



The Child With Neurofibromatosis 1

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Learning that a child has—or may have—neurofibromatosis can be a very difficult experience. Very often it comes as totally unexpected news about a child who appears to be perfectly healthy save for the presence of some innocent-looking brown spots on the skin. Often these spots have gone overlooked for years, passed off as simple "birthmarks". Now, suddenly, a child is labeled as having "neurofibromatosis", an unpronounceable word that many doctors have to look up in their textbooks to explain. Everything seems uncertain. Some people have no major health problems due to neurofibromatosis, whereas others are severely affected, and there is no way to predict what the future holds. Even the diagnosis itself is often uncertain and nobody can say at what point a definite diagnosis might be possible. Finally there may appear to be no place to turn to for reliable information or support. Most existing brochures and support groups seem to stress the more severe manifestations of neurofibromatosis. How do these apply to the child with mild signs, children with only a few cafe-au-lait spots? It is the purpose of this brochure to attempt to place mild or early neurofibromatosis in perspective. To some extent neurofibromatosis is an unpredictable condition, and uncertainty is inevitable. It is hoped, however, that access to accurate medical information will make this uncertainty easier to live with and understand.

What is Neurofibromatosis?

"Neurofibromatosis" is actually a term, which encompasses at least two distinct disorders. Neurofibromatosis type 1 (NF1) is the more common, affecting about 1/4000 people throughout the world. Its major features are skin spots called cafe-au-lait spots and neurofibromas. It can affect nerves throughout the body, including in the brain and spinal cord. Neurofibromatosis type 2 (NF2) affects about 1/40,000 people. It is characterized by the appearance of tumors of the hearing and balance nerve (vestibular schwannomas), as well as other tumors of the nervous system. Both NF1 and NF2 are genetically determined disorders. Generally, all affected members of a family have the same form of NF. It is possible that other types of NF exist, but this has not yet been firmly established.

This brochure is mainly directed at families with children who have, or may have, NF1. The features of NF2 are often not apparent at all in early childhood. If NF2 is being considered in your family, you should consult your physician or the Children's Tumor Foundation for further information.

The Diagnosis of Neurofibromatosis Type 1

The most common way for a person with neurofibromatosis type 1 to be discovered to be affected is by finding multiple cafe-au-lait spots. Cafe-au-lait spots are flat brown skin spots. They are called "cafe-au-lait" from the French term for "coffee with milk", because of their color. Sometimes they are noticed at birth, but more commonly they begin to appear in the first few months of life and may continue to increase in number for a period of several years. The cafe-au-lait spots in themselves are harmless. It is not unusual for them to be passed off as mere "birthmarks". Indeed, anyone can have 1 or 2 cafe-au-lait spots without having neurofibromatosis. The only significance to the cafe-au-lait spot is that it suggests the possibility that a person might have NF1.

People with NF1 usually have many cafe-au-lait spots, sometimes hundreds, and almost always more than 6. It is generally accepted that NF1 should be suspected in any individual with 6 or more spots. The spots must be at least 5 mm in size to be counted in a child before puberty, or at least 15 mm after puberty. It should be stressed that there is no connection between the number of cafe-au-lait spots on a person and the degree of severity of neurofibromatosis. It doesn't matter if a child has 6 spots, 60, or 600, the other features of neurofibromatosis will be the same.

Although the presence of multiple cafe-au-lait spots strongly suggests the diagnosis of NF1, it does not prove it. There may be rare individuals who have as many as 6 cafe-au-lait spots but do not seem to have other features of NF. The diagnosis of neurofibromatosis can only be confirmed if other features of the condition are present. The features commonly looked for are listed in the table below. Looking for these features involves doing a careful physical examination, including an examination of the eyes, usually done by an ophthalmologist. The diagnosis of NF1 is considered to be established in anyone having any two features on the list. For example, a child with more than 6 cafe-au-lait spots who also has Lisch nodules would be considered to be affected.

DIAGNOSTIC CRITERIA FOR NEUROFIBROMATOSIS 1

1. Six or more cafe-au-lait spots measuring at least 5 mm before puberty or 15 mm after puberty
2. Two or more neurofibromas or one plexiform neurofibroma
3. Freckles in the under the arms or groins
4. Lisch nodules on the iris of the eye (Lisch nodules are clumps of pigment cells which are completely harmless to vision.)
5. Optic glioma
6. Characteristic skeletal abnormality (bowing of shin bone, abnormality of orbit)
7. NF1 by above criteria in a parent, sibling, or offspring.

One problem with using these clinical diagnostic criteria is that many of these features of neurofibromatosis are age-related. This means that they are often not present in very young children with NF1, but only appear with time. Usually this

means late childhood, around age 7-10, or even not until adolescence. Puberty is a particularly common time for other features of neurofibromatosis to appear.

As a result, it is often impossible to make a definite diagnosis of neurofibromatosis in a young child with multiple cafe-au-lait spots. There is a high chance that such a child is, in fact, affected, but often it takes years before another feature of the disorder appears to confirm the diagnosis. It is common practice to reexamine such children, usually once a year, to look for the appearance of new signs of neurofibromatosis such as skin-fold freckles or Lisch nodules. If they are found, the diagnosis is clear; if not the question remains unsettled.

It is often asked, "If year after year no additional features appear, is there an age when the possibility of neurofibromatosis is ruled out?" At this point, there is no clear answer to that question. Most people with NF1 develop signs in addition to cafe-au-lait spots by puberty, but not necessarily all. There is no age when we can be sure that an individual having only cafe-au-lait spots is not affected with neurofibromatosis.

This uncertainty about the diagnosis would be remedied if there were a diagnostic test for neurofibromatosis. Unfortunately, no such test currently exists for the child with multiple cafe-au-lait spots and no family history of the disorder. Sometimes a biopsy may be done, or an X-ray taken, to determine if some feature of neurofibromatosis is actually present. But there is as yet no blood test or other laboratory test which can definitely rule in or out a diagnosis of NF1 in a child with only cafe-au-lait spots. It is hoped that this will change in the near future as we learn more about the NF1 gene.

Prognosis of Neurofibromatosis

Neurofibromatosis is truly an unpredictable disorder. It varies widely in severity from one person to the next, even between two people in the same family. Some go through life with only a few skin spots and perhaps a few bumps on the skin, and may be completely unaware that they are affected. Others may have major cosmetic or medical problems due to NF, and these may begin at any time in life, even at birth. Such uncertainty may make it very difficult to know what to expect for a child with only cafe-au-lait spots.

There are a few things that can be said with confidence, however. First, severe complications of NF are by no means inevitable. Much of the medical literature on neurofibromatosis tends to stress the more severe problems, and makes these seem more common than they really are. There is a natural tendency for the medical literature to be "biased" towards the more severe cases. In part this is because only the more severely affected people are likely to be reported to the medical community. For every severely affected person who comes to medical attention there may be several who are mildly affected and therefore do not seek medical care for their disorder.

Second, some complications of neurofibromatosis are apparent early in life. These include deformities of the facial or leg bones, which are usually apparent in infancy. A child who is 5 years old and has only cafe-au-lait spots has escaped at least some of these severe complications of NF1. That is not to say that cosmetic or other severe problems cannot appear later on, but major bone deformities associated with neurofibromatosis do not develop overnight in an otherwise normal-appearing child with cafe-au-lait spots.

Third, although there are many things that can occur in a person with neurofibromatosis, virtually no one with the disorder gets all the possible complications, and most of the severe ones are, individually, uncommon. Of course, the definition of what constitutes a "severe" problem may differ from one person to the next. But it appears that people with NF1 live long and productive lives and do not develop life-threatening complications. Many will experience some degree of cosmetic impact from the condition, but in many cases this is not difficult to manage. Living with NF does involve some degree of adjustment both to possible medical problems and to uncertainty of when and whether they will occur. This burden should be placed in perspective, however, and should not be allowed to be overwhelming.

Having pointed this out, it should also be recognized that severe complications of neurofibromatosis can occur to any person with the disorder at any time in life. A person can always develop severe cosmetic or medical problems. Neurofibromatosis is a condition which must always be respected by affected individuals, their family members, and medical professionals for its potential to cause trouble.

Management of Neurofibromatosis

There is so far no medical or surgical treatment which can cure neurofibromatosis, or reverse or prevent medical complications. This largely reflects our continuing lack of knowledge of the basic mechanisms whereby the neurofibromatosis gene mutation affects the body. A major goal of research is to do away with this ignorance, and develop effective means of therapy.

Until this is achieved, medical management of neurofibromatosis is limited to the early detection of complications which can be treated. Treatment in this sense means surgery to remove or reduce the size of neurofibromas, assessment and management of learning disabilities, etc. Anticipation of such problems and prompt intervention generally can improve the outcome of treatment.

Usually it is recommended that a person with neurofibromatosis have a complete medical evaluation at least once a year. This should be done by a physician who is familiar with neurofibromatosis and has access to appropriate medical consultants to help deal with any problems found. The medical evaluation generally consists of a medical history, physical examination, neurological examination, and eye examination. Careful attention is paid to any change in the skin manifestations of neurofibromatosis, in particular any growth of or pain in a neurofibroma. Any new signs or symptoms should be investigated. The child's cognitive development and school progress should be discussed.

All of this applies equally to a person with confirmed neurofibromatosis and to a child with multiple cafe-au-lait spots in whom the diagnosis is suspected but not confirmed. Such a child may well be at risk of developing neurofibromatosis-related complications and so should be followed just as though they have neurofibromatosis.

Often the question is raised "Should all people with neurofibromatosis have X-rays, CT scans, or MRI scans?" There is no single "correct answer" to this question. It is generally agreed that any signs or symptoms of neurological problems should be fully investigated, and often that includes obtaining a CT or MRI scan of the brain. The value of such a scan in the absence of signs or symptoms of neurological impairment is not as clear. Some physicians prefer to obtain as complete a picture as possible of how NF has affected an individual. Others feel that scanning is unnecessary in the absence of symptoms or signs of problems, since in such a

situation nothing "treatable" would be found. Probably more important than seeking a consensus on this issue, there should be an open discussion between a physician and the family about the risks and benefits of screening tests.

Specific Complications of Neurofibromatosis

Parents of a young child with neurofibromatosis often ask what specific NF-related problems are likely to occur. Some of the more common or typical NF complications are described below, according to the age at which they are most likely to appear.

Newborns and Infants:

Most newborns that have the neurofibromatosis gene mutation show few or no signs. Cafe-au-lait spots are usually noticed in the first few weeks of life, or may appear earlier. Their absence in a newborn that is at risk of inheriting NF1 from a parent is not a good indication that the baby has not received the NF1 gene, since the spots may show up later.

Neurofibromas are not often found in infancy. One exception is the plexiform neurofibroma. This is a neurofibroma which affects multiple branches of a nerve, usually a fairly large nerve. Occasionally, such plexiform neurofibromas are noticed in the newborn period, where they may appear as a soft swelling under the skin. Not finding a plexiform neurofibroma does not assure that one will not appear later in life. This is particularly true for plexiform neurofibromas which are located deep under the skin, which may not be apparent until after they have grown.

Although they do not occur frequently, there are two types of bone deformity which are typical for NF1, and these occur at birth when they occur at all. One involves the long bones, most commonly the shin bone (tibia). Infants affected tend to have a bowing or curvature of the lower leg. Some degree of curvature is normal, but an excessive degree indicates the possibility of this problem, which is referred to as tibial dysplasia. If tibial dysplasia is suspected, an X-ray is usually performed. If it is found, the child should be referred to an orthopedist. The abnormal region of the tibia is very prone to fracture, and the fractures tend not to heal well. Orthopedic care is usually directed towards prevention of fracture, or management of fractures if they occur.

The other typical bone deformity is abnormality of the bony wall behind the eye, called the orbit. Some newborns with NF1 have a defect of the bone behind the orbit, the sphenoid. This is often associated with bulging or recessing of the eye, and sometimes downward displacement of the eye. In addition, there may be plexiform neurofibroma within the orbit and enlargement of the upper eyelid. This can be quite deforming, and often tends to grow over the years. The abnormality of the sphenoid bone is detected by X-ray or CT scanning. It is not usually necessary to do anything about the absence of the sphenoid bone. The cosmetic deformity associated with orbital dysplasia is to some extent amenable to correction by plastic surgery. Fortunately, this problem is relatively rare, and generally some signs are visible during the first year of life.

Other than the bony deformities noted above, neurofibromatosis is not usually associated with congenital malformations. The heart and major organs are usually not involved.

Preschool Years:

Cafe-au-lait spots are usually clearly visible by the first year of life. Plexiform

neurofibromas may grow, or may be noticed for the first time at this point. Sometimes a few freckles may be seen in the armpits or groins, and a few small neurofibromas may be noticed on the skin. The neurofibromas usually appear as small bumps on the skin, which are soft to the touch and have a pink or purple hue. They are not painful and rarely cause problems other than cosmetic. Young children usually do not have more than one or two small neurofibromas, and may have none. Some children, however, develop multiple neurofibromas early in life. Such children do not necessarily develop additional severe complications of NF1 during childhood.

Two abnormalities of growth are commonly noticed in preschool children. One is short stature. Children with NF1 are often shorter than would be expected from the size of others in their family. The cause of this short stature is not known; medical testing is rarely productive, except in cases where growth rate suddenly and unexpectedly changes. The other abnormality of growth is increased size of the head. This generally does not cause discomfort to the child, and is usually not correlated with neurological problems. The head grows at a faster rate than normal, but at a steady, consistent rate. As long as this is the case, it is usually not necessary to do an examination such as a CT scan. In rare instances, the head growth may be associated with symptoms such as vomiting or headache. In such cases, a CT or MRI scan is usually done to be sure that increased pressure of fluid inside the brain (hydrocephalus) has not developed.

Brain tumors can occur at any point in life, including early childhood. Fortunately, they are not common. One form of tumor which is particularly associated with early childhood is the optic glioma. This is a tumor of the nerve to the eye, the optic nerve. When it occurs in a symptomatic form, it may cause loss of vision, pain, bulging of the eye, or affect pituitary hormone secretion. Such symptomatic optic gliomas are diagnosed by CT or MRI scanning and can be treated, usually by radiation treatment or chemotherapy. It is not uncommon to find evidence by CT or MRI scan of thickening of the optic nerve in children with NF1 who manifest no signs or symptoms of optic glioma. This may represent an abnormality of the development of the optic nerve in some children with NF1. Only rarely do symptoms of progression occur requiring treatment. It is recommended that all children with NF1 have ophthalmologic exams, done at least annually, to insure early diagnosis of symptoms of optic glioma.

School Age:

Any of the features of NF1 mentioned above may begin to appear or continue to appear through school age. Thus, skin-fold freckles may increase, iris Lisch nodules may appear, plexiform neurofibromas may grow, and neurofibromas may become visible on the skin. It is not unusual to become aware of learning difficulties in the school aged child with NF1. The exact frequency of learning disabilities in children with NF1 is not known, but estimates run as high as 25-50%, making this one of the most common of serious problems related to neurofibromatosis. The exact form of learning disability and degree of severity varies from child to child. Some experience difficulty with visual and spatial skills, some with speech and language, some with reading or math, or any combination of these skills. In addition some have difficulty in focusing attention, although true hyperactivity does not appear to be especially common in children with NF1. The cause of learning disabilities in children with NF1 is not understood, although it is believed that the NF gene mutation may somehow affect the development of the brain. It is rare for the learning disability to be associated with an abnormality on neurological exam or with a specific visible abnormality in the nervous system. The learning disorder is not progressive; that is, it generally does not get worse with time. The management of learning disabilities in

children with NF1 is the same as for any child with a learning problem. A thorough assessment of the child's skills and areas of weakness should be undertaken, and an educational program designed to meet the child's special needs. This is generally done along with the school system. It is important to be aware of the possibility of learning disorders, since if these go undiagnosed a child can experience demoralizing failure at school instead of receive the special help he or she needs.

Adolescence:

Adolescence is generally a time of change, and often this includes a change in the manifestations of neurofibromatosis. Individuals who have not developed neurofibromas during childhood often begin to see skin neurofibromas during puberty. Pre-existing plexiform neurofibromas often grow at this time. Skin freckling may also increase. The cause of these changes is not well understood, but it is believed that changes in hormones may be responsible. Similar appearance or growth of neurofibromas is also seen in many women with NF1 during pregnancy. This has raised the question of whether oral contraceptives should be avoided by women with NF1. In fact there is no clear evidence that oral contraceptives can be responsible for progression of neurofibromas, although the issue has not been carefully studied.

Adulthood:

It is impossible to predict the course of NF1 in anyone with the disorder. Manifestations of neurofibromatosis generally do not disappear once they develop, although cafe-au-lait spots sometimes fade in later life. Neurofibromas can appear at any time, as can symptoms of nerve compression. Although bone deformities are generally present from birth, cosmetic impairment from a neurofibroma can develop at any time in life. Learning disabilities do not disappear in adulthood, but adults with NF1 and learning disability can lead productive lives if their learning problems were recognized early and appropriate support provided.

Life-Threatening Complications of Neurofibromatosis 1

As has been mentioned already, most individuals with NF1 live long and generally healthy lives. Yet it must be recognized that some complications of neurofibromatosis can be life-threatening. The most frightening to many people is cancer. Neurofibromas are not cancerous growths; they do not spread through the body, even though they may appear in many places on the skin. In some persons, however, a cancer may develop within a neurofibroma. This does not usually happen to the small skin neurofibromas, but seems to be more likely to occur in the plexiform neurofibromas. The signs of malignancy would be the appearance of pain in a previously painless mass, and sudden growth. It is common for plexiform neurofibromas to be painful if bumped or otherwise traumatized, but this is different from the pain associated with malignancy. Pain indicative of cancer is more likely to occur spontaneously, without any evidence of injury to the mass. Likewise, not all growth indicates malignancy. Neurofibromas commonly grow, especially the plexiform neurofibromas. Sudden growth of a portion of the neurofibroma is more indicative of malignancy than slow, steady growth of a larger mass. Malignancy related to neurofibromatosis is estimated to occur in about 5% of affected individuals. Although this might seem like a large number, it must be compared with the fact that 25% of all people—with or without neurofibromatosis—will develop a malignancy sometime in their lives. The malignancies related to neurofibromatosis

can be treated, usually with a combination of surgery, radiation, and chemotherapy. The outcome depends largely on how early the cancer is detected.

In addition to malignancies, the possibility of tumors in the brain and spinal cord must be considered. These, too, occur in relatively few persons with NF1, although the risk to people with NF1 of developing a brain tumor is much higher than the risk to the general population. These are usually detected after symptoms such as headache, vomiting, seizures, visual disturbance, or behavioral change are detected. There may be an abnormality noted on neurological examination. The tumor would be diagnosed by CT or MRI scan. Sometimes the tumor will be biopsied, or even removed, by surgery. The treatment is usually radiation therapy, or, in some cases, chemotherapy. It should be stressed that not all headaches in persons with neurofibromatosis mean that a brain tumor is present. Ordinary headaches, tension headaches and migraines, occur at least as commonly in persons with NF as in the general population. Persistent or especially severe headaches should be reported to a physician.

What to Watch For in a Child with Neurofibromatosis

The child with NF1 should not be treated as ill, or as excessively fragile. There is no need to restrict activity, unless there is known to be a particular complication of neurofibromatosis, which would be prone to injury. It is also not necessary to carefully document every skin spot or bump. These will be noted by the child's physician during annual follow-up visits. The major things to be watching for are sudden changes in the size or appearance of a neurofibroma, unexplained pain, or, as noted above, persistent or severe headaches. Both the family and school teachers should be aware of the possibility of learning disabilities.

When to Tell a Child About Neurofibromatosis

One of the most common and difficult questions asked by parents of children with NF1 is when and how to explain the disorder to the child. There is no single correct approach to this. Much depends on the adjustment of the parents, the maturity of the child, and the specific manifestations of neurofibromatosis present in the child. Ultimately, though, every child with NF1 will begin to question why he or she must go to a special doctor, or why he or she looks different from other children. If any general advice can be given here, it is to answer the child's questions honestly, giving as much information as the child seems to be able to understand. One need not go into great detail about possible complications of neurofibromatosis with a young child, but evasive answers often provoke fear rather than provide reassurance, and false answers may impair later trust. Moreover, sooner or later the child will learn about neurofibromatosis, if not from his or her parents, then from friends or articles in magazines or newspapers. This can lead to misinformation and consequent fear well out of proportion with the risks associated with the disorder. If the parents and physicians serve as the main source of information about neurofibromatosis, one can be more certain that the information is accurate and balanced.

Should Teachers be told about Neurofibromatosis in a Child?

Parents often ask whether the school system or teachers should be informed that their child has—or may have—neurofibromatosis. The concern is often raised that this might result in the child being labeled as "learning disabled", setting up a self-fulfilling prophesy. Actually, it is common for more harm to be done by not informing the school teachers, and having them fail to recognize learning disabilities, and mislabeling a child as a "behavior problem". A frank discussion with a child's teachers

can often correct common misconceptions about neurofibromatosis, and lead to earlier detection and treatment of learning problems related to the disorder.

Genetic Implication of Neurofibromatosis

Neurofibromatosis is a hereditary disorder, due to an abnormality in a gene. All people have two copies of every gene, one they get from their mother and one from their father. In a condition like neurofibromatosis, only one of the two copies of this gene need be affected to produce the disorder. We say that the condition is **dominant** because of this. An affected individual has a 50% chance of passing the abnormal gene copy to any child he or she might have. A child who inherits the abnormal gene will also have neurofibromatosis.

Many children diagnosed as having neurofibromatosis appear to be the only members of their families to have the condition. Neither parent may seem to be affected, and no relative is known to have had the condition. There are two possible explanations for this situation. One is that one of the parents actually does have neurofibromatosis, only its manifestations are so mild that he or she may be unaware of being affected. Alternatively, the genetic change, or mutation, that caused neurofibromatosis may have first arisen in the sperm or egg cell that produced the child. In this case, neither parent will be affected. Deciding between these alternatives can be important. In the first case, where one parent is affected, the risk of reoccurrence of NF1 in future offspring is 50%. In the latter case, where the child is affected due to new mutation of the NF gene, the risk to future offspring of the parents will be very low, practically the population risk. At present, the best way to resolve the issue is to thoroughly examine each parent, generally with a skin examination and eye examination looking for Lisch nodules. If neither parent is found to have signs of neurofibromatosis the child is most likely a new mutation. It is not impossible for the parents to have other affected children, but it is unlikely. Similarly, if neither parent is affected, it is unlikely that brothers or sisters of the affected child will be affected, although they should be examined for signs of neurofibromatosis to be sure.

Regardless of whether a person with NF1 is the first one in the family to be affected or whether the condition has been present for many generations, all persons with NF1 have a 50% risk of transmitting the condition to any child. There is no way to predict the degree of severity of the condition in offspring: severely affected parents may have mildly affected children and *vice versa*. Genetic testing ("DNA testing") is currently being developed which, in some cases, may permit prenatal diagnosis. A physician or genetic counselor can provide additional information about the availability of such testing.

If it is decided that a child has NF1 on the basis of new mutation of the gene, it is natural to ask, "How did this happen?" Parents often wonder if there is something they did which caused the mutation, such as exposure to radiation, medications, alcohol, etc. In fact, the cause of mutations in the NF1 gene is unknown. No environmental exposure has yet been implicated as a cause. In fact, genetic mutations occur commonly. Whenever a cell divides, an enormous volume of genetic information must be copied faithfully. It is not unusual for a bit of information to be copied incorrectly, resulting in mutations. Such random errors may well be the "cause" of mutations leading to neurofibromatosis, although further study of the NF1 gene will be necessary to be sure.

Sources of Support

Mastery of the medical facts about neurofibromatosis may be the first step towards adjustment to living with the disorder. This cannot relieve uncertainty, but ignorance about the condition often produces a picture, which is worse than reality. It is therefore important to maintain open communications with health professionals who are involved in caring for a child with neurofibromatosis. Family and friends can likewise be a source of support. Sharing accurate information with them can prevent them from satisfying their curiosity with inaccurate accounts in the lay press. Many seek professional guidance from clergy or counselors. Finally, there is the resource of other families with neurofibromatosis, who can share experiences, concerns, and advice. The Children's Tumor Foundation can provide needed information, and opportunities to meet others who are dealing with the condition.

The Children's Tumor Foundation

1 -800-323-7938 212-344-6633

Hope Through Research

Research on neurofibromatosis has entered an exciting phase of rapid progress. This is due largely to the application of new techniques of genetics, which have led to the identification of the genes for NF1 and NF2. This has already resulted in the development of some new means of diagnosis. It is ultimately hoped that an effective treatment, or cure, will result from this work. Scientists are actively pursuing the disorder at centers around the country. Your physician can provide up-to-date information on recent progress. The Children's Tumor Foundation newsletters are a particularly good source of information about recent research.