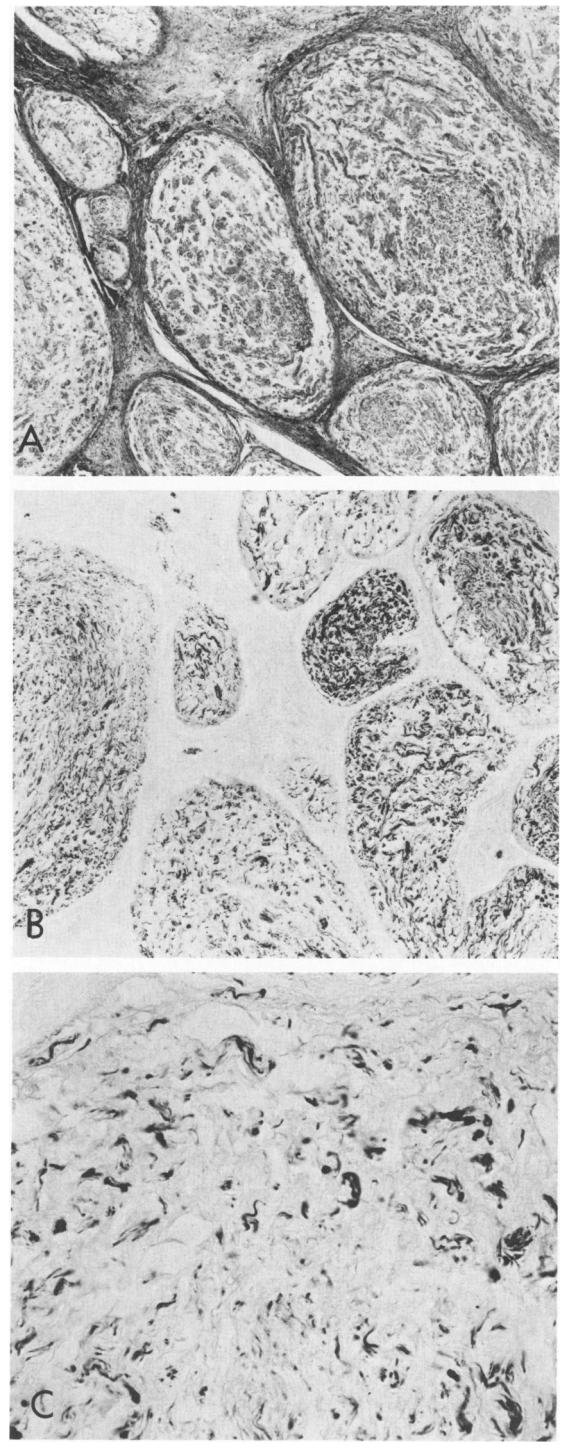


**Figure 2**—Plexiform neurofibroma. (**A**, H&E, ×50; **B**, S-100 immunoperoxidase without counterstain, ×50) Reaction product is present in tumor cells within nerve fascicles. The perineural sheaths and the connective tissue between nerve fascicles remain unstained. **C**—S-100 immunoperoxidase without counterstain, ×250. Higher magnification demonstrating reaction product within cytoplasm and nuclei of tumor cells; axons and connective tissue remain unstained.

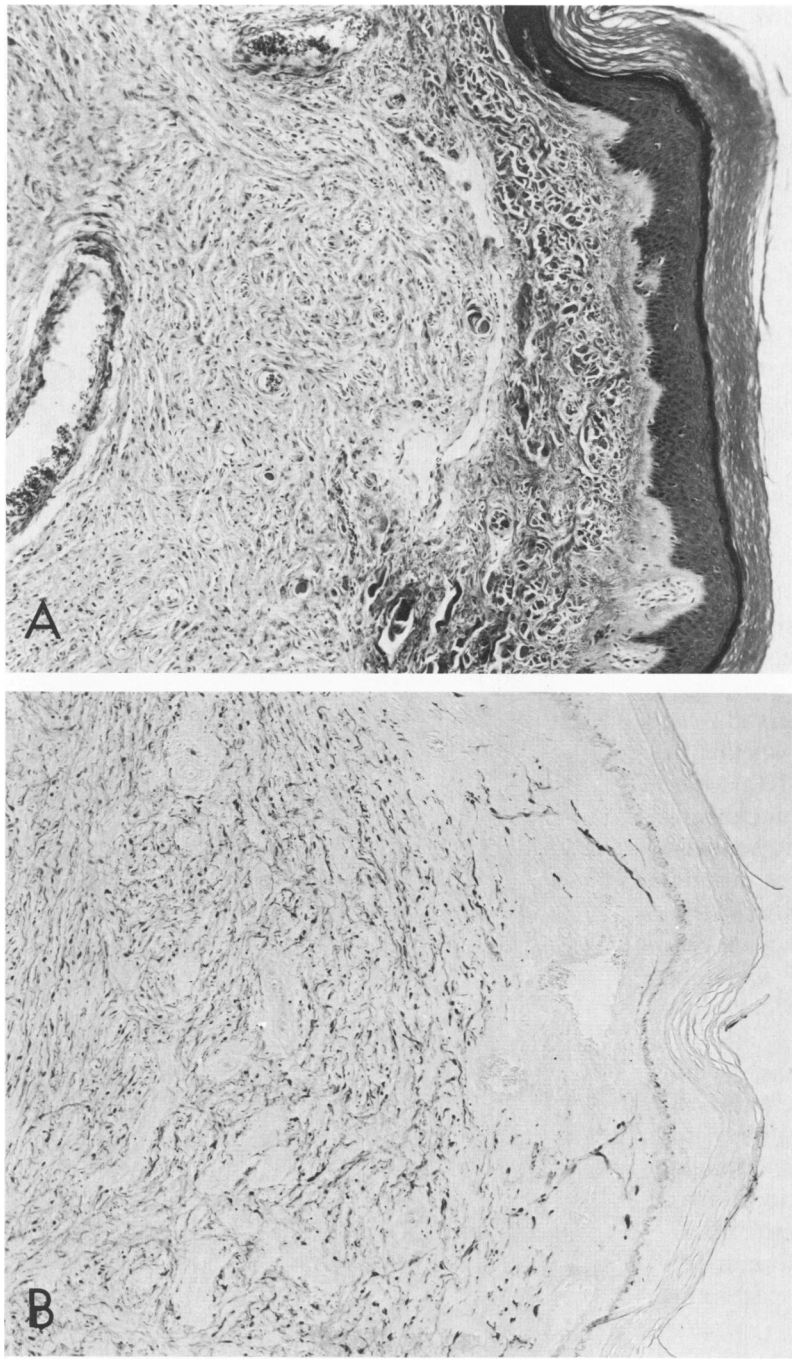


**Figure 3**—Cutaneous neurofibroma. (**A**, H&E, ×100; **B**, S-100 immunoperoxidase without counterstain, ×100). The reaction product is present within tumor cell cytoplasm and nuclei and Schwann cells associated with cutaneous nerve fibers. Adjacent dermal and subcutaneous tissues remain unstained.

and suggestions that these tumors are derived from perineurial sheath cells are still found in the current literature (for reviews see Rosai[19] and Russell and Rubinstein[20]). In normal peripheral nerves of rats and humans S-100 is present in the Schwann cells surrounding myelinated and unmyelinated axons but not in the cells making up the perineurial sheath.[9] Most of the cells in both the dense Antoni A and edematous Antoni B tissue contain S-100. It is therefore most likely that these tumors are derived from Schwann cells, since they express an antigen found in normal Schwann cells but not in perineurial sheath cells.

Axons within neurofibromas arising in peripheral nerves or nerve plexuses are frequently surrounded by plasmalemmal extensions of tumor cells, an ultrastructual feature of normal Schwann cells.[18-22] There has therefore been little controversy about the pres-

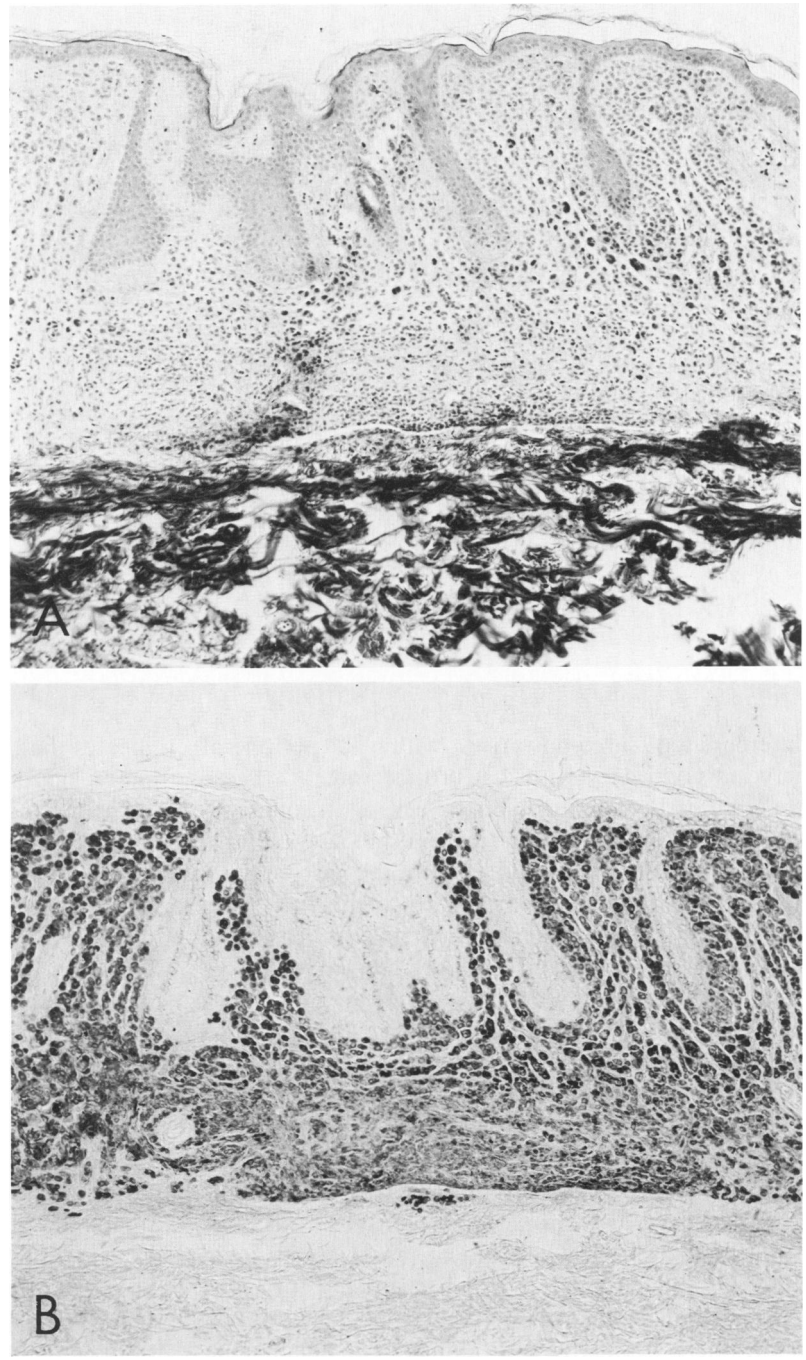


**Figure 4**—Intradermal nevus. (**A**, H&E, ×100; **B**, S-100 immunoperoxidase without counterstain, ×100) Reaction product is present within cytoplasm of nevus cells; many of the nevus cells nuclei remain unstained. The adjacent dermal and subcutaneous tissues are unstained.

ence of Schwann cells within these tumors. Although fibroblasts are also found within these tumors, most ultrastructural investigations have shown that the predominant cell type resembles Schwann cells. But some investigators have suggested that the perineurial sheath cell might be the cell type from which neurofibromas are derived.[23] The cutaneous neurofibromas, whether arising as multiple lesions in patients with neurofibromatosis or as solitary lesions, usually do not have many axons within them. Most axons found within these tumors appear to be branches of cutaneous nerves trapped by the neoplastic proliferation. Nevertheless, the predominant cell type in both the plexiform and cutaneous neurofibromas contains S-100, thereby adding weight to the argument for the Schwann cell origin of these tumors.

Malignant Schwannomas are most frequently diagnosed in patients with neurofibromatosis when an un-

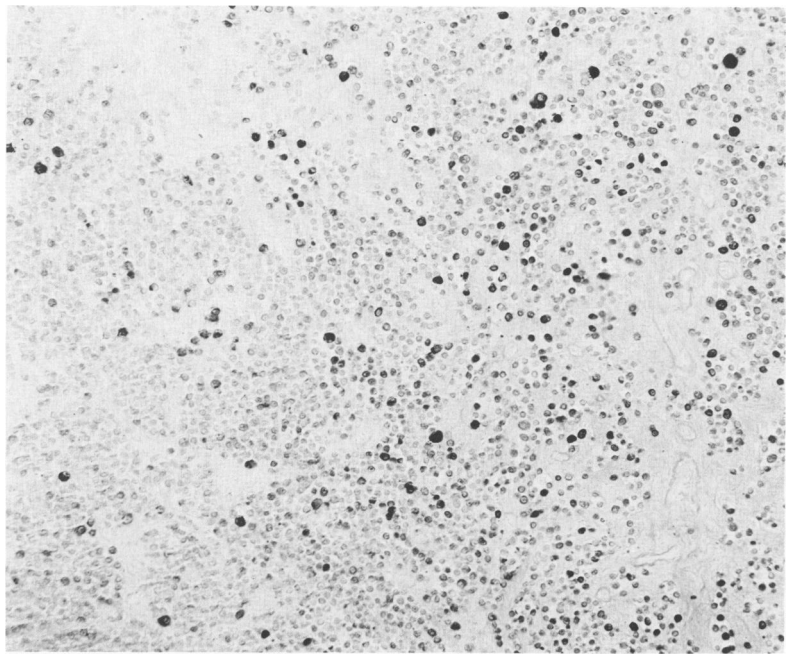

**Figure 5**—Malignant nonpigmented melanoma in deep subcutaneous tissue. The staining intensity varies considerably from cell to cell, but all the tumor cells are stained. Reaction product is present in melanoma cell cytoplasm and many but not all nuclei. Blood vessels and connective tissue stroma are not stained. (S-100 immunoperoxidase, × 100)

differentiated sarcoma arises within a peripheral nerve in continuity with a neurofibroma.[24-26] These are composed of spindle-shaped cells with some histologic and ultrastructural features that suggest a relationship to Schwann cells.[27-29] But the morphologic features are far from sufficient to identify the cells constituting these sarcomas as Schwann cells. The sarcomas arising in plexiform neurofibromas that we examined did not contain S-100, although the adjacent neurofibromas were stained. It is impossible to know from this finding whether these malignant neoplasms were composed of dedifferentiated Schwann cells that had lost their capacity to synthesize S-100 or whether they arose from some other cell type.

The original concept of the origin of nevus cells from neuroectoderm proposed by Masson[30] has been confirmed by many histologic and embryologic studies.[31-34] Therefore, it is not surprising for us to find S-100 in neoplasms derived from melanocytes. While there is usually little difficulty in diagnosing maligant melanoma in the skin, lesions first detected in other locations may be difficult to diagnose in routine paraffin-embedded sections.[35] The presence of S-100 in metastatic malignant melanomas indicates that the immunohistochemical search for this protein might be of value in tumors in which a diagnosis of melanoma is in question. A few metastatic tumors from patients in whom a previous diagnosis had been made of malignant melanoma in a primary skin lesion did not contain S-100. This finding indicates that some, but not all, tumors that acquire a more aggressive behavior no longer synthesize this protein.

The presence of S-100 in tumors derived from Schwann cells and melanocytes indicates that these cells, which are both considered to arise from neural crest, may be even more closely related ontogenetically than previously thought. Certainly neoplasms derived from melanocytes may show neural differentiation,[36,37] and otherwise typical neurofibromas and Schwannomas may contain melanin.[38,39,40]

Other cell types of neural crest origin do not contain S-100. In an examination of tissues outside of the central nervous system, S-100 was not found in the epitheliod cells of the adrenal medulla, the chromaffin cells of the intestinal tract, the pancreatic islets, or the interstitial cells of the thyroid; and it is not present in neurons of the autonomic nervous system.[9] Nor has it been detected in tumors considered to arise from these cell types. S-100 was not found in neuroblastomas, meningiomas, medullary carcinoma of the thyroid, or oat cell carcinomas of the lung.

S-100 therefore appears to be a rather specific marker for tumors derived from one subclass of cells of neural crest origin, which only includes melanocytes and Schwann cells. Antiserum against S-100 should prove to be a valuable tool in the classification of cells of uncertain embryologic origin and in the classification of some neoplasms in which morphologic identification of cells is uncertain.

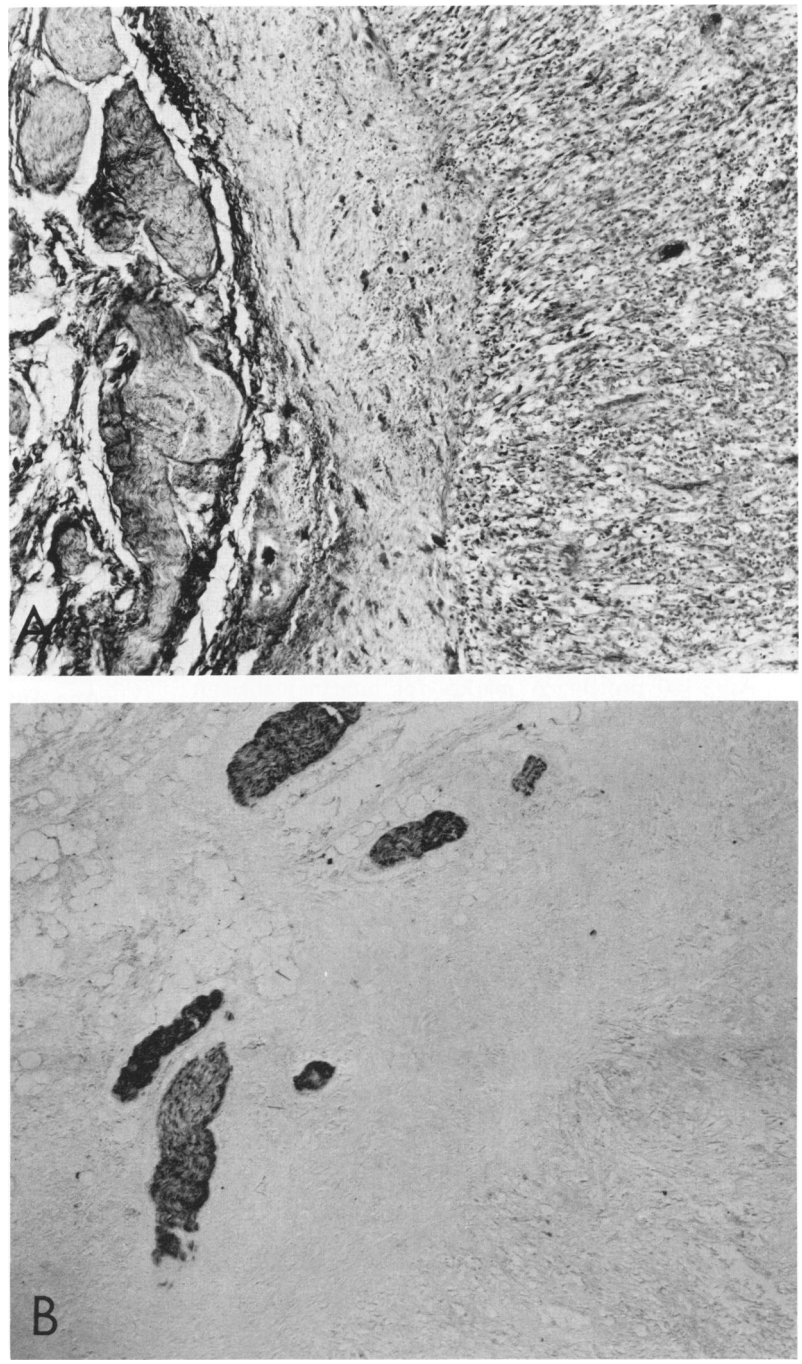


**Figure 6**—Rhabdomyosarcoma in deep subcutaneous tissue of a leg. **A**—Tumor is at right, nerve trunk at left. **B**—The Schwann cells associated with the nerve fascicles at the left are stained; the tumor tissue on the right and the connective tissue remain unstained. (**A**, H&E, ×50; **B**, S-100 immunoperoxidase without counterstain, ×250)

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