FAMILIAL INVOLVEMENT OF THE NERVOUS SYSTEM BY
MULTIPLE TUMORS OF THE SHEATHS AND
ENVELOPING MEMBRANES

HEREDITARY, CLINICAL, AND PATHOLOGICAL STUDY OF CENTRAL AND
PERIPHERAL NEUROFIBROMATOSIS

OSCAR A. TURNER, M.D., AND W. JAMES GARDNER, M.D.
(From the Cleveland Clinic, Cleveland, Ohio)

Von Recklinghausen (1) in 1882 recognized the fact that the presence of
“multiple neuromas” could not be considered as a purely acquired disease,
but Thomson (2) in 1900 was the first to point out clearly that the condition
was hereditary. Since that time the hereditary and familial character of the
disease has been fully established and is generally recognized. Cases of
multiple neurofibromatosis with diffuse involvement of the central nervous
system are unusual. The association of this condition with multiple meningeal
tumors is rare and more so when there is a distinct hereditary back­
ground. The present communication is a clinico-pathological study of fa­
milial von Recklinghausen’s disease of the central and peripheral nervous sys­
tem associated with meningeal and glial tumors.

REVIEW OF THE LITERATURE

Multiple neurofibromatosis or von Recklinghausen’s disease may be looked
upon as a congenital anomaly of the nervous system in a hereditary and dys­
ontogenetic sense, according to Hosoi (3). Penfield (4) describes the con­
dition as a “familial disease of diffuse character in which meningeal fibro­
blastomas, gliomas and sarcomas may occasionally be encountered.” Preiser
and Davenport (5) reviewed the literature and collected 30 cases of the fa­
milial type. They were able to show that the condition appears in both sexes
and follows the mendelian law as a dominant trait. Hoekstra (6) in 1922
also pointed out the hereditary tendency in this condition.

While multiple neurofibromatosis is a system disease affecting mainly the
Peripheral nerves (7), involvement of the central nervous system, though un-
usual, is by no means rare. German (8), reporting upon the changes in the ear in bilateral acoustic nerve tumors, states that over 30 cases of central neurofibromatosis have been recorded. Cases with acoustic nerve involvement have been reported recently by van Bogaert (9), Lewin (10), de Kleijn and Gray (11), and others. Of interest in this respect is the occurrence of bilateral acoustic nerve tumors. Although these may rarely occur without evidence of von Recklinghausen's disease elsewhere in the nervous system, at the present time it is generally conceded that they represent a local manifestation of a general disease process. Gardner and Frazier (12), in a review of the literature, were able to collect 44 cases of bilateral tumors of the acoustic nerve, 37 of which were associated with neurofibromatosis. In addition, they report a family in which 38 members were affected with bilateral deafness which in the autopsied cases was shown to be due to bilateral acoustic tumors. The condition in this family was transmitted as a mendelian dominant. Roger, Alliez and Sarradon (13) have described a family in which bilateral acoustic nerve tumors were verified at autopsy in one member and clinical evidence of a cerebellar tumor was present in four others. These writers believe that there is not sufficient evidence to warrant the full acceptance of Gardner and Frazier's view that bilateral acoustic nerve tumors, as a part of neurofibromatosis, are transferred as a mendelian dominant. In reviewing the literature Roger and his associates (13) were able to find only 7 convincing family histories of intracranial involvement.

The combination of central and peripheral neurofibromatosis with other tumors of the nervous system has been reported from time to time. This association has been looked upon as more than casual. Cushing (14) considered it as an anomaly in development of the nervous system and regarded bilateral acoustic nerve tumors as merely an expression of a more widely disseminated disease. Hosoi (15), in a study of multiple meningiomas, found 21 cases in the literature and added another. Of these patients, 8 had bilateral acoustic nerve tumors, 4 of which were associated with multiple neurofibromatosis. Hosoi suggests that the association of meningeal tumors with multiple neurofibromatosis is not an a priori relationship, but an expression of the predisposition or susceptibility of the individual through hereditary and dysontogenetic influences. Rarely, this combination has been reported on a familial basis. In Schaltenbrand's case (16) the mother had bilateral acoustic nerve tumors and innumerable small meningeal growths over the brain and spinal cord. The daughter had a large meningeal tumor of the falx and "neurinomas" of the spinal nerve roots throughout almost the entire cord and vagus nerve, including the intracranial portion of the latter. In addition, the upper spinal cord of the daughter contained a glioma of spongioblastic type. Skin growths, nodules and tumors along the course of the peripheral nerves were present in both instances.

Although the most common are the meningeal growths, other tumors may also be associated with central neurofibromatosis. Gliomas and even angiomatoses may be encountered. Schaltenbrand's case has been referred to above. Katzenstein (17) reported the case of a twenty-eight-year-old patient who at autopsy showed multiple tumors of the meninges, spinal nerve roots, and spinal cord. Histologic study of these disclosed them to be endotheliomas,
neuromas, neurofibromas, and gliomas. In addition, there was marked diala-
tation of the central canal of the spinal cord. Similarly, Kernohan and
Parker (18) reported the presence of 4 distinct gliomas of the astrocytic and
ependymal types in the spinal cord of a patient with extensive central neuro-

![Family tree diagram]

**Chart I. Familial Incidence of Multiple Tumors of the Sheaths and Enveloping
Membranes of the Nervous System: Authors' Cases**

The first generation is labeled A, the second B, and the third C and D.

A-I. Although it is known that this member of the family had "lumps in the skin" and that
she became blind and paralyzed before death, further information is lacking.

B-1. Reported in detail as Case 1. Mrs. K. R., aged thirty-two years at death. There were
multiple intracranial, intraspinal, and cutaneous tumors.

B-2. Reported in detail as Case 2. Mrs. L. B., aged thirty-nine years at death. There were
multiple intracranial tumors and skin nodules. The spinal cord was not examined.

B-3 and B-4. These members were not examined. Information furnished by relatives and
from other sources indicates that at the present time they are free from clinical manifestations of
the disease.

C-1. Reported in detail as Case 3. O. R., girl aged eleven years. This patient has multiple
skin tumors.

C-2. Reported in detail as Case 4. K. R., girl aged nine years. This patient has multiple skin
tumors.

D-1. Reported in detail as Case 5. M. M. B., girl aged nine years at death. There were no
external manifestations of the disease but autopsy revealed intracranial tumor formation.

D-2. J. R. B. is a ten-year-old boy, the twin of D-3. He has been examined and is free from
clinical evidence of the disease at the present time.

D-3. Reported in detail as Case 6. L. M. B., ten-year-old girl who, from clinical evidence, is
regarded as probably having early intracranial involvement.

D-4. P. A. B., four-year-old girl, is free from clinical evidence of the disease at present.

fibromatosis. Syringomyelia was also present with a presyringomyelic stage
at each end of the cavity. Foerster and Gagel (19) reported a case in which
5 different types of tumor were present. A large meningeal growth was
situated close to an acoustic nerve tumor. Within the medulla was a "cen-
tral neurinoma" and scattered throughout the brain were localized collec-
tions of hyperplastic glia cells and several angiomatous nodules. In the case reported by Penfield and Young (20) the brain, meninges, spinal nerve roots, and sympathetic nervous system were the seat of extensive tumor formation. The tumors proved to be neurofibromas, perineurial and meningeal fibroblastomas, and gliomas. Practically all the cranial nerves were involved and bilateral acoustic nerve tumors were present. The spinal cord contained several discrete tumors of the astrocytic and ependymal types.

Worster-Drought and his associates (21) have reported recently two cases of central neurofibromatosis, in both of which there were associated multiple meningeal tumors. One patient had, in addition to "meningio-angiomatosis" of the cerebral cortex, intramedullary tumors and syringomyelic cavitations of the spinal cord. These writers have reviewed the literature to date and have offered a clinical classification of the different forms of the disease.

**Authors' Cases**

The present report concerns six members of a single family who have been examined and studied carefully. Information obtained from other members of the family indicates that one of those who was not examined had evidence of neurofibromatosis. The diagram on page 341 shows the relationship of the various members and the extent of the disease in the family.

The following histologic methods were employed in the examination of the tumors: hematoxylin and eosin, Mallory's phosphotungstic acid-hematoxylin, Mallory's and Masson's trichrome methods, Fincher's modification of Hortega's lithium silver carbonate method, Cajal's method for unmyelinated nerve fibers, Perdrau's silver impregnation for connective tissue, and various methods for the demonstration of myelin sheaths.

**Case 1 (B-1): Clinical History:** Mrs. K. R., age twenty-eight years, was first seen in July 1931, with enlargement of the right side of the neck and increasing deafness of the right ear. At that time a mass had been present on the right side of the neck for four years but it had shown little tendency toward enlargement. The deafness had been present for about a year and had been associated with tinnitus. Some auditory impairment had been present in the right ear since childhood.

Examination revealed several small masses in the skin of the arms and legs, fixed to the skin, soft, and slightly tender. On the right side of the neck was what was regarded as an enlargement of the cervical lymph nodes. This was discrete, firm, and tender, and caused considerable bulging of the right lateral pharyngeal wall and tonsillar fossa. There had been no dizziness but some staggering to the right had been present. Audiograms showed a total loss of hearing on the right with slight reduction in acuity for low tones on the left. The patient was discharged and returned in three months, at which time a tumor was removed from the right side of the neck.

When the patient was seen one month after operation a right facial paralysis had developed. This was followed in another month by paralysis of the right vocal cord. Both conditions improved to some extent but the tinnitus apparently became more marked. By April 1932, the tumor in the neck had recurred and was associated with the early manifestations of a right-sided Horner's syndrome. The patient was again seen in August 1934, with bilateral deafness and a staggering gait. Both corneal reflexes were absent and there was a horizontal nystagmus which became more marked on left lateral gaze. Both optic discs were hazy but there was no measurable edema. Vision was 6/7.5 in the left eye and 6/12 in the right eye. Perimetric examination disclosed slight constriction of both visual fields, more marked for color in the left eye. The voice was husky, the tongue was deviated to
the right, and there was a complete paralysis of the right vocal cord. The pharyngeal reflex was absent. There was mild dysmetria on finger-to-nose tests and Romberg's sign was positive. Caloric tests indicated functionally inactive labyrinths and hearing was absent in both ears except for a slight tone heard in the right ear at 2048 v.m. Bone conduction was absent.

Roentgenograms of the skull disclosed no abnormality. The patient was discharged with the diagnosis of bilateral acoustic nerve tumors and central neurofibromatosis. Her condition steadily became worse and in February 1935 there was an apparent increase in the ataxia and dysmetria. She was last seen in August 1935, when she was admitted to the hospital in a comatose condition following self-administration of an overdose of allonal. At this time there was choking of the right optic disc, 2.5 diopters; the left could not be seen because of corneal ulceration. Lumbar puncture gave an initial pressure of 400 mm. of water which dropped to about 200 mm. following the intravenous administration of 100 c.c. of 50 per cent solution of sucrose. Death occurred the following day. In the hope

FIG. 1. CASE 1: MID-SAGITTAL SECTION THROUGH THE HEAD

Note the two large meningeal tumors arising from the falx and projecting into the right hemisphere.

that information could be obtained that would be of value in the treatment of her two daughters, the patient had requested that her body be dissected.

**Gross Pathology:** Subcutaneous tumors were present on the dorsum of the left hand, thorax, abdomen, legs, and scalp. One was present on the back, and another on the lateral aspect of the thigh measured $1 \times 2$ cm. Extending along the course of the right sternocleidomastoid muscle, at the site of the previous operation, was a firm, nodular mass which on section revealed a pinkish-gray tumor having a homogeneous surface. There were no tumors of the viscera and the sympathetic system appeared normal on gross examination.

The head was removed, fixed in formalin, and sectioned with a band-saw.

**Dura Mater:** Attached to the falx in the left frontal region, but also extending to the right for a distance of about 1 cm., were two well defined growths, each measuring about 3 cm. in diameter (Fig. 1). The more anterior of these was attached over an area which measured about 1.5 cm. in diameter, and invaginated the medial surface of the left hemisphere about 1.5 cm. from the superior sagittal sinus. The second tumor was adherent to both the falx and superior sagittal sinus and was situated superior and posterior to the first.
The two growths were in contact but appeared to be independent. They seemed similar in character, each having a granular, homogeneous, yellowish-gray cut surface.

Two small independent tumors, identical with those described above, were attached to the dura over the left fronto-parietal region (Fig. 2A). They measured 1.0 × 0.75 cm. and 1.0 × 1.5 cm. and projected about 1 cm. above the surface. Multiple smaller growths of similar character were present on the inner surface of the dura, covering the convexities of the brain, the tentorium, and falx cerebri. Similar tumors were present on the inner surface of the spinal dura, particularly in the cervical and upper thoracic regions. In general, these small meningeal growths measured from a millimeter to a centimeter in diameter and, while most of them were solid, like the larger growths described above, a few were quite friable and wart-like.

**Fig. 2. Case 1: Anterior and Posterior Views of a Coronal Section through the Left Side of the Head**

Note the cerebellopontine angle tumor and the meningeal growths. The midline growth is the extension of the parasagittal tumors through the falx.

**Cranial Nerves:** The left cerebellopontine angle was the site of an encapsulated growth which measured approximately 3.5 × 2.5 × 3.0 cm. (Fig. 2). The tumor was confined to the subtentorial region and compressed and markedly indented the left lobe of the cerebellum and brain stem. The cut surface varied in color from a yellowish-gray to pinkish-yellow, and while some portions appeared solid and fleshy, other areas were the seat of gross degeneration. Several foci of hemorrhage were seen but no gross cysts. A similar growth measuring 2 × 2 × 2.5 cm. was present on the right (Fig. 3). It was irregularly shaped and appeared to have eroded the surrounding bony structures as well as compressed the left cerebellar lobe and brain stem.

**Spinal Nerve Roots:** Attached to the dorsal nerve roots and in rare instances to the anterior nerve roots were multiple, shiny white or yellowish-white encapsulated tumors (Fig. 4). These were very firm and cut with marked resistance. The cut surface was generally
slightly granular and homogeneous and in only a few instances, in the larger tumors, were
gelatinous areas observed. The largest tumor measured 2.2 cm. in diameter and was at­
tached to the right seventh thoracic root. It compressed the cord and reduced it to about
one third its normal diameter. At the eighth cervical level was a group of tumor nodules,
the largest of which measured 1 cm. in diameter. In addition, the dura in this region was
the site of three small tumors, the character of which has been described. A similar group
of tumors was present over the lower thoracic and upper lumbar cord. Other growths, too
numerous to mention, were present. Most of these appeared to originate from the free por­
tion of the nerve roots while an occasional one was found at the point of emergence of the
root from the cord.

Practically every root of the cauda equina was the seat of one or more tumor nodules

(Fig. 3). These varied between 2 and 4 mm. in diameter and upon close examination each
appeared as a localized swelling upon a single nerve fiber. From some nerves the tumors
appeared to hang in small bunches, several fibers of the same nerve having been involved in
the same place.

**Spinal Cord:** Incorporated within the substance of the spinal cord were four tumors
which were manifested upon external examination by slightly elevated, moderately firm areas.
Two were at the second cervical level and upon section appeared yellowish-white and rather
firm. The first measured 2 × 3 mm. and was confined to one posterior column, compressing
the tissues and displacing in its growth the posterior longitudinal sulcus to the opposite side.
The second was half the size of the first and was situated on the tip of an anterior funiculus.
One margin of it bordered on the anterolateral sulcus and here the tumor tissue was sharply
circumscribed; on the other side there was definite infiltration of the adjacent white matter.
Neither of the two growths involved the gray matter of the cord but the leptomeninges
overlying the second tumor were infiltrated and incorporated in the tumor.

The third intramedullary tumor was at the seventh and eighth thoracic levels. It meas­
ure 6 mm. and began at the point of most marked compression by the large extra­
medullary tumor described above. Beyond the region of compression, the growth replaced
practically the entire gray matter and infiltrated the adjacent fiber tracts to the extent that
it almost reached the surface of the cord anteriorly.
The fourth intramedullary tumor appeared at the first lumbar level. It involved the dorsolateral surface of the cord and appeared fairly well circumscribed. The tissue was firmer than the cord itself and the cut surface had a yellowish-white color. The lesion measured about 3 mm. in diameter.

**Microscopic Pathology:** Sections of the tumor removed from the right side of the neck showed it to be a fairly typical neurofibroma with few areas of fibroblastic overgrowth.

**Dural Tumors:** These all proved to be types of the meningeal growths described by various writers as meningiomas, psammomas, arachnoidal fibroblastomas, and meningeal fibroblastomas, the latter name given by Penfield. Of the two large tumors described as originating from the falx, the first was composed of sheets of elongated cells which showed fairly marked streaming but less marked whorl formation. A moderately heavy intercellular collagenous carpet was present but no thick collagen bundles were observed. Psammoma bodies were rare. Invasion of the brain was not observed, but in one place there was evidence of infiltration of the leptomeninges. The second tumor was not unlike the type described by Globus (22) under the name of pachymeningioma or dural fibroma. There was considerable intercellular collagen, both in the form of intercellular fibrils and broad, heavy bands. Only occasionally was there whorl formation but calcified psammoma
Fig. 6, above, is a typical area from the large tumor attached to the seventh thoracic dorsal root. Note the characteristic palisading of nuclei and streaming of the cell-bundles. Hematoxylin and eosin. × 160.

Fig. 7, below, is a section from one of the neurofibromatous nodules attached to a nerve of the cauda equina. Note the tangled and disorderly arrangement of the tissue and the suggestion of palisading in the center of the field. Hematoxylin and eosin. × 175.
bodies were present in abundance. The brain showed no invasion but gave evidence of long-standing compression.

Of the various similar tumors described on the inner surface of the dura, none showed any marked degree of whorl formation. Some appeared to correspond to the above mentioned dural fibroma while others resembled varieties of Globus' leptomeningioma. In several instances there was obvious invasion of the overlying dura and occasionally tumor tissue could be seen on both sides of the dura. Sections of dura, which in the gross appeared to have a granular, friable layer of tissue on the under surface, microscopically proved to be the seat of a thin layer of tumor tissue.

Cranial Nerves: Sections taken from the tumor in the right cerebellopontine angle showed it to be composed of tissue, the greater part of which was typical of Penfield's perineurial fibroblastoma. In these areas the cells contained elongated or rod-shaped nuclei and cytoplasm which tended to be bipolar but which stained lightly with the eosin and was difficult to delimit. There was typical palisading of the nuclei and the Perdrau stain revealed bundles of argentophilic fibers which, through their interlacing course, gave the tumor its characteristic appearance. In other parts of the tumor, the arrangement was less orderly and suggestive of the appearance of the neurofibroma. The corresponding tumor on the left resembled the above except that palisading of nuclei was much less frequently seen and occasional areas were even more suggestive of the neurofibroma. Cajal's stain for unmyelinated nerve fibers revealed occasional scattered fibers coursing through the tumor tissue. These were observed more often in the left tumor than in the right. Both tumors, despite the presence of many vessels of moderate size, were the seat of extensive degeneration.

Spinal Nerve Roots: The histological picture of most of the tumors arising from the spinal nerve roots was typical of the perineurial fibroblastoma (Fig. 6), although in most instances it was possible to observe small areas which resembled neurofibromatous tissue. In every instance, however, the presence of nerve fibers could be demonstrated within the tumor tissue, although in many tumors these were relatively scarce.

Examination of many of the nodules attached to the nerves of the cauda equina demonstrated the fact that it was possible to observe the various stages from neurofibroma to fibroblastic overgrowth (Fig. 7). In some of the preparations, the nerve root could be seen to divide at the tumor capsule, a portion of the fibers sweeping about the periphery of the tumor and the remainder scattering throughout the tumor tissue (Fig. 8). In all instances nerve fibers were observed within these tumor nodules. In one preparation several large bundles of partially degenerated myelinated nerve fibers were present, some just beneath the capsule and others within the tumor but at a short distance from the periphery.

Spinal Cord: Both tumors of the second cervical level appeared to be of the same type. They were composed of streams of elongated unipolar and bipolar cells. These bands of cells showed a tendency to interlace so that many were cut in cross-section. The processes of the cells stained poorly with Mallory's phosphotungstic acid hematoxylin, and glia fibers were not observed. The growths were poorly vascularized and contained no collagen or reticulum. Both were regarded as spongioblastomas.

The intramedullary tumor at the seventh and eighth thoracic level was even more typically a spongioblastoma (Fig. 9). The bands of cells showed a greater tendency to interlace, and microscopically the tumor bore a superficial resemblance to a fibroblastoma. The cell processes took the eosin stain rather deeply. The phosphotungstic acid hematoxylin stain demonstrated many patches of neuroglia and numerous astrocytes. Cajal's gold sublimate method impregnated small groups of large, well formed astrocytes, both at the periphery and in the center of the growth.

The tumor appeared to be vascularized better than those seen at the second cervical level. With several of the special staining methods, the processes of the spongioblasts occasionally could be seen to pass over the vessel wall. The growth was regarded as a spongioblastoma which showed some tendency toward differentiation in the direction of the astrocytoma.

The intramedullary lesion at the first lumbar level proved to be a fairly typical neurofibroma. The tissue consisted of a tangle of cells and fibers which showed only a slight tendency toward streaming and a suggestion of nuclear palisading. The growth was sur-
rounded by an area of softening and early gliosis. A lesion which was not seen in the gross examination was present in the corresponding position on the opposite side of the cord. It proved to be a degenerative process with no definite tumor tissue present.

At the fourth cervical level there was a small area of softening and overgrowth of connective tissue at the point of emergence of the dorsal root. This was interpreted as being due to pressure from a small neurofibroma which was attached to the corresponding root in this position. No tumor tissue could be identified within the substance of the cord at this level.

**Sympathetic System:** Microscopically there was neurofibromatous alteration of many of the sympathetic ganglia. In those affected, the ganglion cells appeared to be fairly well preserved but were embedded in a disorderly tangle of interlacing cells and fibers. Nuclear palisading was not observed and there was little disposition toward streaming or whorl formation. The bundles of nerve fibers which normally constitute part of the ganglia could be identified even in the hematoxylin and eosin preparations. The picture was one of early involvement of this part of the nervous system.

**Case 2 (B-2): Clinical History:** The clinical information on this case is limited. It is known that the patient, Mrs. L. B., had been deaf for at least ten years. Three weeks prior to death she had several epileptiform attacks. When brought to the hospital she was semicomatose and deeply jaundiced. After rallying several times, she lapsed into unconsciousness and died.

**Gross Pathology:** The autopsy findings, aside from the brain, consisted of marked central necrosis of the liver, bilateral hypostatic pneumonia, and advanced chronic cholecystitis and cholelithiasis. The spinal cord was not removed.

1 The writers are indebted to Dr. H. G. Little, pathologist at the Ohio Valley General Hospital, Wheeling, W. Va., for the available necropsy specimens and clinical information.
There were several firm subcutaneous nodules and lightly pigmented areas on the external surface of the body. Two pedunculated tumors, each measuring from 1.5 to 2.0 cm. in diameter, were the largest of the external growths. One was situated on the medial surface of the right wrist and the other on the scalp in the occipital region.

*Dura:* The dura over the frontal lobes of the brain and that lining the middle cranial fossa, especially over the petrous portion of the temporal bones, was nodular and thickened. The same was true of the dura forming the superior longitudinal sinus and falx cerebri. Each frontal lobe of the brain showed a small area of compression corresponding to two olive-sized tumor nodules in the dura. In addition to the above, two large tumors were attached to the dura (Fig. 10). One which was present over the superior frontal gyrus on the right measured $5.5 \times 4.0 \times 4.0$ cm. It was firm to palpation and cut with marked resistance, revealing a yellowish-gray, granular cut surface in which several areas of hemorrhage were visible. The second measured about 3.5 cm. in diameter and covered portions of the medial surfaces of the right superior frontal and cingulate gyri. This tumor differed from the former only in that it was less granular in the cut section and had a pinkish-gray color. Also, the relationship between dura and tumor was less intimate than in the former tumor.

*Cranial Nerves:* Tumors were present on either side of the brain stem. On the right was a large, encapsulated growth measuring $4 \times 3 \times 2$ cm. It cut with considerable resistance and the cut surfaces had a smooth, homogeneous, pinkish-yellow appearance, altogether different from that described above. It was intimately related to and compressed the roots of the 7th, 8th, 9th, and 10th cranial nerves. The 7th and 8th nerve roots also contained several independent tumor nodules which measured 1 to 3 mm. in diameter. On the left side, the tumor consisted of a cluster of small growths attached to the roots of these same nerves. In addition, small nodules were present on the roots of the 5th nerve on the right and the 3rd nerve on the left.

*Brain:* Attached to the choroid plexus and appearing to have arisen from the glomus portion was a small, spherical tumor in the right lateral ventricle (Fig. 10). It measured 1 cm. in diameter and was quite firm. The cut surface was yellowish-gray in color and had a finely granular, homogeneous appearance. The spinal cord was not examined.

*Microscopic Pathology:* Microscopic examination of one of the cutaneous tumors showed it to be a fairly typical neurofibroma. In some areas there were palisading of the nuclei and streaming of fibers, while elsewhere the general pattern of the tissue was less orderly. In occasional places the tissue had an irregular, tangled appearance. Several medium-sized nerve trunks were seen passing through the center of the growth.

*Dural Tumors:* Preparations made from various portions of the tumor which were present over the right superior frontal gyrus revealed different pictures. In one portion the
tissue was extremely vascular and many of the vessels were surrounded by broad, heavy bands of collagen (Fig. 11). Here the tumor tissue was reduced to intervascular islands in many places and the picture was that of the hemangiomatous pial meningioma described by Globus (22). In other portions the tissue consisted of whorl-like cell groups with larger cell bundles passing between them. The demarcation between tumor and brain was not as sharp as is usually seen in meningeal growths and in several places small islands of tumor tissue were observed within the substance of the brain. In one preparation a strand of pia-arachnoid could be traced from the depths of a sulcus to where it blended with the overlying tumor.

The tumor which overlay the right cingulate gyrus was not unlike the second picture described above except that whorl formation was more marked and streaming more evident. The tissue contained a moderate amount of intercellular collagen. There was no evidence of invasion of either the dura or brain.

FIGS. 11 AND 12. CASE 2

Fig. 11 (left) is a section of the meningeal tumor which presented over the right superior frontal gyrus; stained for connective tissue to show the vascularity of a portion of the growth. Perdrau silver impregnation. X 75.

Fig. 12 (right) is a section of the fibroblastoma from the right lateral ventricle. Note the fibrous character of the growth and the many psammoma bodies. Hematoxylin and eosin. X 80.

Intraventricular Tumor: The tumor attached to the choroid plexus in the right lateral ventricle resembled in many respects the pachymeningioma of Globus. The cells contained oval or elongated nuclei and the cytoplasm tended to be bipolar in distribution, although cytoplasmic boundaries were indistinct. Considerable collagen was present in the form of coarse and fine intercellular fibrils. Psammoma bodies, in all stages of development and calcification, were present in abundance, both in the tumor and attached choroid (Fig. 12).

 Cranial Nerves: Tissue was not available for study from all the tumors attached to the cranial nerves, but those which were examined proved to be neurofibromas in which a varying amount of fibroblastic overgrowth had taken place. Some showed palisading of nuclei and interlacing bundles of argentophilic fibers, while in others the nuclear palisading was less evident and the tissue had a less orderly and often tangled appearance. Bielschowsky preparations revealed the presence of fragmented and distorted nerve fibers within the tumor tissue.

Case 3 (C-1): D. R., an eleven-year-old girl, was first seen in November 1935. General examination at this time gave essentially normal findings aside from two small cu-
taneous tumors, one on each side of the abdomen, measuring respectively 1.5 and 1.0 cm. in diameter. These were typical neurofibromas clinically. Hearing was normal but rotation tests of the vestibular apparatus caused no response from the horizontal canals after 10 turns in 10 seconds and a weak response after 20 turns in 10 seconds.

The patient was again seen in May 1936, with no complaints other than occasional tinnitus in the right ear. There had been an apparent increase in size of the skin tumors. Examination with the audiometer disclosed a 15 to 25 sensation unit loss of hearing bilaterally. Bone conduction was normal but the Weber test lateralized to the right. Caloric tests showed no abnormalities.

The patient was last seen in September 1937. Vision was 6/60 in each eye. Ophthalmoscopic examination was normal except for some temporal pallor and a peculiar gray color, similar to that of the medullated nerve fibers, of the macula in the left eye. Hearing was reduced 10 to 15 units from normal. Bone conduction was normal as were the results of caloric tests. There was some nystagmus on left lateral gaze.

The patient was discharged with the clinical diagnosis of von Recklinghausen's disease.

CASE 4 (C-2): K. R., a nine-year-old girl, was seen in October 1935, with visual impairment and occasional tingling of the lower extremities. Examination revealed no cause for the latter complaint. Vision was 6/20 in the right eye and 6/15 in the left. Ophthalmoscopic examination revealed a large, gray opacity in the posterior part of the lens of the right eye. The disc and vessels were normal. The left eye did not appear unusual. The skin contained several typical neurofibromatous nodules. Roentgenograms of the skull showed no abnormalities. Caloric tests revealed functionally inactive vertical and horizontal canals on either side but when repeated one year later gave normal results. Hearing was normal.

In October 1936 the patient was re-examined. There was an indefinite complaint of tinnitus when she was lying down. Tests of auditory acuity revealed about 15 to 25 units loss due to conductive deafness. The Weber test lateralized to the right. Caloric examination disclosed a normal right labyrinth and a slightly hyperactive left labyrinth. Vision was 6/30 in the right eye and 6/60 in the left. Ophthalmoscopic examination showed no changes other than those found in the previous examination. The skin tumors had not increased in size.

The patient was last seen in November 1937. Vision was 6/20 in the right eye and 5/60 in the left. The right eye contained the same polar mass in the lens, and the retina was the seat of a small hemorrhagic lesion. In addition, the macula had a peculiar gray color and elliptical conformation. Audiometer examination was not unusual. The Schwabach test was lengthened and the Weber lateralized somewhat to the right. Caloric tests were similar to those previously obtained.

The patient was discharged to return at intervals for further observation. The clinical diagnosis was von Recklinghausen's disease.

CASE 5 (D-1): Clinical History: M. M. B., an eight-year-old girl, was seen in August 1936, complaining of protrusion and blindness of the left eye, deafness of the left ear, and facial paralysis. She had been an apparently normal, 8-pound baby who had developed normally, both mentally and physically, until about four years of age. At that time headaches and a left, non-pulsating exophthalmos associated with blindness in the same eye developed. During the year previous to hospital admission these symptoms had progressed and deafness in the left ear became apparent. For two or three months a staggering gait, difficulty in swallowing, and huskiness of the voice had been present. A left facial paralysis developed suddenly one month before admission. At no time had there been nausea or vomiting.

Examination revealed no skin tumors or areas of pigmentation. The left eye-ball protruded and was the seat of a moderately severe keratitis. Ophthalmoscopic examination showed 3 to 4 diopters of edema of the right disc and, although there was obvious edema of the left disc also, this could not be measured because of the clouding of the cornea.

Complete neurological examination disclosed evidence of marked involvement of the brain stem. The left eyelid drooped and could not be elevated voluntarily. There was a bilateral internal strabismus and the pupils were unequal, the left larger than the right. There was obvious paralysis of the 3d, 4th, and 6th cranial nerves on the left. A coarse
horizontal nystagmus was present on left lateral gaze. The left masseter, temporal, and pterygoid muscles were definitely weak and there was anesthesia of the face over an area corresponding to the distribution of the left trigeminal nerve. Both corneal reflexes were absent. Facial asymmetry was present due to an obvious left facial paralysis.

Examination with the audiometer disclosed a complete 8th nerve deafness on the left. Hearing on the right was reduced about 50 per cent. Caloric tests showed a horizontal nystagmus to the right on stimulation of the left vertical canals and no response from the left horizontal canal after five minutes. Perverted nystagmus also was obtained after stimulation of the right vertical canals. The gait was ataxic. Speech was indistinct and the voice had a husky quality. The patient experienced difficulty in swallowing and there was a tendency for fluids to regurgitate through the nose. The gag reflex was diminished on the right. The tongue deviated to the right and there was paresis of the soft palate.


Cerebellar tests disclosed marked ataxia, greater on the left. Romberg's test was positive. Babinski's and Gordon-Oppenheim signs were positive bilaterally.

Roentgenograms of the skull showed a large, deep sella turcica. There was erosion of the right sphenoid bone on both the lesser and greater wings. No calcification was evident. Lumbar puncture, performed on the third hospital day, revealed a pressure of 500 mm. of water. The fluid was clear and colorless, contained 1 cell per cubic millimeter and showed a faint trace of globulin. The total protein content was 55 mg. per 100 c.c.

The clinical diagnosis was left cerebellopontine angle tumor with marked compression of the brain stem and suspected central neurofibromatosis. Because of the advanced lesion and the probability of multiple intracranial tumors, the patient was discharged without operation. Death occurred about seven months later.

Gross Pathology: Only the findings referable to the nervous system will be discussed. The head was removed and after fixation in 40 per cent formalin was sectioned with a bandsaw. A large tumor which practically filled the middle cranial fossa was found on the left side. Medially, the growth impinged upon the sella turcica and basiocciput, eroding and
invading the bone and extending beyond the midline (Fig. 13). The lateral limit of the growth was within 1.0 cm. of the outer surface of the greatly compressed left temporal lobe. Posteriorly it extended into the posterior cranial fossa, where it compressed the left lobe of the cerebellum and brain stem. The tentorium was invaded and could be identified within the large mass of tumor tissue (Fig. 14B). The colliculi were reduced to a flat plate of tissue by the upward extension of the tumor but the pineal body appeared intact.

Anteriorly, the tumor extended into the orbit, where it displaced the eyeball forward. The optic nerve sheath was enveloped in tumor tissue and the extra-ocular muscles were compressed against the orbital walls. The floor of the orbit appeared to have been invaded and there was tumor in the upper part of the maxillary sinus (Fig. 14A). It is probable that the tumor originated at the sphenoidal ridge. It was difficult, however, because of the manner in which the growth was also adherent to the squamous and petrous portions of the temporal bone, as well as to the occipital bone and tentorium, to determine the exact point of origin.

The large mass of tumor which occupied the middle cranial fossa measured about 5 cm. in diameter. The external surface was nodular and covered by a poorly defined, thin capsule. The demarcation from brain was less distinct than is usual in meningeal growths. The tumor was firm and cut with marked resistance. The cut section had a coarsely granular, gray surface in which no areas of calcification or cysts were grossly visible.

In the left temporal lobe, about 3 cm. from the pole, was a small area which appeared not unlike a localized focus of encephalomalacia. It was pale, soft, poorly defined, and was subcortical in its major extent.

The cranial nerves were free from tumors. Aside from a questionable slight enlargement of the central canal, the spinal cord appeared normal on gross examination.

Microscopic Pathology: Dural Tumor: The microscopic appearance of the large tumor in the middle cranial fossa coincided for the most part with that of the leptomeningioma as described by Globus (22). The tissue consisted of whorl-like cell groups with less marked

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**Fig. 14. Case 5: Anterior and Posterior Views of a Coronal Section of the Left Side of the Head in Which the Brain Tissue Has Been Removed to Show the Extent of the Tumor**

A. Anterior view showing the anterior extent of the growth. The arrow points to the tumor-filled posterior part of the orbit. The sheath of the optic nerve can be seen in cross-section.

B. Posterior view in which the tentorium can be seen in the midst of the tumor mass (arrow).
cell bundles passing between them. The individual cells contained deeply staining, oval
nuclei and a moderate amount of cytoplasm which had poorly defined boundaries. Small
vessels were abundant and could be seen for the most part in the center of the cell whorls.
The Perdrau stain revealed a network of fine argentophilic fibers, most of which passed
between the cell groups. There was definite invasion of the adjacent brain (Fig. 15). Psammoma bodies, some of which showed calcification, were scattered throughout the tumor.
The portion of the tumor in the orbit did not vary microscopically from that in the
middle and posterior cranial fossa. The sheath of the optic nerve was infiltrated with

![Image](image_url)

**Fig. 15. Case 5: Infiltration of the Brain by the Large Meningeal Tumor Shown in Fig. 14. Hematoxylin and Eosin. X 150**

tumor tissue and there was definite invasion of the nerve itself. The ciliary nerve was likewise involved and appeared to be completely destroyed.

**Brain:** The lesion in the temporal lobe proved to be a completely necrotic and partially calcified vessel which was surrounded by an irregular layer of acellular and densely hyalinated connective tissue. The tissue surrounding the latter was composed of large, atypical astrocytic cells and many neuroglia fibers so that portions of the lesion appeared to assume the characteristics of a small astrocytoma. The tissue was fairly well vascularized but was nevertheless quite necrotic and the seat of focal calcification.

In the brain stem at the level of the motor decussation was a centrally located tumor
which was so small that it was completely overlooked in the gross examination. The growth was situated so as to involve the central canal and was composed of closely packed glial cells which contained oval or elongated nuclei. The cytoplasm was difficult to define and there was an abundance of intracytoplasmic and intercellular neuroglia fibers which showed marked parallelism. Mitotic figures were not observed, although occasional multinucleated cells were seen. The tumor was regarded as a pilocytic astrocytoma.

Sections of the brain stem above the site of the tumor disclosed a slight dilatation of the central canal and proliferation of the ependymal lining. The latter was so marked in places as to cause a papilliferous projection of the lining cells into the lumen of the central canal. The surrounding tissue was the site of small collections of ependymal cells, some of which were in formations highly suggestive of rosettes.

**Spinal Nerve Roots:** Sections from various dorsal root ganglia disclosed no evidence of tumor formation.

**Spinal Cord:** Aside from a moderate diffuse demyelination and concomitant gliosis, the spinal cord showed nothing unusual on microscopic examination.

**Case 6 (D-3): Clinical History:** L. M. B., a ten-year-old girl, was first seen in December 1936, complaining of pain in the left eye. Although the history was not definite, it appeared that the pain, associated with diminution of vision, had been present for about a year. The latter symptom was apparently the earlier one. About three months before admission an earache developed. This was followed by a right facial weakness which persisted for about a month and then gradually improved. There had been no dizziness, staggering, nausea, or vomiting. Headache had not been present, nor had there been difficulty in swallowing, tinnitus, or vertigo.

The child was well nourished and of average weight and height. No skin nodules or areas of pigmentation were present. General and neurological examinations gave negative findings with the exception of changes in the eyes and a slight lower facial weakness on the right. Vision was completely absent in the left eye but normal in the right. The latter showed nothing unusual at perimetry. Ophthalmoscopic examination disclosed fullness of the right optic disc which was interpreted as early edema. In the left eye there was a small, sharply circumscribed area on the temporal side of the nerve head. It occupied about a quarter of the disc and was interpreted as a new growth but with the reservation that it might represent a localized area of edema. In addition, there was some slight generalized choking of the nerve head.

Roentgenograms of the skull were entirely normal. Lumbar puncture gave an initial pressure of 160 mm. of water which rose to 320 mm. with jugular compression. The fluid obtained was clear and colorless and contained 1 cell per cubic millimeter. The Pandy reaction was negative and the total protein content of the fluid was 35 mg. per 100 c.c.

Examination with the audiometer disclosed a very slight bilateral reduction in acuity, but the tuning forks were all well heard. Caloric examination of the vestibular apparatus gave normal results. The patient was discharged on the twentieth hospital day. Because of the family history and the similarity of the mode of onset of the illness to that of her sister, i.e., blindness in the left eye, it was suspected that she had central neurofibromatosis. The patient was examined again in October 1937, at which time she had no additional complaints. There had been no headache, vomiting, tinnitus, or impairment of hearing in the interval.

Examination was essentially the same as previously. There were no cutaneous lesions of neurofibromatosis. The lower right facial paresis was as before, evident only upon testing. Blindness was complete in the left eye but both pupils were regular in outline and equal in size and both reacted normally to light and accommodation. Ophthalmoscopic examination disclosed a slightly hazy outline to the disc and definite macular damage in the left eye, but the findings otherwise were not unusual. There was no measurable edema of either optic disc and the tumor-like lesion seen previously on the left nerve head was absent. Vision was 6/6 in the right eye and the perimetric field was normal. There was a 15 to 20 degree divergence of the left eyeball. No evidence of malingering or hysteria was found to account for the absence of vision in the left eye.

Audiometer examination disclosed no loss of hearing and all tests of the vestibular apparatus gave normal findings. Encephalography on the third hospital day was entirely normal. The patient was discharged to return at intervals for further observation.
Despite the absence of localizing signs and the normal encephalogram, the clinical diagnosis was probable early central neurofibromatosis.

**DISCUSSION**

For the purposes of the present discussion, one may disregard the individual character of the lesions except to note that where a member of the family is affected the lesion originates from the sheaths or enveloping membranes of the nervous system. When this is done it becomes apparent from a genetic point of view that the trait, whatever its character may be, acts as a dominant and further that it follows the mendelian law. Thus, assuming a single unit trait \( T \), in the simplest genetic equation, \( Tt \times tt \), the result would be \( \frac{1}{2} Tt \) and \( \frac{1}{2} tt \); that is, one-half the offspring would show the trait. This can be applied to the family tree in the following fashion. By assigning to A-I the dominant trait in its simplest form, \( Tt \), and assuming the mate to be free from it (\( tt \)) we have the genetic equation which should result in half the offspring carrying the trait as a heterozygous dominant (\( Tt \)) and half being free (\( tt \)).

It can be seen that 2 of the offspring from this union suffered from the disease in a severe form (B-1 and B-2, Cases 1 and 2), and 2 are free from the defect at the present time (B-3 and B-4). Similarly, matings of the 2 hybrids of the second generation (B-1 and B-2) with apparently normal individuals gave rise to 2 branches of the family in which, in one instance, both offspring were affected (C-1 and C-2, Cases 3 and 4) and in the other 1 of the 4 offspring was definitely affected (D-1, Case 5) and 1 probably had early intracranial involvement (D-3, Case 6).

From the above it can be seen that the objective behavior of the unit character under discussion has been that of a dominant trait. Whether the trait has been the expression of a purely dominant single character, however, or whether this character appears dominant only in the presence of a secondary or complementary factor cannot be determined from the material presented here.

The central nervous system was proved to be the site of tumor formation in 3 members of the family. In addition, it is probable that there was central involvement in 2 other members, A-1, by inference from the family history, and D-3, who in view of the clinical observations probably has early involvement despite normal encephalograms.

It must be remembered that, while neurofibromatosis makes itself apparent as a rule at the time of puberty, in a great number of instances the manifestations of the disease appear or first become evident in middle life. Similarly, the incidence of meningeal tumors reaches the peak at about forty-five years of age and below fifteen years these tumors are relatively infrequent. The absence of more obvious manifestations of the disease process in the central or peripheral nervous system in several members of the third generation may be explained by the above. The oldest living member in the third generation when last seen was eleven years old, far below the age at which either the meningeal or nerve sheath tumors are usually found.

The first case reported here closely simulates those reported by Kernohan and Parker (18) and Penfield and Young (20). Attention was directed by
the latter authors to the fact that, in addition to the neoplasms, there were areas of hyperplasia of the same cells which elsewhere, in their case, had become neoplastic. They were able to show this in the nerve trunks, meninges, and central nervous system. The presence of small, wart-like elevations on the under surface of the dura is of interest. In Penfield's case these were regarded as hyperplasia of arachnoidal cells, while in the first case described here the lesions, although minute in size, were definitely recognizable as tumor. The advanced character of the general disease process is illustrated by the fact that the degree of fibroblastic overgrowth in practically every nerve tumor was sufficient to obliterate almost completely the neurofibromatous character of the lesion. Foci of hyperplasia within the central nervous system were found only in case 5. The tumors within the spinal cord in the first case were well differentiated growths composed mainly of spongioblasts.

The first two cases are peculiar in that, although both patients had well-advanced central neurofibromatosis, the involvement of the meninges by tumor was as marked as the involvement of the nerves by their specific growths. The principal lesion in Case 5 was a large, infiltrating meningeal tumor and this may be an instance in which the rapid growth of the meningeal tumor caused the patient's death before the lesions of von Recklinghausen's disease had become evident. Thus it may be that von Recklinghausen's disease should be regarded less as a specific disease process of the nerve sheaths (neurofibromatosis) and more in the light of a condition affecting all the sheaths and enveloping membranes of the central and peripheral nervous system. On this basis it would seem that at any one time the disease process might be more marked in either the nerves or the meninges and that in isolated or familial cases one form might become clinically evident or cause death before the other had become manifest. Penfield and Young (20) have made the observation that, in the case described by them, none of the tumors were of neurogenic origin; that is, in every instance the type cell of the neoplasm itself was not of nervous tissue origin. In a broad sense, then, the defect may be looked upon as one of the binding tissues of the nervous system in which the neuroglial elements may also respond, either in the form of hyperplasias or true neoplasms.

Worster-Drought and his associates (21) offer the term "neuro-fibroblastomatosis" as being more accurate from a pathological standpoint. They believe that the term "von Recklinghausen's disease" should be confined to the purely peripheral subcutaneous form of the disease. While the basic concept is apparently sound, the objection to the introduction of the term suggested is that not only is it unwieldy but it also fails to include in its scope the changes in the glia, hyperplastic and neoplastic, which so often form an integral part of the disease process.

With respect to the microscopic pathology and the pathogenesis of von Recklinghausen's disease, the exact relationship between the latter and the nerve sheath tumor which is frequently seen as a solitary lesion of the cranial, spinal, or peripheral nerves is not fully understood at the present time. Further, there is considerable controversy over the nature of each of these individual lesions. The solitary nerve sheath tumor with its characteristic palisading of nuclei and streaming of cell bundles has been variously described as
neurilemoma, neurinoma, schwannoma, and perineurial fibroblastoma. Penfield regards these tumors as arising from the mesodermal elements of the sheaths of the nerves or nerve roots and considers the type cell to be the connective-tissue perineurial or endoneurial cell. Masson (23), on the other hand, believes that these tumors are derived from cells of neuro-ectodermal origin, the cells of the sheath of Schwann, and from his experimental studies believes that these cells are capable of elaborating collagen.

Penfield supports his stand upon the fact that these nerve sheath tumors contain fibroglia, collagen, and elastin, all shown to be products of cells essentially mesodermal and fibroblastic. He points out that the long collagen fibrils which form the stroma of the tumor, and bear a striking resemblance to the perineurium or reticulum of the nerve, are totally unlike neuroglia fibers and could not be expected to have arisen from the schwannian cells, which are analogous to neuroglia.

The neurofibroma itself is regarded as an overgrowth of the tissues composing the nerve, axis cylinders as well as sheath cells taking part in the process (24). True neoplastic change may occur in the form of a fibroblastic overgrowth which may obliterate the neurofibromatous character of the initial lesion, except, however, for the presence of nerve fibers within the tumor. The latter may be said to constitute the diagnostic criterion for the neurofibromatous background of tumors of this variety.

SUMMARY

1. A family has been described in which one or more tumors of the sheaths and enveloping membranes of the nervous system appeared as a hereditary trait and was transmitted as a mendelian dominant. Six cases in this family have been reported in detail.

2. Of the 14 members of the family, 7 gave evidence of having been affected. In the latter group, 3 were proved at autopsy and 2 were proved clinically by the presence of typical skin nodules of von Recklinghausen's disease. One member of the family had clinical signs which were regarded as probably due to early intracranial tumor formation and the family history indicated that another member had peripheral and possibly central neurofibromatosis at the time of death.

3. It has been suggested that von Recklinghausen's disease be regarded as a disease process which involves all of the sheaths and enveloping membranes of the nervous system and that this concept, in a broad sense, be extended to include the glial elements as well. Placing the defect in the "binding tissues" of the nervous system would account not only for the various types of growths associated with central neurofibromatosis but also for the preponderance of one of these types over the other.

REFERENCES