CHAPTER 9
Spinal Cord: Clinical Considerations

Disease affecting the spinal cord is a frequent cause of chronic neurological disability. Often, young adults are involved as in injuries due to war, motor vehicle accidents, motorcycle accidents, diving and skiing accident. Special units have been developed for the care, and rehabilitation of the unfortunate victims of these injuries. Early recognition and management of a potential spinal cord compromise is essential.

It is important to differentiate extrinsic (compressive) and intrinsic diseases of the spinal cord.

Continued spinal cord compression will produce irreversible damage. For extrinsic diseases, surgical therapy is then indicated as early as possible.

In general, extrinsic compressive lesions (Table 9-1) manifest a number of local segmental features at the level of the lesion as well as long tract findings below the level of the lesion.

TABLE 9-1. CONSEQUENCES OF EXTRINSIC COMPRESSION OF SPINAL CORD

Symptoms and signs	Anatomical correlation
1. Radicular pain at level of compression.	Posterior root and ganglion
2. Radicular sensory symptoms at level of compression	Posterior root and/or posterior horn
3. Segmental atrophy, weakness and fasciculations, at level of compression	Segmental lower motor neuron findings due to involvement of the anterior horn cells and anterior roots.
4. Segmental depression of deep tendon stretch reflexes	Involvement of the anterior root and anterior horn or of posterior root and or horn. The monosynaptic reflex arc has been interrupted as regards its afferent or efferent component
5. Long tract findings below the level of the lesion:	**a.** Spastic (UMN) weakness, increased deep tendon reflexes & Babinski sign (extensor plantar response) due to damage to descending pyramidal tracts. **b.** Spastic neurogenic bladder due to bilateral involvement of UMN control with release of the segmental bladder stretch reflexes. **c.** Deficits in position, vibration, and other proprioceptive and light touch sensation due to posterior column damage. **d.** Deficits in pain and temperature sensation due to lateral spinothalamic pathway damage.

Acute spinal cord compressions or transactions: The phenomena of spinal shock and the pattern of reflex recovery: After the acute and sudden loss of supra segmental control, a temporary depression of segmental reflex activities occurs. Deep tendon stretch reflexes are depressed. Cutaneous and autonomic reflexes may also be affected. The excitability of alpha and gamma motor neurons and of interneurons is depressed. This is more prominent in man than in species such as the cat or dog related to the progressive encephalization of function that has occurred in the primates. In the frog, the duration is fleeting; in the cat, spinal shock lasts a matter of minutes or hours. In the monkey duration is a matter of days or weeks. In humans, the duration is usually of several weeks. In the cat or dog spinal shock follows damage to the vestibulospinal and ventral reticular spinal tracts. In primates, spinal shock depends more on damage to the cortical spinal tracts. It is important to note that the depth and duration of spinal shock depends on the rapidity (acuity) and completeness of spinal cord section. Slowly evolving chronic spinal cord compressions are not char-

E. M. Marcus et al., *Integrated Neuroscience*

acterized by spinal shock. Fever or infection will prolong the duration of spinal shock or may result in a recurrence of spinal shock once recovery has occurred. Immediately after an acute transection, the patient will demonstrate a depression of all the deep tendon stretch reflexes and to a lesser degree the flexion reflexes. The limbs will be flaccid and paralyzed. The bladder will be flaccid that is hypotonic or atonic due to depression of the bladder stretch reflex. Within a short period of time (1 - 5 weeks), the flexion reflexes including the sign of Babinski will recover and remain prepotent. The flexion reflex, (the withdrawal of the foot and leg on painful stimulation) is a polysynaptic reflex. The afferent component of the reflex arc is mediated by group II and III myelinated fibers and group IV unmyelinated fibers, from a variety of receptors in skin, muscle, and joints. Initially in the human, the flexion reflex may be manifested as a mass reflex. When fully developed, this mass reflex may consist of generalized reflex flexor spasms of the muscles of the trunk and lower extremities accompanied by sweating, emptying of the bladder and in males penile erection and ejaculation. Initially, the receptive field for triggering this response is quite extensive, involving any tactile or nociceptive stimulus to the foot, leg, abdomen or thorax. With the passage of time, the mass reflex becomes less prominent and local sign develops. The more specific reflex movement then depends on the more specific location of the stimulus. For example, a painful stimulus to the outer border results in flexion, inversion, and adduction as opposed to a similar stimulus to the inner border of the foot that results in flexion, eversion, and abduction. The mass reflex may return if fever or infection occurs. Over a number of weeks to months depending on the completeness of transection (longer if complete), stretch reflexes with other extensor reflexes and postures will return. The deep tendon stretch reflexes will then become hyperactive. There will be a spastic rather than a flaccid weakness. Bladder emptying and bowel evacuations return 3 to 4 weeks after injury. The bladder will subsequently become hypertonic that is spastic with small capacity. The extensor capabilities may consist of crossed extension, (the contralateral lower limb extends when the ipsilateral will lower limb is responding to a painful stimulus by flexion). Sweating below the level of transection may not return for 3-4 months. In the cat and dog-alternate flexion/extension, alternate stepping and in high cervical preparations inter limb reflexes may occur (the upper limb movements are appropriately triggered by lower limb responses). With marked extensor tone, a partial capacity for brief periods of standing may return. Clearly there is a phylogenetic factor; such extensor capabilities are more limited in the spinal human. In comparison the capabilities of the frog or chicken with a high cervical transection are well described in common terminology.

The Brown Sequard hemisection syndrome (Table 9-2): Transactions of the lateral one-half of the spinal cord or lateral compressions of the spinal cord for example by tumors such as Schwannomas, meningiomas or metastases will produce a classical syndrome which reflects the anatomy of the spinal cord and of the spinal cord pathways.

The progressive subacute or chronic anterior midline compression syndrome: The spinal cord is gradually compressed backwards against the bony canal elements. Based on the clinical and experimental studies of Tarlov, the following sequence is often noted.

Initially the symptoms and signs will be relevant to posterior columns followed by symptoms and signs of lateral column involvement and finally by symptoms and signs relevant to the lateral spinothalamic system. From a clinical standpoint, the initial symptoms may consist of a numbness of the lower extremities and a sensory ataxia. An ascending spastic weakness of the lower extremities will then develop followed by an ascending deficit in pain and temperature sensation. Such a pain and temperature deficit will initially involve the sacral segments then lumbar segments followed by the thoracic segments and finally the lower cervical segments. This sequence reflects the lamination pattern of the lateral spinal thalamic system in which sacral segments are most extrin-

TABLE 9-2 CLINICAL SIGNS IN BROWN SEQUARD SYNDROME

Deficit	Cause of Clinical Deficit
A spastic weakness below and ipsilateral to the side of transection/damage	Injury to the lateral column/cortical spinal system.
Deep tendon reflexes increased below and ipsilateral to the side of transection/damage	Injury to lateral column/ cortical spinal system.
The sign of Babinski will also be present ipsilateral to the side of transection/damage	Injury to pyramidal tract in the lateral column.
Ipsilateral loss of vibration, position sense and all other proprioceptive sensory modalities below the level of transection/compression	Injury to posterior column
A contralateral loss of pain and temperature sensation beginning 1 or 2 segments below the level of the transection/compression	Involvement of the lateral spinothalamic tract.
An ipsilateral band of weakness atrophy and fasciculations may be present at the level of transection	Damage to the anterior root and or the anterior horn.
Ipsilateral depression of deep tendon stretch reflexes at the level of transection/ compression	Damage to the afferent or efferent components involved in the monosynaptic stretch reflex arc.
An ipsilateral band of loss of pain, temperature and touch sensation may be present at the level of transection	Damage to the posterior root and posterior horn

sic and cervical segments most intrinsic. As a general rule then, extrinsic lesions do not have sacral sparing. The earlier involvement of posterior and lateral columns may reflect the sequence of structural compression or the greater vulnerability of the heavily myelinated fibers.

It is important then to realize that the apparent upper level of sensory level for pain and temperature may not be the actual level of compression. When the patient is seen early in the course of spinal cord compression the apparent level of sensory deficit will be considerably lower than the actual level of compression.

It is important to recognize that slowly evolving extrinsic lesions (such as intradural meningiomas and neurofibromas) despite considerable distortion of spinal cord may produce only minimal symptoms and have a good response to surgical therapy. In contrast, rapidly evolving lesions such as metastatic epidural tumors, more often present a relatively acute or subacute course and often have a poor response to therapy. At times such metastatic lesions are complicated by vascular compromise.

SPECIFIC EXTRINSIC LESIONS OF THE SPINAL CORD.

Fracture dislocations: *(Fig.9-1)* In civilian life, most injuries to the cord do not represent actual lacerations of the spinal cord but are a result of crush injuries caused by fracture dislocations in the cervical or thoracic area. Vascular effects often complicate such crush injuries. Infarction (related to compression of anterior spinal artery and of veins) and hemorrhage may occur often in a central cord location (the latter is referred to as hematomyelia). After resorption of a hemorrhage, a cystic cavity may remain. Falls transmit force to the thoracic vertebrae; the resulting compression fractures may collapse the vertebrae and caused a sharp angulation of the axis of bony support. A similar compression and collapse; may also occur from other non-traumatic causes such a tuberculosis of the spine (Pott's disease), metastatic carcinoma and osteoporosis. Injuries to the cervical spine resulting from fracture dislocation are common in auto accident, and in diving accidents. In rheumatoid arthritis, the odontoid is commonly fractured and dislocated. It is important to note that fractures of the vertebrae may occur without a marked degree of dislocation. In such cases great care must be taken in moving these patients. Thus, in fractures of the cervical spine, the patient should remain supine with the neck immobilized to avoid flexion and extension during transportation. (Utilize a makeshift collar or sandbags.) Once the patient arrives at a treatment center,

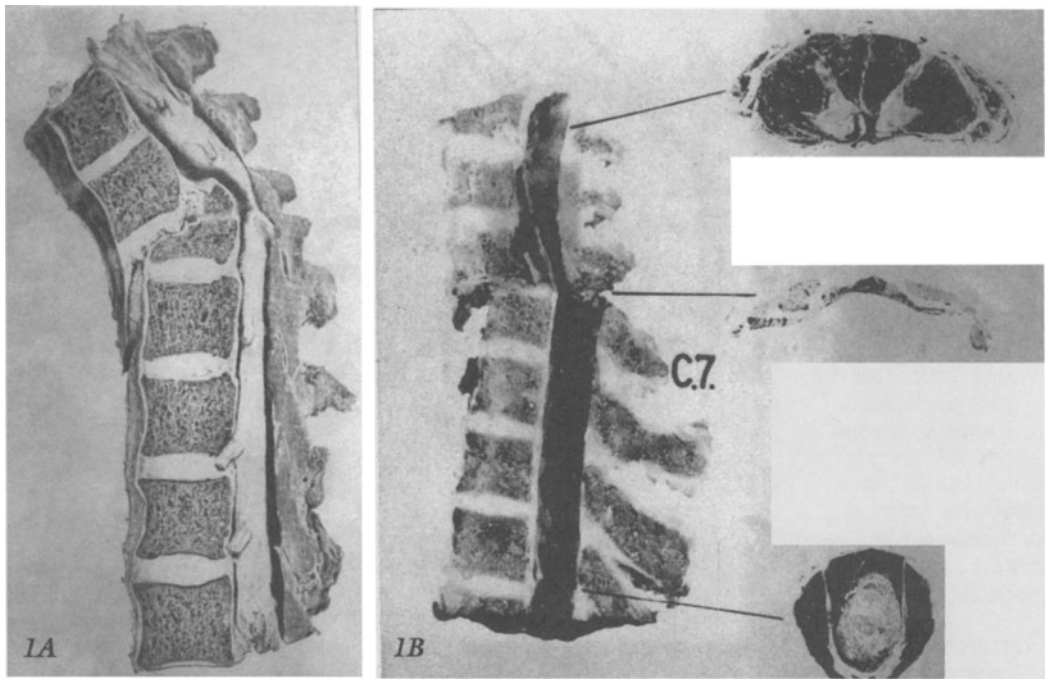

Figure 9-1. Traumatic lesions of the spinal cord: A) Fracture dislocation of thoracic vertebra has crushed and almost transected the thoracic spinal cord. B) A fracture dislocation of the cervical spine (due to an auto accident 2 weeks prior to death) has produced an almost complete transection of the spinal cord at the C7 level. (From Blackwood, W., Dodds, T.C., and Somerville, J.C.: Atlas of Neuropathology, 2nd Edition, Baltimore, Williams and Wilkins, 1964, p. 147).

additional measures such as traction or spinal fusion must be considered. The use of very high dosage corticosteroids may have some value in reducing the edema of the spinal cord.

Cervical disk disease: Acute ruptures and chronic cervical spondylosis with cervical spinal cord compression: This is probably the most common cause of cervical spinal cord compression. Acute lateral or midline rupture of disk material may occur in the cervical area related to trauma or sudden coughing or straining. The term cervical spondylosis refers to a more chronic process. The disk degenerates with increasing age, the disk material begins to bulge, the disk space narrows, and the secondary formation of osteophytes (bony spurs) occur. The osteophytes may project laterally into the neural foramina producing nerve root compression and/or may be located in a midline location producing spinal cord compression *(Fig. 8-17)*. Not all bulging disks and osteophytes compress the spinal cord. In some patients, the vertebral canal is sufficiently wide that no compromise of the spinal cord occurs. In other patients, the bony canal in relatively narrow (spinal stenosis) and compromise occurs. The pattern of ascending and descending degeneration found at autopsy following spinal cord compression in a patient with cervical spondylosis is demonstrated in *Figure 9-2*. This 64 year old male had a 6 year history of progressive spastic paraparesis with atrophy and fasciculations at C4-C8, bilateral corticospinal and posterior column findings in the lower extremities and a deficit in pain sensation below the T 10 level. Softening of the spinal cord was present at the cervical 7 levels. The following case illustrates the syndrome of spinal cord compression secondary to cervical disk disease.

Case 9-1: This 34-year-old female after 2 weeks of prolonged hyperextension of her neck while painting walls and ceilings developed a transient 6-hour period of weakness in both her legs. She then developed pain in the right side of her neck, her right shoulder and right

upper arm, followed by weakness in the right leg. Shortly thereafter she noted intermittent prickly sensations (paresthesias) in both lower extremities. And she was unable to walk.

Neurologic exam: *Motor:* weakness was present in the right upper extremity most prominent at the triceps and wrist extensors (4/5) with a lesser degree of weakness at deltoid, pectorals, wrist flexors and finger abductors plus a minor degree of weakness at right ankle dorsiflexion (4.5/5). Gait was ataxic. *Reflexes:* Bilateral ankle clonus was present with bilateral Babinski signs. *Sensation:* Vibratory sensation was decreased in the right lower extremity at toes ankle and knee with associated proprioceptive deficits. Pain sensation was decreased in the left lower extremity from the toes to the groin. The entire buttock and the perianal area were also involved in this deficit.

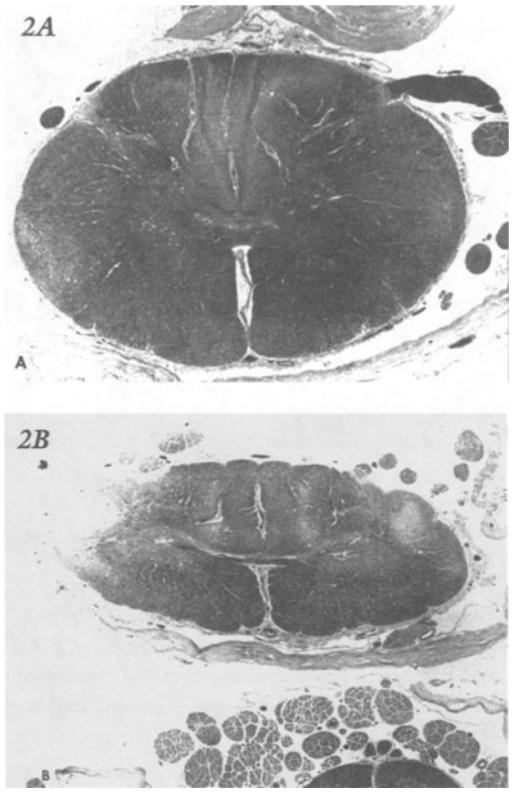

Figure 9-2. Ascending and Descending Degeneration: Cervical Spondylosis with Spinal Cord Compression Myelin stains. A) Upper cervical spinal cord above level of compression: ascending degeneration predominantly in posterior columns. B. Lower cervical cord just below area of softening: descending degeneration predominantly in lateral columns. (Courtesy of Dr. Jose Segarra, Boston Veterans Administration Hospital).

Clinical diagnosis: Partial Brown-Sequard syndrome due to acute ruptured cervical disk involving the right side of cervical cord.

Laboratory data: *CT myelogram* demonstrated a probable extruded disk at the C5-C6 level to the right of the midline displacing the spinal cord posteriorly and to the left *(Fig.9-3).*

Cerebral spinal fluid protein was significantly elevated to 141 mg % (normal is less than 45mg %), consistent with a spinal cord block.

Subsequent course: She was unwilling to have an MRI or any neurosurgical procedure undertaken to remove the disc. With the use of a cervical collar, she had had rapid resolution of her symptoms and continued to do well over the next 8 years. Refer to CD ROM for additional details.

The MRI scan remains the study of choice in patients with cervical spine pathology as demonstrated in *Figure 9-4.* This 31-year-old male jumped off a truck carrying an 80-pound bag on his shoulder. The following morning, he awoke with severe pain throughout the spine on coughing. And intermittent tingling of both hands for approximately 4 months Nine months later, he still had an equivocal plantar response and MRI demonstrated a ruptured disc at the C5-6 interspace.

Metastatic carcinoma: May involve the vertebrae without producing spinal cord or nerve root compression. However continued growth of the tumor or vertebral collapse may lead to spinal cord compression. The tumor may spread to the epidural space from the vertebral involvement producing spinal cord compression. Vertebral collapse may also produce spinal cord compression from bony elements of the vertebrae. A metastatic tumor may also appear in the epidural space without direct involvement of the vertebrae. In such cases, tumor within the thoracic or abdominal cavity may have spread through the neural foramina into the epidural space. Lymphomas in the thoracic or abdominal cavity in a paravertebral

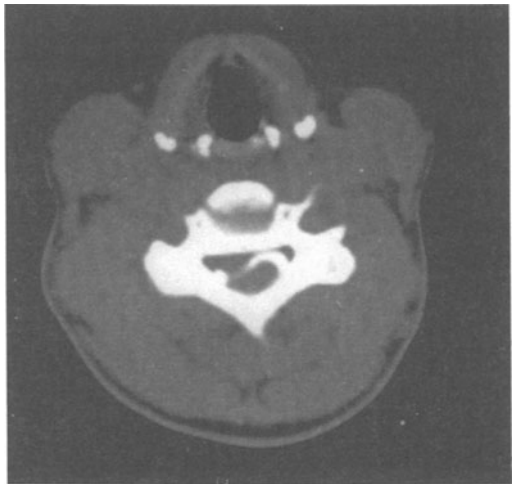

Figure 9-3. Cervical Disc Rupture: Brown Sequard Syndrome, Case History # 9-1: CT Scan of cervical cord post metrizamide myelography. Refer to text.

location often spread in this manner. Spread of metastatic tumor may also occur via the venous plexus or via other hematogenous routes. The majority of metastatic tumors involve the thoracic and lumbar areas. The majority of cases originate from primary disease in the lung, breast, prostate and kidney. Based on the autopsy studies of Barron in 1959, 5% of all systemic cancers will eventually develop spinal epidural spread. A significant proportion of patents presenting with epidural spinal cord compression secondary to metastatic disease may not have been previously known to have a malignancy. In a series from a large general hospital (The London Hospital) in 1982, 47% of the patients were in this category. 14% of patients never had the primary location determined. **Case 9 - 2** demonstrates the consequences of metastatic carcinoma producing spinal cord compression.

Case 9-2: This 55 year-old white housewife first noted pain in the thoracic-right scapular area, 5 months prior to admission Three months prior to admission, a progressive weakness in both lower extremities developed resulting in a bed ridden state in which she was unable to move her legs or even to wiggle her toes .She had also noted a progressive pins and needles sensation involving both lower extremities. At the same time she developed difficulty

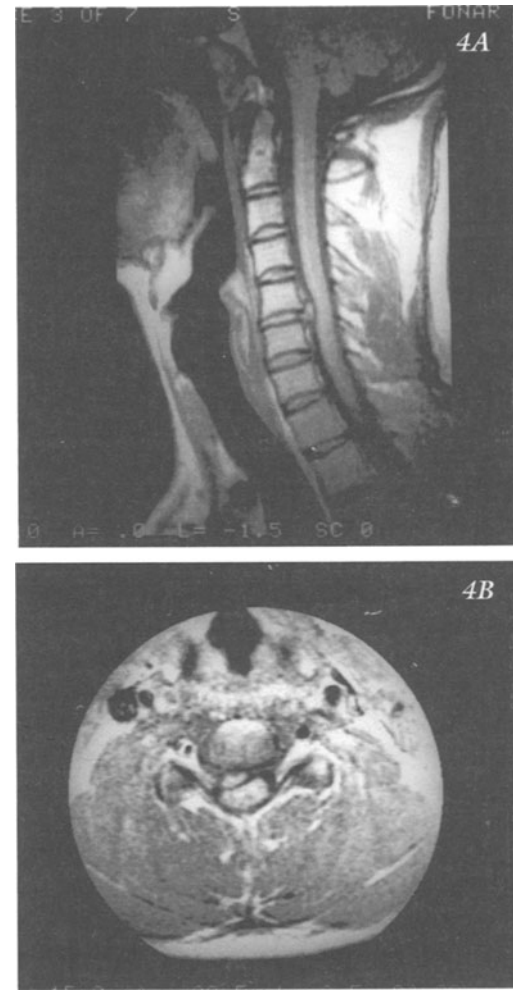

Figure 9-4 Acute Rupture of cervical disc midline and right lateral at C5-C6. A) MRI T1 weighted sagittal section of cervical spinal cord slightly to right of midline demonstrating a ruptured intervertebral disc at C5-C6 interspace. B) Transverse sections at C5-C6 interspace refer to B for correlation of levels- slice- 9 and 10. Cross-section at approximately C5, C6 demonstrating an extra dural mass to the right of the midline displacing the spinal cord posteriorly and to the left.

with the control of bowel movements and urination. At age 40, 15 years prior to this admission, she had undergone a left radical mastectomy for an infiltrating carcinoma of the breast with regional lymph node involvement.

Neurological examination: *Motor system:* a marked flaccid weakness in both lower extremities with retention of only a flicker of flexion at the left hip. *Reflexes:* Plantar respons-

es were extensor bilaterally (bilateral sign of Babinski). *Sensory system:* Position sense was absent at toes, ankles, and knees and impaired at the hip bilaterally. Vibratory sensation was absent below the iliac crests bilaterally. Pain sensation was absent from the toes through the T 6-T 7-dermatome level bilaterally with no evidence of sacral sparing. Tenderness to percussion was present over the midthoracic vertebrae (T4 and T5 spinous processes)

Clinical diagnoses: Spinal cord compression at T4-T5 vertebral level most likely secondary to metastatic epidural tumor.

Laboratory data: *XRay Studies:* The patient had multiple metastatic lesions in lungs, T4, T5 vertebrae and head of femur. An emergency *myelogram* demonstrated a complete block to the flow of contrast agent at the T5 level due to an extradural lesion displacing the spinal cord to the left.

Subsequent Course: An emergency thoracic T3-T4 laminectomy demonstrated adenocarcinoma presumably metastatic from breast in the vertebral processes, laminae and epidural space displacing the spinal cord. Following removal of tumor from epidural space and subsequent radiotherapy, movement in the lower extremities had returned to 30% of normal and pain sensation had returned to the lower extremities to a moderate degree.

In this case, a myelogram was performed, at the present time; the most appropriate diagnostic procedure would be an MRI scan. However in circumstances where that study cannot be performed, on an emergency basis then an emergency myelogram (or myelogram-CT) is appropriate. The presence of persistent mid thoracic - scapular back pain in a patient with a past history of breast malignancy should always prompt a search for metastatic lesions in vertebrae. In any case, the earliest development of motor or sensory symptoms in a patient with a past history of malignancy and back pain should lead to prompt neurological evaluation and investigation. (The present standard of investigation would include appropriate MRI study of the spine, which has the advantage of allowing studies not only of the specific area of compression but also of the spinal cord above and below the area of compression. Thus other epidural lesions may be identified). The best treatment of metastatic spinal cord compression is a high index of suspicion and early recognition to prevent the results seen in this case.

Acute epidural abscess: The dura mater of the spinal cord is separated from the periosteum of the surrounding bony canal by a narrow space containing fatty tissue (the epidural space). This space may be infected by an infection in adjacent tissues for example skin (furuncles) or bone (osteomyelitis involving the vertebrae). Alternatively, hematogenous spread of infection from distant sources may occur. The usual organism is staphylococcus aureus .The usual site is midthoracic. The epidural abscess is rare compared to the epidural tumors just considered and rare compared to meningitis and brain abscess. Nevertheless early recognition is necessary. Prompt drainage, decompressive laminectomy and antibiotic therapy are essential to avoid the poor prognosis of continued spinal cord compression.

The early symptoms of severe back pain and fever are followed by radicular pain or weakness and then the acute or subacute development of the signs of spinal cord compression. Approximately half the cases evolve over days to 2 weeks; half evolve over a period greater than 2 weeks. These latter cases are usually secondary to vertebral osteomyelitis. If treatment is delayed, functional transection of the spinal cord is the usual outcome related both to the direct effects of compression and the indirect effects of compression on the blood supply and the involvement of the blood vessel walls by the infectious process. The diagnosis is established by the appropriate clinical history, an MRI study or myelogram-demonstrating blockage of the subarachnoid space by an epidural mass and subsequent aspiration of pus from the epidural space.

Tuberculous involvement of the vertebrae with secondary spinal cord compression: Tuberculosis was once a common disease in urban centers of the United States and Europe. In other parts of the world for example, India, tuberculosis remains a common dis-

ease. Tuberculous involvement of joints, tuberculous arthritis, is a complication of untreated tuberculosis in children. A very common site of involvement is the dorsal spine. The process often appears to begin in the disc space and then involves the adjacent vertebrae. The disease process, tuberculous spondylitis (or Pott's disease), results in destruction of the body of the vertebrae and of the intervertebral disc. Collapse of the vertebrae and severe angulation of the bony canal occurs. In addition the chronic infection may spread into the epidural space as a local mass of infection or may accumulate as a mass under the ligament posterior to the vertebral bodies. All of these factors may contribute to spinal cord compression. Diagnosis can now be established by MRI scan. Treatment consists of drainage of any mass pockets of infection compressing the spinal cord, anti tuberculous chemotherapy, immobilization and possibly fusion of the spine.

Intradural - extra medullary spinal cord tumors (meningiomas and Schwannomas): In many earlier operative series this category of extrinsic tumor internal to the dura but external to the substance of the spinal cord, accounted for the largest percentage of spinal cord tumors. Such series accumulated prior to the advent of the MRI tended to underestimate epidural metastatic tumors because such patients were usually not admitted to specialized neurological-neurosurgical units. For example among 567 cases of spinal cord tumors collected from the literature by Merritt, in 1967, 59% were intradural extra medullary, 25% were extradural and 11% were intramedullary. The extradural tumors have already been considered in relationship to metastatic spread of carcinoma and lymphoma. The intramedullary tumors will be considered later under intrinsic lesions: gliomas and ependymomas. Essentially 2 types of tumor constitute in a relatively equal proportion all of the intradural lesions: meningiomas and Schwannomas (neuromas). Both types are benign in the sense that they are not locally invasive and do not spread to distant sites.

Meningiomas: These tumors arise from the arachnoidal cell clusters. Since the more common location is the cerebral hemisphere a more complete discussion of histologic types will be found in a later chapter. The typical gross appearance of this tumor in relation to the spinal cord is shown in *Figure 9-5.*

These tumors occur most frequently in middle-aged females (many meningiomas have estrogen receptors). The most frequent location is the thoracic portion of the spinal cord,

Figure 9-5. Gross appearance of meningioma compressing the ventrolateral aspect of thoracic spinal cord. (From Russell, D.S., and Rubinstein, L.J.: Pathology of Tumors of the Nervous System, 2nd Edition. Baltimore, Williams and Wilkins, 1963, p. 45).

in part because the thoracic segments constitute the longest extent of the spinal cord. Other areas however are not immune. In the upper cervical area these tumors may arise in relation to the foramen magnum producing both lower brain stem and upper cervical cord symptoms. The symptomatology of a typical meningioma arising in the thoracic spinal cord area might include thoracic back pain that radiated around to the interior chest in coughing

and straining at stool. Ascending sensory upper motor neuro symptoms in the lower extremities might evolve slowly over 6 to 12 months. Examination might demonstrate the findings of the bilateral transverse or Brown Sequard hemisection discussed above. In addition local tenderness would be present over the spinous processes at the level of involvement. Note that local tenderness over the spinous processes is common in extradural and intradural extra medullary tumors. MRI scan (or CT- myelogram if MRI is not available) would reveal an intradural extramedullary tumor with partial or complete block to the flow of CSF. CSF protein would be increased. These tumors require early neurosurgical intervention to avoid progression to a chronic paraplegic state. With the slow growth of the tumor, the capacity for recovery of function despite considerable distortion of the spinal cord is usually quite surprising once the compression has been relieved.

Schwannomas: These benign tumors arise from the cells of the nerve sheath. These tumors as noted above may arise in relationship to peripheral nerve, cranial nerves or nerve root. As discussed above those that arise in relation to nerve root with in the bony canal may compress nerve root and/or the spinal cord depending on location and size of the tumor. The symptoms and signs may be very similar to those of a meningioma. Because these tumors arise from the nerve root radicular pain is often more common than in meningiomas. The use of MRI to image Schwannomas is demonstrated in Figure 9-6. This 43 year old male had several months of pain in the cervical area that radiated into the anterior chest on coughing plus tingling from this area to the sacral area on sneezing. He had a marked decrease in all deep tendon reflexes in the right upper extremity. and percussion tenderness over the C6-7 spinous processes. All symptoms resolve following removal of the tumor. Note that the tumors may attain considerable size and produce only minimal spinal cord symptoms. As with all spinal cord lesions, the preferred neuroimaging technique is the MRI scan.

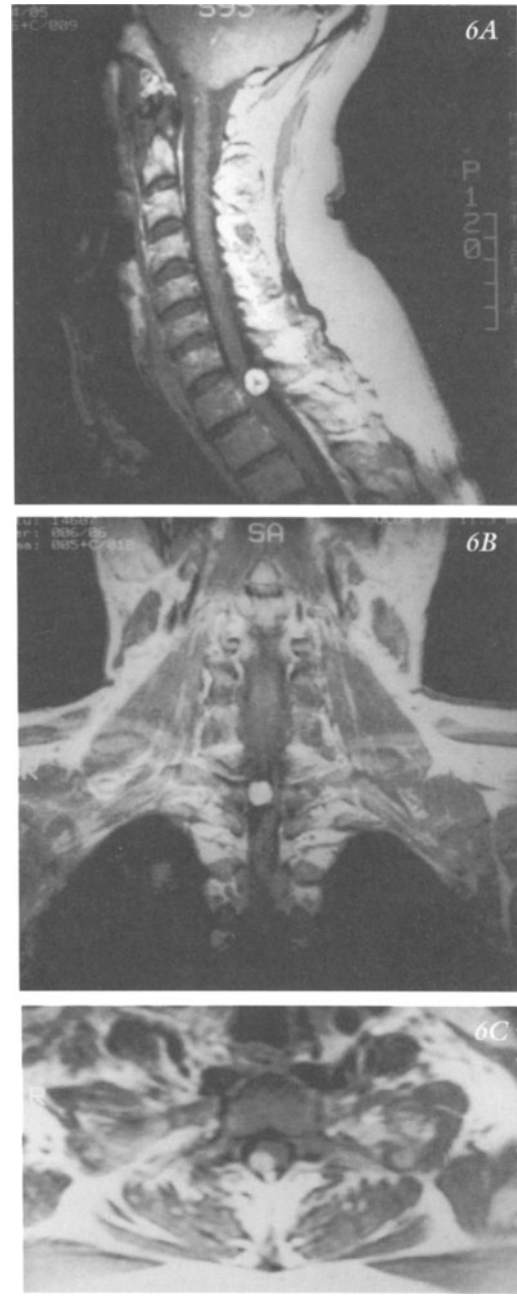

Figure 9-6. Schwannoma with compression of spinal cord. MRI with contrast enhancement. A) Sagittal section-midline. B) Coronal section between posterior arches and dorsal surface of spinal cord. C) Transverse section-T1-vertebral level.

Case history 9-3 presented on the CD ROM demonstrates the course of an Schwannoma compressing spinal cord.

Neurofibromatosis Type I (von

Recklinghausen's disease): This is an autosomal dominant inherited disease characterized by multiple peripheral neurofibromas (tumors composed of Schwann cells, collagen and reticulin fibers). There are also various anomalies of the skin (multiple > 6 cafe au lait spots and cutaneous neurofibromas), iris (Lisch nodules –pigmented hamartomas) and skeletal system. Large plexiform neurofibromas may produce marked facial deformities. Patients may also manifest meningiomas or intrinsic gliomas involving the optic nerve, brain or spinal cord but such central lesions are less common than in type II neurofibromatosis considered below. This form of neurofibromatosis is also referred to as peripheral neurofibromatosis; and occurs once in 3,000 live births. The mutated NF1 gene has been localized to chromosome 17q. The CT scan and MRI appearance of Schwannomas involving nerve roots has been presented in chapter 8.

Neurofibromatosis Type II: This type also known as central neurofibromatosis is also an autosomal dominant but is rare compared to neurofibromatosis type 1 occurring 1 in 50,000 births. The mutated NF 2 gene has been localized to chromosome 22. In contrast to type 1, peripheral manifestations are uncommon. Skin and bone lesions do not occur. Instead the patients have multiple types of tumors of the central nervous system. Most patients eventually develop bilateral acoustic neuromas (actually vestibular Schwannomas). This problem will be discussed in greater detail in the brain stem chapter.

INTRINSIC DISORDERS OF THE SPINAL CORD

Three general categories of intrinsic disease must be distinguished:

1. *Local disease affecting one or more adjacent segments:* a). Infarcts produced by occlusion of the anterior spinal artery b) transverse myelitis c) intramedullary spinal cord tumors: gliomas and ependymomas d) syringomyelia

2. *System diseases affecting one or more neuronal or fiber systems:* a) motor neuron disease, b) tabes dorsalis c) combined system disease d) spinal cerebellar degeneration

3. *Multifocal disorders*: various levels of the nervous system are affected. At any given level, a specific lesion is not restricted to a specific neuronal or fiber system: a) multiple sclerosis, b) other demyelinating disorders c) collagen-vascular disease lupus erythematosus and vasculitis.

SPECIFIC INTRINSIC SYNDROMES

LOCAL DISORDERS:

Vascular disease: anterior spinal artery occlusion: Primary vascular disease affecting the spinal cord is not common although a secondary vascular component may be present in many of the spinal cord compression syndrome discussed above. Any understanding of the clinical syndrome found in vascular disease of the spinal cord is dependent on knowledge of the anatomy of the arterial supply of the spinal cord *(Fig.9-7)*. The major artery of the spinal cord is the anterior spinal artery that is located in a midline position at the anterior median fissure. This single thin midline vessel has a bilateral origin from the intracranial portions of each vertebral artery. The arterial flow as this vessel descends is dependent on additional supply from the radicular arteries. These radicular arteries are derived from the cervical portion of the vertebral artery particularly at C3 and C 5 levels and the inferior thyroid artery at the C6 level. Additional radicular arteries originate from the aorta as the intercostal thoracic lumbar and sacral arteries. Most of the radicular arteries of the thoracic area do not contribute a significant supply. However, the middle thoracic artery usually at T 7 and the artery of the lumbar enlargement, (the artery of Adamkiewicz) which usually arises between T10 and L2 are of particular importance. There are then border zones of blood supply in the rostral-caudal axis between the cervical and lumbar segments of major supply. The actual border zones of circulation are at segments T4 and L1.

When the transverse anatomy is considered:

1. Anterior spinal artery: This midline vessel supplies the anterior and lateral columns and almost all of the gray matter except for the posterior horns.

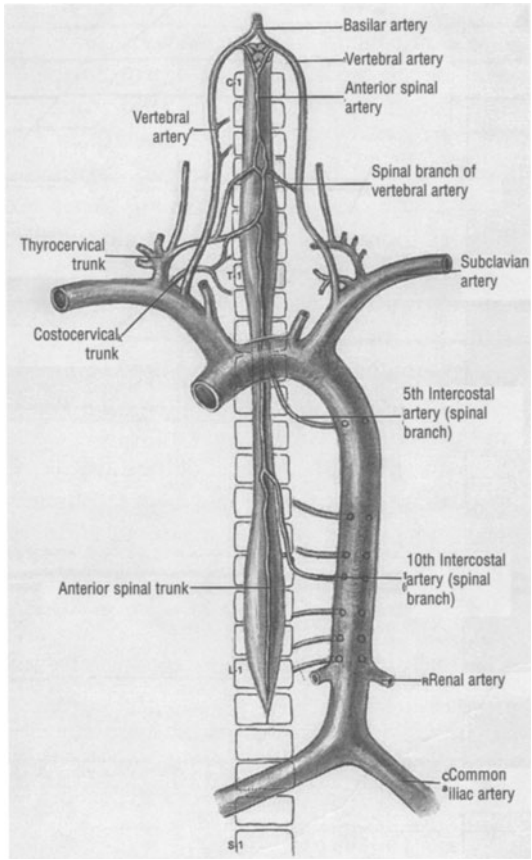

Figure 9-7. Vascular Anatomy of the spinal cord. Anterior spinal artery: the major radicular (segmental) blood supply is diagrammed. From Clemente, C., Gray's Anatomy, 30th Ed, Philadelphia , Lea and Febiger, 1988.

2. Posterior spinal arteries: These paired vessels supply the posterior horns and the posterior columns, each derived from the intracranial segment of a vertebral artery. These posterior spinal arteries also receive contributions from the posterior branches of the radicular arteries.

3. Anastomotic Vessels. At each level, coronal arteries at the periphery of the spinal cord connect the anterior spinal artery and the posterior spinal arteries. These anastomotic vessels at the periphery also serve to interconnect the blood supply of adjacent segments. A transverse border zone or watershed must also exist in the central gray matter where penetrating branches of the anterior spinal artery meet the penetrating branches of the posterior spinal arteries.

Since the largest area of the spinal cord is supplied by a single anterior spinal artery, it is not surprising that most vascular disease involving the spinal cord presents as the syndrome of the anterior spinal artery that is infarction of the territory supplied by this vessel *(Fig.9-8)*. This 71-year-old male had the acute onset of a flaccid paraplegia with an absence of deep tendon reflexes in the lower extremities and a pain sensory level at T7-8.No recovery occurred.

Actual occlusion of this vessel is rare. The usual cause of the syndrome relates to diseases of the aorta or to surgical procedures involving the heart, aorta, or related vessels. Clamping of the upper aorta for the surgical treatment of an aneurysm of the aorta may result in a decrease in blood flow in the critical intercostal branches supplying the spinal cord. A dissecting aneurysm of the aorta (a tear within the wall of the vessel with blood under high pressure dissecting down the media of the wall of the blood vessel) often results in the occlusion of intercostal and other vessels arising from the aorta. Other arteries arising from the arch of aorta such as vertebral and carotids may also be occluded. In other instances, the occlusion of intercostal branches particularly at T 10 may occur during surgical procedures on the kidney

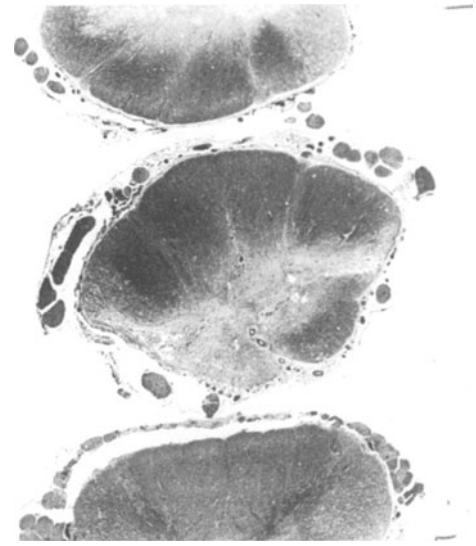

Figure 9-8. Infarction of spinal cord in distribution of anterior spinal artery secondary to occlusion of radicular artery at T6. Courtesy of Dr. Jose Segarra

or lumbar sympathetic ganglia.

The resultant neurological syndrome is manifested by the acute onset of a paraplegia which is usually flaccid due to spinal shock and a bilateral deficit in pain and temperature below the level of lesion with preservation of vibratory and position sense. If the area of infarction involves the lumbar sacral area the anterior horn cells will also be destroyed. The legs will then remain flaccid, muscle atrophy will develop, deep tendon stretch reflexes will never recover and spasticity will never develop. The prognosis then for a significant degree of recovery is usually poor. Theoretically, if the thoracic spinal cord were infarcted, with preservation of the lumbar and sacral segments, deep tendon reflexes could recover and spasticity without atrophy in the lower extremities could develop after several days.

In distinguishing other acute processes producing paraplegia, the rapidity of onset and the anatomical pattern of infarction seen in occlusion of the anterior spinal artery should be considered. Other processes such as trauma or hemorrhage into the spinal cord (hematomyelia) from rupture of a malformed blood vessel may produce an acute syndrome. The history, and findings as well as the MRI scan and the CSF examination would be distinguishing factors. Spinal arteriovenous malformations may also produce a progressive syndrome with episodes of acute exacerbation related to infarction and hemorrhage, but the anatomical pattern will differ from the acute anterior spinal artery syndrome. Multiple sclerosis may also produce a relatively acute onset of symptoms but the anatomical pattern will differ and lesions will usually be present elsewhere in the nervous system. Acute transverse myelitis and the spinal cord compressions discussed above do not produce the anatomical pattern of the anterior spinal artery syndrome.

The syndrome of acute or subacute transverse myelitis: When all other causes of an acute or subacute myelopathy have been excluded, there remain a group of patients without evidence of an extrinsic compressive or intrinsic vascular lesion. Usually the upper or mid thoracic spinal cord is involved. In the 1978 series of Ropper and Poskanzer, (in which all patients had myelography, since this was prior to the modern era of neuroimaging) 138 patients presented from 1955 to 1975 with an acute myelopathy or myelitis. In this overall group, 82 (59%) had an anatomical mass lesion usually an epidural metastatic tumor, four (3%) had a dissecting aortic aneurysm and presumably an anterior spinal artery syndrome, and 52(38%) remained in the transverse myelitis category.

Of the 52 patients in this residual transverse myelitis category, 33% had a prior viral illness and presumably could have had a post infectious myelitis. 6% had cancer of the lung, ovary, or prostate but without spinal cord compression and presumably had a remote effect of malignancy. 13% of patients eventually developed multiple sclerosis with the transverse myelitis as the presenting syndrome. The remaining 48% had no specific possible etiology.

In 21% of these patients the appearance of symptoms was acute with mid thoracic back pain, weakness of legs, sensory deficit below the level of lesion and urinary retention evolving over less than 1 to 12 hours. In 69% of patient's the symptoms progressed in an ascending manner over 14 days and then stabilized with the findings of a spastic paralysis and spastic bladder. In 10% of patients, the course was a stuttering progression over 10- 28 days. The progressive patients had a better prognosis than those with the acute onset. In the era prior to MRI scans, myelograms were usually normal but occasional patients were found to have mild swelling of the spinal cord.

In cases of transverse myelitis, pathological examination of the spinal cord reveals an acute or subacute necrotic process involving a number of segments. In other cases, areas of demyelination are present.

The MRI is able in most cases to image these pathologic changes. In mild cases, the MRI may be normal.

Case 9-4 presented on the CD ROM and in *Figure 9-9A* illustrates the diagnostic dilemma provided by such cases of transverse

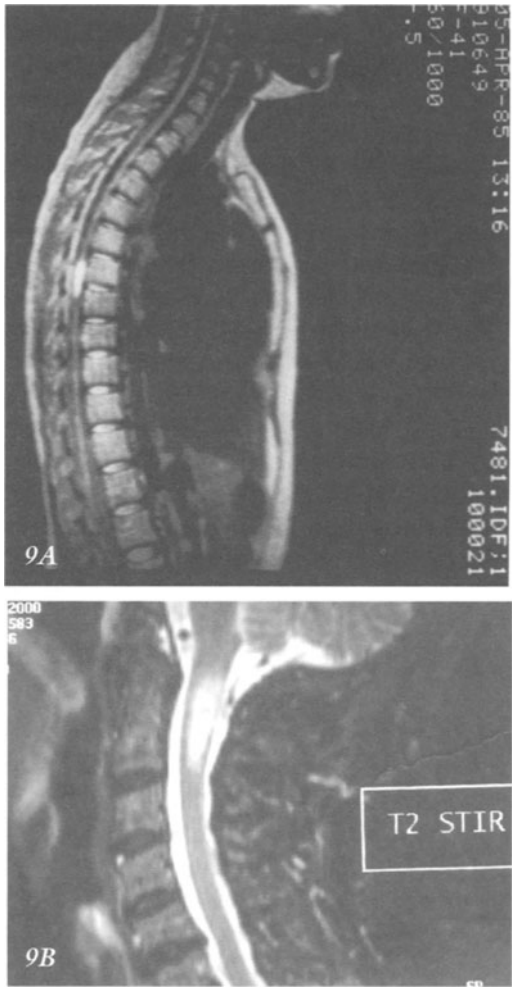

Figure 9-9. Transverse myelitis: A)Case 9-4 MRI (T1)(CASE ON CD ROM) This 42 year old female had the sudden onset of back pain at T6-8, followed by tingling and weakness in the lower extremities plus urinary retention evolving over 12 hours and then improving. B) This 54 year old female with a prior history of non Hodgkin,s lymphoma developed a progressive quadriparesis over 6 days ,and then rapidly improved possibly related to high dosage corticosteroids.

myelitis A 42 year old woman had the relatively sudden onset of back pain at T6-T8 and a tingling in the lower extremities. Over the next 12 hours, she developed weakness in the lower extremities and urinary retention. She then had improvement over the next 24 hours. A CT myelogram indicated a widened spinal cord at T7-8. Eventually clinical and MRI improvement occurred over several months.

Devic's syndrome (neuro myelitis optica) is a variant of transverse myelitis in which a relatively acute transverse myelitis is associated with an acute unilateral or bilateral optic neuritis. Some of these cases represent a variant of multiple sclerosis; others a variant of a post infectious myelitis, or rarely a paraneoplastic syndrome.

Subacute –chronic HTLV associated progressive myelopathy HAM/ tropical spastic paraparesis: This is a myelopathy produced by the retrovirus HTLV that causes human T cell leukemia. A chronic meningoencephalomyelitis is associated with demyelinating lesions in posterior and lateral columns. A sensory level may be present in the thoracic area. In tropical areas, the incidence may be as high as 128/100,000. The risk factors for transmission of the disease include many of the factors found with HIV infection: sexual transmission, intravenous drug use and blood transfusions. The CSF and MRI findings are similar to multiple sclerosis (which actually has a lower incidence in tropical as opposed to temperate areas). Differentiation may be made by a determination of antibody levels in serum and CSF.

Intrinsic spinal cord tumors: Rarely metastatic tumors may be found within the substance of the spinal cord. However most intramedullary tumors are intrinsic arising from the glial (astrocytic or ependymal) components. The glioma arising from the astrocytic series of cells is the most frequent intrinsic tumor of the spinal cord found in the cervical-thoracic spinal cord. Most spinal cord ependymomas arise at the lower end of the spinal cord in the filum terminale. Intrinsic tumors of the spinal cord are rare compared to intrinsic tumors of the cerebral hemispheres and compared to extrinsic tumors of the spinal cord.

Ependymomas are often relatively localized and are to some extent discrete tumors. Astrocytomas on the other hand often tend to infiltrate the surrounding tissue without any particular limiting border. Several or many adjacent segments may be thus involved by the tumor. In some children, the tumor does appear to have limiting borders and thus may be shelled out at surgery. A cystic component is often present and the cyst may be drained at

surgery. The overall diameter of the spinal cord is increased and this may be visualized at myelography or on MRI scans. The increased mass of the spinal cord produces pressure on the pedicles of the vertebrae. Plain x-ray films of the spine may demonstrate the resultant increased interpeduncular distance. From a histological standpoint the spinal cord astrocytoma is usually of a uniform appearance with a relatively low to moderate grade of malignancy (grade 1-2). This is reflected in the usual clinical course that extends over a period of several years with a 5-year survival after surgery of up to 90% of patients. Contrast this to the astrocytoma that infiltrates the cerebral hemispheres which has a much more malignant histological grade of 3-4, and a much shorter survival.

A typical case is that of a young adult or child who presents with a several year history of a slowly progressive lower motor neuron weakness and atrophy of 1 extremity involving multiple segments. Sensory symptoms in that extremity might develop at the same time or subsequently with or without radicular pain. As the process continues upper motor neuron weakness of the ipsilateral leg might be followed by a similar involvement of the opposite leg. Subsequently a slowly progressive lower motor neuron weakness might develop in the opposite upper extremity. Depending on the pattern of infiltration, long tract sensory findings might be present or absent. Bladder function would usually be well preserved. Very little local tenderness would be present over the vertebrae in contrast to extrinsic tumors. The changes in plain spine x-rays, myelography/CT and MRI scan have been noted above. The patient would improve following laminectomy, drainage of any cystic component and in some cases removal of tumor in cases (usually pediatric) where the tumor could be discreetly separated from the surrounding tissue. Radiotherapy would also produce considerable improvement.

Syringomyelia: this disease usually affects the cervical portion of the spinal cord but may extend into thoracic and lumbar segments. The basic pathology involves the formation of an irregular cavity (syrinx) in a central or paracentral location *(Fig.9-10)*. The cavity is surrounded by a border of gliosis, (an area of proliferation of astrocytes with the production of glial fibers. The cavity is usually ventral to and distinct from the central canal that is lined by ependymal cells .As the disease progresses, the syrinx may however extend into the central canal. The location of the syrinx is critical for understanding the early symptoms and signs that develop. The syrinx initially involves those pain and temperature fibers crossing the midline in the anterior white, commissure. Thus the initial symptoms and signs relate to a selective loss of pain and temperature sensation in the cervical segments producing a cape like deficit *(Fig.9-11)*. Since, initially touch, vibratory and proprioceptive sensation are preserved, this is referred to as a dissociated sensory deficit. The patient often reports painless burns and painless trauma to the hands and arms. Although these symptoms and findings are usually bilateral, occasionally because of the irregular shape of the syrinx the symptoms and signs may be predominantly unilateral. The subsequent course of syringomyelia is variable since the syrinx often varies in its shape and pattern of expansion. The anterior horns however are often subsequently involved resulting in local atrophy fasciculations and local flaccid paralysis of hand or upper extremity muscles with a segmental loss of deep tendon stretch reflexes. As the syrinx continues to expand, lateral and at times posterior columns may be involved with resultant long tract motor and sensory findings. Although the process is most

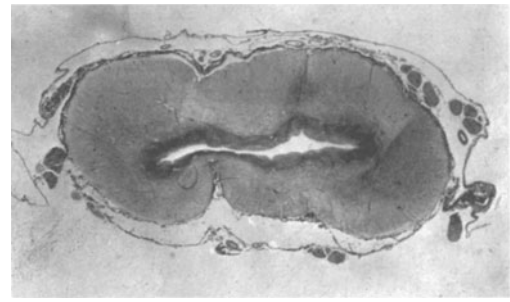

Figure 9-10. Syringomyelia producing enlargement of the cervical spinal cord, destroying the anterior white commissure and the anterior horn. A dense border of gliosis is evident around the cavity. (Holzer stain for glia). (Courtesy of Dr. E. Ross).

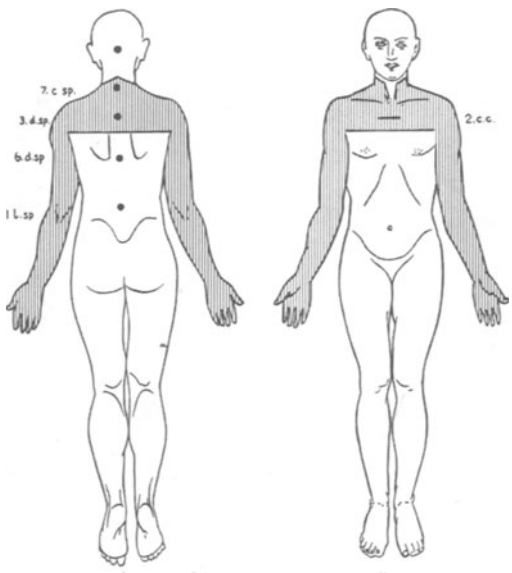

Figure 9-11. Syringomyelia with dissociated sensory loss. The cape-like distribution of a selective pain and temperature deficit with intact touch sensation over the upper extremities is demonstrated.

prominent in the cervical spinal cord, the syrinx may extend into the thoracic and lumbar spinal cord. In addition, the process may extend into the medulla as syringobulbia. In such cases, the syrinx is usually present as a slit like cavity extending in a ventral lateral direction from the floor of the 4th ventricle (the continuation of the central canal) into the dorsal lateral medullary tegmentum. In this location, many of the symptoms and signs relevant to the medulla will be similar to those of the lateral medullary infarct to be discussed in the brain stem chapter. The symptoms and signs of syringobulbia are often predominately unilateral although bilateral lesions may occur with involvement of the nucleus ambiguous. The slit like cavity may be difficult to visualize on MRI scans of the brain.

The precise etiology of syringomyelia is variable, and the underlying pathophysiology is often not clear.

In *type I syringomyelia*, there is an abnormality, usually developmental at the cervicomedullary junction. The Chiari or Arnold Chiari malformation is a frequent association. Two types of the Chiari Malformation are recognized: type I and type II. In *type I Chiari malformations*, the cerebellar tonsils extend down through the foramen magnum compressing the cervical medullary junction. In *type II Chiari malformations,* there is caudal displacement of the lower end of the medulla and 4th ventricle as well as of the cerebellar tonsils through the foramen magnum .As a result, the brain stem is elongated and distorted with an abnormal bend. Other abnormalities at this junction may include the Dandy Walker malformation in which the 4th ventricle is markedly dilated due to a closure or failure of development of the foramina of Magendie and Luschka. In other cases a meningioma may be present at the junction or inflammation of the meninges (arachnoiditis) may have occurred. In all of these abnormalities at this junction, a dilatation of the central canal (hydromyelia) usually occurs, and the syrinx appears to develop from this dilated central canal. In some of these cases hydrocephalus is also present.

In *type II syringomyelia*, no specific etiology is present. These cases referred to as idiopathic constitute approximately 60% of all cases.

In *type III syringomyelia,* the syrinx appears to relate to other disease of the cervical spinal cord.

In approximately 8 - 16% of patients with syringomyelia, there is an associated intramedullary tumor.

Syringomyelia may also follow severe spinal cord trauma or following spinal cord compression, developing late after the event from areas of necrosis (myelomalacia).

Diagnosis can be made based on the clinical findings with confirmation by MRI studies of the spine and brain.

The following case 9-5 provides an example of syringomyelia.

Case 9 - 5: This 33 year-old female credit union manager had a 3-year history of intermittent pain and paresthesias extending from the left cervical area to the left arm and hand predominantly involving the middle finger. In the last 3 months, weakness of the left arm and had developed and paresthesias of the left arm had become more continuous.

Neurological examination: *Motor system:*

A mild weakness was present at the left triceps muscle. *Reflexes:* There was depression of all deep tendon stretch reflexes in the left upper extremity. *Sensory system:* There was a selective cape like decrease of pain and temperature sensation in the left upper extremity (shoulder and arm). In addition, there was a selective decrease in pain sensation over the T 3-T5 dermatomes on the right.

Clinical Diagnosis: syringomyelia

Laboratory data: *MRI scan* of the spinal cord demonstrated an extensive irregular cavity extending from C2 to T 9 with a major enlargement of the spinal cord at the T 4 vertebral level *(Fig.9-12)*.

MRI scan of the head demonstrated a type 1 Arnold Chiari malformation with displacement of the cerebellum below the foramen magnum *(Fig.9-13)*.

Subsequent course: Dr. Alex Danylevich performed a laminectomy at T4 and shunted the large cavity into the subarachnoid space.

Figure 9-14 and **Case 9-6** (presented on the CD ROM) represent a more complex and more advanced example of syringomyelia and syringobulbia.

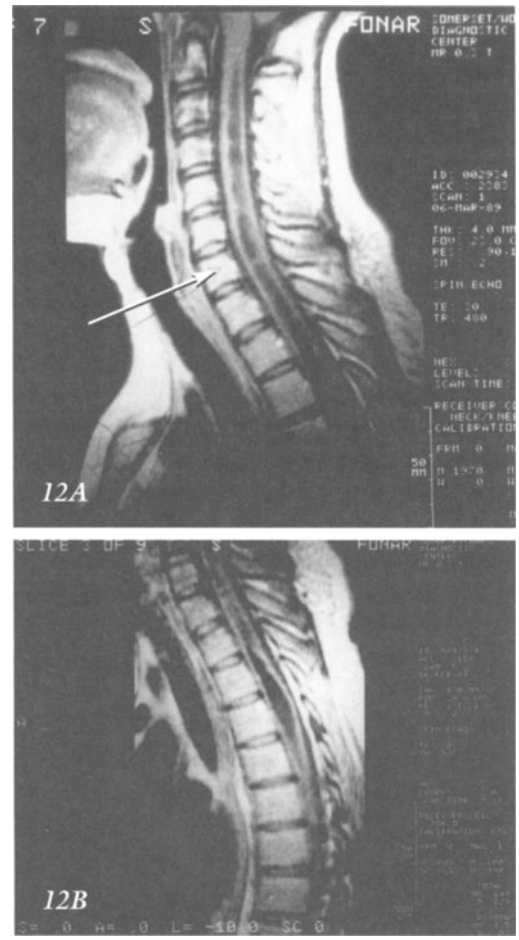

Figure 9-12. Syringomyelia. Case 9-5 MRI Scan. A) Cervical 2-Thoracic 5: Sagittal Section 10mm to left of midline-the arrow is on the cervical 7 vertebral body. B) Cervical 6- Thoracic 9: Sagittal section 10 mm right of the midline. The point of widest enlargement of the spinal cord is opposite the T4 vertebral body.

SYSTEM DISEASES OF THE SPINAL CORD:

These are diseases in which there is a relatively selective involvement of particular neuronal cell groups and/or their fibers. At times, several related cell or fiber systems are involved. System diseases are not of a uniform etiology. Nutritional deficiencies, infections and degenerative disorders are found in this category.

SPECIFIC SYSTEM DISEASES:

Disorders of the anterior horn cell:

Acute anterior poliomyelitis: This disease is caused by a filterable virus that invades the central nervous system. The virus spreads from the gastrointestinal tract by means of a viremia or by spreading up the axis cylinders of the autonomic nerve fibers. On reaching the central nervous system, the virus then involves preferentially the large motor neuron of the spinal cord and brain stem resulting in damage, degeneration, or death of these neurons and

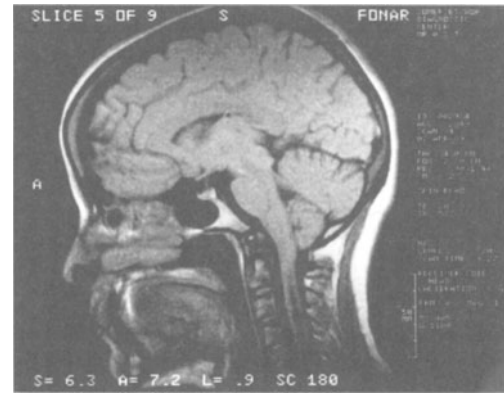

Figure 9-13: Arnold Chiari malformation associated with syringomyelia Case 9-5 MRI (See text)

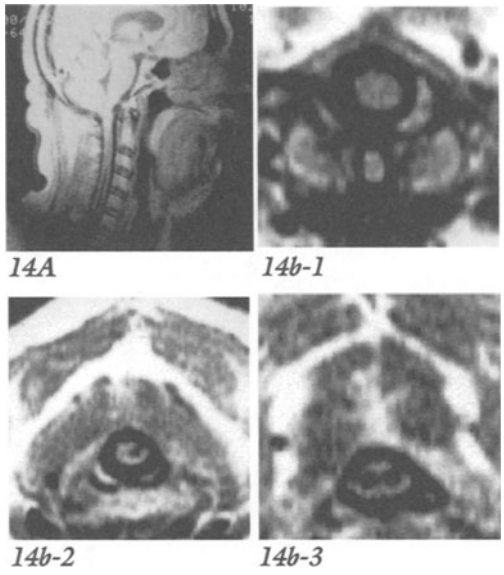

Figure 9-14 Syringomyelia. Case History #9-6. (CASE ON CD ROM). MRI Scan. This 60 year old male had clinical findings of syringomyelia and syringobulbia. A) Midline Sagittal Section demonstrating a central cavity beginning at the cervical two segment and extending well into the upper thoracic segments. B) Transverse Sections demonstrating the irregular nature of the central cavity. 1) Cervical 1-level, no definite cavity. 2) Cervical 2 Level-cavity is predominately right sided extending into right posterior column, 3) Cervical 4 Level-bilateral cavities.

inflammatory changes in the surrounding tissue *(Fig.9-15)*. Neurons in the posterior horn and interneurons of the spinal cord are to a lesser degree often involved in the acute stage.

The correlated clinical phenomena consist of a prodromal period of fever, malaise, headache plus gastrointestinal and upper respiratory symptoms. This is followed in some patients, by a stage of meningeal irritation and then in some patients, by the development of a flaccid paralysis. This involves in an irregular manner, many of the muscles of the extremities and trunk (the spinal form) or the muscles supplied by the bulbar motor nuclei (the bulbar form). Muscles affected in the bulbar form include the facial, palatal, pharyngeal and tongue. In the acute phase cramps are often a significant symptom. Respiratory paralysis may occur in severe cases because of the involvement of the motor nuclei of the diaphragm and

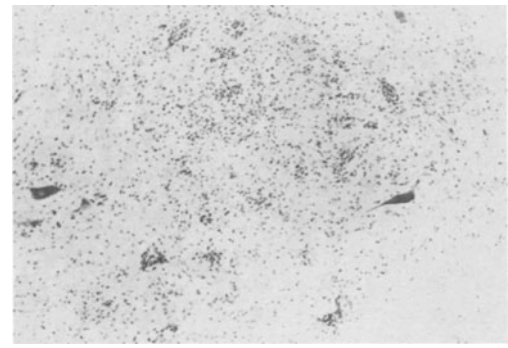

Figure 9-15. Acute anterior poliomyelitis. Lumbar spinal cord, with a loss of large anterior horn motor neurons and replacement by clusters of mononuclear cells. Cresyl violet stain (X100) (Courtesy of Dr. Jose Segarra).

intercostal muscles or from damage to the respiratory centers in the medulla. The spinal fluid findings are typical of aseptic meningitis with a predominantly lymphocytic response; however very early in the disease polymorphonuclear cells may predominate. The majority of patients with anterior poliomyelitis make a complete or significant recovery. A significant proportion may actually be labeled as nonparalytic cases because a paralysis fails to develop even in the acute state. However an estimated 20 -30% of all cases have a significant residual deficit or disability: a flaccid paralysis with atrophy, fasciculations, and loss of deep tendon stretch reflexes. In many cases, one limb, often a lower extremity is predominantly involved. In bulbar cases, many patients remain respirator dependent. We may presume that in the majority of cases many neurons invaded by the virus manifest a transient dysfunction but are not destroyed.

Recent interest has centered on the development of additional weakness and atrophy many years after the acute episode called the post polio syndrome. The underlying pathological basis for this progression is not entirely clear. The muscles involved however appear to be those previously affected in a clinical or subclinical manner with or without residual paralysis. Electromyography in many patients after the acute phase of poliomyelitis demonstrates changes in many muscles that were not clinically affected by the acute disease.

With the development of the Salk vaccine (formalin inactivated virulent strains) and the Sabin (attenuated live virus) vaccine, infections with the poliomyelitis virus are now extremely rare in the United States and other developed countries. Worldwide eradication is now possible but economic factors and warfare has prevented such eradication in many parts of Africa, and Asia. In countries where the natural disease (due to the "wild," naturally occurring virus) has been eliminated rare cases are still encountered as a result of infection from immunization with the live attenuated virus. In addition, adults who have not been immunized may be infected by exposure to infants or children who have just been immunized with the live attenuated virus.

Case 9-7 presented on the CD ROM presents an example of poliomyelitis in an adult who had not been immunized.

Spinal muscular atrophies: This is a group of genetic disorders that involve the anterior horn cell, without involvement of the corticospinal or sensory systems. All are autosomal recessive. Four types are identified based on age of onset. The later the age of onset, the slower the progression. The earlier the age of onset, the more likely that bulbar motor neuron involvement and respiratory failure will be present in addition to the findings of anterior horn cell involvement. The incidence of the infantile and juvenile forms of the disease is estimated as 1 in 6,000 - 20,000 births. The major disease to be differentiated is usually a disease of muscle i.e. a myopathic process. EMG studies, muscle biopsy and genetic studies are useful in establishing the diagnosis. Types are based on age of onset.

Type I, infantile form (Werdnig-Hoffman Disease): onset: last trimester of pregnancy-6 months: floppy.

Type II (Intermediate/arrested form of spinal muscular atrophy):onset <18 months: delayed motor dates.

Type III Juvenile form (Kugelberg-Welander Disease):onset 5-15 years: proximal limb weakness.

Type IV, Adult onset spinal muscular atrophy: onset>20years:very slowly progressing proximal limb weakness. Note overlap with progressive muscular atrophy form of amyotrophic lateral sclerosis discussed below.

Underlying molecular basis: types I, II, III have all been mapped to chromosome 5 at region 5q11.2--5q13.3 where a survival motor neuron (SMN) gene is located. Deletions in exons on this gene occur in these patients. The genetic defect responsible for the type IV, adult onset cases is unknown.

X-Linked Recessive Bulbospinal Neuronopathy (Kennedy's Disease): This adult onset disease affects males over the age of 30 years. Degeneration of motor neurons in spinal cord and brain stem occurs. There are minor sensory findings. The disease is rare compared to the progressive muscle atrophy form of amyotrophic lateral sclerosis to be considered below but somewhat more common than the adult onset type of spinal muscular atrophy. The importance of this disorder relates to the underlying molecular basis: an abnormal increase in the trinucleotide cytosine –adenine-guanine (CAG) repeats in the region of the androgen receptor gene on the X chromosome. Many of these patients will have gynecomastia; some will have testicular atrophy. In normal individuals, there are 17-26 repeats. In the patients, there are 40-65 repeats. A similar expansion in the number of CAG trinucleotide repeats occurs in other diseases involving different aspects of motor function and affecting different chromosomes: Huntington's disease and the spinocerebellar degenerations. The CAG trinucleotide repeats encodes poly glutamine. With excessive function, protein aggregation occurs in the motor neuron nucleus resulting in degeneration. As in these other disorder,s the higher the number of repeats, the earlier the age of onset.

Disorders of the motor system affecting both the lower motor neuron and the upper motor neuron

Amyotrophic lateral sclerosis (motor neuron or motor system disease, ALS): this is a relatively common degenerative disease of unknown etiology affecting predominantly adults of 40 to 60 years of age. Prevalence is

estimated at 4- 10 per 100,000. Approximately 10% of cases are inherited usually as an autosomal dominant rarely as an autosomal recessive. In 15-20 % of the autosomal dominant families, a mutation has been mapped to the gene locus for superoxide dismutase on chromosome 21. This enzyme is involved in the detoxification of the free radical superoxide to hydrogen peroxide. Whether injury from free radicals is responsible for the neuronal degeneration in sporadic cases is uncertain.

Clustering of cases of ALS has been noted among the Chamorros on Guam, on the Kii peninsula of Japan and in western New Guinea. In these clusters, there is an overlap with cases of Parkinson - dementia complex. In these areas, the prevalence of ALS was formerly 100 times that of sporadic cases in other parts of the world when studied in the 1950's. With improvement in nutrition and in water supplies, the incidence has decreased. Thus possible toxic factors have been suggested, although a possible predisposition may also be present in these populations. As regards the etiology in most sporadic cases of ALS, the hypothesis of glutamate excitotoxicity has gained prominence in recent years. Glutamate serves as the major excitatory transmitter in the central nervous system. Excessive long-term ingestion of the chick pea (Lathyrus sativus) that contains a neurotoxin, a glutamate receptor agonist may produce a neurological syndrome (lathyrism) in which selective damage to upper motor neurons in the motor cortex occurs. As we will discuss later in relationship to dementia, an epidemic of food poisoning related to contaminated mussels occurred in the Canadian Maritime Provinces in the early 1980s with manifestations of motor neuron disease and dementia. Domoic acid, a potent glutamate receptor agonist was found to be the specific neurotoxin. Related to glutamate excitotoxicity is the role of the subsequent influx of excessive amounts of intracellular calcium. Intracellular calcium binding proteins protect against the effects of excessive intracellular calcium. Those neurons that degenerate in ALS such as the large cortical pyramidal cells the bulbar motor neurons and the alpha motor neurons of the spinal cord have low activity of these calcium-binding proteins. In contrast, those neurons which are not affected in ALS; the oculomotor nuclei, the sensory neurons, the cerebellar Purkinje cells and the nucleus relevant for the bladder (Onuf's nucleus) have a high level of immunoreactivity for calcium binding proteins.

An additional hypothesis as to etiology, concerns possible failure of action of nerve growth factors. Table 9-3 outlines the clinical features and the neuropatholic correlation in ALS.

The majority of cases referred to as *classical ALS* eventually have involvement of all of the systems listed in Table 9-3. However the disease may begin with involvement of the bulbar motor neuron or the spinal cord lower motor neuron or the upper motor neuron. The onset may be very asymmetrical and limited to one limb. The terms applied to those cases with only one of the systems involved are presented in table 9-3.

The diagnosis in those cases with a classical ALS syndrome can be established on the basis of the clinical symptoms and signs. Those cases with a progressive bulbar symptomatology may require MRI studies to exclude other brain stem pathology such as a brain stem glioma. Those cases with a progressive cortical spinal syndrome will require MRI study of brain and cervical spinal cord to exclude other treatable conditions such as parasagittal or foramen magnum meningioma. Those cases with a progressive spinal muscular atrophy syndrome will require nerve conduction studies and electromyography to exclude motor neuropathies. These latter patients may also require studies for immunological and toxic causes.

Electromyography in anterior horn cell disease will show evidence of both denervation and reinnervation. Some of the muscle fibers of a motor unit that have lost their innervation may be reinnervated by axonal sprouting from surviving anterior horn cells. Muscle biopsy will demonstrate grouped motor unit atrophy (as in figure 8-16) Thus a group of muscle fibers all innervated by the same anterior horn cell will be atrophic where as a neighboring

group of muscle fibers innervated by an intact anterior horn cell will be well preserved. MRI studies of the brain particularly in patients with prominent upper motor symptoms and signs will demonstrate atrophy in the motor and premotor areas.

Overall median duration of disease ranges from 23 - 52 months. 20 to 25% of all patients live longer than 5 years and 8 -16% of patients survive beyond 10 years. The prognosis of patients with ALS depends on the type of disease and on the initial manifestations as indicated in Table 9-4.

Note that questions have been raised been raised as to whether cases of primary lateral sclerosis and progressive muscular atrophy represent diseases that are distinct from classical ALS. Cases that remain as pure anterior horn cell involvement longer than 36 months are usually classified as PMA. The age of onset is usually younger as well. Overall younger patients have a better prognosis.

The following **case history 9-8** demonstrates the full clinical extent of a classical case of ALS.

Case 9-8: This 66 year-old married white male merchant, 9 months prior to evaluation had the insidious onset of a progressive weakness and atrophy involving the lower extremities and subsequently a similar but lesser involvement of the upper extremities. Three-month prior to evaluation, the patient had the onset of thickness of speech, a difficulty in swallowing solids and to a lesser degree liquids. At the same time stiffness in both lower extremities developed. There had been no sensory symptoms, no urinary symptoms, and no change in mental status. There had been a weight loss of 30 lb.

Neurological examination: *Cranial nerves:* V: the jaw jerk was hyperactive (deep tendon stretch reflex). VII: A bilateral peripheral paralysis was present involving the upper and lower face with a paucity of facial expression. IX, X: Although a gag reflex was present, elevation of the uvula was poor. The voice was hoarse and speech was of low volume. XII. Ridges of atrophy and fasciculations were present along the lateral borders of the tongue. *Motor system:* Widespread muscular atrophy, fasciculations and weakness were present in all four extremities. *Reflexes:* The deep tendon stretch reflexes at the biceps, triceps, and patellar were hyperactive at 3 +. However the right Achilles reflex was 2 + and left was decreased at 0 to 1. The plantar responses were both extensor (bilateral sign of Babinski). *Sensory system:* Intact.

Clinical Diagnosis: amyotrophic lateral sclerosis (fully developed-classical type).

Laboratory data: *The EMG studies* muscle and biopsy were consistent with the diagnosis.

Subsequent course: The patient experienced additional difficulty in swallowing. He expired 3 months after the above evaluation, approximately 1 year after the onset of his disease.

Other diseases with selective involvement of the cortical spinal tracts:

TABLE 9-3. CORRELATION OF CLINICAL SIGNS AND NEUROPATHOLOGY IN ALS AND RELATED DISORDERS

Clinical Sign	Location of Neuropathology	If this system only is involved
1. atrophy, fasciculations, flaccid weakness and loss of deep tendon stretch reflexes (DTR's)	Alpha motor neurons of anterior horn	Progressive muscular atrophy (PMA)
2. bulbar palsy (CN 5,7,9,10,11,12)	Bulbar motor neurons of medulla and pons	Progressive bulbar palsy
3. upper motor neuron findings of spastic weakness, increased DTR's and sign of Babinski	Degeneration of corticospinal tracts secondary to loss of large/giant pyramidal cells in motor cortex (Fig.9-16)	Primary lateral sclerosis (PLS)
4. Pseudobulbar findings of increased jaw jerk and gag plus pseudobulbar speech.	Bilateral degeneration of corticobulbar tracts secondary to loss of large/giant pyramidal cells in motor cortex	Progressive pseudobulbar palsy

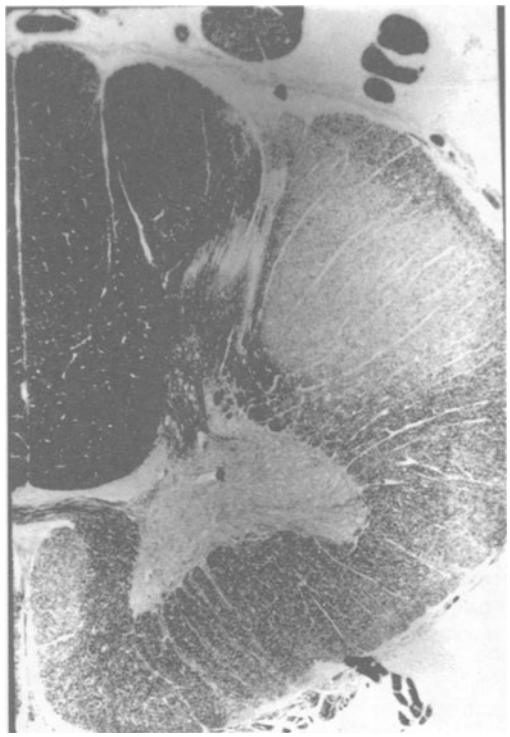

Figure 9-16. Amyotrophic Lateral Sclerosis. Degeneration of the corticospinal tracts is demonstrated in this myelin stain. (Courtesy of Dr. Emanuel R. Ross).

In addition to primary lateral sclerosis, another very slowly progressive disorder has been identified: hereditary (or familial) spastic paraplegia. The prevalence of this disease may be as high as 1 in 10,000. In 70-85% of cases the transmission of the disease occurs as an autosomal dominant. Genetic studies have indicated linkage to different chromosomes for different families: 14q or 15q or 2 p. Less often an autosomal recessive pattern is present. In most cases, onset of disease occurs in childhood or adolescence, less often, after age 35. Initially the lower extremities are primarily involved, with delays in motor development or clumsiness in walking or athletic activity. As the disease progresses the spastic paraparesis becomes evident. As in many of these degenerative disorders a deformity of the feet, pes cavus may occur. Later in the disease, the upper extremities may be involved. In addition a minor decrease in vibratory sensation in the lower extremities may be noted, and pathological examination of the nervous system demonstrates a minor degeneration of the posterior columns in addition to the marked degeneration of the corticospinal tracts.

TABLE 9-4: SURVIVAL RELATED TO ONSET OR TYPE (DERIVED FROM MATSUMOTO ET AL, 1998 AND MACKAY, 1963)

Classical ALS	Duration (mean)	Relatively Pure forms	Duration
OVERALL	36 months		
Bulbar onset	17 months*	Pogressive bulbar palsy	17 months
Corticobulbar onset	24 months		
Spinal motor neuron onset	33 months	Progressive muscular atrophy (PMA)	159 months (13 years)
Corticospinal onset	36months	Primary lateral sclerosis (PLS)	224 months (19 years)**

* Worst prognosis **Best prognosis

Degeneration of the posterior columns secondary to disease of the posterior root:

Tabes dorsalis *(Fig.9-17)*: this is a late complication of the sexually transmitted disease syphilis caused by the spirochete, Treponema pallidum. Three stages of the disease are recognized: Primary, secondary, and tertiary. A lesion of abraded skin and or mucous membranes that begin as a painless papule, which then subsequently ulcerates to form the chancre, characterizes the primary stage. The chan-

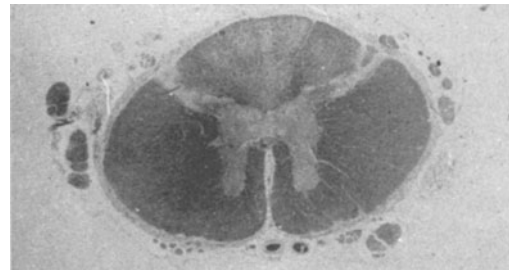

Figure 9-17. Tabes Dorsalis. Ascending degeneration of the posterior columns in a 67-year-old white male with tabes dorsalis, abdominal crises, luetic aortitis, and luetic optic neuritis. Myelin stain (Courtesy of Dr. Jose Segarra).

cre may involve the genitalia or lips or oral cavity or anus. The *primary lesion* develops after an incubation period of approximately 20 days, and may persist for an additional 14 -40 days. There is an associated painless lymphadenopathy. Primary lesions involving the vagina or cervix or anus may go unrecognized and in other locations may be mistaken for other transient diseases. In approximately a one-third of these patients asymptomatic spread to the nervous system may be documented by a cerebral spinal fluid examination. The *secondary stage of disease* begins at a variable interval of 2 - 12 weeks after contact. It is characterized by a generalized maculopapular rash which may be confused with other infectious exanthems and constitutional symptoms such as fever fatigue and generalized lymphadenopathy. The symptoms may be so mild that the patient has little awareness of this stage of the disease. Again approximately one-third of patients would demonstrate a meningeal infection were spinal fluid examination to be performed. However only 1 to 2% of patients in the secondary stage actually have symptoms of meningitis. After a variable period following infection of months to 30 years, the late or tertiary manifestations involving the nervous system and the cardiovascular system appeared in 28% of all patients in the pre antibiotic era. Symptomatic neurosyphilis developed in 7-9% of all patients in that era. Prior to the antibiotic era, tertiary neurosyphilis constituted a major neurological problem. A resurgence of the disease may occur in the future. The various types of tertiary neurosyphilis are listed in Table 9-5.Note that the primary process in almost all these syndromes relates to the late effects of meningeal infection and inflammation.

The Clinical Symptoms and Signs of Tabes Dorsalis are listed in table 9-6.

Case 9-9 provides an example of tabes dorsalis.

Case 9-9: This 40 year old male had a 4-year history of severe lancinating type pains in either leg worsened by exposure to cold weather or hot water. This was accompanied by a progressive deterioration of gait, which was particularly impaired in the dark. He could not determine where his feet were placed. He would often go 18-20 hours without voiding.

Neurological examination: *Cranial nerves:* pupils were small, did not respond to light but did respond to accommodation. *Motor system:* A gross ataxia of gait and stance was present worse with eyes closed (positive Romberg sign). *Reflexes:* Deep tendon reflexes were absent in the lower extremities. *Sensory system:* Position and vibratory sensation was absent at toes and ankles. Pain sensation was decreased over the nose and nipples.

TABLE 9-5:THE SYNDROMES OF TERTIARY NEUROSYPHILIS (DERIVED FROM MERRITT, ADAMS &SOLOMON, 1946)

Type and % of all tertiary neurosyphilis (predominant syndrome)	Location of Pathology	Delay in onset after infection
Acute meningitis	Meninges plus cranial neuropathies	2 months to 26 years usually <1 year
Meningo-vascular (16%)	Meninges and arteries in subarachnoid space (arteritis with infarcts in brain and spinal cord)	Several months to 20 years, average of 7 years
General paresis (12%)	Invasion of cerebral cortex by the spirochete with dementia and personality changes (see chapter 30)	20 years
Tabes dorsalis (30%)	Inflammation and infection of posterior roots and secondary degeneration of posterior columns plus (see table 9-6 below)	10-25 years.
Mixed usually general paresis and tabes	Combined cerebral cortex and posterior roots plus (see table 9-6 below	10-25 years
Chronic granulomas (gummas)	Skin, bones, CNS Rare	
Asymptomatic (31%)	Asymptomatic meningitis	Usually 1year

Clinical diagnosis: Tabes dorsalis

Laboratory data: The diagnosis was confirmed by positive serological tests for syphilis in serum and CSF.

The diagnosis of tabes dorsalis is dependent on the recognition of the clinical pattern of disease. It may not be possible to obtain a reliable history of the primary or secondary lesions. The clinical diagnosis is confirmed by serological tests of the serum and by cerebrospinal fluid examination demonstrating a positive serological test, some mild increase in mononuclear cells, a mild elevation of protein and an increase in gamma globulin. The serological test are of 2 types: 1) the nonspecific reagin antibody tests such as the RPR and the VDRL. 2) The specific treponemal antibody test such as the fluorescent treponemal antibody absorption test (FTA ABS). As regards the nonspecific antibody tests, a positive serum test alone indicates only previous infection without necessarily indicating neurosyphilis. Moreover a false positive test may occur in other febrile illnesses and other immunological disorders. A false negative nonspecific test in the serum may occur in up to 30% of patients with chronic neurosyphilis. The specific antibody tests on serum are positive in almost all cases of neurosyphilis. The positive nonspecific test of the spinal fluid when contamination of the spinal fluid by blood has been ruled out is diagnostic of neurosyphilis.

Penicillin is the treatment of choice of neurosyphilis. The current recommendations of the U.S. public health service are that the patient receive 24,000,000 units a day intravenously for at least 14 days. This should eliminate the activity of the organism. However many of these symptoms and signs will persist since the chronic damage to nerve roots and nervous system from the meningeal or the meningoencephalitic inflammation or vascular components has already occurred. A reexamination of the spinal fluid at 6 months may continue to show a weakly positive serological test for syphilis but all other abnormalities should clear. The serum nonspecific serological tests may continue to remain weakly positive.

TABLE 9-6: TABES DORSALIS: CORRELATION OF CLINICAL FINDINGS AND LOCATION OF NEUROPATHOLOGY

Clinical Sign	Location of Pathology
1. Loss of conscious proprioception: involving the lower extremities	Degeneration of heavily myelinated fibers entering the posterior columns
2. Loss of unconscious proprioceptive information.	Loss of medium diameter fibers, in the posterior root and possibly posterior horn on their way to neurons in the nucleus dorsalis (Clarke's column)
3. Unsteadiness of stance and gait: sensory ataxia. Positive Romberg sign	Loss of proprioceptive information in posterior columns from lower extremities to cerebellum and cerebrum
4. Loss of the deep tendon stretch reflexes manifested as an absence of the patellar and Achilles reflexes.	Loss of the heavily myelinated Ia fibers in the posterior root.
5. Bladder dysfunction - hypotonic flaccid dilated bladder occurs, atonic neurogenic bladder	Loss of the afferent fibers in the posterior roots of S2, S3 and S4 conveying stretch information from detrusor muscle of the bladder (interferes with reflex contractions of the detrusor muscle and subsequent emptying of the bladder)
6. Fleeting sharp pains in the legs the back, the body or face so-called ightening lpains. At times the viscera may also be involved.	Damage to small diameter fibers conveying pain sensation, in the posterior roots
7. Loss of sensation in the feet and subsequent trauma may result in trophic ulcers	Damage to sensory fibers from the leg with degenerative changes in the joints (Charcot's joints)
8. Abnormalities of the pupillary response to light (the Argyll Robertson pupil). Pupil is small (miotic), irregular, fails to respond to light and to sympathetic stimulation. Pupil does accommodate.	Lesion in pretectal region of upper midbrain or possibly in ciliary ganglion

Combined degeneration of the posterior and lateral columns:

Subacute combined degeneration: Combined system disease due to vitamin B12 deficiency: The combination of posterior and lateral column degeneration may be seen in several diseases involving the spinal cord. Of these various causes, the most important characteristic syndrome is that of subacute combined degeneration secondary to vitamin B12 (cobalamine) deficiency. In most cases the basic defect is a lack of intrinsic factor, the enzyme produced by the parietal cells of the gastric mucosa, the same cells that produce gastric acid. In most cases, this occurs on a genetic or immunological basis or as a result of a previous gastrectomy. Intrinsic factor is necessary for the absorption of vitamin B12 that occurs in the distal ileum. In a few cases, the deficiency of vitamin B12 does not indicate a deficiency of intrinsic factor but rather reflects an overall severe nutritional deficiency (eg. a diet deficient in this vitamin) or represents a failure of the absorption of vitamin B12. Such a malabsorption syndrome may occur with a tropical or non-tropical sprue. In other instances a blind loop has occurred and bacterial growth has resulted in consumption of vitamin B-12. The presence in the small intestine of the fish tapeworm d. Latum may also result in the consumption of vitamin B12.

Two active forms of cobalamine have been identified in humans. Methylcobalamin functions as the cofactor for the conversion of homocysteine to methionine. When the reaction fails to occur, folate metabolism is impaired and as a result there is a defect in DNA synthesis. As a result, megaloblastic maturation fails to occur and the characteristic megaloblastic picture of pernicious anemia results. The methionine that results from this conversion is also utilized for the production of choline and choline containing phospholipids. When defective, the formation and maintenance of myelin may be impaired. The second form of cobalamine, adenosylcobalamin is necessary for the conversion of methylmalonyl -coenzyme A to succinyl -coenzyme A. As a result, abnormal fatty acids may be synthesized and incorporated into neuronal lipids. Although the precise metabolic defect responsible for the neurological syndromes is not entirely clear, the first reaction is considered to be the more likely explanation.

Approximately 30 to 70% of all patients with pernicious anemia develop neurological symptoms and signs. Even when severe anemia is present the neurological state may be relatively normal and the explanation is unclear. On the other hand, severe signs of neurological involvement may be present in the absence of anemia. In some instances folic acid may been present in the absence of vitamin B12. Folic acid will correct the anemia but will not affect the progression of the neurological syndromes.

The neurological syndromes relate to the degeneration of myelin and subsequently of axons.

1. The major site of involvement is the spinal cord *(Fig. 9-18)*. Initially the process is most severe in the heavily myelinated fibers of the posterior columns. This results in paresthesias in the extremities and a sensory ataxia accompanied by a + Romberg sign a

2. At the same time, the same process affecting the heavily myelinated sensory fibers also affects peripheral nerves resulting in paresthesias and a loss of deep tendon reflexes.

3. Subsequently the heavily myelinated fibers of the lateral columns are involved predominantly affecting the lateral cortical spinal tracts. Bilateral Babinski signs will be found. Hyperactive deep tendon reflexes are not likely

Figure 9-18 Combined Systems Disease. Degeneration of posterior and lateral columns is demonstrated in this myelin stain of cervical spinal cord. (Courtesy of Dr. Emanuel R. Ross).

because of the effects of the peripheral neuropathy.

4. Less often the cerebral hemisphere white matter may be involved. Rarely for unknown reasons this site predominates producing a progressive dementia.

5. Occasionally the optic nerve is involved producing an optic neuropathy.

Diagnosis: Clinical syndrome + low B12 level (<200pg/ml) + Schilling test demonstrating low absorption and subsequent excretion (<8%) of labeled vitamin B 12 in urine with improvement after combined B12 and intrinsic factor.

Treatment: Monthly injections (IM) of 1000mcg of vitamin B12, after loading during the first month, 1000mcg daily X 5 days, then weekly X 3 weeks.

Case 9-10 demonstrates the symptoms and signs of a typical case of combined system disease.

Case 9-10: This 48 year-old house painter had a 16-week history of progressive impairment of gait mainly unsteadiness and imbalance worse in the dark than in the light and tingling paresthesias of all his toes. Twelve weeks prior to admission, tingling began in his fingers. Weakness had not been a major complaint although he had noted shortly before admission some sense of heaviness in his legs on climbing steps.

Neurological examination: *Motor system:* walking a tandem gait with eyes closed was difficult. The Romberg test was positive. *Reflexes:* Achilles deep tendon stretch reflexes were absent. Bilateral Babinski sign was present. *Sensory system:* vibratory sensation was absent at toes, ankles and knees. Position sense was decreased at toes. There was a minimal decrease in pain and touch sensation over the toes.

Clinical diagnoses: Combined system disease.

Laboratory data: consistent with the diagnosis. Serum B12 level: none detected. Schilling test demonstrated 1% excretion of radioactive B12 in the urine which increased to 12% with intrinsic factor.

Subsequent course: The patient was treated with vitamin B12 injections with improvement in symptoms.

Spinal forms of spinal cerebellar degeneration: Spinocerebellar degenerations represent overlapping groups of degenerative diseases that are usually of unknown etiology. In some cases and families the predominant pathology involves peripheral nerve; in others the cerebellum, in others, the cerebellum and brain stem, in others, the cerebellum, brain stem and basal ganglia. In the type to be considered in the section, the predominant involvement is of the spinal cord. However as will be evident, peripheral nerve is also often involved during the course of these cases.

Friedreich's Ataxia: In most series of hereditary ataxia, this type accounts for 50% of all cases. It is the most common of the autosomal recessive type and is certainly the most common of the early onset hereditary ataxias. The prevalence of this disease in Europe and the United States is 1-2 cases per hundred thousand. The initial symptom: an ataxia of gait appears in childhood or adolescence although rarely symptoms may appear in the young adult years. Subsequently, pyramidal tract findings and dysarthria may appear. Approximately 50% of the patients have a distal wasting suggesting a peripheral nerve involvement. Most patients have a distal loss of deep tendon reflexes and a distal sensory neuropathy involving large diameter fibers. Deformities of the foot including pes cavus *(Fig.9-19)* are common. Deformities of the vertebral spine such as scoliosis (curvature) or kyphoscoliosis are also common. In some cases, blindness due to optic nerve involvement and deafness due to 8th cranial nerve involvement is prominent. The majority of patients have abnormal electrocardiograms. Cardiac arrhythmias and ventricular enlargement/hypertrophy are common due to myocardial muscle and conduction system involvement. Ten % of patients has overt diabetes mellitus. The disease slowly progresses with a mean age of death in the 30s usually due to the cardiac involvement and to the bed ridden state.

Pathological examination *(Fig.9-20)* demonstrates a loss or degeneration of axons

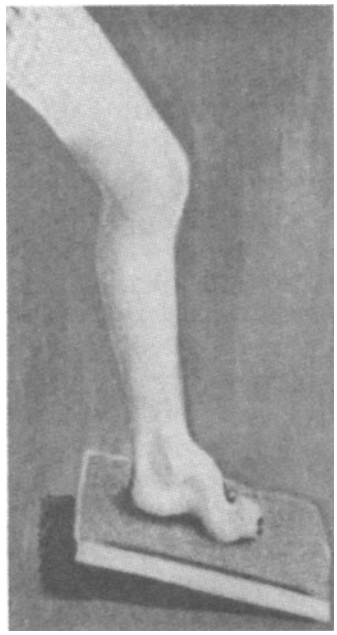

Figure 9-19. Friedreich's Ataxia: Pes Cavus. A similar abnormality of the foot may occur in other disease states. (From Wechsler, I.: Clinical Neurology, 9th Edition. Philadelphia, W.B. Saunders, 1963, p. 123).

that is most severe in the posterior columns of the cervical spinal cord and is accompanied by a significant loss of cells in the posterior root ganglion. The corticospinal and spinocerebellar (lower extremities) and cuneocerebellar (upper extremities) pathways also demonstrate degeneration of axons. There is also a loss of neurons in Clark'scolumn, the cells of origin of the spinocerebellar pathway. In some cases, there is a minor loss of Purkinje cells in the

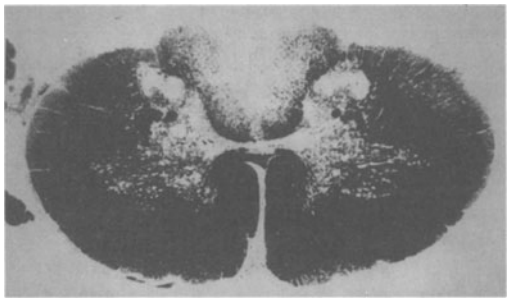

Figure 9-20. Friedreich's Ataxia. Degeneration of posterior columns and, to a lesser extent, of lateral columns is demonstrated in this myelin stain of cervical spinal cord. (From Wechsler, I.: Clinical Neurology, 9th Edition, Philadelphia, W.B. Saunders, 1963, p. 28)

superior vermis of the cerebellum, the termination of the spinocerebellar pathway. There is usually a mild loss on neurons in the dentate nuclei of the cerebellum and of the inferior olivary nuclei of the medulla which projects to the cerebellum. A more significant loss of neurons is found in the nuclei for cranial nerves 8, 10 and 12. Mild degenerative changes may be noted in the optic nerves. In contrast the peripheral nerves demonstrate a more significant distal loss of large myelinated axons.

From the standpoint of clinical pathological correlation, the ataxia is primarily a sensory ataxia due to the involvement of posterior columns, dorsal root ganglia, peripheral nerve and a lesser degree, the spinocerebellar pathways. However some cerebellar component is also present. The dysarthria reflects involvement of cranial nerves 10 and 12 in addition to some possible cerebellar component.

The underlying genetic basis of the disease is an unstable expansion of a trinucleotide repeat GAA (guanine adenine adenine) which maps to the chromosome locus 9 q 13 .On normal chromosomes, the number of GAA repeat ranges from 7 to 22. In contrast, 96% of patients with Friedreich's ataxia have both alleles expanded to 100 to 2,000 repeats. Patients with a larger number of repeats have an earlier age of onset and a more severe form of the disease. They are also more likely to have a cardiomyopathy. The trinucleotide expansion apparently results in a decrease in a protein which has been labeled frataxin and which may function as a mitochondrial iron transporter. The buildup of untransported iron could then result in defects of free radical regulation and oxidative metabolism.

Case history 9-11 presented on the CD ROM demonstrates the typical history and findings in a case of Friedreich's ataxia followed over a long period of time.

MULTIFOCAL DISORDERS AFFECTING THE SPINAL CORD:

Two categories of pathology produce multifocal symptoms and signs affecting central nervous system disease: demyelinating disease

and vascular disease particularly small vessel disease such as vasculitis. When the spinal cord is considered the first variety occurs frequently; the second is encountered less frequently.

Demyelinating diseases: In this category of disease we mean a pathological process in which there is a primary destruction of normally formed myelin. We have already indicated other disorders in which damage to myelin in system disorders is but one step in the destruction of the axon. In addition, destruction of myelin and axons may occur as a consequence of vascular infarction. There is another rare group of disorders, the leukodystrophies occurring in childhood, adolescence or early adult life, in which an extensive diffuse loss of myelin occurs. The loss however involves the destruction of defectively formed myelin.

Multiple sclerosis: Among the primary demyelinating diseases, the most common variety is multiple sclerosis also referred to as disseminated sclerosis. This is a relatively common disease of unknown etiology primarily affecting young or middle-aged adults with most patient's first demonstrating symptoms between the ages of 18 and 50. The frequency of disease varies based on geographical origin. Those who reside in the northern temperate zone for the first 18 years of their lives are at greatest risk as opposed to those who have spent those years in a more tropical climate Within a given geographic area whites are at higher risk than blacks. Approximately 1 in 1,000 individuals of northern European origin who have resided in temperate climates during those early critical years will develop multiple sclerosis at some point during their lifetime. An autoimmune disorder of the central nervous system has been suggested and therapy has been directed at this suspected etiology. As with many autoimmune disorders, frequency is higher in females than in males, (ratio of 1.6/1.0). As discussed recently by Noseworthy (1999), while it is unlikely that a viral invasion of the nervous system directly causes the disease, it is possible that molecular mimicry-the antigenic similarity between viral organisms and neural tissue - may trigger the autoimmune reaction. Viral infections may also trigger exacerbations of the disease. Genetic and familial clustering has also been noted.

The disease is characterized by the dissemination of the pathological process in time and space. Thus there is a diagnostic criterion that various lesions be acquired at different times. At any given moment, the various lesions than will be at a different stage of development. It is also a diagnostic criterion that multiple levels of the central neural axis are affected. At a given level the lesion cuts across various fiber systems; it is not a system disease.

The pathological picture varies with the stage of the disease. The initial areas of involvement are perivenous with infiltration of mononuclear cells; plasma cells and lymphocytes .A slight degeneration of oligodendrocytes may be noted. There is a destruction of myelin. There is than a stage of infiltration by macrophages in which the destroyed myelin is removed. There is then a stage of astrocytic proliferation with the production of glial fibers. These areas of gliosis result in the firm sclerotic gray appearance of old lesions and thus the name multiple sclerosis *(Fig.9-21)*. In some early cases, re myelination by oligodendrocytes may occur. As the disease progresses actual destruction of the axons may occur as demonstrated at pathological examination and by MRI scans. Perivascular infiltration of plasma cells and lymphocytes is the probable source of production of the increased amounts of immunoglobulin -G in the cerebrospinal fluid of most patients with active multiple sclerosis. Among all patients with multiple sclerosis 40 - 60% will have such an elevation. Immuno-electrophoresis of the CSF will demonstrate a more specific abnormal population of oligoclonal bands within the IgG in 75 to 85% of patients. A moderate increase in the number of lymphocytes will also be found in the CSF during acute exacerbations These CSF finding however are not specific for multiple sclerosis, also being present in neurosyphilis, and post infectious encephalomyelitis.

Cases are classified according to the anatomical level involved in the initial acute stage for example spinal, cerebellar- brain stem, optic nerve, cerebral hemisphere. A more

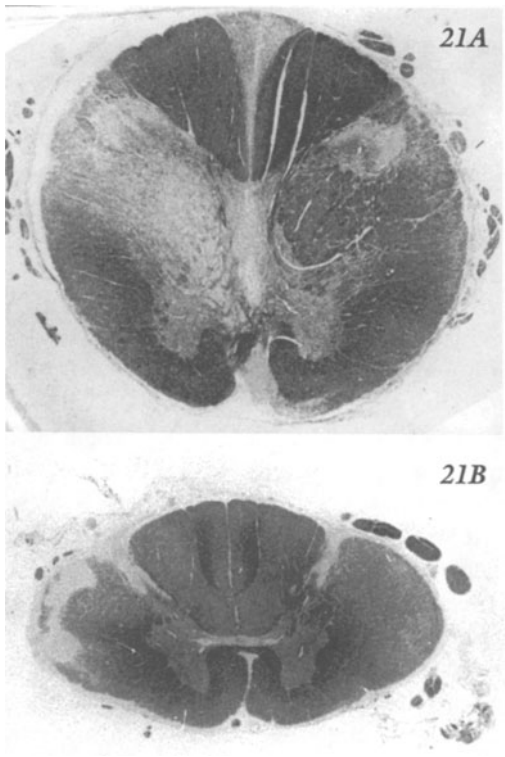

Figure 9-21. Multiple sclerosis affecting the spinal cord. A) A 58-year-old male with a long history of progressive multiple sclerosis. At postmortem examination multiple plaques of variable age were present in the nervous system. (Courtesy of Dr. Jose Segarra). (8-26A) B) This 44-year-old male 20 years previously had experienced a single acute episode of possible multiple sclerosis involving spinal cord and was asymptomatic in the interim until his acute death from an unrelated cause. (Courtesy of Dr. Jose Segarra).

important classification takes account of the pattern of evolution of the disease for example: relapsing- remitting, primary progressive or secondary progressive. Some patients have a benign disease with only 1 or 2 episodes with a relatively complete remission. Overall 85% of patients began with a relapsing /remitting course and 15% with a primary progressive course.

Diagnosis of multiple sclerosis is based on the clinical history and examination. When patients have clear-cut evidence of lesions disseminated in time and space they are referred to as manifesting definite multiple sclerosis. When dissemination in time or in space is present the label of probable multiple sclerosis has been employed. When patients of appropriate age present with the initial findings of syndromes that are seen commonly in multiple sclerosis such as transverse myelitis, or optic neuritis, or the brain stem syndrome of internuclear ophthalmoplegia or an acute cerebellar syndrome they are labeled as possible multiple sclerosis.

The main ancillary technique for diagnosis is the MRI scans. The MRI scan has simplified the diagnosis since many cases of possible or probable now have been shifted into the definite category at first presentation. The visual evoked potential may also be of value in providing evidence of an optic nerve lesion in patients with involvement of other areas of the nervous system.

The following **case 9-12** is an example of multiple sclerosis beginning with an episode affecting spinal cord, but in which the MRI scans demonstrated not only the suspected spinal cord lesion but also, cerebral lesions.

Case 9-12: This 32 year old female registered nurse had a 6 month history of tingling paresthesias in the lower extremities beginning in the toes on the right foot and then the left and gradually spreading to the rib margin on the right and slightly lower on the left. Three months later she developed tingling of the ring and 5th fingers bilaterally. Six weeks prior to evaluation, a positive Lhermitte's sign developed: flexion of the neck produced electric shock sensations that extended down from the buttocks into lower extremities.

Neurological examination confirmed the positive Lhermitte's sign. There was no local cervical tenderness. *Reflexes:* The left plantar response was extensor; the right equivocal. *Sensory system:* Pain and cold were decreased up to the L1-L2 vertebrae posteriorly (but possibly at times to the rib margin on the right), and anteriorly up to D7 dermatome on the right and to D9 dermatome on the left. Vibratory sensation was bilaterally decreased at toes, ankles, and knees with a greater defect on left than right.

Clinical diagnosis: Cervical myelopathy. While the Lhermitte's sign could be seen in multiple sclerosis, this sign also could be pro-

duced by compression of posterior columns.

Laboratory data: *MRI of the cervical spine (Fig.9-22)* demonstrated a large area of demyelinating at C2 involving the right lateral column and to the lesser degree the left posterior column. *MRI brain (Fig 9-23)* demonstrated multiple demyelinating lesions in both cerebral hemispheres.

CSF studies were consistent with the diagnosis in terms of an increased count of 18 lymphocytes plus a markedly elevated Immunoglobulin G index). Two oligoclonal bands were present (normal = 0-1). **Subsequent course:** The patient received a 5-day course of high dose (1000mg/day) intravenous methylprednisolone with some improvement in the sensory symptoms in the legs. She had subsequent episodes affecting spinal cord and brain stem and was treated with beta interferon.

Case history 9-13 presented on the CD ROM includes several episodes indicating clear-cut clinical involvement of the spinal cord in a patient with multiple sclerosis followed over a number of years. In addition several episodes relevant to brain stem are documented. The history of the patient's brother with a single episode of probable transverse myelitis is also presented.

Present clinical and MRI studies indicate that most patients with relapsing/remitting multiple sclerosis do have an increasing lesion load resulting eventually in symptoms or signs that do not resolve. The present approach then is to utilize early in the disease course agents that modify the immune system. Agents such as the beta interferons decrease relapses and secondary progression. The effects are evident from both a clinical and MRI standpoint. Many would now advocate beginning such therapy after the first episode in a patient who had clear-cut MRI evidence of multiple lesions such as case 9-12.

Acute exacerbations are usually treated with high-dose intravenous corticosteroids with the patient receiving 1,000 mg a day of methylprednisolone for 5-7 days. This shortens the course of the exacerbation with the possibility of less residual disability. There is no clear-cut therapy for primary progressive multiple sclerosis although various major immunological therapies have been investigated.

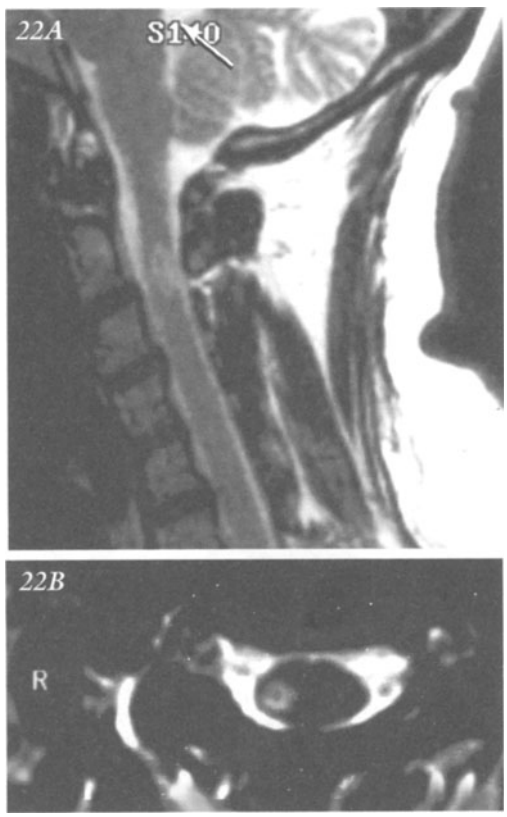

Figure 9-22: Multiple sclerosis involving the spinal cord. Case 9-12 see text. MRI A) Sagittal section. B) transverse section.

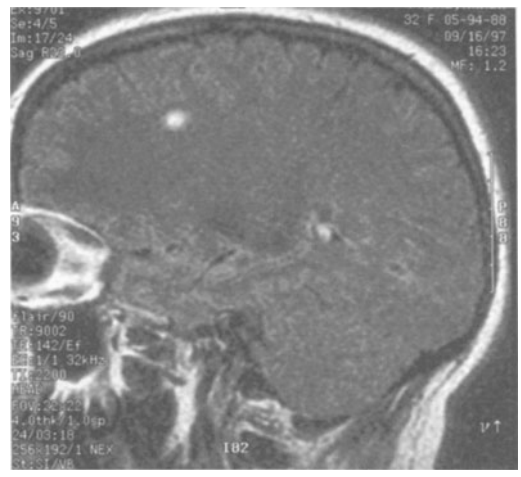

Figure 9-23: Multiple sclerosis involving brain. Case 9-12. MRI. See text.