Reassessment of rectal approach to neuropathology in childhood

Review of 307 biopsies over 11 years

E. M. BRETT and B. D. LAKE

From The Hospital for Sick Children, London


In GM1 and GM2 gangliosidosis, Batten’s disease, and certain other neuronal storage diseases rectal biopsy is a reliable diagnostic alternative to brain biopsy. However, the need for biopsy has diminished with improvement in other diagnostic methods, particularly enzyme assay, the availability of which should determine the extent to which biopsy is used. It is suggested that rectal biopsy is necessary in the various forms of Batten’s disease and in the neurovisceral storage disease with supranuclear ophthalmoplegia described by Neville et al. (1973). In certain diseases its use is unjustified, either because the result would be negative or because other less traumatic, reliable investigations are available. On rare occasions it is justifiable to use rectal biopsy either as an ‘excluding investigation’ to exclude Batten’s disease for certain in a healthy sib of a known case with this disorder or to detect the disease before onset of clinical symptoms. The need for a full thickness biopsy and for a full range of staining methods is emphasized. Without these the investigation cannot be expected to give diagnostic information and may be misleading, giving ‘false negative’ results.

Rapid advances in paediatric neurology have been made in the past 15 years, particularly in the field of progressive degenerative neurometabolic diseases. The classification of these conditions has changed as a result of progress in biochemistry, histochemistry, and enzymology. The basic enzyme deficiency is now known in many disorders while in other conditions this stage has not yet been reached. In the earlier, pre-enzymological era, biopsy of neural tissue was needed to establish the diagnosis in most of these diseases. The disadvantages of cerebral biopsy led to the introduction of intestinal biopsy as an alternative, using rectum or appendix.

The concept of rectal biopsy as a diagnostic test in neurological disease may have originated in the work of Ludwig Pick, who in 1927 reported changes in the intestine at necropsy in several cases of Niemann-Pick disease. Neurons in Auerbach’s and Meissner’s plexuses were filled with deposits and changes were also seen in smooth muscle cells and muscularis mucosae. Landing and Freiman (1957) found at necropsy in cases of ‘amaurotic idiocy’ and Niemann-Pick disease similar changes in neurons of the central nervous system (CNS) and myenteric plexus of the large intestine. Martin, Landing, and Nakai (1963) reported a series of 75 rectal biopsies, of which only 11 were undertaken to advance the neurological diagnosis, the rest being in cases of Hirschsprung’s disease and similar conditions. Though no neurological diagnoses resulted from these biopsies, the
authors believed that rectal biopsy might provide a reliable alternative to brain biopsy in the 'neural lipidoses'.

General experience has shown this to be true (Nelson, 1974). At The Hospital for Sick Children, rectal biopsy has been used for this purpose since 1962 and a total of 307 biopsies were performed between then and 1973. The first report was in 1963 (Bodian and Lake) of 49 biopsies, including a review of 21 necropsies in which the CNS and gastrointestinal tract were examined and complete concordance was shown between neuronal changes in the two systems. It was found that a diagnosis of metachromatic leucodystrophy could be made by examination of included peripheral nerves. 10 biopsies (20%) were diagnostic and others were reported to show nondiagnostic changes. The second report on 165 biopsies (Brett and Berry, 1967) included 33 (20%) which were diagnostic. There were 11 cases of metachromatic leucodystrophy, a disease which even then could be diagnosed without biopsy (and for which, if biopsy is desired, a peripheral nerve biopsy would be more appropriate).

Brett and Berry (1967) suggested that increasing refinement of chemical and other methods might in time render the use of biopsy obsolete in many patients with neurulipidosis. This has occurred with advances in biochemistry and enzymology leading to reclassification of the 'neurulipidoses'. The gangliosidoses have been separated from those disorders formerly known collectively as 'amaurotic familial idiocy' and associated with the names of Batten, Bielschowsky, Jansky, Spielmeyer, Vogt, and others. Zeman and Dyken (1969) have suggested the term 'neuronal ceroid lipofuscinosis' for this group of disorders in which the basic biochemical and enzymatic defect has not yet been determined. Although the stored material in neurons is thought to be ceroid (Saikotos et al., 1970) this has not yet been proved, and though a deficiency of peroxidase activity has been shown in granulocytes (Armstrong, Dimmitt, and Van Wormer, 1974; Patel et al., 1974) the exact significance of this is not yet clear and the reliability of the test is doubtful. In this group of disorders, which will be referred to as Batten's disease, biopsy of neural tissue is still needed as a diagnostic test, though the results of neuropsychological investigations (electroencephalography (EEG) and electroretinogram (ERG)) have been found to correlate closely with the various forms of the condition (Harden, Pampiglione, and Picton-Robinson, 1973; Pampiglione and Harden, 1973; Santavuori, Haltia, and Rapola, 1974). Doubts have been cast on the value of rectal biopsy in diagnosis of neuro-metabolic brain disease in children in general, with the suggestion that it is difficult to interpret, rarely useful, and dangerous (Myers, Hedley-Whyte, and Fagan, 1973). Some have claimed that cerebral biopsy is still necessary for the diagnosis of Batten's disease (Gordon, Marsden, and Noronha, 1972) and others (Carpenter, Karpati, and Andermann, 1972) have suggested that electron microscopic examination of sweat glands in a skin biopsy is a reliable diagnostic method.

For these reasons and because we feel that the present status of investigation should be reviewed, a report of a further series of 93 rectal biopsies together with an analysis of the total series of 307 is presented.

Methods

The surgical technique for taking an adequate biopsy is described elsewhere (Smith, Dickson, and Lake, 1975). The biopsy is collected from theatre and brought to the laboratory where a small portion (about 1/20th) of mucosa and smooth muscle is removed and fixed in buffered 4% formaldehyde for subsequent processing for electron microscopy. The remainder of the biopsy is frozen in hexane at −79 °C in a solid carbon dioxide/acetone bath. Sections are cut at 5–7 μm in a cryostat and stained by methods described by Bodian and Lake (1963) with the addition of the demonstration of acid phosphatase activity and examination of an unstained, unfixed, mounted section under ultraviolet light for autofluorescent deposits (Lake, 1973a). Neither formalin-fixed frozen sections nor paraffin wax-embedded sections are prepared. Occasionally other methods are required to obtain more specific information. Water-soluble acidic mucosubstances can be shown by the toluidine blue method of Haust and Landing (1961) and β-galactosidase activity can be shown by an indoxyl method (Lake, 1973b).

Normal appearance—neurons. There is a range of normal appearance of neurons which varies with age. Until the age of about 5 years there is generally no evidence of lipid deposition. Neurons from older patients may show a few granular deposits of a substance which is P.A.S.-positive, often stains with Sudan Black, and shows an orange-yellow autofluorescence; but this substance does not stain with Luxol- Fast Blue. It corresponds to wear and tear pigment or lipofuscin, and occurs increasingly with age. Not all neurons are affected.

Smooth muscle of the circular and longitudinal muscle coats, muscularis mucosae, and of blood vessels shows no lipid or lipofuscin deposits but will often show glycogen deposits at the nuclear poles.

Acid phosphatase activity consists of a few fine discrete granules in the cytoplasm of neurons and considerable activity in the mucosal epithelium and in histiocytes of the lamina propria. Muciphages are often present in the
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lamina propria, occurring more frequently towards the luminal surface but may also occur in deeper regions. These muciphages stain with the celloidinized P.A.S. method but usually fail to stain with any of the other methods. They display a silver autofluorescence and have no diagnostic significance unless their numbers are large and/or they occur below the muscularis. In this situation a diagnosis of metachromatic leucodystrophy could be considered and the included peripheral nerves should be carefully examined.

Results

Ninety-three full thickness rectal biopsies were taken between 1967 and 1973 in 93 children with neurodegenerative brain disease was suspected. 35 biopsies were diagnostic, 56 were normal, and 2 showed nondiagnostic abnormalities. The diagnoses are shown in Table I.

<table>
<thead>
<tr>
<th>Table I</th>
<th>Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batten's disease</td>
<td>28</td>
</tr>
<tr>
<td>Gaa-gangliosidosis</td>
<td>2</td>
</tr>
<tr>
<td>Clinical Tay-Sachs disease</td>
<td>2</td>
</tr>
<tr>
<td>Late onset variety</td>
<td>1</td>
</tr>
<tr>
<td>Gm1-gangliosidosis</td>
<td>1</td>
</tr>
<tr>
<td>Early onset</td>
<td>1</td>
</tr>
<tr>
<td>Late onset</td>
<td>1</td>
</tr>
<tr>
<td>Syndrome with vertical supranuclear ophthalmoplegia (Neville et al., 1973)</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
</tr>
</tbody>
</table>

Batten's disease. 18 of the 28 cases of Batten's disease were classified as late infantile (or Bielschowsky-Jansky) type. One case was later considered on review to be an example of the condition described by Finnish authors as 'the infantile type of so-called neuronal ceroid-lipofuscinosis' (Santavuori et al., 1973; Haltia et al., 1973), a form we call the early infantile variety. This boy's sister had an identical clinical picture and had been investigated by cerebral biopsy.

One child with the late infantile form of Batten's disease also had a brain biopsy and similar changes were seen in both biopsies. 9 of the patients with Batten's disease conformed to the juvenile (Spielmeier-Vogt) variety and a tenth, though clinically of the juvenile type, showed changes in her biopsy more suggestive of those seen in the early infantile form.

On rectal biopsy two main types of change can be distinguished, corresponding closely to the clinical presentations of the late infantile and juvenile forms of the disease. Recent experience has also allowed distinction to be made between the early infantile variety and the late infantile and juvenile forms. The changes present in biopsies from patients with late infantile Batten's disease are not marked and could be missed without the whole battery of stains outlined in Methods.

The neurons are not enlarged but contain a granular substance which stains only weakly grey/black with Sudan Black and weakly yellow/orange with Oil Red O. P.A.S. reaction does not show the granules, but a diffuse P.A.S. positivity is often present in the neuronal cytoplasm. There is no metachromasia with Feyrer's thionin. Luxol-Fast Blue shows the granules as blue/black deposits and also shows larger aggregates of substance (Fig. 1). The acid phosphatase reaction is very strong and the reaction product is coarsely granular. The substance shows yellowish autofluorescence in an unstained, unfixed section. The smooth muscle cells are also involved and show deposits usually at the poles of the nuclei. These deposits have a more variable set of staining reactions but are usually visible in either the Sudan Black or acid phosphatase preparation and are also autofluorescent. Neurons of Meissner's plexus are often involved to only a minor degree, emphasizing the need for a full thickness biopsy.

In early-infantile Batten's disease the changes found are similar to those in late-infantile Batten's disease but the deposits do not stain with Luxol-Fast Blue. There may also be an excess of P.A.S. and Sudan-Black-positive muciphages in the lamina propria.

The changes in juvenile Batten's disease are more marked and show differences from the infantile forms of the disease. The neurons may be enlarged and the deposited granular substance stains positively with P.A.S., Sudan Black (Fig. 2), and Luxol-Fast Blue. No large aggregates are found in neurons in Luxol-Fast Blue preparations. In general no metachromasia is detected with Feyrer's thionin but sometimes an occasional neuron may show strong metachromasia similar to that found in the gangliosidoses. The neuronal deposits are autofluorescent (Fig. 3) and ultraviolet microscopy also shows deposits of a yellow autofluorescent substance in smooth muscle cells. The intensity of fluorescence is greater in the juvenile form of the disease than in the other types.

Acid phosphatase reaction shows a number of intensely reactive histiocytes among the smooth muscle bundles. These cells are only present in the juvenile form of the disease and have been present consistently. In one child presenting as the juvenile form of the disease the staining reactions...
and ultrastructure were more like those of the early infantile disease. The neuronal deposits did not stain with Luxol-Fast Blue and there were no acid phosphatase positive histiocytes in the smooth muscle.

**G_{M2}-gangliosidosis.** Two children in this group were clinically examples of Tay-Sachs disease. Enzyme assays of white blood cells in one patient showed the usual pattern of marked deficiency of hexosaminidase A and in the other an activity of hexosaminidase indistinguishable from the normal. (This patient has been referred to by Brett et al., 1973.)

Two patients were examples of late onset G_{M3}-gangliosidosis, showing slowly progressive neurological deterioration from 4 years of age without macular changes or other features suggesting Tay-Sachs disease. 2 sisters with the late infantile variety of G_{M3}-gangliosidosis, with onset at 19 and 21 months of age and necropsy confirmation, were included in the previous series of patients with 'neurolipidosis' diagnosed by rectal biopsy (Brett and Berry, 1967). These 4 cases were included in the series of 8 reported by Brett et al. (1973).

The changes are identical in all types of G_{M3}-gangliosidosis and will be described together.

Neurons are the only cell type affected in rectal biopsies from G_{M3}-gangliosidosis. Neurons in Meissner's and Auerbach's plexuses are equally affected, being grossly enlarged, and their cytoplasm contains a granular deposit staining strongly with P.A.S. and weakly with Sudan Black, Oil Red O, and Luxol-Fast Blue. An immediate metachromasia is produced with Feyerter's thionin. Acid phosphatase reaction in the neurons shows a diffuse reaction throughout the cytoplasm and the discrete deposits normally observed are lost. Excess ganglioside G_{M3} can be shown by thin layer chromatography of a lipid extract of the biopsy (Lake, 1973a). Normal rectal mucosa and muscle show an essentially neutral pattern of gangliosides and only a trace of G_{M3} is visible under standard conditions. The histochemical method for showing β-acetyl hexosaminidase activity does

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**FIG. 1.** Late infantile Batten's disease. Cryostat section stained with Luxol Fast Blue—Neutral Red. Neurons in Auerbach's plexus containing fine granular deposits (F) and coarser aggregates (C) of the stored substance.
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FIG. 2.—Juvenile Batten's disease. Cryostat section stained with Sudan Black. Neurons in Auerbach's plexus containing a fine granular substance which stains grey-black. Smooth muscle cells also contain a similar substance (arrows).

not differentiate between the activities of A and B components, so that only the total deficiency of hexosaminidase typical of Sandhoff’s disease can be detected.

G$_{M_1}$-gangliosidosis. One child with early onset and another with late onset G$_{M_1}$-gangliosidosis had diagnostic rectal biopsies. Bone marrow biopsy showed abnormal storage cells in both cases and peripheral blood contained vacuolated lymphocytes in the early onset case only. Deficiency of β-galactosidase activity was found in both cases.

In both types of this disease the pathological changes in the rectum are very similar. The neurons are enlarged, as in G$_{M_2}$-gangliosidosis, but the degree of involvement is greater in Meissner’s plexus than in Auerbach’s. Staining reactions of the neurons are the same as those in G$_{M_2}$-gangliosidosis as might be expected, since the reactive groups of the two gangliosides are the same. In addition to neuronal storage there is deposition in large histiocytes in the lamina propria of a substance which has the properties of a water soluble acid mucosubstance showing metachromasia and basophilia with Haust and Landing’s (1961) toluidine blue method. Almost complete absence of β-galactosidase activity is readily demonstrable in the mucosal epithelium, in histiocytes of the lamina propria, and in neurons.

Neurovisceral storage disease with vertical supranuclear ophthalmpoplegia. A 4-year-old Greek girl had a progressive neurological illness with a supranuclear vertical gaze palsy and distinctive cells in the bone marrow conforming to the clinical and pathological picture described by Neville et al. (1973). Rectal biopsy showed a pattern of neuronal and histiocytic storage which
Brett and Lake

Fig. 3.—Juvenile Batten's disease. Examination of an unfixed, unstained section with ultraviolet light (360 nm; dark ground) shows strongly autofluorescent deposits in neurons.

distinguished it from other forms of neuronal storage disease, changes similar to those found in the appendices of 2 patients in the series of Neville et al. (1973).

Neurons in this condition show a variable amount of stored substance which stains with the celloidinized P.A.S. method (Fig. 4), but not with P.A.S. after fixation. There is weak staining with Sudan Black and no staining with Luxol-Fast Blue. Feyrter's thionin shows metachromasia; there is no autofluorescence and no involvement of smooth muscle. The acid phosphatase reaction is strong in neurons and in the numerous histiocytes present in the lamina propria and around the lymphoid follicles.

Normal rectal biopsies in patients with proved progressive degenerative brain disease. Among patients with normal rectal biopsies were 6 in whom diagnoses of specific neurological diseases were later made during life or at necropsy. One had subacute sclerosing panencephalitis and another sudanophilic diffuse sclerosis (necropsy diagnosis). In one boy biopsied at 17 months of age, in whom Krabbe's globoid body leucodystrophy of late onset was suspected, biopsy showed no changes in included peripheral nerves despite extensive sectioning. Diagnosis of Krabbe's leucodystrophy was later established by enzyme assay of white blood cells. (The absence of peripheral nerve involvement in the late onset form of Krabbe's leucodystrophy has been reported by Crome et al. (1973) and contrasts with the presence of such involvement in the commoner early onset variety.) In 2 other patients with normal rectal biopsies diagnoses of juvenile Huntington's chorea and of Lafora body disease were made at necropsy.

A 13-year-old African boy with a progressive neurological illness with myoclonus, horizontal supranuclear ophthalmoplegia, splenomegaly, and normal rectal biopsy was later shown to have Gaucher's disease by liver biopsy and enzyme assay in cultured skin fibroblasts. In this respect, therefore, the juvenile form of Gaucher's disease resembles the infantile type, in which intestinal neuronal storage and smooth muscle involvement are absent.

Electron microscopy. Electron microscopy of smooth muscle and neurons can occasionally be helpful in confirming a diagnosis but is never used
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Nondiagnostic abnormalities. Rectal biopsies of 2 children were abnormal but not diagnostic. In one biopsy some neurons were large and vacuolated but with no particular staining reactions. No diagnosis has been made in this boy, who appears clinically to have a progressive brain disease. In the other biopsy from a girl of 7 years the only abnormality seen was the presence of large foamy endothelial lining cells in some blood vessels; the diagnosis is uncertain in this patient but a myopathy with abnormal mitochondria is suspected from examination of a muscle biopsy.

Complications

The procedure, if properly performed, is safe, and since 1971 when a minor change in the surgical technique was introduced there have been no complications in over 70 biopsies (Smith et al., 1975). Previously, postoperative bleeding was occasionally a problem, occurring in 8% of the 165 cases reported by Brett and Berry (1967), 5 of whom needed blood transfusion.

Discussion

Refinements in the understanding and diagnosis of progressive neurometabolic diseases have greatly reduced the need and justification for rectal biopsy. Our own experience has caused us increasingly to limit its use since diagnosis by other means, particularly by enzyme assay, has become possible. Biopsy may in time become unjustified as the enzyme defect in other conditions becomes known and enzyme assay becomes more reliable and widely available. The present situation with regard to various diseases is summarized in Table II.
FIG. 5.—Preclinical late infantile Batten's disease. Electron photomicrograph of neuron in Auerbach's plexus showing membrane-bound curvilinear bodies.

FIG. 6.—Same case as Fig. 5. Curvilinear bodies are also present within smooth muscle cells.
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TABLE II
Choice of rectal biopsy and other investigations in some childhood neurological diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Rectal biopsy positive</th>
<th>Other simpler or more reliable diagnostic methods available</th>
<th>Favoured investigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaa-gangliosidosis (all types)</td>
<td>Yes</td>
<td>Yes</td>
<td>Hexosaminidase assay in leucocytes</td>
</tr>
<tr>
<td>Gaa-gangliosidosis (types I and II)</td>
<td>Yes</td>
<td>β-galactosidase assay in leucocytes; bone marrow biopsy;</td>
<td></td>
</tr>
<tr>
<td>Niemann-Pick disease (types A and B)</td>
<td>Yes</td>
<td>spine x-rays may help; Bone marrow biopsy;</td>
<td></td>
</tr>
<tr>
<td>Syndrome with vertical supranuclear ophthalmoplegia (Neville et al., 1973)</td>
<td>Yes</td>
<td>Bone marrow biopsy; sphingomyelinase assay in leucocytes if possible, otherwise liver biopsy</td>
<td></td>
</tr>
<tr>
<td>Gaucher's disease</td>
<td>NO</td>
<td>Bone marrow biopsy; rectal biopsy</td>
<td></td>
</tr>
<tr>
<td>Mucopolysaccharidoses</td>
<td>Yes, but not diagnostic of type</td>
<td>Yes</td>
<td>Glucocerebrosidase assay in leucocytes or fibroblasts; biopsy of bone marrow, liver, or lymph nodes</td>
</tr>
<tr>
<td>Metachromatic leucodystrophy</td>
<td>Yes, (changes in included nerves)</td>
<td>Yes</td>
<td>Urine mucopolysaccharides; metachromasia in leucocytes; enzyme assay in leucocytes and cultured fibroblasts; x-rays</td>
</tr>
<tr>
<td>Krabbe's globoid body leucodystrophy</td>
<td>NO</td>
<td>Yes</td>
<td>Galactocerebrosidase-β-galactosidase activity in leucocytes and/or fibroblasts; nerve conduction studies; sural nerve biopsy helpful but not essential if other methods available</td>
</tr>
<tr>
<td>Batten's disease, early infantile, late infantile, and juvenile types</td>
<td>Yes</td>
<td>?</td>
<td>Rectal biopsy; (white blood cell peroxidase assay claimed by some to be a reliable diagnostic method; also skin biopsy for electron microscopy)</td>
</tr>
<tr>
<td>Subacute sclerosing panencephalitis</td>
<td>NO</td>
<td>Yes</td>
<td>EEG; CSF Lange curve; measles antibodies in blood and CSF</td>
</tr>
<tr>
<td>Sundanophilic diffuse sclerosis (aplastic and X-linked)</td>
<td>NO</td>
<td>Yes</td>
<td>Adrenal function tests (in X-linked variety); brain biopsy may be needed, but is not always diagnostic</td>
</tr>
<tr>
<td>Cerebral neoplasms</td>
<td>NO</td>
<td>Yes</td>
<td>EEG; neuroradiological methods; occasionally brain biopsy</td>
</tr>
<tr>
<td>Nonspecific and nonprogressive mental retardation, epilepsy, and cerebral palsy</td>
<td>NO</td>
<td>Yes</td>
<td>Biochemical, serological, chromosomal, radiological, neurophysiological, and other tests secundum artem</td>
</tr>
</tbody>
</table>

Where reliable facilities exist for measurement of the appropriate enzyme, as in the gangliosidoses, it is logical to abandon biopsy. Where such facilities are lacking, biopsy will continue to be needed. In conditions such as metachromatic leucodystrophy, in which several alternative diagnostic methods exist, biopsy is no longer justifiable. In Niemann-Pick disease, types A and B, assay of sphingomyelinase activity in white blood cells is possible but facilities for this are still not widely available and biopsy is therefore necessary. Liver biopsy is the logical choice here but where the patient's life may be endangered by a general anaesthetic suction rectal biopsy without anaesthetic has been diagnostic (Lake, 1974). However, it must be emphasized that suction rectal biopsy should only be used in a few conditions, namely, Niemann-Pick disease and Gm1-gangliosidosis, in which the diagnosis can be based on changes in the mucosa alone (Lake, 1973b, 1974). In the syndrome with vertical supranuclear ophthalmoplegia, described by Neville et al. (1973), the enzyme defect is not yet known and biopsy remains essential. In this disorder bone marrow biopsy gives useful information but should not be relied on for a definitive diagnosis.

In the various forms of Batten's disease the clinical picture and closely correlated neurophysiological findings usually point clearly to the diagnosis (Harden et al., 1973; Pampiglione and Harden,
Brett and Lake

1973; Santavuori et al., 1974). Assay of peroxidase activity in white blood cells is not yet reliable enough in our opinion to obviate the need for biopsy, though this stage may soon be achieved. At present it is in Batten’s disease that rectal biopsy is most useful. In this group of disorders, and in the other diseases in which rectal biopsy is positive, it seems to us unjustified to continue cerebral biopsy.

Rectal biopsy is occasionally justified as an ‘excluding investigation’ when a family history of Batten’s disease raises the possibility of the diagnosis in a sib without symptoms. In this situation the more drastic brain biopsy is impossible to justify. A normal rectal biopsy at an age which an affected sib has had a positive biopsy excludes the disease. This can be helpful in reassuring anxious parents, whose previous tragic experience causes them to see deterioration where none exists, and in giving similar reassurance to anxious doctors. However, even in a clinically and electrophysiologically normal younger sib, a diagnostic positive biopsy can be obtained well before the disease becomes apparent to the parent, physician, or electrophysiologist (see Fig. 5 and 6). Increasing reliability of neuropathological investigations and other methods should, however, make this excluding role of biopsy unnecessary. In order to be of any value, and to avoid the erroneous conclusions reached by Myers et al. (1973), biopsy must be adequate and must be examined with a full range of stains.

REFERENCES


Correspondence to Dr. E. M. Brett, The Hospital for Sick Children, Great Ormond Street, London WC1N 3JH.
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