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NEUROPATHOLOGICAL DIAGNOSIS OF CHILDHOOD NEURODEGENERATIVE DISORDERS BY BIOPSY: INVITED TOPIC*

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Key words: biopsy, diagnosis, neurogenerative disorders, skin, ultrastructure

Identifying a child's progressive neurodegenerative disorder during life aims at genetic counselling, prognostication and assessing the possibilities of curable diseases since many neurodegenerative diseases currently remain largely without cause-directed treatment, while supportive therapy not neccesarily requires a precise nosological diagnosis. In view of these therapeutic limitations, accurate recognition of the individual child's neurodegenerative disease may, for various reasons, have to be postponed until death when the central nervous system may become available for comprehensive morphological and eventual biochemical investigations. However, if such an autopsy is not intended or a respective request for autopsy is denied, the individual child's disease may not only remain unidentified but knowledge of the respective neurodegenerative disease may also be withheld from the entire family, thus preventing appropriate genetic counselling with sometimes dire consequences to additionally born siblings or cousins of the original diseased and deceased child.

These latter socio-medical aspects may often prompt clinicians to seek the correct diagnosis of a neurodegenerative disease during the child's life at considerable cost, i.e., by biopsy. Gravity of the illness, risks involving the biopsy procedure and the significance of anticipated results will have to be considered as to when and where to perform a biopsy. Before the biopsied tissue becomes available for diagnostic studies to the neuropathologist, the neurochemist, and/or the neuromicrobiologist, it will be these experts who have to counsel the clinician on which diagnoses to expect from the respective biopsied tissues. When dealing

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with neurodegenerative diseases of childhood the role of the neuropathologist is crucial as he is the one who will receive the tissue for further adequate investigations. He, himself, will chiefly employ the electron microscope as his diagnostically most valuable tool[1].

Principally, brain, rectum, peripheral nerve, muscle, skin, conjunctiva, lymphocytes, liver, and rarely kidney[2] may be targets for biopsies in neurodegenerative diseases, while renal biopsy in Fabry's disease although affecting the kidney foremost, is unwarranted in view of the severely damaged small vessels in skin and conjunctiva.

Brain biopsy. Brain biopsy as the most risky procedure should be entertained in only those neurodegenerative diseases that are morphologically and biochemically confined to the brain, but the affected tissues should provide sufficient findings to permit a precise nosological diagnosis, largely disease-specific findings. In the past, refined surgical, anesthesiological, but foremost morphological, e.g., electron microscopic, and biochemical techniques, had prompted brain biopsy in numerous children afflicted with neurodegenerative disorders–but also, for instance, in the slow virus diseases, subacute sclerosing panencephalitis (Fig. 1)-and thus furnished a wealth of data concerning the ultrastructural pathology of the brain in many neurodegenerative disorders. Lysosomal diseases, though

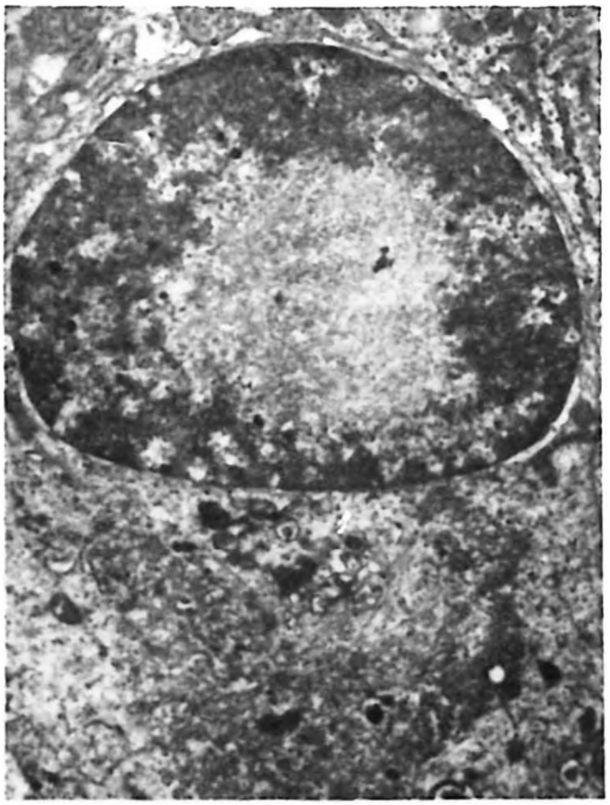

Fig. 1: Subacute sclerosing panencephalitis:
Innumerable paramyxovirus nucleocapsids in nucleus and cytoplasm (X 8,000).

known since the end of the last century as Tay-Sachs disease or amaurotic familial idiocy, have been successfully delineated by ultrastructural studies of biopsied brain tissue identifying membranous cytoplasmic bodies (Figs. 2a, b) as the disease-specific hallmark of the gangliosidoses or disease-specific lysosomal inclusions in oligodendrocytes and macrophages of metachromatic (Fig. 3a) and globoid cell (Fig. 3b) leukodystrophies. From these studies it also became apparent that largely those neurodegenerative diseases could be recognized that morphologically affect the cerebral cortex and the cerebral white matter while diseases of the basal ganglia and other subcortical regions were not accessible to diagnosis by brain biopsy. Among the non-lysosomal diseases Lafora, Canavan, and Alpers diseases, and infantile neuroaxonal dystrophy (Fig. 4) were investigated.

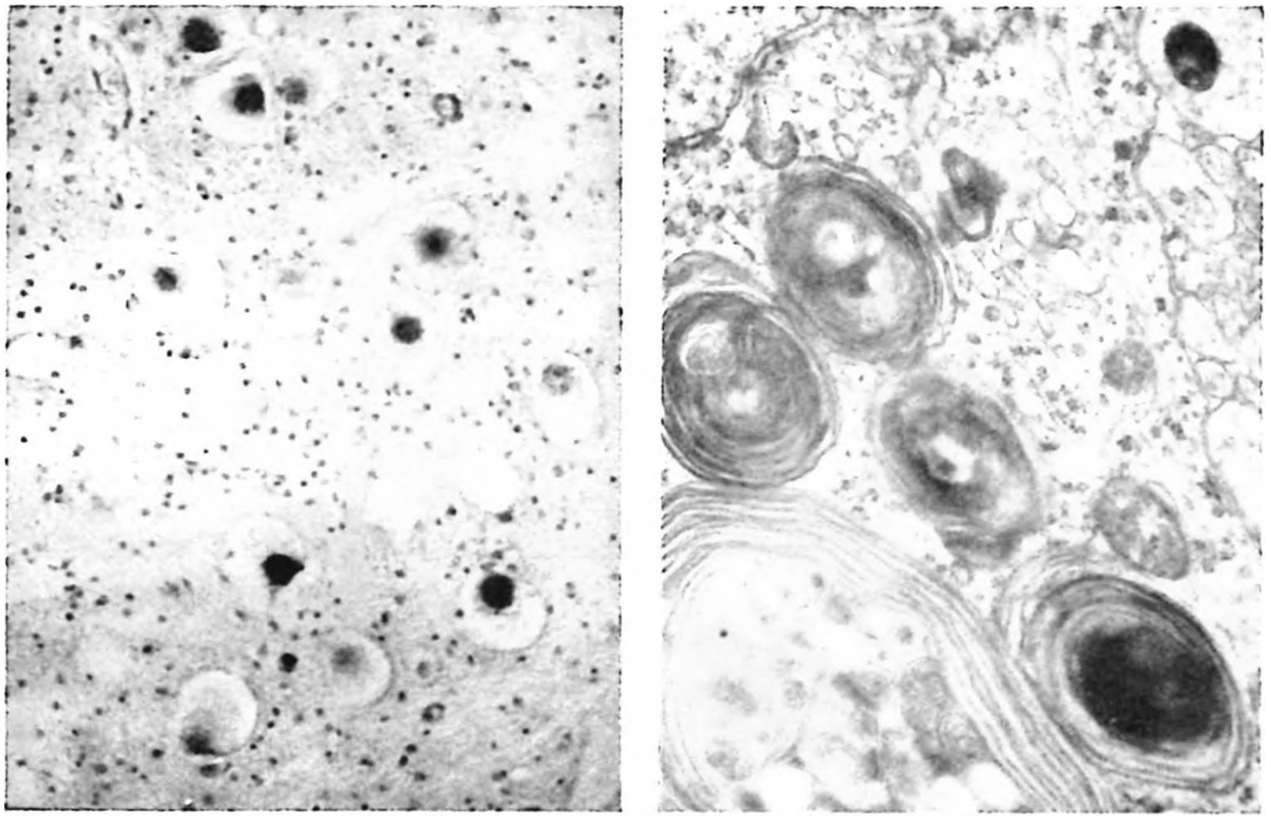

Fig. 2: GM_2-gangliosidosis:
a) Enormous enlargement of neuronal perikarya (Cresyl violet X 300).
b) Typical membranous cytoplasmic bodies (X 17,600).

When it became apparent that other non-cerebral tissues are often affected in neurodegenerative disorders, even without clinical symptoms derived from the non-affected non-cerebral tissues, brain biopsy became obsolete because it still is a risky procedure and today may only be justified in generalized Alexander's disease. However, variants of Alexander's disease localized to subcortical regions, e.g., the brainstem[3] will escape diagnostic detection.

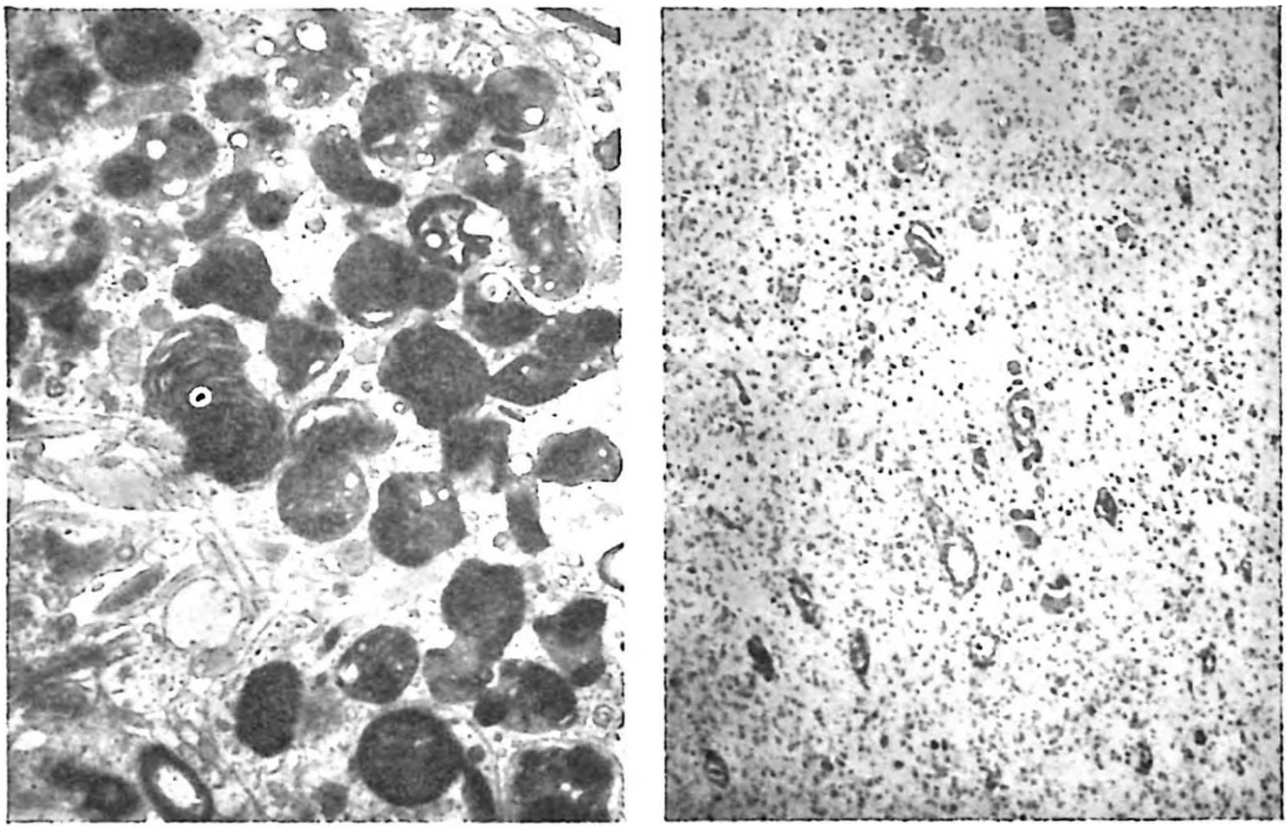

Fig. 3: Leukodystrophies:
a) Metachromatic type, numerous membranous lysosomal residual bodies within oligodendrocytes (X 2,120).
b) Globoid cell (Krabbe) type, numerous large globoid cells, often in small clusters, cerebral white matter (LFB-PAS X 45).

While stereotactic surgery may render subcortical brain regions accessible to biopsy a lack of disease-specific morphological and biochemical findings, e.g., in Huntington's chorea or dystonia have not favored this procedure. Conversely, the in vivo diagnosis of these disorders may hopefully be more reliably gained from radiological and genetic investigations.

Biopsy of non-cerebral tissues. Again, it was the rapidly expanding concept of and knowledge about the lysosomal diseases, i.e., lysosomal enzyme deficiencies with which every cell of the patient's body is endowed and their morphological manifestation in visceral organs, sometimes in an almost ubiquitous fashion as in type II glycogenosis and neuronal ceroid-lipofuscinosis (NCL) that has reduced the number of diagnostic brain biopsies in children to virtually nil and supplanted them by biopsies of those non-cerebral tissues that are easily amenable to biopsy, e.g., the skin and conjunctiva as well as circulating lymphocytes.

Biopsy of peripheral nerves. Surgical removal of a peripheral nerve segment for in vivo diagnostic purposes is, to many pediatricians and pediatric neurologists, still a matter of controversy. Three groups of peripheral nerve disorders are to be

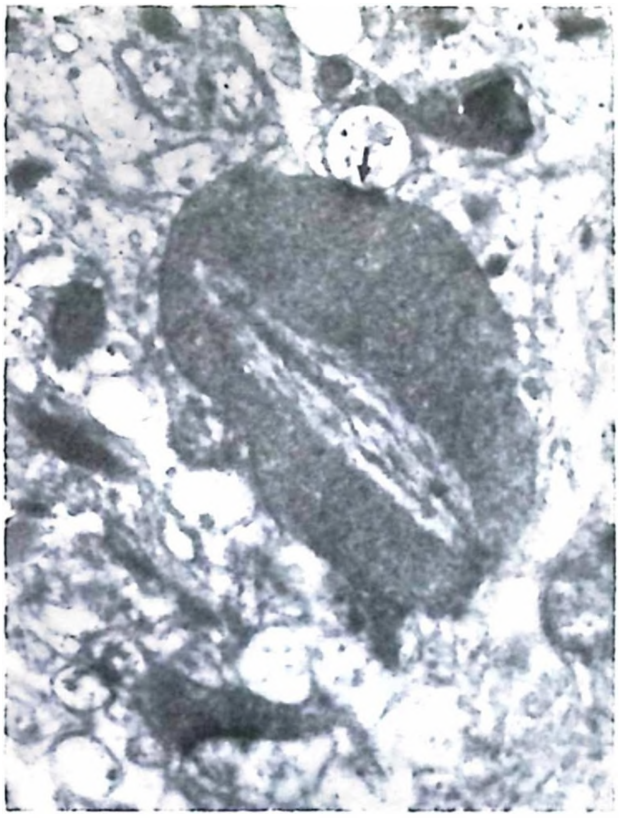

Fig. 4: Infantile neuroaxonal dystrophy:
Distension by tubulo-cisternal profiles of a cerebrocortical synaptic complex (arrow) (X 17,440).

Fig. 5: Hereditary sensory-automatic neuropathy IV:
Too few unmyelinated axons (arrow) among numerous myelinated ones, sural nerve (X 6,840).

considered as regards biopsy. Firstly, those disorders that exclusively affect the peripheral nervous system in childhood, e.g., the hereditary sensory-motor neuropathies and hereditary sensory-autonomic neuropathies, especially HSAN IV (Fig. 5). Secondly, those neurodegenerative disorders that both affect the central and the peripheral nervous system and allow precise nosological diagnosis from a biopsied peripheral nerve, e.g., the globoid cell and metachromatic leukodystrophies (Figs. 6a, b), adrenoleukodystrophy[4] or giant axonal neuropathy (Fig. 7). Thirdly, those neurodegenerative disorders of childhood that although affecting both the central and the peripheral nervous system, manifest themselves clinically and by non-clinical and non-morphological criteria more pronounced in the central nervous system, e.g., certain mitochondrial disorders such as the Leigh syndrome, the Kearns-Sayre syndrome, mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) or the Cockayne syndrome. In these disorders, however, peripheral nerve involvement is subtle and non-specific and thus peripheral nerve biopsy usually does not contribute to the in vivo diagnosis. Sometimes, the assumption that biopsy of a peripheral nerve may elucidate a CNS disorder is even carried further when indiscriminately resorting to a peripheral nerve biopsy in any progressive neurodegenerative

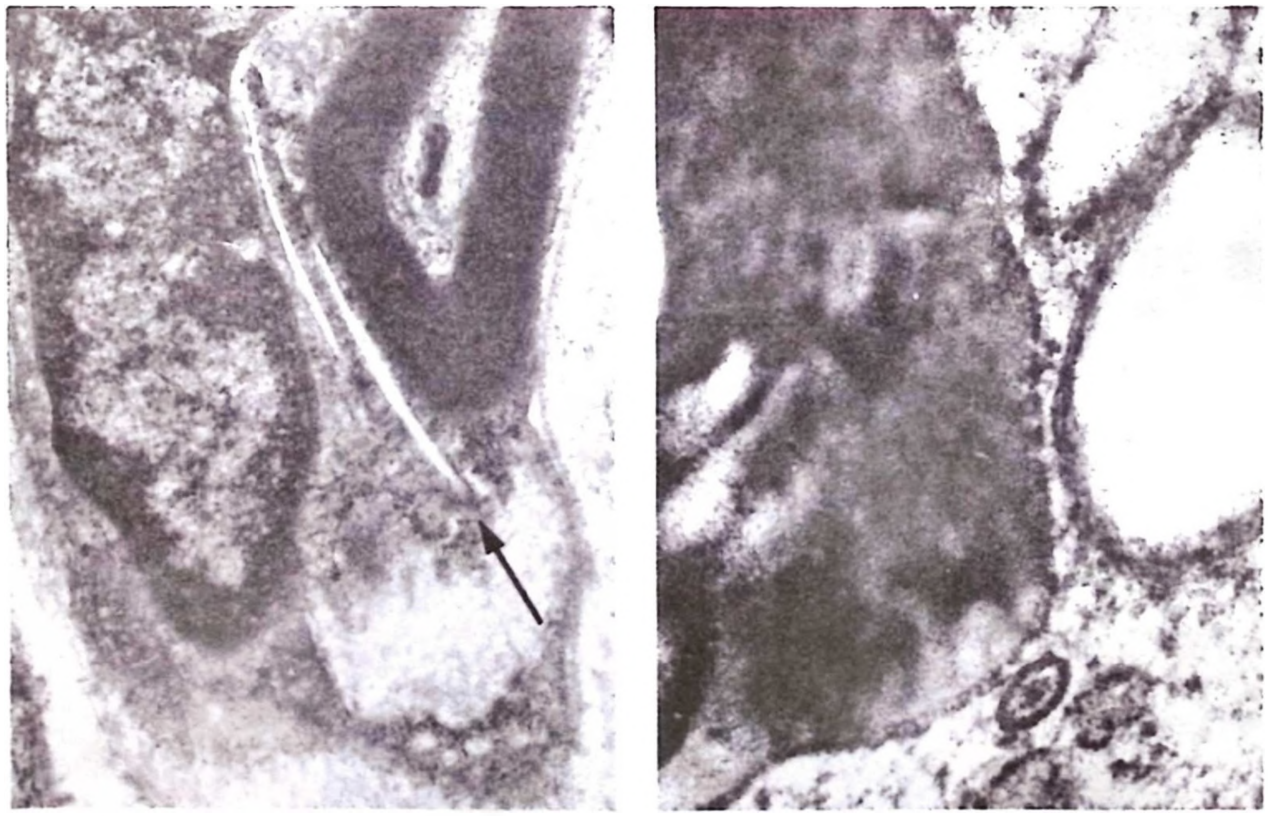

Fig. 6: The peripheral nervous system in lysosomal leukodystrophies:
a) Globoid cell (Krabbe) type with characteristic needle-like inclusions (arrow) within a myelinating Schwann cell (X 22,500).
b) Metachromatic type with characteristic prismatic lysosomal inclusion (X 64,000).

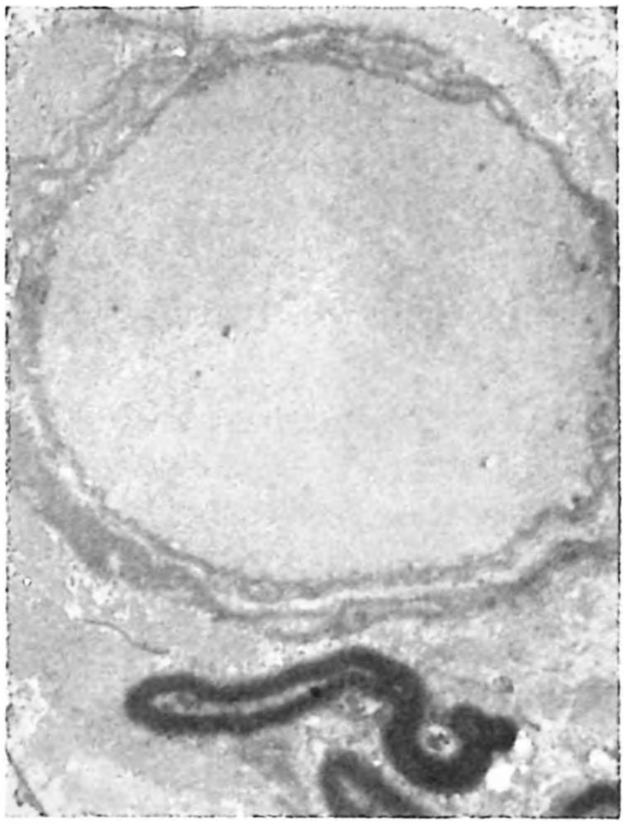

Fig. 7: Giant axonal neuropathy:
An axon without a myelin sheath is distended by numerous neurofilaments, sural nerve (X 3,750).

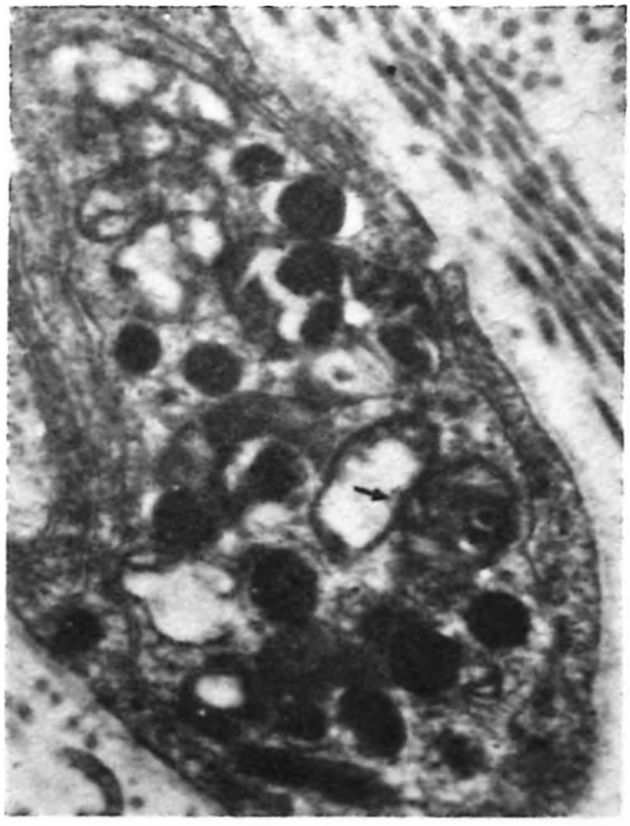

Fig. 8: Mucolipidosis IV:
Axonal enlargement by dense and membranous (arrow) bodies, skin (X 68,600).

disorder of the CNS; then, a peripheral nerve biopsy becomes unnecessary and unjustified because its morphological results may not reveal the underlying CNS disease and thus disappoint clinicians, patients, and their relatives, alike. Even when the peripheral nerve may disclose disease-specific morphological findings, e.g., in the NCL, other tissues such as skin, conjunctiva, and lymphocytes are not only more easily biopsied but are also diagnostically more reliable and thus rewarding[5]. For instance, the Leigh syndrome may be associated with a demyelinating disorder[6], but evidence of demyelination is certainly not pathognomonic for the Leigh syndrome.

Biopsy of skin (and conjunctiva). Skin specimens may be successfully investigated morphologically, i.e., largely electron microscopically, and biochemically, the latter by culturing fibroblasts. The cytological diversity of the skin, especially when one incorporates nerve fascicles and axonal terminals[7] (Fig. 8) into the ultrastructural study, allows identification of numerous lysosomal diseases which, however, need to be confirmed by biochemical studies of the respective enzyme deficiencies from simultaneously cultured fibroblasts, and of those disorders of which enzyme defects are not yet known (Fig. 9), especially the NCL (Figs. 10a, b), and also of non-lysosomal diseases such as infantile neuroaxonal dystrophy (Fig. 11), Lafora disease (Fig. 12), and giant axonal neuropathy. Adrenoleukodystrophy,

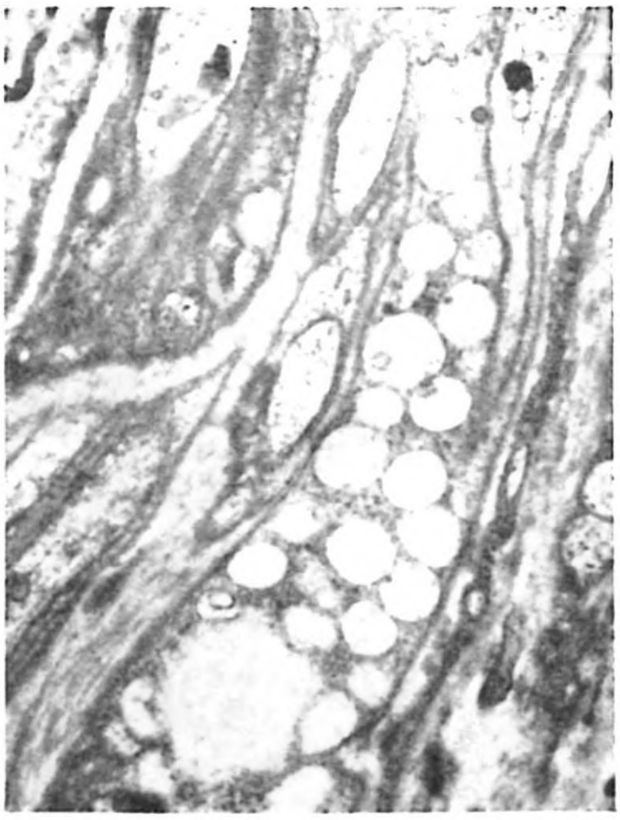

Fig. 9: Salla disease:
Lysosomal vacuolation in dermal Schwann cells (X 13,990).

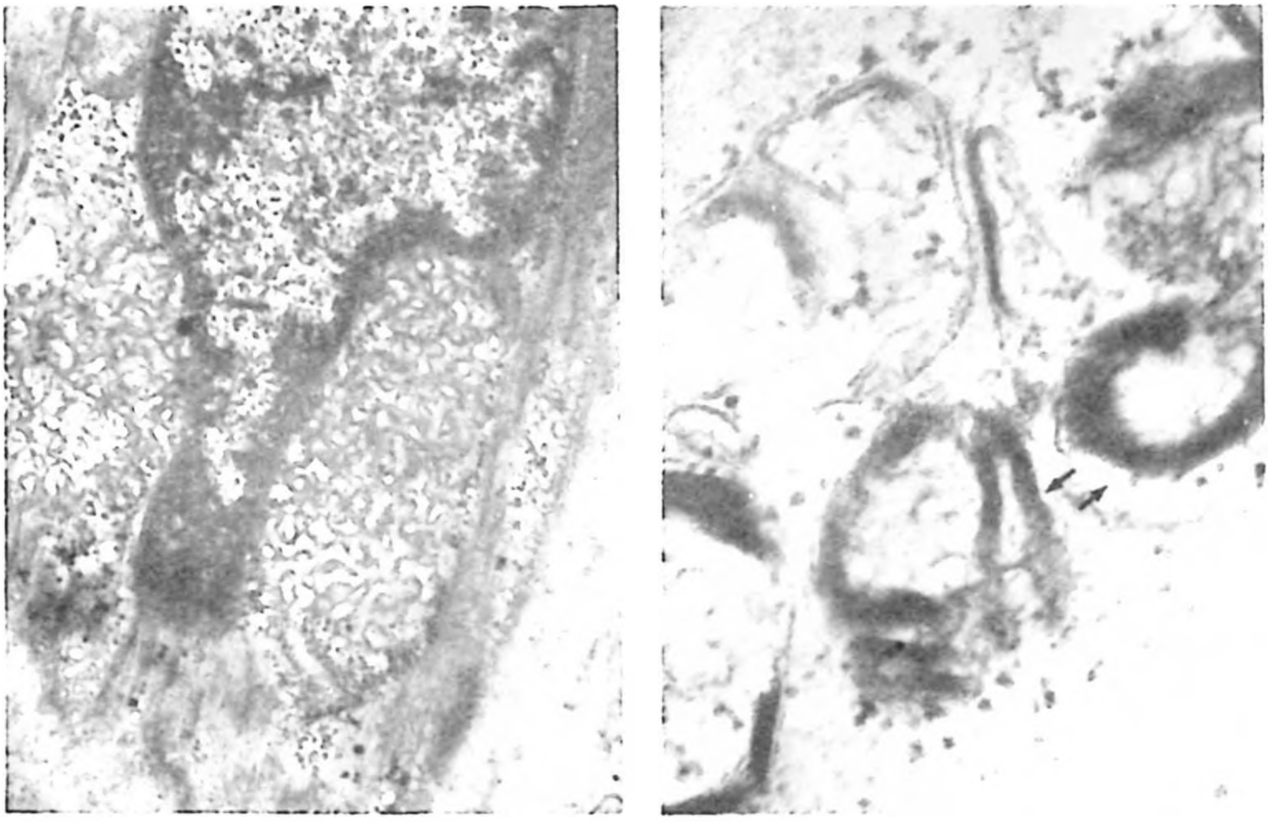

Fig. 10: Neuronal ceroid-lipofuscinoses:
a) Late infantile type, marked by numerous curvilinear bodies in dermal smooth muscle (X 16,500).
b) Juvenile type, marked by additional fingerprint (arrow) profiles, skin (X 59,780).

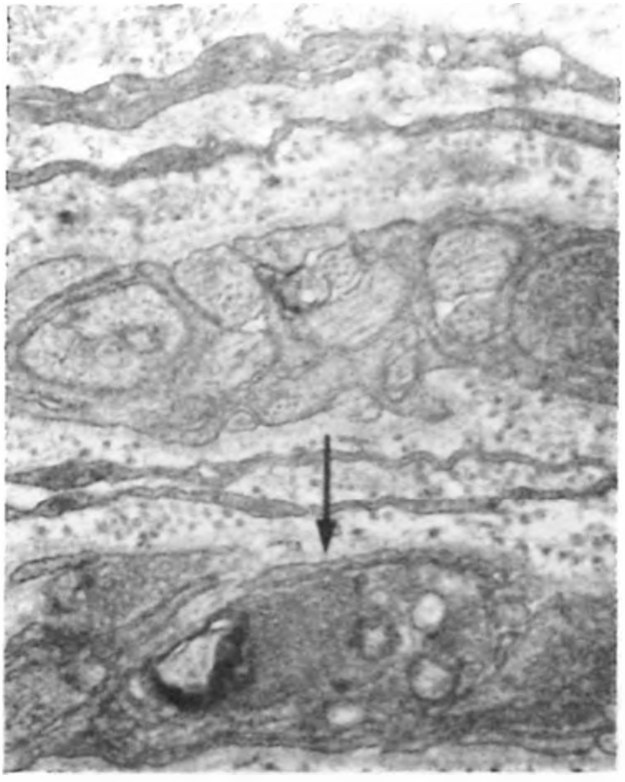

Fig. 11: Infantile neuroaxonal dystrophy:
Unmyelinated axons, enlarged (arrow) by tubulo-cisternal profiles, skin (X 21,000).

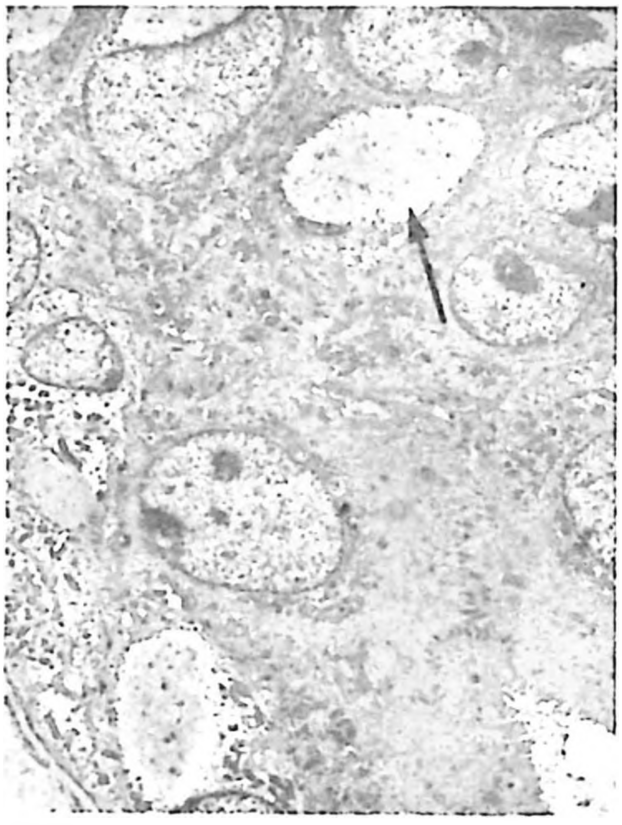

Fig. 12: Lafora disease:
Numerous light inclusions (arrow) within sweat gland epithelial cells (X 2,660).

among the peroxisomal disorders, requires the presence of myelinated axons to identify the disease-specific needle-like inclusions within Schwann cells of myelinated axons[8], while abnormally structured mitochondria may give evidence of a mitochondrial disorder, e.g., an encephalomyopathy[9]. The number of lysosomal and non-lysosomal neurodegenerative entities in childhood morphologically demonstrable in the skin is impressive[10,11] and even the almost exclusively neuronal disorders, among them the GM_2-gangliosidoses, may be typically expressed in dermal terminal axons[12]. Since conjunctiva yields similarly abundant pathological findings (Fig. 13) it remains up to the clinician to decide which of the two tissues, skin or conjunctiva, he may biopsy. The combined efforts of the ophthalmologists and electron microscopists have, indeed, resulted in recording ample ultrastructural pathology in the conjunctiva in neurodegenerative, primarily lysosomal disorders[13].

Lymphocytes. While non-lysosomal ultrastructural pathology of circulating lymphocytes is confined to the tubulo-reticular or undulating profiles (Fig. 14) of immune mediated disorders such as dermatomyositis or the acquired immunodeficiency syndrome (AIDS), among the neurodegenerative disorders only lysosomal conditions are known to be morphologically manifested in lymphocytes as vacuolar or non-vacuolar lysosomal residual bodies[14]. The former are found in

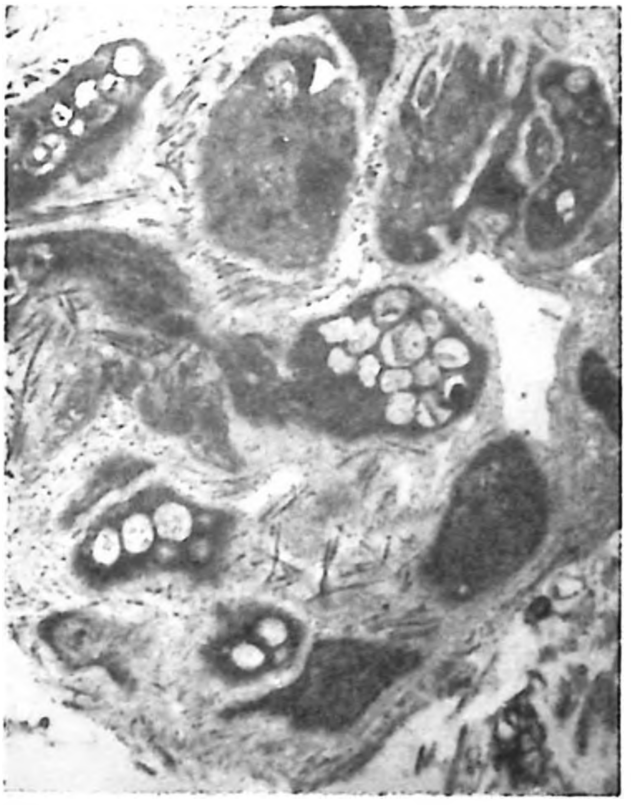

Fig. 13: I-cell disease:
Numerous vacuolated cells within a nerve fascicle of the conjunctiva (X 2,500).

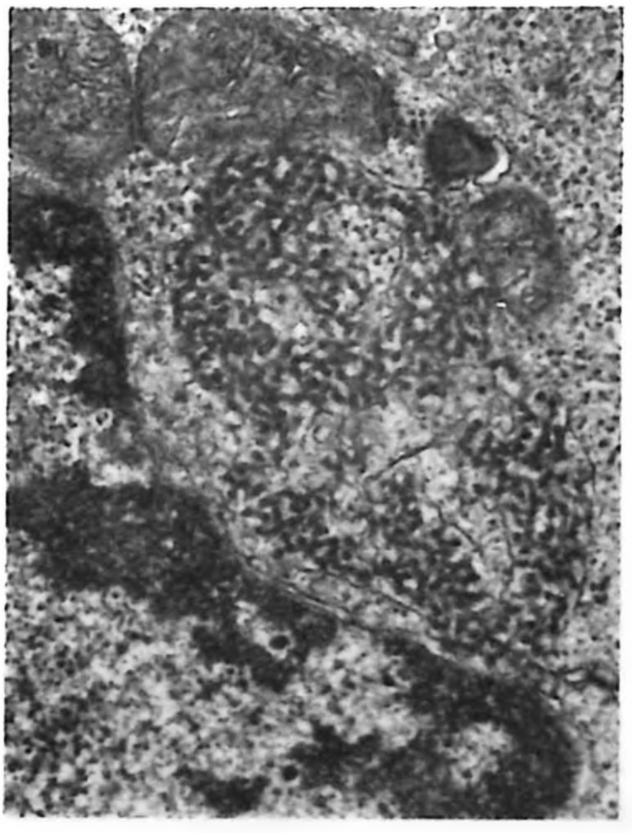

Fig. 14: Dermatomyositis:
Tubulo-reticular or undulating profiles within a circulating lymphocyte (X 33,750).

mucopolysaccharidoses, mucolipidoses I-III, certain oligosaccharidoses including Salla disease and the juvenile form of NCL (Fig. 15), in which fingerprint profiles need to be identified within lysosomal vacuoles (Fig. 15) to distinguish this condition from other lysosomal disorders. Mucolipidosis IV and the infantile (Fig. 16) and late infantile NCL as well as type II glycogenosis (Fig. 17) comprise the entities associated with non-vacuolar lysosomal inclusions. In type II glycogenosis the "non-vacuolar" aspect depends on the preservation of the intralysosomal glycogen.

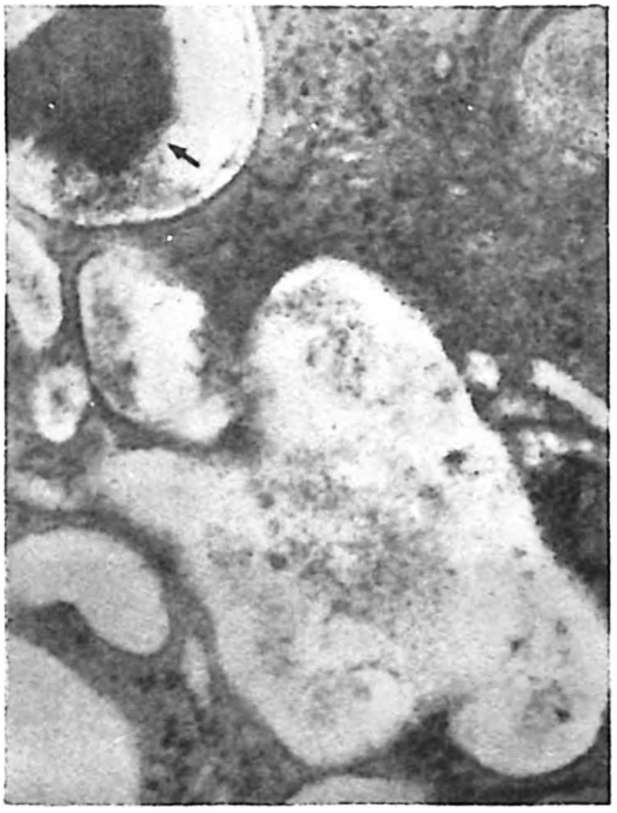

Fig. 15: Juvenile neuronal ceroid-lipofuscinosis:
Lysosomal vacuoles, one with fingerprint profiles (arrow) in a circulating lymphocyte (X 10,000).

Skeletal muscle. Striated muscle fibers–and other cell types within the skeletal muscle, e.g., mural cells of vessels, fibroblasts, cells of intramuscular nerve twigs–may be affected by lysosomal diseases, primarily the NCL[15] and in neurodegenerative diseases such as Lafora disease (Fig. 18), type IV glycogenosis[16], and generalized polyglucosan body disease[17] in which the particulate-fibrillar inclusions devoid of a limiting membrane are identical to that seen in polyglucosan body myopathy and share antigenicity with similar material in other disorders[18]. In Lafora disease, the material within muscle fibers appears membrane bound (Fig. 18). The presence of axons is essential in identifying giant axonal neuropathy and infantile neuroaxonal dystrophy, the latter condition especially when motor endplates are incorporated within the biopsied muscle

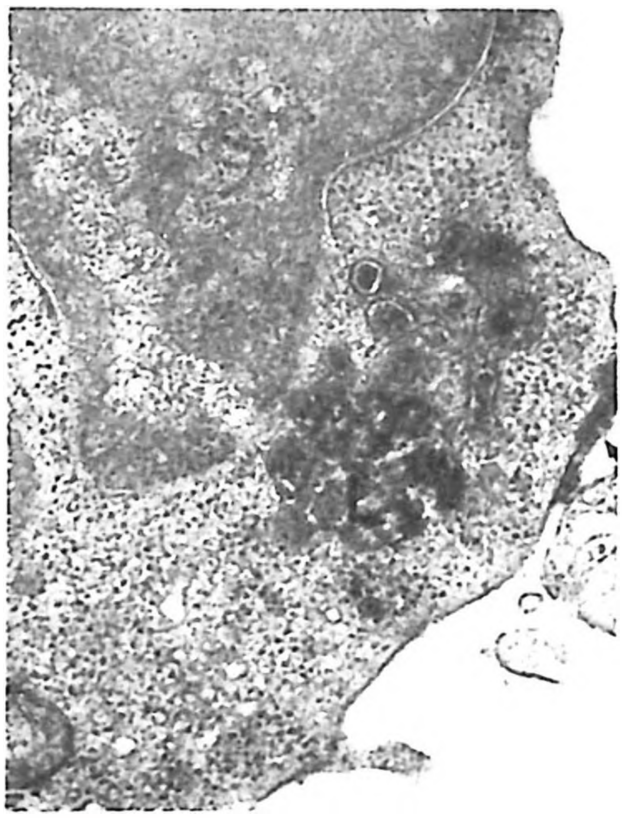

Fig. 16: Infantile neuronal ceroid-lipofuscinosis:
A solid-granular lipopigment (L) body in a labeled (arrow) circulating T-lymphocyte (X 57,000).

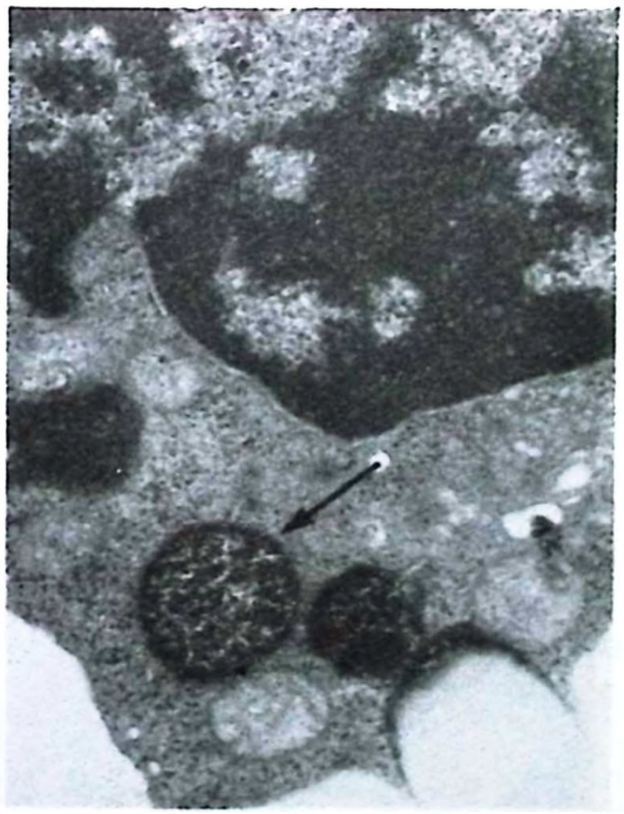

Fig. 17: Type II glycogenosis:
Lysosomal glycogen (arrow) within a circulating lymphocyte (X 25,650).

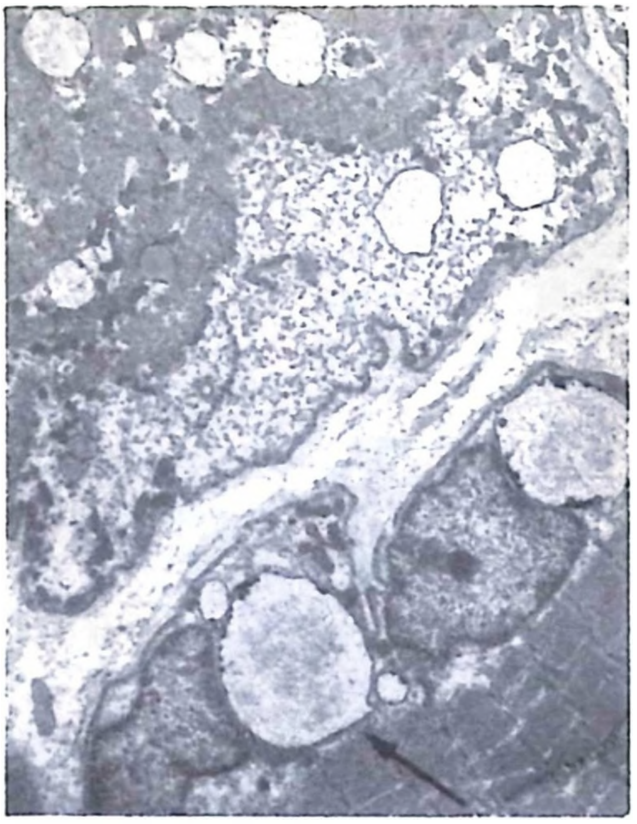

Fig. 18: Lafora disease:
Membrane-bound inclusions (arrow) within skeletal muscle fibers (X 3,040).

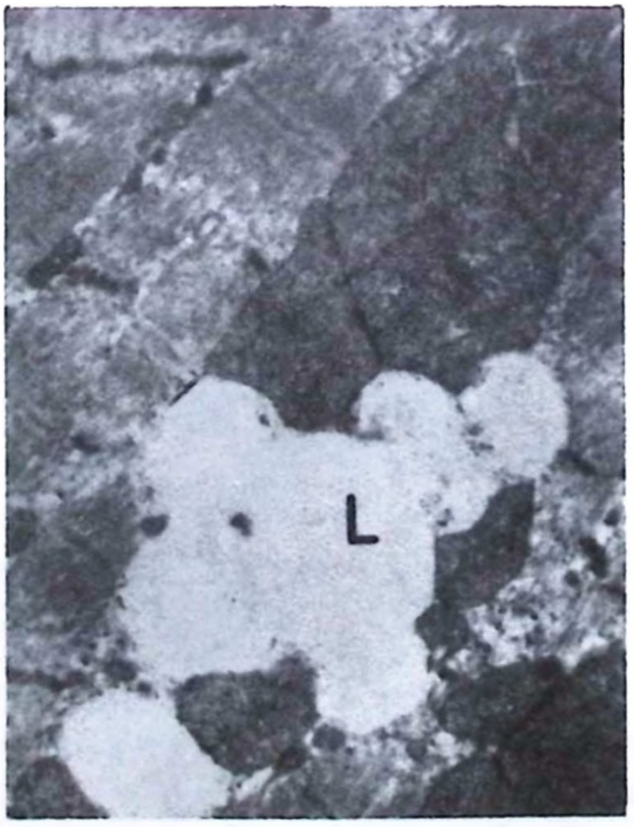

Fig. 19: Carnitine deficiency:
Aggregates of lipid (L) droplets within a striated muscle fiber (X 10,240).

tissue. In systemic carnitine deficiency, clinically associated with encephalopathic episodes, lipid droplets may abound within muscle fibers such as in other lipid myopathies (Fig. 19).

However, it is the rapidly growing number of encephalomyopathies, i.e., mitochondrial diseases that affect the skeletal muscle and the brain, that require a muscle biopsy for adequate morphological and biochemical evidence of abnormal mitochondria (Figs. 20a-c). Biochemical characterization of several encephalomyopathies, e.g., due to complex IV or cytochrome c oxidase deficiency of the respiratory chain as well as deficiencies of the pyruvate dehydrogenase complex has been based on muscle tissue studies. Tissue-specific isozymes in certain mitochondria-related encephalomyopathies, however, should caution the investigator in automatically applying to brain tissue, data retrieved from muscle tissue.

Rectum. As numerous lysosomal disorders predominantly affect the nerve cells, rectal biopsies were utilized early in diagnosis[19,20] while appendectomy furnishing appendiceal neurons served a similar purpose[21]. Since infantile neuroaxonal dystrophy is marked by proliferation of tubulo-cisternal profiles especially in synaptic regions, i.e., terminal segments of axons, it has also been successfully diagnosed in the rectum[22]. As among the neurodegenerative diseases, many are expressed in non-neural cells and such non-neural cells are present in more easily accessible tissues such as skin and conjunctiva. Since rectal tissue is frequently obtained by suction which may rarely or not at all contain neural elements, rectal biopsy has also become obsolete in the diagnostic regimen of neurodegenerative diseases of childhood.

Liver. While the liver is conspicuously affected in numerous lysosomal diseases[23], especially in Niemann-Pick disease (Fig. 21), the majority of these may be more easily recognized in other tissues. Only Gaucher disease which, however, more often than not is not a neurodegenerative disorder displays prominent hepatic-and splenic, i.e., Gaucher cells-involvement. The liver is also affected in Lafora disease accreting a particulate-fibrillar material similar to that in skeletal muscle fibers and neurons. It is, however, a recently disclosed group of peroxisomal disorders[24], especially those affecting infants, that has reemphasized the diagnostic biopsy of the liver by evaluating presence or absence, number and size of hepatic peroxisomes. In view of the easy accessibility of skeletal muscle, especially by needle biopsy, liver has not been diagnostically studied extensively in encephalomyopathies although the existence of tissue-specific mitochondrial isozymes promises to enrich our knowledge regarding this group of disorders.

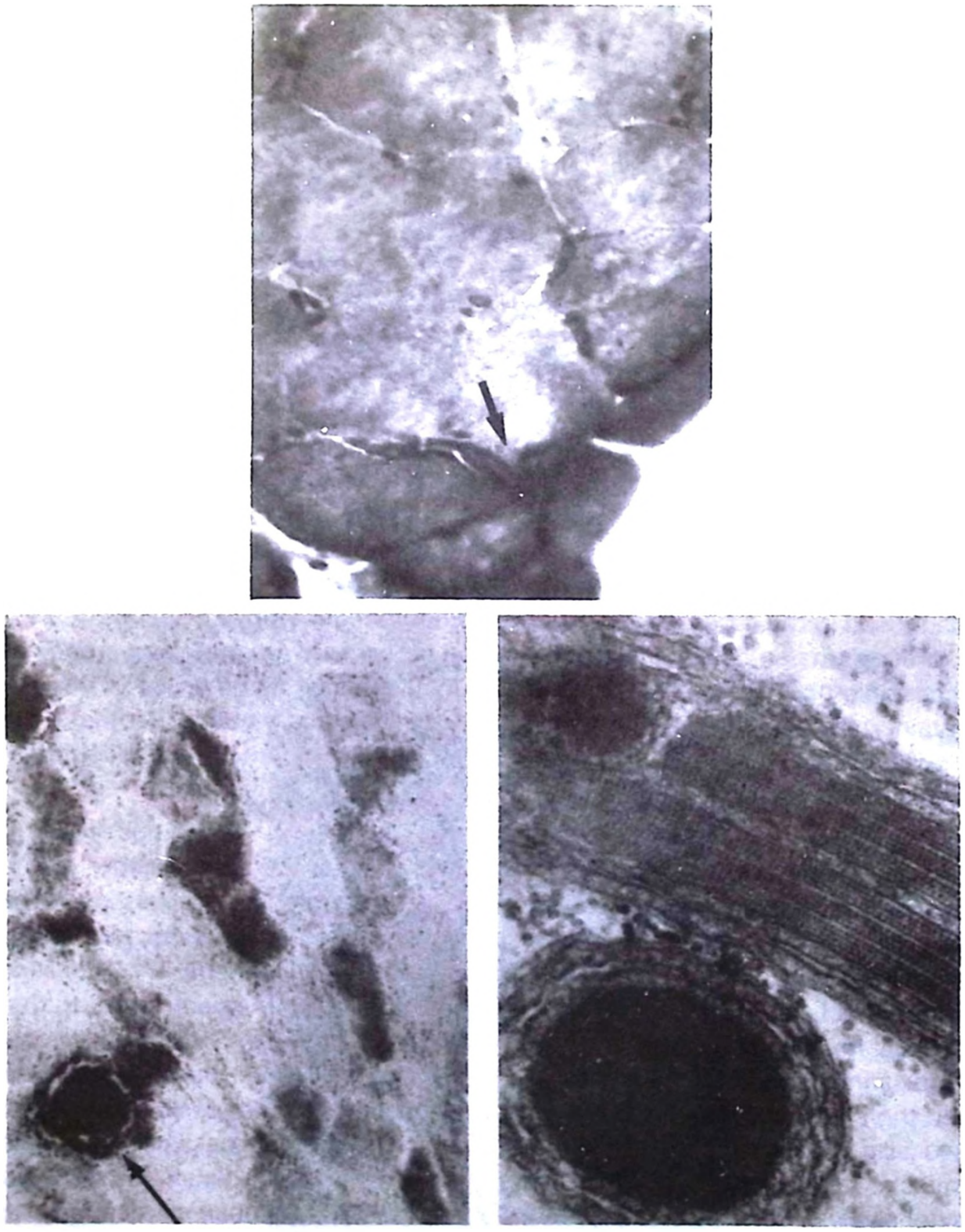

Fig. 20: Mitochondrial myopathy:
a) Ragged red fibers (arrow) (modified trichrome stain X 300).
b) Strong menadione-linked-alpha-glycerophosphate dehydrogenase activity (arrow) identifies "ragged red fibers" (X 132).
c) Abnormally structured mitochondria in a myofiber are marked by type I crystals and homogeneous dark inclusions (X 79,350).

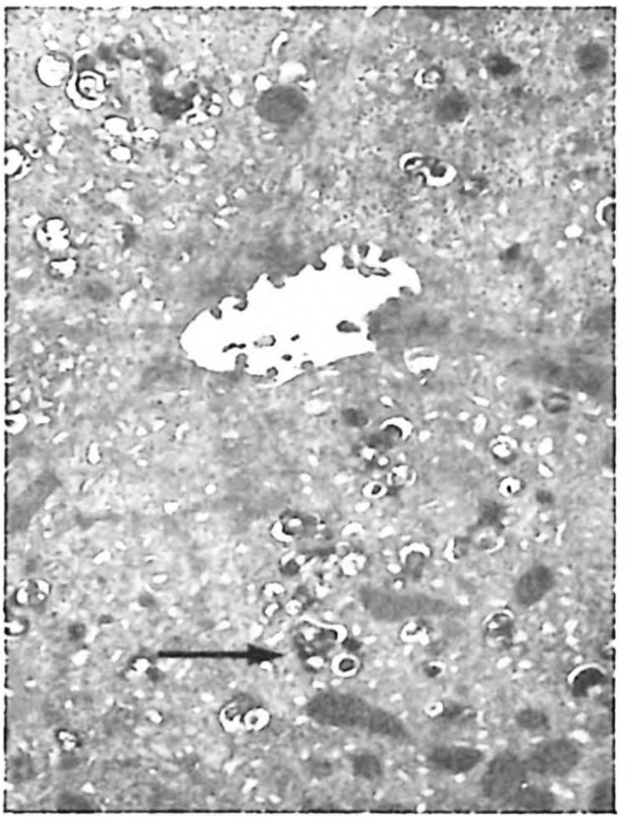

Fig. 21: Niemann-Pick disease:
Multiple membranous lysosomal inclusions (arrow) within hepatocytes (X 7,860).

Conclusions

Hesitation of the clinician to biopsy the brain and exploratory advances by the electron microscopist have procured a shift in diagnostic emphasis on non-cerebral tissues in the neurodegenerative disorders and largely eliminated diagnostic brain biopsies. Although numerous lysosomal and non-lysosomal neurodegenerative disorders may now be morphologically recognized and thus diagnosed in visceral tissues, the entire topographic spectrum of all individual neurodegenerative diseases of the nervous system has not been completely elucidated by electron microscopy. Furthermore, involvement of eccrine sweat glands in Lafora disease and identification of enlarged terminal axons in infantile neuroaxonal dystrophy require an electron microscope. Thus, only application of electron microscopy to every tissue and organ available to diagnostic biopsy will map the complete non-cerebral topography of neurodegenerative diseases. It is further conceivable that even certain neurodegenerative diseases of which gross and histological lesions are not known or appear non-specific may harbor disease-specific abnormalities to be elucidated only with the electron microscope within and/or outside of the central nervous system. Thus, it is mandatory when studying biopsied tissues from a child with a neurodegenerative disorder to always be prepared for electron microscopy–and often for biochemistry as well,

regardless of the organ or tissue biopsied and the neurodegenerative disease suspected. Although cultured fibroblasts are extremely useful in biochemical diagnosis, it is our and the experience of others that they are not suitable for morphological diagnosis.

Prenatal diagnosis by amniocentesis and chorionic biopsy largely aims at elucidating neurodegenerative and other disorders marked by chromosomal aberrations and biochemical defects. A light microscope or electron microscope is not required to ascertain such disorders. Currently, only the NCL may be successfully diagnosed in fetal cells obtained by amniocentesis, chorionic biopsy, or possibly in fetal lymphocytes. Whether infantile neuroaxonal dystrophy is already manifest in fetal skin, is not known to date.

Summary

Since brain biopsy as a means of achieving a correct antemortem diagnosis of a progressive neurodegenerative disease in childhood has largely been abandoned, the neuropathologist has resorted to studying non-neural tissues instead. Due to the fact that almost any progressive neurodegenerative disease of childhood that can be reliably recognized by brain biopsy can also be safely diagnosed in non-neural tissues, these diagnostic achievements from non-neural tissues rendered brain biopsy obsolete. The skin/conjunctiva is the tissue most suited for such in vivo diagnostic investigations while studies of other non-neural tissue such as circulating lymphocytes, rectum, peripheral nerves, skeletal muscle, and liver play only a minor role. The cytological wealth in skin specimens provides morphological information, largely based on electron microscopy, in numerous lysosomal and quite a few non-lysosomal neurodegenerative diseases of childhood.

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