Memoranda / Mémorandums

Prevention and control of neurofibromatosis: Memorandum from a joint WHO/NNFF meeting*

Neurofibromatosis (NF) is a serious, common, genetically determined neurological disorder; with a prevalence of about 1:4000 births it affects both sexes and all races and ethnic groups. The two major forms are referred to as NF1 and NF2, as suggested in 1987 by a National Institutes of Health Consensus Development Conference on Neurofibromatosis.

In NF1, the disease phenotype is more variable and complex than in NF2. Complications can occur in any of the body systems in tissues of ectodermal, mesodermal and neural tube origin; there is marked variation of disease phenotype even within families. The NF2 gene, in contrast, only seems to be expressed in tissues of ectodermal origin and its expression is more uniform both within and between families. The recent discovery and isolation of the gene responsible for the NF1 mutation has practical applications in the field of molecular genetics which could modify the approaches for diagnosis, treatment and prevention of NF.

This Memorandum summarizes the discussions and recommendations of the participants at a joint WHO/National Neurofibromatosis Foundation (NNFF) meeting, held in Jacksonville, Florida, USA, on 27–28 January 1991.

Introduction

Neurofibromatosis (NF) is a serious, genetically determined neurological disorder, with a prevalence of about 1:4000 births, affecting both sexes and all races and ethnic groups. The term "neurofibromatosis" encompasses at least two distinct disorders which have in common a predisposition to the development of tumours of the nerve sheath. Both forms (known as NF1 and NF2) are genetically transmitted as autosomal dominant traits and are distributed throughout the world with no apparent racial or ethnic predilection. Clinical management of persons with NF is complicated by a wide range of variability of expression, often impeding accurate diagnosis, and making it difficult to predict the clinical course (*1–3*).

Until the last decade, very little research had been undertaken into the cause of the different forms of NF because the challenge presented by this disorder may have actually hampered such studies. The problems caused by NF can take a patient to any of the major medical specialties and are individually relatively infrequent, so that no one group of health professionals realizes the overall health burden of the disease. Prior to the advent of DNA technology relatively little basic research into NF had been carried out. The recent discovery and isolation of the gene responsible for the NF1 mutation has made it highly appropriate to discuss the applicability, at the practical level, of the new findings that could modify the approaches to diagnosis, treatment and prevention of NF.

* This Memorandum is based on the report of a joint WHO/NNFF (National Neurofibromatosis Foundation) meeting held in Jacksonville, Florida, USA, on 27–28 January 1991. The participants were: J. Carey, Salt Lake City, UT, USA; E.K. Ginter, Moscow, USSR; S.M. Huson, Oxford, England (*Rapporteur*); B. Korf, Boston, MA, USA (*Chairman*); R. Martuza, Boston, MA, USA; V.F. Mautner, Hamburg, Germany; M. Niimura, Tokyo, Japan; V. Penchaszadeh, New York, NY, USA; A. Rubenstein, New York, NY, USA; and B. Seizinger, Boston, MA, USA. *NNFF Secretariat*: P. R. W. Bellermann. *WHO Secretariat*: V. Bulyzhenkov, Hereditary Diseases Programme, World Health Organization, Geneva, Switzerland.

Requests for reprints of this article should be addressed to the Hereditary Diseases Programme, Division of Noncommunicable Diseases and Health Technology, World Health Organization, 1211 Geneva 27, Switzerland. A French translation of this article will appear in a later issue of the *Bulletin*.

Reprint No. **5263**

Definition, frequency and heterogeneity

The NF1 and NF2 nomenclature for the two major forms was suggested in 1987 by a National Institutes of Health Consensus Development Conference on Neurofibromatosis (*4*); their diagnostic criteria are given in Tables 1 and 2. NF1 is more common, affecting approximately 1:4000 individuals worldwide; its characteristics are café-au-lait spots, Lisch nodules, and neurofibromas; other manifestations include optic gliomas, skeletal dysplasias, plexiform neurofibromas, learning disabilities, etc. NF2 is far less common, with a frequency of about 1:100 000; it is characterized by the occurrence of bilateral acoustic neuromas, as well as meningiomas, schwannomas, neurofibromas, and bilateral posterior subcapsular cataracts. NF1 is the disorder sometimes referred to as von Recklinghausen or "peripheral" neurofibromatosis. NF2 has been called bilateral acoustic or "central" neurofibromatosis.

Table 1: **Diagnostic criteria for NF1**

NF1 should be considered if two of the following are present in an individual, provided no other disease accounts for the findings:

1. On examination in room light, there are at least 5 café-au-lait macules (over 5 mm in greatest diameter), if prepubertal; or 6 café-au-lait macules (over 15 mm in greatest diameter), if post-pubertal.
2. Based on the history or on clinical grounds, there are 2 or more neurofibromas of any type, or 1 plexiform neurofibroma.
3. Multiple freckles in the axillary or inguinal regions.
4. Sphenoid wing dysplasia or congenital bowing or thinning of long bone cortex, with or without pseudoarthrosis.
5. Optic nerve glioma.
6. Two or more iris Lisch nodules on slit-lamp examination.
7. A first-degree relative (parent, sibling or offspring) has NF1, by the above criteria.

Table 2: **Diagnostic criteria for NF2**

NF2 should be considered if either of the following is present in an individual:

1. Evidence, by computer tomography (CT) or magnetic resonance imaging (MRI), of bilateral internal auditory canal masses, consistent with acoustic neuromas.
2. A first-degree relative has bilateral acoustic neurofibromatosis and *one* of the following:
   - — CT or MRI evidence of a unilateral internal auditory canal mass, consistent with acoustic neuroma.
   - — A plexiform neurofibroma or two of the following: meningioma, glioma, neurofibroma at any site.
   - — Imaging evidence of an intracranial or spinal cord tumour.

Other inherited syndromes may include some features of neurofibromatosis, but they may be distinct entities; whether they represent allelic or gene locus heterogeneity will depend on their molecular genetic characterization. A list of neurofibromatosis-like syndromes is given below:

- — segmental neurofibromatosis
- — Noonan syndrome / neurofibromatosis
- — Watson syndrome
- — gastrointestinal neurofibromatosis
- — spinal neurofibromatosis
- — familial café-au-lait spots
- — schwannomatosis.

Segmental NF represents the appearance of features of NF1 confined to restricted segments of the body (*5*). In some cases the features are limited to either café-au-lait spots and skinfold freckles, or to neurofibromas without pigmentary changes. Precise criteria for diagnosis of segmental NF have not been determined. The hypothesis has not been tested at the molecular level. The majority of reported cases have been sporadic, but there are a few cases reported of parents with segmental NF having children with classical NF1, suggesting germline involvement.

Several persons with NF1 have been found to have some features of Noonan syndrome, including short stature, pulmonary stenosis and characteristic facial appearance (*6*). This has led to the suggestion that this syndrome and NF1 may be due to mutations at contiguous genes, but there is no genetic evidence to support this hypothesis. Alternatively, the Noonan-like features may be a manifestation of some NF1 mutations, and may be genetically distinct from true Noonan syndrome. A number of families have been described with pulmonary stenosis, café-au-lait spots, and neurofibromas, a constellation referred to as Watson syndrome.

Several syndromes are characterized by multiple neurofibromas or schwannomas occurring in a restricted set of tissues. These include gastrointestinal neurofibromatosis, spinal neurofibromatosis, and schwannomatosis. Finally, a few families have been found in which café-au-lait spots occur without other signs of NF (*7*). The trait appears to segregate as an autosomal dominant. It is important to consider this disorder in a child who manifests only café-au-lait spots, although it appears to be much rarer than NF1. It is not known whether this entity is allelic to NF1.

Pathogenesis

Proposed mechanisms of pathogenesis for the different forms of NF have to explain the disease

phenotype: how the tumours form and what causes other associated features. In NF1 the disease phenotype is more variable and complex than NF2. The complications can occur in any one of the body systems in tissues of ectodermal, mesodermal and neural tube origin. There is marked variation of disease phenotype even within families. The NF2 gene, in contrast, only seems to be expressed in tissues of ectodermal origin and its expression is more uniform both within and between families. The mechanism of tumorigenesis in both NF1 and NF2 is of major interest and will be important not only in our understanding of NF, but also for histologically similar tumours which can occur in isolation.

The majority of work up until 1985 is reported in conference proceedings from that year (*44*). The only possible clues to pathogenesis had come from studies of nerve growth factor (NGF) in people with NF. NGF is a polypeptide necessary for the growth and maintenance of sympathetic and certain sensory neurones, and possibly other neural-crest-derived tissues including Schwann cells. Early studies in small numbers of cases suggested that there may be an increased NGF activity in the serum of people with NF1 and NF2; in each form the activity was detected in different assay systems and it was proposed that the two forms may result from different abnormalities of NGF. However, NGF activity was investigated in a much larger number of people with NF1, using an improved assay system, and no abnormalities were found, thus throwing doubt on the earlier reports. The increasing clinical interest in NF in the late 1970s and early 1980s, and the lack of understanding of its pathogenesis made it the right time for the application of DNA technology and the so-called reverse genetic or positional cloning approach (*8*); these endeavours began in the early 1980s.

Molecular genetics

The advent of DNA technology provided the means by which genetic diseases could be studied at the molecular level, directly, rather than at the biochemical or cellular level. Instead of approaching the disease from phenotype to genotype, in the reverse genetic approach the gene itself is first isolated, studied at the molecular level and its product then identified. The first step in this approach is to localize the disease gene to a chromosome, followed by fine mapping of a small area of that chromosome and the eventual cloning of the gene, which is usually achieved by genetic linkage studies looking at the segregation of DNA markers in families with the disease. There may be possible shortcuts to the gene localization, which would include the study of candidate disease genes (e.g., NGF for NF1 and NF2) or the identification of patients with the disease and a chromosome rearrangement.

The NF1 gene: localization and cloning

For NF1, none of the clues to chromosome localization gave the answer. In particular, studies of polymorphisms in the NGF gene in NF1 families showed no linkage, confirming the earlier suggestion that NGF was not the NF1 gene. Linkage studies from 114 markers were eventually undertaken (*9*) before a positive linkage was found with markers which mapped on chromosome-17 (*10, 11*). Progress towards the eventual cloning of the gene in 1990 was rapid and aided by the formation of a consortium of the scientists involved. The group has been able to hold regular meetings due to the generous sponsorship of the National Neurofibromatosis Foundation (NNFF).

Shortly after the gene localization by linkage analysis, a balanced chromosone translocation involving band 17q11.2 was described in a person with NF1 suggesting that this may be the subchromosomal localization of the NF1 gene (*12*). The finding of a second similar case added support to this (*13*). The localization was confirmed using linkage analysis of chromosome-17 markers. The markers which were shown to flank the NF1 gene by linkage studies flanked the translocation breakpoints by physical mapping methods (*14*). With the identification of closely linked family-flanking markers, the first clinical application of the research was possible, and from 1989 prenatal and presymptomatic diagnosis of NF1 using linked markers was possible in families with a suitable pedigree structure (*15*).

Subsequent physical mapping studies identified the markers which detected the translocation breakpoints on pulsed field gels and showed the breakpoints to be about 50 kilobases (kb) apart (*16, 17*). Efforts then focused on the identification of candidate transcripts from the region defined by the translocation. The first three transcribed genes identified, however, showed no mutations in NF1 patients and were therefore unlikely to be the NF1 gene (*18, 19*).

A transcribed region was subsequently identified which encodes a 13 kb RNA which is expressed in all tissues but most abundantly in the CNS. This gene showed mutations in NF1 patients and was concluded to be the NF1 gene (*18–20*). The gene stretches across at least 200 kb of genomic DNA. The first three transcribed genes identified in this area (EVI-1, NF1-C2, and the oligodendrocyte myelination glycoprotein) lie within an intron in the NF1 gene and are transcribed in the opposite direction to the NF1 gene (*18, 19*). Whether their presence affects the NF1 phenotype in any way remains to be determined.

Cloning and sequence analysis (still incomplete) of the NF1 gene showed homology between a portion of this sequence to the GTPase-activating protein (GAP) family. This homology extends down to yeast (*21*). GAP proteins are involved in the regulation of the signal transducing oncogenes of the ras family which are involved in the control of cell proliferation. GAP proteins hydrolyse ras-GTP (the active form) to ras-GDP (the inactive form). In the simplest hypothesis of NF1 gene action, loss of NF1 activity would lead to a preponderance of active ras, which in many (but not all) situations is associated with unregulated cell growth. Three groups have now provided evidence that NF1 has GAP activity and can interact with mammalian and yeast ras proteins (*21–23*).

The mechanism of tumorigenesis in NF1 remains unclear. There has been much speculation as to whether the NF1 gene is a tumour suppressor gene, in which tumour growth would be caused by a recessive mechanism, or whether tumour growth results by a negative dominant mechanism, in which the lack of function of one allele is sufficient for tumour formation (*24*). It has been postulated that the benign neurofibromas seen in NF1 may be the result of one mutation in the NF1 gene and the multiple neurofibrosarcomas are the result of multiple mutations, with a second mutation at the NF1 gene and mutations at other genes involved in tumour progressions (e.g., P53). In studies to date, only phaeochromocytomas have shown allele loss at the NF1 gene, although neurofibrosarcomas have shown loss of the short arm of chromosone-17 and specifically P53 mutations (*25*). It must be concluded that the mechanistic role of the NF1 gene in tumorigenesis at this time is uncertain. If the mechanism is recessive, as demonstrated for other familial tumour syndromes such as retinoblastoma and indeed NF2, a mechanism would still have to be found to explain NF1 symptoms not related to tumour formation.

Molecular studies of NF2

From the clinical viewpoint, NF2 is much more like other family cancer syndromes where tumours have been shown to develop due to a recessive mechanism. The tumours in NF2, principally acoustic neuromas and meningiomas, can occur in isolation and when they occur in the familial form they tend to present at a younger age group and tend to be multiple. Indeed, the first clue to the chromosome localization of NF2 was from studies of chromosomal and DNA rearrangements in tumours.

Studying meningioma tissue cytogenetically showed frequent loss of chromosome-22 (*26*). As DNA techniques became available, Seizinger et al. compared DNA polymorphisms in the blood and tumour tissue from patients with both isolated acoustic neuromas and NF2: frequent and specific deletions of chromosome-22 were seen (*27*). That chromosome-22 was the localization of the NF2 gene was subsequently confirmed by linkage studies (*28*). These studies placed the NF2 gene on the long arm of chromosome-22 (22q11.1–22q13.1). Subsequent studies have bracketed the NF2 gene to a region of approximately 13 centimorgans (cM) between the markers D22S1 and D22S28 (*29*).

In contrast to NF1, subsequent progress has been relatively slow owing to the limited number of people with NF2 available for study. As NF2 is a relatively infrequent disease, there are only a few large families available for linkage studies and therefore it has not been possible to entirely exclude non-locus heterogeneity. There have also been no patients identified till now with a chromosome translocation which might have given a short-cut to the cloning of the gene. However, a translocation has recently been reported in a meningioma with a breakpoint at 22q11 in the region where linkage studies suggest the NF2 gene is located (*30*). The translocation therefore may provide the vital clue to the exact position of the NF2 gene. Another possible short-cut was that when the NF1 gene was cloned, a structural homologue on chromosome-22 would be found. Although a region containing apparently homologous sequence has been found on chromosome-22, it remains unclear whether it is in the region of the NF2 gene (Marchuk, personal communication).

The NF gene-cloning and function consortium, sponsored by the NNFF, now includes the groups working on NF2. It is likely that with regular exchange of ideas and material the NF2 gene will be cloned in the near future.

Clinical diagnosis and management

Diagnosis of NF1 and NF2

The diagnosis of NF is based on clinical criteria which are updated versions of those suggested by the National Institutes of Health Consensus Development Conference in 1987 (Tables 1 and 2). The criteria were designed to avoid false positive diagnoses, but it is likely that at some point in their lives many persons who truly have NF1 or NF2 may not satisfy the criteria. The features of NF tend to be age-dependent, so it is often necessary to follow a person for some years before the diagnosis can be confirmed. The distinction between a person having NF1 and NF2 is of great clinical importance. Persons with NF1 are not at high risk of developing acoustic

neuroma, and do not need to be closely monitored for that complication. On the other hand, problems such as learning disabilities and optic glioma do not appear to be specifically associated with NF 2.

Diagnosis of NF1. The most common presenting sign of NF1 is multiple café-au-lait spots, the presence of more than six spots being highly indicative of NF1 (*2, 31*). It should be noted that the studies of café-au-lait spots in the general population are all based on white-skinned individuals; it is not known how frequently café-au-lait spots occur in black or Oriental persons, for example. Café-au-lait spots do occur in other disorders and therefore are not pathognomic of NF1. These disorders include Russell-Silver syndrome, Fanconi anaemia, McCune-Albright syndrome, ataxia telangiectasia, X-linked ocular albinism, familial spinocerebellar ataxia, tuberous sclerosis, multiple lentigines syndrome, and Bannayan-Riley-Ruvalcaba syndrome. These are usually easily distinguished from NF. Café-au-lait spots may also occur in persons with NF2, but usually in numbers fewer than six.

Another cutaneous manifestation of NF1 is the occurrence of skinfold freckling (*32*). This usually begins in childhood, and involves the axillae, groins, and other skinfold areas. The sensitivity of this sign in the diagnosis of NF1 in various populations has not been established.

Neurofibromas are the hallmark of NF1, but may not appear until late childhood or adolescence. They commonly come to attention as skin lesions, involving cutaneous nerves, but can occur anywhere in the body. They must be distinguished from cutaneous lipomas, which are often misdiagnosed as being neurofibromas. Plexiform neurofibromas, in which a large nerve trunk is involved with neurofibroma growth, may be present congenitally. Some plexiform neurofibromas are associated with hypertrophy and deformity. Isolated neurofibromas occur rarely in the general population, and many of the syndromes considered to be possible variant forms of NF can lead to the development of neurofibromas. Both neurofibromas and schwannomas occur in NF2, although schwannomas are more characteristic of that disorder (*33*).

Iris Lisch nodules can be a helpful sign in establishing a diagnosis of NF1. These are hamartomatous lesions which have no impact on vision (*34*). They are found in almost all persons with NF1 after puberty, and are very rarely, if ever, seen in persons with NF2. The examination for Lisch nodules should be done by an experienced ophthalmologist. A slit-lamp must be used to distinguish Lisch nodules, which are raised, from iris naevi, which are flat and not associated with NF1.

Optic glioma is a characteristic tumour associated with NF1. Optic nerve thickening is commonly found by CT scanning or magnetic resonance imaging (MRI) of NF1 patients, but only a minority of these manifest symptoms of visual loss, proptosis, or hypothalamic dysfunction (*35*). Persons with optic glioma should be carefully examined for other signs of NF1, and persons with NF1 should be followed for the possible development of symptomatic optic glioma.

Two types of skeletal dysplasia are typical for NF1, and serve as diagnostic criteria. These are deformities of the orbit and of long bones, most commonly the tibia. Both are congenital lesions. Orbital dysplasia is usually associated with plexiform neurofibroma of the orbit and complete or partial absence of the greater wing of the sphenoid (*1, 2*). Tibial dysplasia presents as anterolateral bowing of the lower leg (*1, 2*). Early recognition and orthopaedic management of tibial dysplasia is important to prevent the occurrence of fracture and formation of pseudoarthrosis.

NF1 is genetically transmitted as an autosomal dominant trait, so the occurrence of NF1 in a first-degree relative satisfies one diagnostic criterion. The penetrance of NF1 is very high, and about 50% of cases appear to represent new mutations (*36*). The diagnosis of NF1 in young children with only multiple café-au-lait spots and no family history of the disorder presents a particularly difficult problem, since most of the features of the disorder are age-dependent. Such children must be carefully examined and followed up for the development of features of NF, or for the presence of other syndromes listed above which can be associated with café-au-lait spots.

Diagnosis of NF2. The hallmark of NF2 is the occurrence of bilateral acoustic neuromas (*3*). These are rarely clinically apparent before the second decade of life, and may not appear until much later. Clinical signs include high-frequency hearing loss, tinnitus, loss of balance, and spatial disorientation. The most sensitive clinical test is the gadolinium-enhanced MRI, which can reveal pre-symptomatic lesions in the size range of millimetres (*37*). Audiometry and brainstem auditory-evoked potentials can also be helpful in diagnosis. In addition to the acoustic nerves, schwannomas may occur on other cranial nerves in association with NF2. Other tumours of the nervous system include meningiomas, gliomas, and ependymomas. Schwannomas of spinal nerve roots are of particular importance because of their potential to cause radiculopathy or spinal cord compression.

Unlike NF1, cutaneous features of NF2 are few and may be subtle. Café-au-lait spots are usually

fewer than six; both neurofibromas and schwannomas may occur on the skin, or along peripheral nerves. NF2 should be considered as a possible diagnosis in a person with one or two café-au-lait spots or cutaneous neurofibromas and no other signs of NF1.

The recent discovery of posterior subcapsular cataract, which occurs in approximately one-half of persons with NF2, provides a useful diagnostic clue (*38*). This may be seen within the first decade, well before the occurrence of acoustic neuromas. Examination for this lesion requires the use of the slit-lamp.

As for NF1, a positive family history is a diagnostic criterion for NF2. Recently it has become apparent that a substantial proportion of persons with NF2 have no family history of the disorder, and were affected by a probable new mutation of the NF2 gene.

Management

There is no medical treatment that can prevent or reverse the characteristic lesions. Instead, medical management is focused on the early detection of treatable complications and prompt institution of appropriate therapy. Management is often performed under the aegis of a specialized "Neurofibromatosis Clinic", where considerable expertise representing multiple medical disciplines can be gathered. These disciplines generally include at least neurology, genetics, dermatology, surgery, orthopaedics, and oncology. Wherever health care is provided, however, it is most important that clinicians should be familiar with the disorder and work together as a team.

Aside from providing for the medical care of persons with NF, it is important to be attentive to the needs for psychosocial and genetic counselling. NF can impose a significant psychological burden, related to issues such as disfigurement, uncertainty regarding prognosis, and problems associated with chronic medical illness. Additional practical difficulties with employment or obtaining insurance may further complicate the management. Genetic counselling should be provided to all persons with NF, and to their first-degree relatives. Affected relatives should be identified and advised of the risk of transmitting the disorder to their offspring.

Management of NF1. Major complications of NF1 are listed in Table 3. It should be noted that no estimates are given for the frequency of these complications. The true frequency of most manifestations of NF1 are not known. Wide variations in the frequency of complications reported in the medical literature are probably due to bias (*39*).

Table 3: **Complications of NF1**

System	Complications
Central nervous system	Learning disabilities, megalencephaly, seizures, neurological deficits due to tumours, cord compression
Peripheral nervous system	Neuropathy, malignant schwannoma
Cutaneous	Cosmetic, pruritus
Cardiovascular	Hypertension
Gastrointestinal	Bleeding or obstruction due to neurofibromas, constipation
Endocrine	Short stature, neuroendocrine disturbance due to hypothalamic tumours, abnormal puberty, phaeochromocytoma
Musculo-skeletal (orthopaedic)	Sphenoid wing dysplasia, scoliosis, congenital bowing or pseudoarthrosis, bone cysts, limb overgrowth
Optic (vision)	Orbital malformations, optic glioma

Among the most common problems requiring cosmetic treatment are cutaneous or plexiform neurofibromas. No medication has been demonstrated to cause shrinkage of neurofibromas; the only available treatment is surgery which is rarely indicated to remove small cutaneous neurofibromas. Some surgeons have advocated plastic surgical procedures for persons with innumerable cutaneous tumours, but there is little evidence to show substantial benefit. Plexiform neurofibromas can be particularly aggressive, and result in considerable hypertrophy and deformity; in the absence of malignancy, they do not respond to radiation or chemotherapy. Surgical removal or debulking of excessive tumour mass is the only known treatment. Often multiple surgical procedures are required. Areas of cutaneous hyperpigmentation have been treated with the CO_2 laser, but there is not enough published data to judge its effectiveness and most patients do not find the hyperpigmented lesions a major cosmetic problem.

Tumours of the nervous system, including gliomas and nerve root neurofibromas, are generally recognized by characteristic neurological syndromes (*40*). The possibility of nerve root compression should be considered in investigating unexplained segmental pain. MRI scanning is the most sensitive and precise method for localizing neurological lesions. Although some clinicians have advocated routine screening scans for all patients with NF1, the utility of such screening has not been conclusively

demonstrated and routine neuroimaging is not available in all parts of the world. Regular medical evaluation, with careful attention to the neurological examination should suffice to detect most lesions requiring treatment. Recently, MRI studies of persons with NF1 have revealed the occurrence of foci of bright signals with T2-weighted imaging (*41*). These do not appear to distort the architecture of the brain, and are apparently of no clinical significance.

Optic nerve tumours are noted with high frequency in children with NF1. As noted previously, these are usually asymptomatic, and require no therapy. Progressive optic gliomas respond to radiation therapy (*42*). Experimental protocols using chemotherapy are being tested to treat optic gliomas in young children, in whom the side-effects of radiation treatment may be severe (*43*).

The treatment of tibial fractures due to bony dysplasia of NF1 is a particular problem. A number of approaches have been tried, but none is totally successful in achieving reunion of the fractured bone (*1*). The best treatment is early detection and protection of the involved limb by bracing. Significant tibial dysplasia is easily detected by physical examination.

Malignant schwannoma is one of the few complications of NF1 which has the potential to be lethal (*1, 2*). Usually these tumours occur within plexiform neurofibromas, and present with unexplained pain and growth. Detection of a region of malignant schwannoma in a large plexiform tumour can be difficult, and may require multiple biopsies. Treatment usually involves local control by surgery or radiation, accompanied by aggressive chemotherapy.

One of the most common and serious complications of NF1 is learning disability (*1, 2*). Both the severity and the character of learning disabilities vary widely in different persons; it is estimated that as many as 50% of children with NF1 have some degree of learning disability. The management is the same as for any person with a learning problem: identification of areas of strength and weakness, and institution of a programme of special help at home and at school. The learning disabilities in NF1 are not progressive, and are not correlated with other neurological problems. Parents, teachers, and health care professionals should be alert to the possibility of learning disorders in children with NF1 so that problems can be recognized and treated expeditiously.

Management of NF2. The major lesion associated with NF2 requiring medical treatment is acoustic neuroma. The outcome of treatment, particularly the ability to preserve hearing, is best when therapy is instituted early. The decision of when to intervene, however, is a complex one depending on symptoms, size of the lesions, and the medical condition and age of the patient. The best established mode of therapy is surgical (*3*). Recently, stereotactic radiosurgery with the gamma knife and the computerized linear accelerator have been used to treat acoustic neuromas (*1, 3*). There is currently insufficient data to judge the relative effectiveness of these treatments versus surgery.

Because most persons with NF2 eventually develop acoustic neuromas, it is important to monitor the affected individuals closely for the development of this lesion. This is best done by periodic MRI scanning, although audiometry and brainstem auditory-evoked potentials can also be useful. Screening should be extended to the offspring of persons with NF2, beginning after puberty. Persons found to have acoustic neuroma should be cautioned to avoid situations (such as scuba diving) in which spatial disorientation could be life-threatening.

Most other complications of NF2, including meningiomas, are treated surgically. Spinal neurofibromas can lead to radicular pain, or spinal cord compression. Learning disabilities are not a characteristic feature of NF2.

Prognosis

Both major forms of NF are subject to a wide range of variability of expression, making it difficult to make general statements about prognosis. The medical literature is generally biased by over-reporting of severe complications. One study of affected siblings of probands with NF1 revealed that only one third had severe complications due to the disorder (*41*). The remainder had mild or moderate problems including cosmetic impairment or learning disabilities. Similar findings were reported from a population-based study in South Wales (*39*). Persons with NF1 or NF2 can be reassured that their disorder is compatible with a long and relatively healthy life in most instances.

Further research

Future prospects

The immediate clinical applications of molecular studies are in prenatal and presymptomatic diagnosis. Although very accurate genetic markers are available for use in NF1, the demand for such studies is low; many couples would request a prenatal diagnosis if it could predict disease severity, but this is not possible at present. While the diagnosis of NF1 is usually straightforward even in early childhood, presymptomatic DNA diagnosis is also probably not going to have a huge demand. For NF2, further work

to exclude non-allelic heterogeneity is necessary before clinical application; markers for presymptomatic diagnosis will have enormous practical application. At the present time everybody at 50% risk has to be offered regular follow-up screening; with a presymptomatic DNA test, only those shown to be disease gene carriers would be entered into such programmes.

The cloning of a disease gene is the first and fundamental step towards eventual understanding of its pathogenesis and the development of treatment. To achieve this goal it is crucial that investigators from many different fields should become involved in the research, particularly from neurobiology, cell biology and cancer genetics. The continuation and development of the international gene-cloning and function consortium will have an important part to play in this. It is also important to encourage exchange of material between investigators, including DNA probes and cell lines from patients with unusual disease features. Clinicians caring for people who have NF, but without direct involvement in laboratory research, should be encouraged since they too have an important part to play. It will probably be the study of patients with unusual complications or atypical features that will give further important insights into our understanding of this complex group of diseases.

Consideration should be given to the establishment of NF tissue/tumour banks. Whether this is best done at national or international level needs discussion and potential funding sources should be identified.

Participants at the meeting stressed that the understanding of the genes involved in NF will help many other areas, e.g., in cancer research or our understanding of learning disabilities. As it is important to encourage young investigators to enter into the field, other NF lay organizations may want to follow the NNFF's example of giving Young Investigator awards to young clinical or scientific workers embarking on the study of NF.

Clinical research

Despite recent scientific developments in the field of NF, long-term clinical research is lacking and there are still many issues to be resolved, such as:

(*a*) There is a need for natural history studies of NF in unbiased populations to identify the true incidence of complications and the clinical features predisposing to a particularly poor outcome.

(*b*) Many of the complications are rare and the development of the best approaches for their assessment and treatment is slow because each centre has limited experience. Collaboration between centres is therefore needed to study groups of patients with different complications to answer these questions.

(*c*) Routine MRI scans have been recommended in the management of people with NF1 but there is debate about their value. Given that such scans may detect asymptomatic optic gliomas or abnormalities on T2-weighted images, the nature of which is as yet uncertain, there is a need for some centres to do long-term prospective studies of serial MRI scans in people with NF1 to establish if knowledge about these lesions affects their management in any way.

(*d*) NF is presumed to have relatively equal prevalence worldwide, but population studies have been largely limited to the developed countries. Studies in other parts of the world may show differences in disease phenotype which may give important clues to the pathogenesis, as well as raise local awareness of NF and act as a stimulus for improved patient care.

(*e*) Clinicians caring for patients with NF should be aware of the importance of sharing details about unusual cases of NF tumour material with laboratory researchers.

It is recognized that the NNFF clinical database, which is now being developed, may lead to answers to some of these questions. The database is at present being assessed in a number of trial centres and if it is useful it will be made available to NF centres worldwide so that clinical data could be collected in a relatively uniform manner.

Recommendations

Despite increasing awareness of the problems associated with NF by health care professionals, many patients even in developed countries still receive inadequate care and counselling about their condition. To improve this situation and to get maximum benefit from the potential disease treatments arising from recent scientific developments, the following are recommended:

- It is necessary to consider commissioning the production of booklets about the disease for health professionals, which summarize the diagnostic criteria for the different forms of the disease and guidelines for disease management, as well as recent research developments. Many lay organizations have produced booklets for professionals and for patients with the disease; these should be collated and made available to new centres trying to improve NF care in their area.
- One of the problems for people with NF is due to the lack of disease awareness by health professionals which has led to inadequate care and counselling. Thus, treatment was given by several different

specialists, each looking at a particular disease complication, with no one person taking an overview of the disease as a whole. Several centres in the USA took the lead in establishing the concept of multidisciplinary care of patients with NF and their families (*1*, *2*). Many centres in other developed countries have now followed this example, but there is still marked discrepancy in the levels of care between regions and countries.

• Continuing the education of health care professionals and increasing their awareness of the needs of patients are essential. Owing to the limited resources for health care, there is need to audit the different approaches to the management of NF. With regard to NF2, there is very little debate since all patients and at-risk individuals need the best possible monitoring with brain-stem auditory evoked responses and MRI scans. For NF1, however, there is still considerable debate as to whether any investigation, other than regular physical examination, is needed to screen for complications. Well-established NF clinics should therefore take a lead in auditing their practices to see which investigations, if any, significantly alter the management of persons with NF.

• If key professionals interested in NF can be identified in major medical centres in selected developing countries in Latin America, Africa and Asia, through the WHO Regional Offices, they could be encouraged to increase people's awareness of NF and set guidelines for health care of patients in their country. In developing such services the following are important:

— to set up priorities in the management of NF in the country;
— to develop educational materials for health professionals, the general public, and people with NF for use in their particular society (these can easily be prepared from material already available);
— to stimulate interested colleagues to set up multidisciplinary groups for the care of NF and develop protocols which take into account the local prevailing levels of health care;
— to stimulate the sharing of concerns about NF at regional, national and international levels.

The foundations to such collaboration are already well laid in the International Consortium for Neurofibromatosis Gene-Cloning and Function funded by the NNFF, which holds regular regional and national meetings to raise the awareness of health professionals. Many other lay organizations have undertaken similar tasks in their own countries. In Europe, the interested health professionals and lay groups held their first workshop in 1990 and plan to meet every year. The following activities, if developed, may aid national and international collaboration:

(*a*) WHO, perhaps with the larger lay organizations, might consider co-sponsoring an international symposium on NF.

(*b*) A series of joint WHO/NNFF meetings should be planned in the coming years to address specific issues, such as recommendations for the management of NF sufferers, or of particular complications (e.g., craniofacial plexiform neuromas, optic gliomas), and the delineation of other types of NF.

(*c*) The lay NF groups should consider forming an international organization, which could meet in association with an international meeting of health professionals, and coordinate their activities in the production of literature and audiovisual material.

References

1. **Rubenstein, A.E. & Korf, B.R.** *Neurofibromatosis.* New York, Thieme, 1990.
2. **Riccardi, V.M. & Eichner, J.E.** *Neurofibromatosis: phenotype, natural history and pathogenesis.* Baltimore, Johns Hopkins University Press, 1986.
3. **Martuza, R.L. & Eldridge, R.** Neurofibromatosis 2 (bilateral acoustic neurofibromatosis). *New Engl. j. med.*, **318**: 684–688 (1988).
4. **National Institutes of Health Consensus Development Conference.** Neurofibromatosis: conference statement. *Arch. neurol.*, **45**: 575–578 (1988).
5. **Calzavara, P.G. et al.** Segmental neurofibromatosis: case report and review of the literature. *Neurofibromatosis*, **1**: 318–322 (1988).
7. **Riccardi, V.M.** Pathophysiology of neurofibromatosis. IV. Dermatologic insights into heterogeneity and pathogenesis. *J. Amer. Acad. Dermatol.*, **3**: 157–166 (1980).
8. **Orkin, S.H.** Reverse genetics and human disease. *Cell*, **47**: 845–850 (1986).
9. **Sarfarazi, M. et al.** An exclusion map for von Recklinghausen neurofibromatosis. *J. med. genetics*, **24**: 515–520 (1987).
10. **Barker, D. et al.** Gene for von Recklinghausen neurofibromatosis is in the pericentromeric region of chromosome 17. *Science*, **236**: 1100–1102 (1987).
11. **Seizinger, B.R. et al.** Genetic linkage of von Recklinghausen neurofibromatosis to the nerve growth factor receptor gene. *Cell*, **49**: 589–594 (1987).
12. **Schmidt, M.A. et al.** Cases of neurofibromatosis with rearrangements of chromosome 17 involving band 17q11.2. *Amer. j. med. genetics*, **28**: 771–777 (1987).
13. **Lebetter, D.H. et al.** Precise localization of NF 1 to 17q11.2 by balanced translocation. *Am. j. human genetics*, **44**: 2–24 (1989).
14. **Collins, F.S. et al.** The von Recklinghausen neurofibromatosis region on chromosone 17: genetic and physical maps come into focus (Editorial). *Amer. j. human genetics*, **44**: 1–5 (1989).

15. **Ward, K. et al.** Diagnosis of NF1 by using tightly linked, flanking DNA markers. *Amer. j. human genetics*, **46**: 943–949 (1990).
16. **Foutain, J.W. et al.** Physical mapping of the von Recklinghausen neurofibromatosis region on chromosome 17. *Amer. j. human genetics*, **44**: 58–67 (1989).
17. **O'Connell, P. et al.** Two NF1 translocations map within a 600 kb segment of 17q11.2. *Science*, **244**: 1087–1089 (1989).
18. **Viskochil, D. et al.** Deletions and a translocation interrupt a cloned gene at the neurofibromatosis type 1 locus. *Cell*, **62**: 187–192 (1990).
19. **Wallace, M. R. et al.** Type 1 neurofibromatosis gene: identification of a large transcript disrupted in three patients. *Science*, **249**: 182–186 (1990).
20. **Cawthon, R.M. et al.** A major segment of the neurofibromatosis type 1 gene: cDNA sequence, genomic structure, and point mutations. *Cell*, **62**: 193–201 (1990).
21. **Xu, G. et al.** The catalytic domain of the NF1 gene product stimulates ras GTPase and complements IRA mutants of *S. cerevisiae*. *Cell*, **63**: 835–841 (1990).
22. **Ballester, R. et al.** The NF1 locus encodes a protein functionally related to mammalian GAP and yeast IRA proteins. *Cell*, **63**: 851–859 (1990).
23. **Martin, G.A. et al.** The GAP-related domain of the NF1 gene product interacts with ras p21. *Cell*, **63**: 843–849 (1990).
24. **Ponder, B.A.J.** Inherited predisposition to cancer. *Trends in genetics*, **6**: 213 (1990).
25. **Menon, A.G. et al.** Chromosome 17p deletions and p53 gene mutations associated with the formation of malignant neurofibrosarcomas in von Recklinghausen neurofibromatosis. *Proc. Nal Acad. Sci. USA*, **87**: 5435–5439 (1990).
26. **Zang, K.D.** Chromosomal constitution of meningiomas. *Nature*, **216**: 84–85 (1967).
27. **Seizinger, B.R. et al.** Common pathological mechanism for three tumor types in bilateral acoustic neurofibromatosis. *Science*, **236**: 317–319 (1987).
28. **Rouleau, G.A. et al.** Genetic linkage of bilateral acoustic neurofibromatosis to a DNA marker on chromosome 22. *Nature*, **329**: 5419–5423 (1987).
29. **Rouleau, G.A. et al.**. Flanking markers bracket the NF2 gene on chromosome 22. *Amer. j. human genetics*, **46**: 323–328 (1990).
30. **Lekanne Deprez, R.H. et al.** A t(4;22) in a meningioma points to the localisation of a putative tumor-suppressor gene. *Amer. j. human genetics*, **48**: 783–790 (1991).
31. **Crowe, F.W. & Schull, W.J.** Diagnostic importance of café-au-lait spots in neurofibromatosis. *Arch. int. med.*, **91**: 758–766 (1953).
32. **Crowe, F.W.** Axillary freckling as a diagnostic aid in neurofibromatosis. *Ann. int. med.*, **61**: 1142–1143 (1964).
33. **Halliday, A.L. et al.** Benign spinal nerve sheath tumors: their occurrence sporadically and in neurofibromatosis types 1 and 2. *J. neurosurg.*, **74**: 248–253 (1991).
34. **Lewis, R.A. & Riccardi, V.M.** Von Recklinghausen neurofibromatosis: incidence of iris hamartomas. *Ophthalmology*, **88**: 348–354 (1981).
35. **Lewis, R.A. et al.** von Recklinghausen neurofibromatosis II: incidence of optic gliomata. *Ophthalmology*, **91**: 929–935 (1984).
36. **Carey, J.C. et al.** The genetic aspects of neurofibromatosis. *Ann. N. Y. Acad. Sci.*, **486**: 45–56 (1986).
37. **Jackler, R.K. et al.** Gadolinium-DTPA enhanced magnetic resonance imaging in acoustic neuroma diagnosis and magagement. *Otolaryngol. head neck surg.*, **102**: 670–677 (1990).
38. **Pearson-Webb, M.A. et al.** Eye findings in bilateral acoustic (central) neurofibromatosis: association with presenile lens opacities and cataracts but absence of Lisch nodules. *New Engl. j. med.*, **315**: 1553–1554 (1986).
39. **Huson, S.M. et al.** Von Recklinghausen neurofibromatosis: a clinical and population study in south-east Wales. *Brain*, **111**: 1355–1381 (1988).
40. **Gray, J. & Swaiman, K.F.** Brain tumors in children with neurofibromatosis: computed tomography and magnetic resonance imaging. *Pediatr. neurol.*, **3**: 335–341 (1987).
41. **Duffner, P.K. et al.** The significance of MRI abnormalities in children with neurofibromatosis. *Neurology*, **39**: 373–378 (1989).
42. **Pierce, S.M. et al.** Definitive radiation therapy in the management of symptomatic patients with optic glioma: survival and long-term effects. *Cancer*, **65**: 45–52 (1990).
43. **Packer, R.J. et al.** Treatment of chiasmatic/hypothalamic gliomas of childhood with chemotherapy: an update. *Ann. neurol.*, **23**: 79–85 (1988).
44. Neurofibromatosis. *Ann. N.Y. Acad. Sci.*, **486**: 1–414 (1986).