Neurofibromatosis is one of the most devastating, destructive, and debilitating diseases. It is characterized by neurofibromas or other neural tumors and by focal cutaneous hyperpigmentation (café-au-lait spots) caused by aggregation of melanoblasts in the basal layer of the epidermis. These elements, derived from the neural crest, are primarily affected. Mesenchymal elements are secondarily involved.

Neurofibromatosis is an autosomal dominant trait with full penetrance but variable expression. This differential expression is probably not intrinsic to the mutant gene but to local epigenic factors mediated by cellular interaction.

The frequency of neurofibromatosis has been documented as one case per 2500 to 3300 live births. Skull and facial deformities occur in approximately 22 per cent of cases.

The lesion may be unilateral or bilateral, diffuse or circumscribed (Figs. 1 and 2). There appears to be a relation between the time of the insult and the severity of the malformation—the earlier, the more severe.

Progression of the disease appears to be stimulated by puberty, pregnancy, and trauma. Increase of iris melanocytic hamartomas at or beyond puberty is considered to be an important criterion in evaluating this progression.

An increase in the production of serum nerve growth factor cross-reacting protein has been observed in many patients with neurofibromatosis, but the exact role of the nerve growth factor is still to be elucidated.

An important factor to be considered in patients with neurofibromatosis is the chance of malignant degeneration, as observed by many authors. Percentages vary from a low of 2 per cent to the high incidence of 27 per cent reported by Brasfield and Das Gupta.

HISTORY

Tilesius of Tilenau is credited with the first report on molluscum fibrosum, published as early as 1793.

Robert Smith, a professor of surgery at the Dublin Medical School, reviewed the literature in 1844 and cited 75 references. He also recorded the autopsy findings in two personal cases, but failed to see that neurologic elements were involved.

Von Recklinghausen in 1882 was the first to conclude that the multiple tumors of nerves and skin (neuromas and fibromas) existed simultaneously and were structurally related, thus justifying the name neurofibromatosis. This was 2 years before Frederick Treves, then consulting surgeon for the London Hospital, came to meet John Merrick, who was being exhibited opposite the hospital as the "elephant man."

In search of a diagnosis for this unique combination of skin and bone lesions, Treves presented his case on several occasions to the Pathological Society of London, where Dr. Radcliffe Crocker, a physician from the University College Hospital, made the suggestion that changes in the nerves were responsible for the bodily distribution of the disease.

However, an accurate diagnosis was not made until 1909 by Dr. Parker Weber, physician to the German Hospital in London. By then, Payne in 1887 had already suggested a developmental failure at the mesodermal junction as a possible cause of neurofibromatosis, and the hereditary nature of the disorder had been discussed by Thomson in 1900.

The protean manifestations of neurofibromatosis—affecting not only the peripheral nerves

Orbital Neurofibromatosis

Jacques van der Meulen, MD, PhD*
and the skin but also other tissues and structures such as the central nervous system, the skeleton, the vessels, and so on—were gradually becoming recognized.

Referring to elephantiasis neurofibromatosis (Fig. 3) as Quasimodo’s tumor, McDowell considered these lesions to be malignant in their incurable deforming and in their inexorable killing of major hopes, desires, and ambitions.

PATHOLOGY

Neurofibromatosis involves the central and peripheral nervous systems in a variety of ways.

The Central Nervous System

Optic gliomas, schwannomas, and meningiomas are most commonly seen.
Gliomas of the optic nerve appear as multicentric lesions, affecting this structure by circumferential growth. The nerve itself is relatively spared and so is the chiasm. This is in contrast with optic gliomas in nonneurofibromatosis tumors, which tend to invade the optic nerve or chiasm. The tumor grows as a fusiform expansion of the nerve and tends to spread through the optic foramen, expanding in a dumbbell fashion within the cranium. The major part of the swelling is often due to extension into the enveloping sheath, the optic nerve itself becoming atrophic. Histologically, gliomas are pilocytic astrocytomas. The tumors grow slowly and it may take years before symptoms are sufficiently severe to warrant medical treatment.

The Peripheral Nervous System

Neurofibromatosis is characterized by a high incidence of peripheral nerve tumors: neurofibromas (frequently plexiform) and, more rarely, schwannomas. The neurofibromas are specific for von Recklinghausen’s disease; schwannomas are not distinctive.

Neurofibromas

Neurofibromas are confined by perineurium in early stages, except for the nodules that arise in small terminal branches. They present as a well-defined tumor embedded in a fibrous matrix or as a poorly defined mass loosely arranged in normal tissue. The lesions are caused by a focal increase of an endoneurial myxomatous matrix containing collagen fibers, stellate cells, and mucoid components. Partial hyalinization is sometimes seen and mast cells are frequently observed. The endoneurial mass progressively separates the Schwann’s cell cylinder. These axon-enveloping cords elongate, lose their parallel arrangement, become tortuous, and increase in number. A plexiform neurofibroma (Fig. 4A) is then formed in which intact nerve

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**Figure 4.** A, Schwannoma. B, Plexiform neurofibromatosis. (Modified after Harkin JC and Reed RJ: Tumors of the peripheral nervous system. In Atlas of Tumor Pathology. Second Series. Fascicle 3. Washington, DC, Armed Forces Institute of Pathology, 1969.)
fibers are arranged in a bizarre fashion. The nerve of origin is almost never seen, and if it is found entering the tumor, it disappears into the neurofibromatous mass.

**Schwannomas**

The typical schwannoma (Fig. 4B) is sharply circumscribed by a thin fibrous layer and contains no axons. The cellular elements may be arranged in two different ways. The tumor is generally composed of compactly arranged spindle cells, with long oval nuclei that are frequently oriented with their long axes parallel to each other (Antoni A type pattern). Zones may be observed in which the cells are orderly arranged in palisades at either end of a bundle of parallel fibers. Part of the tumor may show cells arranged in thin, tortuous cords widely separated by an intercellular watery matrix that contains many collagen fibrils (Antoni B type pattern).

The distinction between a neurofibroma and a schwannoma is not always clear-cut. The proportion and growth pattern of each of the composing elements differ and the features of one tumor may blend into the other. Diagnosis is also complicated by the fact that Schwann's cells cannot be distinguished from neuroectodermal-perineural cells by any of the present techniques. They differ only in their location within the nerve sheath. The tumors contain an abundance of collagen and the cells resemble fibroblasts, suggesting a fibroblastic origin. Electron microscopy, however, shows a distinct basement lamina in these cells, a feature not normally characteristic of fibroblasts.

Fisher and Vuzevski demonstrated that collagenous fibrils arise from interdigitating extensions of the basement membrane of Schwann's cells in neurofibromas, but controversy exists as to the cells of origin. The precursor may be the Schwann's cell, both the Schwann's cell and the fibroblast, or a precursor of these cells.

**The Skin**

Plexiform neurofibromas may be associated with diffuse proliferation of compactly arranged spindle cells (fibroblasts). These cells may infiltrate the surrounding tissues, separating the pre-existing collagen bundles in dermis and subcutaneous tissue by loose, fibrous tissue.

Diffuse neurofibromatosis differs from the plexiform type by absence of the characteristic cordlike structures. Histologically, there is no difference.

The origin of dermal neurofibromas is not clear. The presence of Schwann's cells suggests that myelinated fibers are involved, but Meissner's corpuscles have also been described.

**The Skeleton**

Skeletal changes have been described by many authors. Subperiosteal proliferation, deficient tubulation, cyst formation, angulation, indentation, and perforation of bones may be observed.

**The Vessels**

Vascular alterations consist of intimal and adventitial proliferation, tunica media muscular degeneration, elastica fragmentation, and perivascular nodule formation. Luminal obliteration and aneurysmal dilation may result, which is probably responsible for the massive loss of blood that is seen in some patients during surgery and the difficulty to control this.

With respect to the mesenchymal dysplasias observed in patients with neurofibromatosis, an unusual feature of some nerve sheath tumors described by Luse is of interest. “Long-spacing” collagen may be found with cross banding occurring at 1100 to 2200 angstrom intervals, in contrast with the 700 angstrom banding in normal collagen, which is characterized by a quarterstep-staggered overlapping pattern. The significance of this abnormal collagen in relation to the many neural cutaneous, osseous, and vascular lesions and to wound healing is unfortunately not known.

**CLINICAL FEATURES**

Headaches, seizures, and mental retardation due to the presence of glial tumors or cortical architectural anomalies are observed in 8 to 10 per cent of patients with neurofibromatosis. It appears that virtually all motor, sensory, and autonomic nerves may be involved by the disease, separately or in combination. However, nerve function studies are rarely done, and attempts to classify the deformities have not been made to my knowledge. As a result, “orbitofacial neurofibromatosis” is the term commonly used to indicate a wide spectrum of abnormalities affecting the soft tissues and the skeleton.
The Soft Tissues

The Orbit

The optic nerve may be affected by a glioma. It is now generally accepted that neurofibromatosis is present in approximately 25 per cent of the patients seen with this tumor.

The eye itself may show manifestations of the disease in virtually all of its components. Cord-like, nodular, or diffuse neurofibromas have been recorded in the cornea, the sclera, the choroid, and the ciliary body. The iris may contain nodules and melanocytic hamartomas (Lisch spots), which are particularly pathognomonic for the disease. Retinal lesions are unusual and involvement of the lens and vitreous body has not been recorded.

Buphthalmos (Fig. 5) or hydrophthalmia may be observed and is without question the most salient feature of ocular involvement. Intraocu-
lar hypertension is commonly present and probably caused by a neurofibroma of the ciliary body and the choroid or by a schwannoma of the ciliary nerves involving the iridocorneal angle. Normal intraocular pressure has been reported, however, and some authors have therefore suggested that buphthalmos may be, at least in part, an expression of ocular hyperplasia or regional gigantism.

The periocular structures may also be invaded by neurofibromas, and the formation of retrobulbar tumors may gradually result in exophthalmos (Fig. 6), loss of visual acuity, and oculomotor paresis.

The Face

Initially, the abnormal areas seem to be well defined, corresponding to the territorial pattern and extent of an underlying plexiform neurofibroma of one of the facial nerves.

Gradually, the tumors become less well defined and increase in size owing to the proliferation of structural elements, the aggregation of collagen fibers, and the extracellular accumulation of mucoid materials associated with the presence of large numbers of mast cells.

The skin loses its tensile strength and becomes friable, thick, pigmented, and hairy. The

Figure 6. Patient with severe elephantiasis neuromatosa, pulsating exophthalmos with minimal vision, and typical orbital abnormalities. A, Preoperative view. B, Postoperative view, following enucleation of the eye, palpebral reconstruction, medial and lateral canthopexies, and orbital remodeling. C, CT scan showing extent of malformation. D, Peroperative view of exophthalmos.
mucous membranes of the eyelids, the cheek, and the lips may show similar alterations. The muscles may continue to function for prolonged periods of time in some patients but they gradually lose their animating power. Ptosis develops and facial expression disappears.

The soft tissues lose contact with the facial skeleton at places where they are firmly adherent under normal circumstances. They detach themselves from the contiguous structures and develop into a sessile or pedunculated mass, producing a fibroma molluscum or eventually elephantiasis. Abnormal folds, frequently described as a “bag full of worms,” are formed in some areas, whereas other folds, normally existing, disappear.

Four areas of drift in particular may be distinguished: the forehead, the palpebral complex, the nasolabial fold, and the oral commissure.

Frontotemporal fold formation and downward dislocation of the eyebrow, palpebral ptosis, macroblepharia and canthal dystopia, flattening and downward dislocation of the nostril, macrocheilia, and macrostomia and downward dislocation of the oral commissure all may be observed.

 Conjunctivitis, epiphora, salivation, and troublesome mastication are some of the complications that may result.

The Skeleton

Bony malformations such as hypoplasia, intrasosseous cysts, and perforating defects are typical characteristics in patients with craniofacial neurofibromatosis (Fig. 7). Macrocrania, expansion of the middle cranial fossa, and downward tilting of the sella turcica may be observed.

The orbit may be affected by minor abnormalities such as small defects, lacunae and foramina with perforating, cordlike nerves at abnormal sites, or simple enlargement of the optic foramen.

However, major abnormalities are also seen. Aplasia or hypoplasia of the lesser or greater wing of the sphenoid bone may be associated with widening of the sphenoidal fissure, resulting in wide areas of communication between the anterior or middle cranial fossa on one side and the orbit on the other.

Invagination and herniation of the dura mater into the orbit may thus occur and produce a pulsating exophthalmos. Enlargement of the orbit, particularly in its inferolateral part, may be associated with enophthalmos (Fig. 8) and downward displacement of the zygoma, maxilla, and mandible on the ipsilateral side. Downward tilting of the occlusal plane may occur, and because the skeletal changes are usually associated with hypertrophy of the soft tissues, the illusion of hemifacial macrosomia may be created.

SURGERY

The opinion of different authors as to timing and extent of surgery is still controversial. According to Grabb et al., total resection is unjustified and, in fact, not possible unless all affected tissues are removed. They prefer multiple subtotal excision over the years to the sacrifice of normal tissue in a vain attempt to
Figure 8. Patient with severe orbitofacial neurofibromatosis, palpebral ptosis, and enophthalmos. A, Preoperative view. B, Sagittal CT scan showing palpebral abnormalities and enophthalmos. C, Postoperative view following resection of palpebral tumor, remodeling of the eyelids, medial and lateral canthopexies, and elevation of orbital floor. Part of the corneal surface has been invaded by the tumor.

remove all the disease, but admit at the same time that partial excision is never adequate to prevent overwhelming deformities.

Griffith et al. 16 share this opinion and advise excision of lesions that threaten to encroach upon vital structures.

Davis et al. 10 also recommend subtotal resection and express optimism based on the results obtained from earlier surgery, stating that it will preserve both function and appearance and will remove a tumor before it begins to degenerate.

It is highly improbable that early partial excision will preserve function and appearance. The affected tissues are intimately intermingled with normal tissues. As a result, tumor growth will proceed in the nonresected tissues, allowing the deformity to recur.

I believe that selective conservative excision 25 as well as radical resection of the tissues involved may have their indications. Selective removal of orbital tumors and selective resection of tumors in eyelids or cheeks may be warranted when vision and ocular or facial motion are still normal or subnormal. Radical resection of the involved tissues is the treatment of choice in patients who have already lost their functions.

The Orbit

An abnormal position of the eye, due to an increase in volume of the orbital contents (exophthalmos) or to an increase in size of the orbit itself (enophthalmos), and an abnormal size of the eye are the main hallmarks of the disease. Resection or repositioning of the eye and adnexa and remodeling of the skeletal frame are the surgical modalities that may be used for correction. The type of procedure chosen is dictated by the presence or absence of vision.

Presence of Vision

It is generally accepted that the eye should be preserved if it has vision. Removal of the tumor would seem to be the procedure of choice, but this can only be considered when the lesion is isolated and function of the eye and muscles is not compromised by careful dissection. Unfortunately, such patients are rare.

However, examination of patients at an early stage with CT scanning and nuclear magnetic resonance may provide more accurate information regarding the type of nerve involved and the extent of the lesion. This may allow better differentiation between the deformities, improving our ability to predict the natural course of the disease and perhaps ultimately enhancing our therapeutic potential.

At this stage, improvement can be obtained only by repositioning the dislocated tissues and remodeling the orbital framework.

Reconstruction of the orbital roof with a bone graft to correct a cerebral hernia and cure a
pulsating exophthalmos was done as early as 1927 by Dandy. However, this procedure offers no solution for patients with an increase in volume of the orbital contents because exophthalamos will persist.

Remodeling of the orbit by expansion of its roof has therefore been advocated by Marchac to make repositioning possible. Expansion of the orbital roof must be combined with elevation of the floor whenever this is too low. However, Marchac concludes that the results so far have been somewhat disappointing owing to soft-tissue distention and possible recurrence of the cerebral hernia following resorption of a bone graft.

The latter problem can probably be solved by the transfer of a temporal osteoperiosteal flap, as has been described for the correction of Treacher Collins syndrome.

In addition, it should be borne in mind that successful repositioning is not automatically associated with normal vision. Ptosis usually persists, and its correction is complicated if not impossible when both thelevator and frontalis muscles are affected by the lesion.

Remodeling of the orbit by elevation of its floor is indicated in patients with enophthalmos. It may be achieved by means of bone grafting or by the “reverse facial osteotomy” described by Munro and Martin.

Absence of Vision

In the majority of patients with severe neurofibromatosis seen by this author, the eye had been enucleated previously or vision was severely reduced owing to the presence of ocular neurofibromatosis or functional amblyopia.

Because a nonseeing eye may form an obstacle to all attempts at correction of the malformation, I believe that its enucleation is justified. All efforts may then be concentrated on the restoration of a more normal appearance by resection of residual orbital tumors, reconstruction of the orbital roof, and remodeling of the orbital framework as dictated by the circumstances.

Resection of the orbital contents may be radical or partial. Jackson et al. favor radical resection in view of possible recurrence of the tumor and its chance of becoming malignant. They cover the denuded orbital walls with the eyelids and fit the patients with a prosthesis.

I tend to be more conservative in this respect and favor selective removal of the residual tumor masses and preservation of normal structures. If this is not possible, I also perform a radical resection and replace the removed tissues with a bone or cartilage graft, thus reducing the orbital volume. The transfer of a temporo-periosteal flap will also achieve this objective and is therefore being considered. I never resect the conjunctiva and use this tissue as a socket lining.

The Face

The principles that I use to correct the facial abnormalities combine selective conservative and radical excision. This means that a maximum of involved tissues must be removed, preserving only so much of the skin as is necessary to close the resulting defect and only those muscles that are functional and effective.

A functioning muscle may be ineffective when it is unable to activate the soft tissues invaded by the tumor. Resection of the mass—for instance, in the upper eyelid—may restore the effectiveness of the levator. A nonfunctioning muscle is only to be preserved when removal would imply an unacceptable loss of contour.

Such an approach has several advantages. It allows dissection in a less vascular plane, thus avoiding excessive bleeding from the tumor and enhancing hemostasis. It promotes healing by approximation of normal tissue containing normal fibroblasts and producing normal collagen. It limits the amount of involved tissues responsible for further deterioration of normal tissues, reducing the incidence of recurrences or even malignancy.

A second principle to be considered is the site of the incisions, which should be parallel to the lines of minimal tension and be hidden in natural folds or creases. At the same time, they should allow for maximal exposure and full-thickness resection of the affected tissues when this is indicated.

A third principle, frequently neglected, but decisive for the quality of the result, concerns the reattachment of the soft tissues in the areas of drift: the forehead, the palpebral complex, the nasolabial fold, and the oral commissure.

The Forehead

A coronal approach allows for dissection of the affected tissues in an epicranial and subdermal plane. A temporofrontal tumor invading the frontal muscle may thus be removed together with the many terminal nerve branches invading the skin or perforating the skeleton in the orbital region. Resection of tumor masses in the medial canthal area or below the orbital

Orbital Neurofibromatosis
Figure 9. Patient with palpebral neurofibromatosis. A, Preoperative view. B, CT scan showing normal orbital contents. C, Peroperative view demonstrating extent of excision. D, Postoperative view following eyelid reduction, shortening of the palpebral fissure, and lateral canthopexy.

Figure 10. Patient with severe orbitofacial neurofibromatosis. A, Preoperative view: The eye was removed at the age of 1 year. B, Postoperative view following skeletal corrections involving resection of orbital tumors, obliteration of the orbit with bone grafts, reconstruction of eyelids and socket, medial and lateral canthopexies, partial maxillectomy, and reconstruction of nasolabial fold using nasal part of modified Ferguson-Weber incision. C, Modified Ferguson-Weber incision. (From van der Meulen JC, Moscona AR, Vaandrager M, et al: The management of orbitofacial neurofibromatosis. Ann Plast Surg 8:213–220, 1982; with permission.)
Orbital Neurofibromatosis

roof is equally possible. Remodeling of the eyebrow may require separate incisions.

**The Palpebral Complex**

A template of the normal opposite eyelid is first made and then superimposed in the affected one. The surplus of skin and degenerated orbicularis muscle is then removed through appropriate incisions. Full-thickness reduction of the eyelids by wedge excisions in their lateral parts is usually indicated, and the extremities of the eyelid rims are then attached to the orbital wall by means of a lateral canthopexy. The skin lateral to the canthus should be fixed to the underlying periosteum to obtain normal contour and prevent drift. A medial transnasal canthopexy is indicated in all patients with canthal dystopia following extensive removal of tumor masses in that region (Fig. 9).

**The Nasolabial Fold**

Flattening of this area and downward drift of the nostrils cannot be corrected by simple excision of the tissue surplus. Reconstruction of the fold is always indicated. To achieve this objective, radical resection of the subcutaneous tissues is first performed, using a modified interdigitated Ferguson-Weber incision. Burr holes are made in the rim of the piriform aperture and the fold is solidly anchored to the skeleton by passing sutures through these holes (Fig. 10).

**The Oral Commissure**

Macrocheilia and downward drift of the oral commissure complete the list of stigmata. Attempts to correct these deformities by external reduction are usually disappointing because of the trap-door effect created by wrongly placed incisions. Full-thickness resection of the lip using skin incisions in the philtrum and in the nostril sill and mucosal incisions in the buccal sulcus has given better results in my hands than any other approach (Fig. 11).

**SUMMARY AND CONCLUSION**

The origin of neurofibromatosis (the neuroectoderm, the mesectoderm, or both primordia?) is not known. The protean manifestations of the disease cannot be explained, and classification of the various forms of orbital neurofibromatosis on the basis of specific neural involvement has never been attempted. Further studies of the pathogenesis are therefore urgently needed. Differentiation between types of orbital tumors may benefit from advanced computer scanning and nuclear magnetic resonance techniques.

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**Figure 11.** Patient with severe orbitofacial neurofibromatosis. *A,* Preoperative view following enucleation of the blind right eye, resection of the orbital tumors, obliteration of the orbit with bone grafts, reconstruction of eyelids and socket, and canthopexies. *B,* Postoperative view following further obliteration of the orbit, extensive resection of tumors in cheek and upper lid using modified Ferguson-Weber incision, and reconstruction of nasolabial fold and upper lid. The patient is temporarily wearing a conformer. (From van der Meulen JC, Moscona AR, Vaandrager M, et al: The management of orbitofacial neurofibromatosis. Ann Plast Surg 8:213-220, 1982; with permission.)
The results of surgical treatment, although much improved in recent years, are still unsatisfactory. Concentration of patients with neurofibromatosis in specialized centers is therefore indicated.

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