



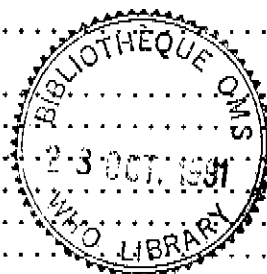
HEREDITARY DISEASES PROGRAMME  
DIVISION OF NONCOMMUNICABLE DISEASES AND HEALTH TECHNOLOGY

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REPORT OF A JOINT WHO/NNFF MEETING ON THE POSSIBILITIES  
FOR THE PREVENTION AND CONTROL OF NEUROFIBROMATOSIS

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## 1. INTRODUCTION

Neurofibromatosis (NF) is a serious common genetically determined neurological disorder, with a prevalence of about 1:4000 births and affects both sexes, all races and ethnic groups.

The term "neurofibromatosis" encompasses at least two distinct disorders which have in common a predisposition to the development of tumors of the nerve sheath. Both forms 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<sup>(1-3)</sup>.

Until the last decade, very little research had been undertaken into the cause of the different forms of NF. It may be that what makes the understanding of NF such a challenge actually hampered it being studied. The problems caused by NF can present to any one of the major medical specialties and are individually relatively infrequent so no one group of health professionals realizes the overall health burden of the disease. The stimulus to undertake research was perhaps therefore not as great as for other common genetic diseases, where the burden of care fell upon just one group of health care professionals (e.g., haemoglobinopathies - haematologists, muscular dystrophies - neurologists). Prior to the advent of DNA technology relatively little basic research into NF had been carried out.

In the light of the recent discovery and isolation of the gene responsible for the NF1 mutation, it was highly appropriate to discuss the applicability, at the practical level, of the new findings in the field of molecular genetics which would modify the approaches for diagnosis, treatment and prevention of NF. The first joint meeting between WHO and the National Neurofibromatosis Foundation (NNFF) was therefore convened.

## 2. DEFINITION, FREQUENCY AND HETEROGENEITY

The two major forms of NF are referred to as NF1 and NF2, in accordance with nomenclature suggested in 1987 by a National Institute of Health Consensus Development Conference on Neurofibromatosis<sup>(4)</sup>. The two disorders are defined by diagnostic criteria which are set forth in Tables 1 and 2. NF1 is the most common form, affecting approximately 1:4000 individuals worldwide. The hallmark features are café-au-lait spots, Lisch nodules, and neurofibromas; other manifestations include optic gliomas, skeletal dysplasias, plexiform neurofibromas, learning disabilities, etc. NF2 appears to be far less common than NF1. It has been difficult to measure the frequency of this disorder, but it is believed to be in the range of 1:100,000. NF2 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.

Other inherited syndromes have been recognized which may include some features of neurofibromatosis, and have been proposed to be distinct entities. The ultimate determination of whether these represent allelic or gene locus heterogeneity will await molecular genetic characterization. A list of these syndromes is provided in Table 3.

Segmental NF represents the appearance of features of NF1 confined to restricted segments of the body<sup>(5)</sup>. In some cases the features are limited to either café-au-lait spots and skin-fold freckles, or to neurofibromas without pigmentary changes. Precise criteria for diagnosis of segmental NF have not been determined. It has been speculated that this represents somatic mutation of the NF1 gene, but this 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, pulmonic stenosis and characteristic facial appearance<sup>(6)</sup>. This has led to the suggestion that Noonan 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 pulmonic 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<sup>(7)</sup>. 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.

### 3. THE PATHOGENESIS OF NF

Postulated mechanisms of pathogenesis for the different forms of NF have to explain the disease phenotype: how tumors 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 tumors which can occur in isolation.

The majority of work up until 1985 is reported in conference proceedings from that year (Neurofibromatosis, Ann. N.Y. Acad. Sci., 1986). 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, with an improved assay system, and no abnormalities were found thus throwing doubt upon the earlier reports. With the increasing clinical interest in NF in the late 1970s and early 1980s, and the lack of understanding of pathogenesis to that time, NF was therefore ripe for the application of DNA technology and the so-called reversed genetic or positional cloning approach<sup>(8)</sup>; these endeavours began in the early 1980s.

#### 4. MOLECULAR GENETICS OF NF

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 to a small area of that chromosome and the eventual cloning of the gene. The first step 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.

##### 4.1 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<sup>(9)</sup> before a positive linkage was found with markers which mapped on chromosome 17<sup>(10-11)</sup>. 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.

Shortly after the gene localization by linkage analysis, a balanced chromosome translocation involving band 17q11.2 was described in a person with NF1 suggesting this may be the subchromosomal localization of the NF1 gene<sup>(12)</sup>. The finding of a second similar case added support to this<sup>(13)</sup>. 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 break points by physical mapping methods<sup>(14)</sup>. 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<sup>(15)</sup>.

Subsequent physical mapping studies identified the markers which detected the translocation breakpoints on pulsed field gels and showed the breakpoints to be about 50 Kb apart<sup>(16-17)</sup>. Efforts then focussed 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<sup>(18-19)</sup>.

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<sup>(18-20)</sup>. 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<sup>(18-19)</sup>. 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<sup>(21)</sup>. 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<sup>(21-23)</sup>.

The mechanism of tumorigenesis in NF1 remains unclear. There has been much speculation as to whether the NF1 gene is a tumor suppressor gene, in which tumor growth would be caused by a recessive mechanism, or whether tumor growth results by a negative dominant mechanism, in which the lack of function of one allele is sufficient for tumor formation<sup>(24)</sup>. 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 tumor progressions (e.g., P53). In studies to date, only pheochromocytomas have shown allele loss at the NF1 gene, although neurofibrosarcomas have shown loss of the short arm of chromosome 17 and specifically P53 mutations<sup>(25)</sup>. 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 tumor syndromes such as retinoblastoma and indeed NF2, a mechanism would still have to be found to explain NF1 symptoms not related to tumor formation.

#### 4.2 Molecular studies of NF2

From the clinical viewpoint, NF2 is much more like other family cancer syndromes where tumors have been shown to develop due to a recessive mechanism or "two hits" as proposed by Knudson in 1971. The tumors 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 tumors.

Studying meningioma tissue cytogenetically showed frequent loss of chromosome 22<sup>(26)</sup>. As DNA techniques became available, Seizinger et al compared DNA polymorphisms in the blood and tumor tissue from patients with both isolated acoustic neuromas and NF2: frequent and specific deletions of chromosome 22 were seen<sup>(27)</sup>. That chromosome 22 was the localization of the NF2 gene was subsequently confirmed by linkage studies<sup>(28)</sup>. 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 cM between the markers D22S1 and D22S28<sup>(29)</sup>.

In contrast to NF1, subsequent progress has been relatively slow due 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 to this time with a chromosome translocation which might have given a short-cut to the cloning of the gene. However, a translocation in a meningioma with a breakpoint at 22q11

in the region where linkage studies suggest the NF2 gene is was recently reported<sup>(30)</sup>. 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.

## 5. CLINICAL DIAGNOSIS AND MANAGEMENT OF NF

### 5.1 Diagnosis of NF1 and NF2

The diagnosis of NF is based on clinical criteria which are updated versions of those suggested by the National Institute 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 often it is necessary to follow a person for some years before the diagnosis can be confirmed. The distinction between a person having NF1 or 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 NF2.

#### 5.1.1 Diagnosis of NF1

The most common presenting sign of NF1 is multiple café-au-lait spots, but the presence of more than six spots is highly indicative of NF1<sup>(2,31)</sup>. 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 pathognomonic 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 lentiginos 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 skin-fold freckling<sup>(32)</sup>. This usually begins in childhood, and involves the axillae, groins, and other skin folds. 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 anyplace 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<sup>(33)</sup>.

Iris Lisch nodules can be a helpful sign in establishing a diagnosis of NF1. These are hamartomatous lesions which have no impact on vision<sup>(34)</sup>. They are found in almost all persons with NF1 after puberty, and are very rarely, if ever, seen in persons with NF1. 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 nevi, which are flat and are not associated with NF1.

Optic glioma is a characteristic tumor associated with NF1. Optic nerve thickening is commonly found by CT or MRI scanning of NF1 patients, but only a minority of these manifest symptoms of visual loss, proptosis, or hypothalamic dysfunction<sup>(35)</sup>. 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<sup>(1,2)</sup>. Tibial dysplasia presents as anteolateral bowing of the lower leg<sup>(1,2)</sup>. Early recognition and orthopedic 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<sup>(36)</sup>. 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 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.

#### 5.1.2 Diagnosis of NF2

The hallmark of NF2 is the occurrence of bilateral acoustic neuromas<sup>(3)</sup>. These rarely are 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 millimeters<sup>(37)</sup>. 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 tumors 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 may occur, but usually fewer than six. Likewise, 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<sup>(38)</sup>. 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, the occurrence of family history satisfies 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 are affected by probable new mutation of the NF2 gene.

## 5.2 Management of NF

There is no cure for either form of NF, or medical treatment which 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, orthopedics, and oncology. Wherever care is provided, however, the most important factors are that clinicians 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 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 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 their risk of transmitting the disorder to offspring.

### 5.2.1 Management of NF1

Major complications of NF1 are listed in Table 4. 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 likely due to bias of ascertainment and reporting<sup>(39)</sup>.

Among the most common problems requiring treatment are cosmetic, due to cutaneous or plexiform neurofibromas. No medication has been demonstrated to cause the shrinkage of neurofibromas; the only available treatment is surgery. It is rarely indicated to remove small cutaneous neurofibromas. Some surgeons have advocated plastic surgical procedures for persons with innumerable cutaneous tumors, but there is little data to document substantial benefit. Plexiform neurofibromas can be particularly

aggressive, and result in considerable hypertrophy and deformity. In the absence of malignancy, plexiform neurofibromas do not respond to radiation or chemotherapy. Surgical removal or debulking of excessive tumor mass is the only known treatment. Often multiple surgical procedures are required. Areas of cutaneous hyperpigmentation have been treated with the CO<sub>2</sub> laser. There is not sufficient published data to judge the effectiveness of this intervention, and most patients do not find the hyperpigmented lesions to impose a major cosmetic burden.

Tumors of the nervous system, including gliomas and nerve root neurofibromas, are generally recognized by characteristic neurological syndromes<sup>(40)</sup>. 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<sup>(41)</sup>. These do not appear to distort the architecture of the brain, and are apparently of no clinical significance.

Optic nerve tumors 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<sup>(42)</sup>. Experimental protocols using chemotherapy are being tested to treat optic gliomas in young children, in whom side effects of radiation treatment may be severe<sup>(43)</sup>.

The treatment of tibial fractures due to bony dysplasia of NF1 is a particular problem. A number of approaches have been tried, but none are totally successful in achieving reunion of the fractured bone<sup>(1)</sup>. 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<sup>(1,2)</sup>. Usually these tumors occur within plexiform neurofibromas, and present with unexplained pain and growth. Detection of a region of malignant schwannoma in a large plexiform tumor 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<sup>(1,2)</sup>. Both the severity and the character of learning disabilities vary widely in different persons with NF1. 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.

### 5.2.2 Management of NF2

The major lesion associated with NF2 requiring medical treatment is acoustic neuroma. The outcome of treatment, and 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<sup>(3)</sup>. Recently, stereotactic radiosurgery with the gamma knife or the computerized linear accelerator have been used to treat acoustic neuromas<sup>(1,3)</sup>. 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 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 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.

### 5.3 Prognosis of NF

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<sup>(41)</sup>. 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<sup>(39)</sup>. Persons with NF1 or NF2 can be reassured that their disorder is compatible with a long and relatively healthy life in most instances.

## 6. FURTHER RESEARCH AND NEEDS

### 6.1 Future prospects

The immediate clinical applications of the molecular studies are in prenatal and presymptomatic diagnosis. Very accurate genetic markers are already available for use in NF1, although the demand for such studies has been relatively low. Many couples decide that they would only want a prenatal diagnosis if it could predict disease severity which is not possible at this time. As 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 our eventual understanding of its pathogenesis and development of disease treatment. To achieve this ultimate goal for NF it is crucial that investigators from many different fields 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 and who have no direct involvement in laboratory research should be encouraged that they too have an important part to play. It will probably be the study of patients with unusual complications or atypical features that give further important insights into our understanding of this complex group of diseases.

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

The researchers participating in this joint meeting stressed the difficulty of obtaining funds for NF research when compared with other genetic diseases, e.g., cystic fibrosis and the muscular dystrophies. Scientists seeking funding from government bodies and lay organizations involved in fund-raising must stress that the understanding of the genes involved in NF will have widespread implications in many other areas and not just for people with NF, (e.g., cancer research, helping our understanding of learning disabilities). Where funds are available to support research, 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 sponsor young clinical or scientific workers embarking on the study of NF.

## 6.2 Clinical research

Despite the rapid scientific developments towards our understanding of NF in recent years, and because of the lack of long-term clinical research until relatively recently, there are still many issues which need to be resolved by the clinical researcher. Some of the main issues are as follows:

- (a) There is a need for natural history studies of NF in unbiased populations so that the true incidence of disease complications and clinical features which predispose to a particularly poor outcome can be identified.
- (b) As many of the complications are rare, development of the best approaches of their assessment and treatment are slow because any one centre only has a limited experience. There is therefore a need for collaboration between centres to look at series of patients with different complications to answer these questions.
- (c) Some authorities have recommended routine MRI scans in the management of people with NF1. There is debate about their value. Given that MRI 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 a limited number of centres to do long-term prospective studies of serial MRI scans in people with NF1 to establish if knowledge about these lesions affects management in any way.

- (d) Although it is assumed that NF has a relatively equal prevalence worldwide, population studies have been largely limited to developed countries. Studies in other parts of the world may show differences in disease phenotype which may give important clues to disease pathogenesis. Such studies often raise the 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 tumor material with laboratory researchers.

It is recognized that the NNFF clinical database which is at present being developed may facilitate answering some of these questions. The database is at present being assessed in a number of trial centres and if it is useful it would then be available to any NF centre worldwide so that clinical data could be collected in a relatively uniform manner.

### 6.3 Scientific research

The major developments and future directions of scientific research are outlined in section three. The main problems seen by scientists involved in NF research at present are as follows:

- (a) Compared with other genetic diseases of similar frequency there is a relative lack of funds for research.
- (b) Given the complex phenotypic nature of NF, particularly NF1, it is likely that scientists from a number of different backgrounds need to be encouraged to undertake research in order that the biology of the disease will eventually be understood. One of the ways of encouraging young scientists to be involved in NF research is by awarding research funding specifically for young investigators.
- (c) Consideration should be given to the formation of an NF tissue/tumor bank at a national/international level.

## 7. CONCLUSIONS AND RECOMMENDATIONS

The last decade has seen increasing awareness of the problems associated with NF by healthcare professionals. However, even in developed countries many patients still receive inadequate care and counselling about their condition. In order to improve this situation and so that maximum benefit can eventually be derived from the potential disease treatments which may arise from the recent exciting scientific developments, the following recommendations were proposed:

WHO should commission the production of booklets about the disease for health professionals summarizing the diagnostic criteria for the different forms of the disease, broad guidelines for disease management and the recent research developments. Many of the lay organizations have booklets available both 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.

Several of the lay organizations have spent a relatively large proportion of their funds on commissioning videos about NF; perhaps WHO could coordinate future efforts so that professional audiovisual materials about the disease are available in different languages.

In the past the problem for people with NF has been that the lack of disease awareness by health professionals has led to inadequate care and counselling. People often found themselves being treated by several different specialists, each looking at a particular disease complication, but 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 multi-disciplinary care of patients with NF and their families<sup>(1,2)</sup>. Many centres in other developed countries have now followed this example but there is still marked discrepancy in levels of care in different regions and countries.

Continuing education of health care professionals and increasing awareness of the needs of patients is essential. Given that in many countries there is increasing demand on 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 amongst the medical profession as to what the best follow-up strategies are. 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. It is therefore important that well established NF clinics take a lead in auditing their practice to see which investigations, if any, significantly alter the management of the person who has NF.

It may help to increase awareness of NF in developing countries if key professionals interested in the disease are identified in major medical centres in selected countries in Latin America, Africa and Asia, through the WHO Regional Offices. These professionals should be encouraged to increase the awareness of NF and set guidelines for health care for people with the disease within their country. In developing services for NF the following points are considered to be important:

- (a) To set up priorities in the management of NF for their country.
- (b) To develop educational materials for health professionals, the general public and people with NF suitable for use in the particular society. These should be able to be easily developed from material already available.
- (c) To stimulate interested colleagues to set up multi-disciplinary groups for the care of NF and to develop protocols which take into account the local prevailing levels of health care.
- (d) 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. The NNFF also holds regular regional and national meetings to raise the awareness of health professionals about NF. 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 now plan to meet together on an annual basis. It is likely as more centres become involved in running specific NF clinics then this kind of endeavour will naturally follow. There are, however, specific activities which if developed may aid national and international collaboration:

- (a) It is recommended that WHO, perhaps with the larger lay organizations, consider sponsoring an international symposium on NF.
- (b) Following the first WHO/NNFF Workshop on NF, it is envisaged that a series of such meetings should be planned in coming years to address specific issues. For example, to agree on recommendations for the management of NF sufferers; detailed discussions about the best management of particular complications (e.g., craniofacial plexiform neuromas, optic gliomas; delineation of other types of NF).
- (c) The lay NF groups should consider forming an international organization, which perhaps could meet in association with an international meeting of health professionals, and serve to coordinate activities in terms of producing literature and audiovisual material.

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TABLE 1

NF1 is considered to be present in an individual with two of the following criteria, provided no other disease accounts for the findings:

1. On examination in room light, at least 5 café-au-lait macules over 5 mm in greatest diameter, if prepubertal; 6 café-au-lait macules over 15 mm greatest if, post-pubertal.
2. Based on clinical or historic grounds, 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 off-spring) with NF1, by the above criteria.

TABLE 2

NF2 is considered to be present in an individual with either of the following criteria:

1. Computer tomography (CT) or magnetic resonance imaging (MRI) evidence of bilateral internal auditory canal masses, consistent with acoustic neuromas; or,
2. A first degree relative with bilateral acoustic neurofibromatosis and one of the following:
  - CT or MRI evidence of unilateral internal auditory canal mass, consistent with acoustic neuroma.
  - A plexiform neurofibroma or 2 of the following criteria:
    - meningioma, glioma, neurofibroma at any site.
  - Imaging evidence of an intracranial or spinal cord tumor.

TABLE 3

Neurofibromatosis and neurofibromatosis-like syndromes

NF1  
NF2  
Segmental neurofibromatosis  
Noonan syndrome/neurofibromatosis  
Watson syndrome  
Gastrointestinal neurofibromatosis  
Spinal neurofibromatosis  
Familial café-au-lait spots  
Schwannomatosis

TABLE 4

Complications of NF1

System	Complications
Central Nervous System	Learning disabilities, megalencephaly, seizures, neurological deficits due to tumors, cord compression
Peripheral nervous System	Neuropathy, malignant schwannoma
Cutaneous	Cosmetic, pruritis
Cardiovascular	Hypertension
Gastrointestinal	Bleeding or obstruction due to neurofibromas, constipation
Endocrine	Short stature, neuroendocrine disturbance due to hypothalamic tumors, abnormal puberty, pheochromocytoma
Orthopedic	Sphenoid wing dysplasia, scoliosis, congenital bowing or pseudoarthrosis, bone cysts, limb overgrowth
Vision	Orbital malformations, optic glioma