Peripheral Neuropathy in Oxalosis. A Case Report with Electron Microscopic Observations

JUAN M. BILBAO, HENRY BERRY, JOSEPH MAROTTA AND RODERICK C. ROSS

SUMMARY: *A 61 year old man had chronic renal failure because of oxaluria and renal calculi. Two years before death, while on hemodialysis, he developed severe progressive peripheral neuropathy. At autopsy calcium oxalate crystals were found in the peripheral nerves and other tissues. Nerve lesions included segmental demyelination, axonal degeneration and crystalline deposits within the myelin sheath. Ultrastructurally there were foci of osmiophilic granular material within myelin lamellae and endoneurium, and pleomorphic lamellar bodies in the perinuclear Schwann cell cytoplasm.*

It is probable that chronic hemodialysis favors the deposition of oxalate in the Schwann cells and the development of neuropathy in patients with primary hyperoxaluria and renal failure.

RÉSUMÉ: *Un homme de 61 ans souffrait de déficience rénale chronique à cause d'oxalurie et de calculs rénaux. Deux ans avant sa mort, pendant qu'il était sous hémodialyse, il développa une neuropathie périphérique sévère progressive. A l'autopsie, on trouva des cristaux de calcium oxalate dans les nerfs périphériques et autres tissus. Les lésions nerveuses incluaient une démyélination segmentale, une dégénération axonale et des dépôts cristallins dans la gaine dy myéline. Au microscope électronique, il y avait des accumulations de matériel granulaire osmiophilique à l'intérieur des lamelles myéliniques et de l'endonèvre, et des corps lamellaires pléomorphiques dans le cytoplasme de la cellule de Schwann périnucléaire.*

Il est probable que l'hémodialyse chronique favorise les dépôts d'oxalate dans les cellules de Schwann et le développement de neuropathie chez les patients avec hyperoxalurie primaire et déficience rénale.

From the Departments of Pathology and Neurology, St. Michaels Hospital, and the University of Toronto.

Reprint requests to Dr. Juan M. Bilbao, Department of Pathology, St. Michaels Hospital, 30 Bond Street, Toronto M5B 1W8, Ontario. Canada.

INTRODUCTION

Disseminated extra-renal deposition of calcium oxalate crystals is characteristic of primary hyperoxaluria (Ying Chou and Donohue, 1952; Dunn, 1955). The clinical picture of this rare genetic disorder is one of recurring renal calculus formation and progressive impairment of renal function resulting in premature death (Hockaday et al., 1964 and Williams and Smith, 1972). The kidneys are invariably involved; crystals are also deposited in bone, testis, the arterial media, and within myocardial fibres, (Katsuni and Sandbank, 1959; Scowen et al., 1959 and Koten et al., 1965). Calcium oxalate deposits have been demonstrated within the central nervous system in only four reported cases of primary hyperoxaluria (Neustein et al., 1955; Scowen et al., 1959; Hughes, 1959; and Barbizet et al., 1971). In two other published cases increased concentration of oxalate in the spinal fluid was demonstrated at post mortem (Scowen et al., 1959; and Hall et al., 1960).

The case to be reported here is of special interest because of the association of oxalate deposits in Schwann cells with peripheral neuropathy occurring during chronic hemodialysis for renal failure.

It is suggested that oxalic acid is, at least in part, responsible for Schwann cell damage, leading to segmental demyelination, and axonal degeneration.

CASE REPORT

This man first developed renal calculi at the age of 20 and nephrocalcinosis and impairment of renal function at the age of 47. Recurrent renal and ureteral calculi, and urinary tract infection ensued. Hemodialysis was begun in July 1970 at the age of 59 because of rising BUN to 192 mgm%. A nephrectomy was performed in September 1970 and histologically there was chronic pyelonephritis and widespread deposition of calcium oxalate cyrstals. Diphenylhydantoin 200 mgms per day, was given for 9 months following one episode of cerebral seizures.

In December 1970 he developed numbness of hands and feet followed by Raynaud's phenomenon and progressive muscle weakness to the point that he could only walk with the help of a cane. By May 1971 there was marked atrophy of the small muscles of both hands with considerable distal weakness to all extremities. Sensory examination revealed a distal loss for all modalities extending up to the lower forearm and to above the ankles. All tendon reflexes were absent, and there was no response to plantar stimulation. Electromyographic examination of the abductor digiti minimi, tibialis anterior and frontalis muscles showed fibrillation potentials, and motor conduction times were markedly slowed in the ulnar, lateral popliteal and facial nerves. Sensory evoked responses were absent at the wrist. X-rays of bone were suggestive of renal osteodystrophy and hyperparathyroidism. Hemodialysis was continued and the BUN remained around 60 mgm%, but there was gradual progression of the neuropathy. He died in November 1972 at the age of 61 of pulmonary edema and bronchopneumonia. The patient's sister had died at the age of 36 of uremia and kidney stones.

https://doi.org/10.1017/S0317167100026020 Published online by Cambridge University Press

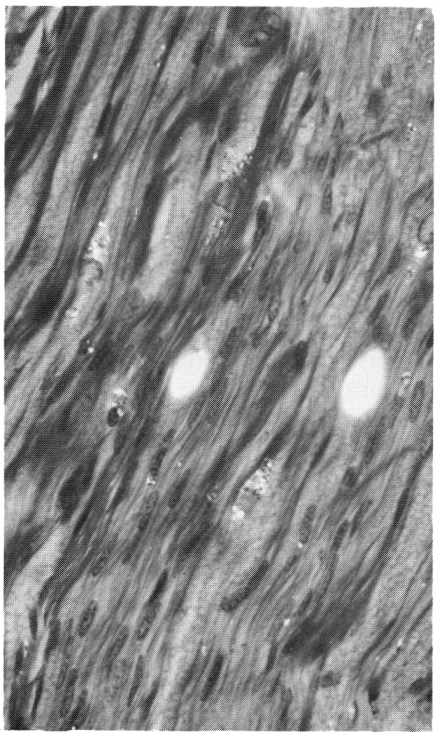

Figure 1—Right median nerve showing large crystals within nerve fibers. Fine refractile material in the vicinity of Schwann cell nuclei. Paraffin. Hematoxylin-phloxine-saffron. Half crossed polarizing filters. x250.

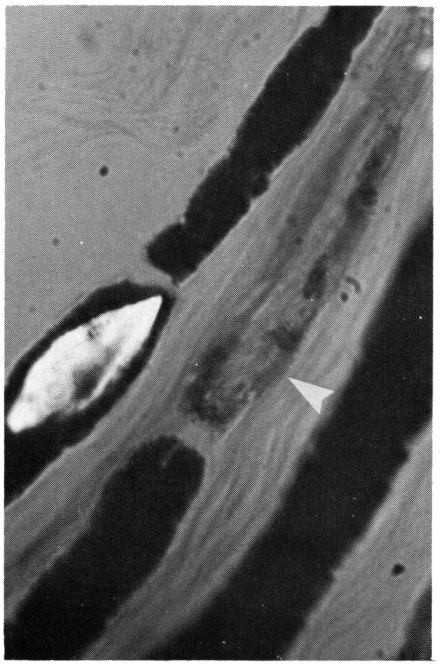

Figure 3—Teased nerve preparation showing a large crystal distending a myelinated fiber, and a demyelinated internode (arrowhead). Osmium. Half crossed polarizing filters. x1,000.

MATERIAL AND METHODS

Tissue from most organs including radial, medial, and sciatic nerves were obtained six hours after death and processed for routine microscopy. Representative pieces of nerve were post-fixed in Osmium Tetroxide after two weeks fixation in buffered formalin, individual nerve fibers were teased and whole mounted. The formaldehyde fixed nerves were post-fixed in Glutaraldehyde and Osmium Tetroxide in Cacodilate buffer and processed for electron microscopic examination. X-ray diffraction was carried out on the sediment obtained after digestion of renal tissue with sodium hydroxide (Johnson, 1972).

FINDINGS

At autopsy the remaining kidney was atrophic and gritty on sectioning. The renal cortex contained several calculi and was scarred. Other findings included an oncocytic adenoma of the parathyroid gland, and changes in bone consistent with secondary hyperparathyroidism and renal osteodystrophy. Moderately severe neurogenic atrophy was found in skeletal muscle of limb girdles. There were massive deposits of oxalate crystals in the kidney, predominantly within the proximal tubules, where crystals formed rosettes with radial striation and fissuring. Crystal deposition was also marked in trabecular bone, aorta, testes, heart and nerve (Fig. 1). The posterior pituitary gland, pancreas and cartilage of a pulmonary hamartoma contained only a few crystals. The crystals did not stain by the Von Kossa method and were identified as calcium oxalate by polarization microscopy, and X-ray diffraction of renal tissue. The brain appeared normal.

Demyelinated internodes were a prominent finding in the teased nerve preparation (Fig. 2) and Wallerian type of degeneration was also present. In addition there were numerous crystals which often appeared to distend an otherwise normal myelin sheath (Fig. 3). Amorphous refractile material was often seen in the vicinity of the Schwann cell nuclei (Fig. 4). A few crystals in

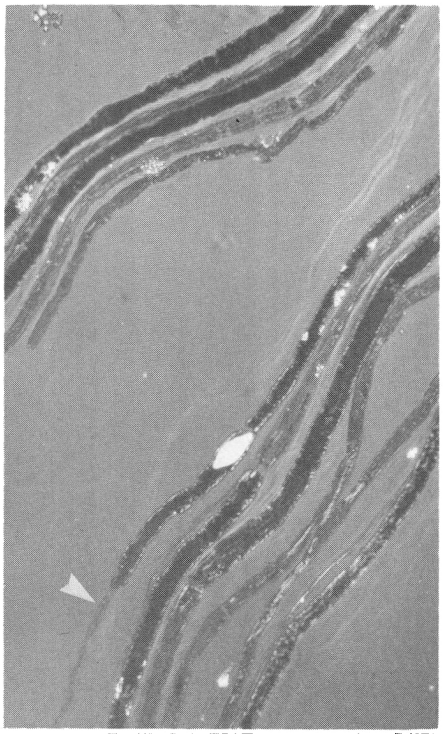

Figure 2—Teased nerve preparation. Crystal within myelin sheath. Demyelinated internode (arrowhead). Amorphous refractile material at the periphery of some myelinated fibers. Osmium. Half crossed polarizing filters. x250.

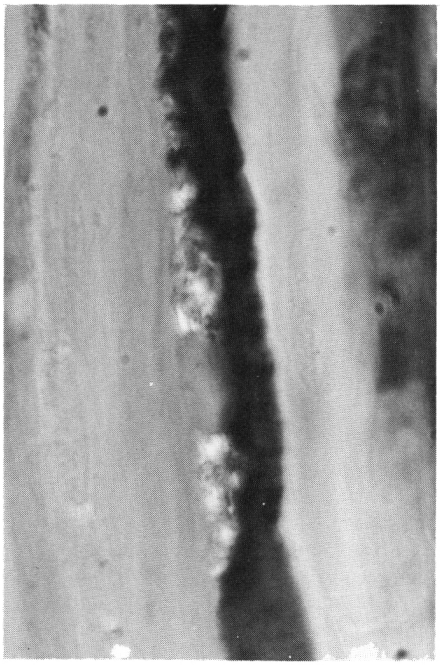

Figure 4—Teased nerve preparation demonstrating amorphous refractile material adjacent to Schwann cell nucleus. Osmium. Half crossed polarizing filters. x1,000.

https://doi.org/10.1017/S0317167100026020 Published online by Cambridge University Press

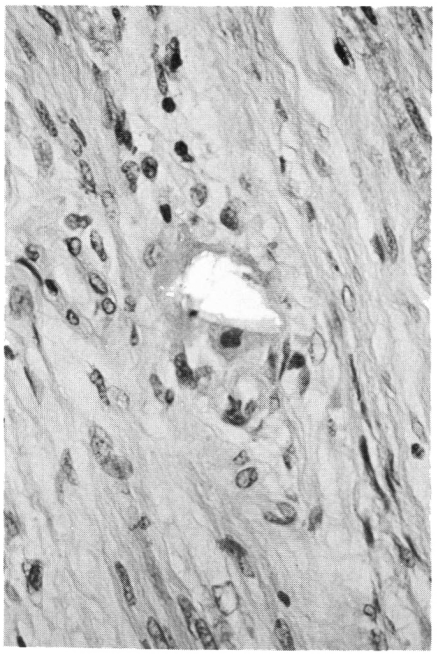

Figure 5—Sciatic nerve. Crystal within histiocyte in endoneurial perivascular space. Paraffin. HPS. Half crossed polarizing filters. x250.

the endoneurium were seen surrounded by, and within giant cells (Fig. 5). Endoneurial and epineurial blood vessels were not involved.

On electron microscopic examination myelinated fibers appeared moderately diminished in number; some of the remaining fibers showed myelin ovoids suggesting segmental demyelination. Demyelinated axis cylinders were common (Fig. 6), as were empty Schwann cells and denervated bands of Bungner. The axons of a few normally myelinated fibers contained aggregates of organelles indicating early axonal degenerative changes. Some myelin lamellae were separated by granular osmiophilic material (Fig. 7). It could not be ascertained whether these granular deposits were primarily between major dense lines or intraperiod lines. The Schwann cell cytoplasm very often contained pleomorphic bodies composed of multi-layered stacks of non-membrane bound osmiophilic substance (Fig. 8) which in other cells showed a more homogeneous core (Fig. 9). Lying free in the endoneurium, adjacent to collagen fibres, there were also masses of finely granular, moderately osmiophilic material similar to the structures shown in Fig. 7.

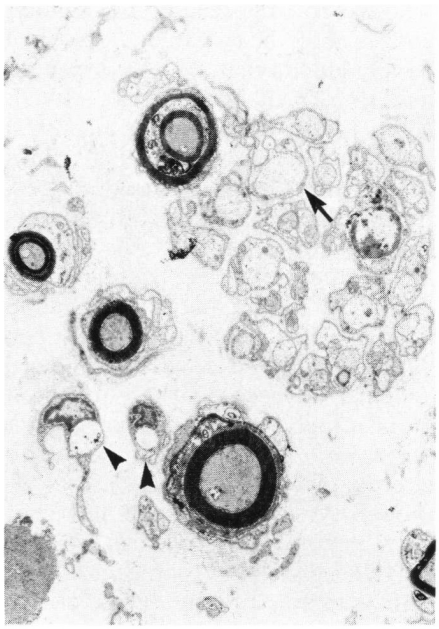

Figure 6—Cross section of radial nerve showing decreased number of myelinated fibers, demyelinated axon (arrow) and empty Schwann cells (arrowhead). x3,490.

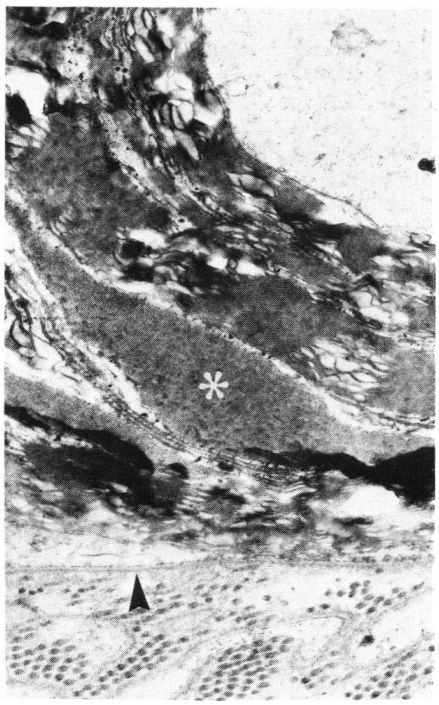

Figure 7—Finely granular osmiophilic material separating myelin lamellae (asterisk). Schwann cell basement membrane (arrowhead). x 23,965.

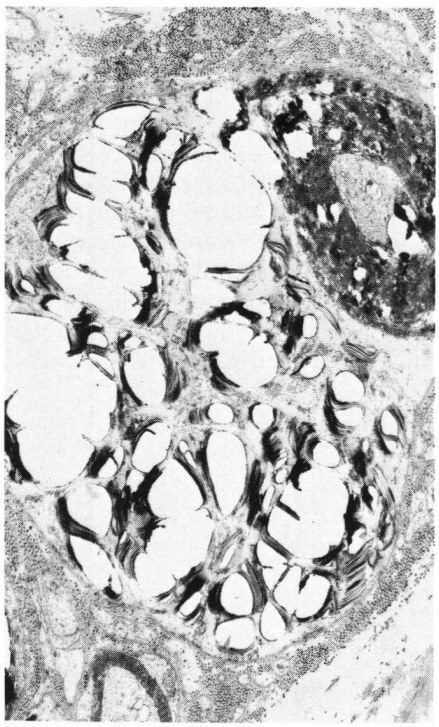

Figure 8—Schwann cell cytoplasm distended by stalks of multilayered bodies. x5,107.

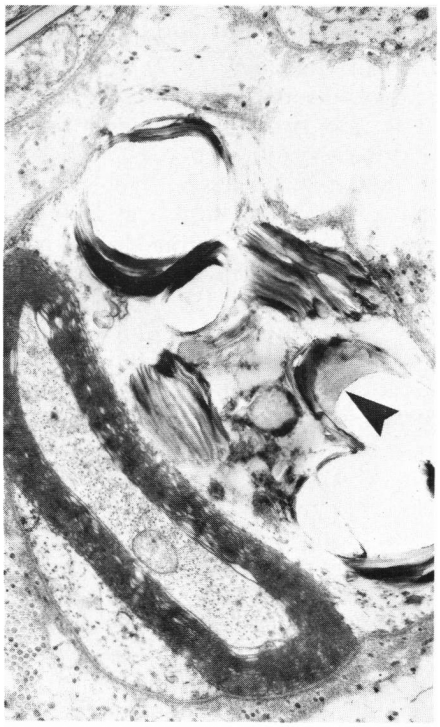

Figure 9—Lamelarr bodies similar to those shown in Fig. 8, with an homogeneous core (arrowhead). x16,751.

https://doi.org/10.1017/S0317167100026020 Published online by Cambridge University Press

DISCUSSION

There have been previous reports of the occurrence of peripheral neuropathy in patients with oxalosis who were maintained by hemodialysis. One of these patients also had developed Raynaud's phenomenon, case No. 3 of Walls et al. (1969). More recently Boquist et al. (1973) reported the histological findings in a patient with primary hyperoxaluria and polyneuropathy following hemodialysis. Some amorphous masses were found in the peripheral nerve, but no crystalline deposits were demonstrated. The patient exhibited severe peripheral vascular disease and an impaired blood supply was though to account for the development of the neuropathy. It is of interest that although cyrstalline deposits have not been reported in oxalosis due to ethylene glycol poisoning, areflexia is a common finding (Pons et al., 1946).

The recognition of crystals of calcium oxalate in myelinated fibers on teased nerve preparations in our case leaves no doubt that oxalic acid entered the Schwann cells and formed precipitates of calcium oxalate. The low toxicity of calcium oxalate (Roscher, 1971) apparently allows prolonged survival of affected cells. The structures shown in Fig. 7 may be the ultrastructural correlate of the crystals seen by light microscopy. However, they bear little resemblance to the needle-shaped particles described in primary oxalosis (Boquist et al., 1973) and the fibrillary material with homogeneous cores seen in experimental ethylene glycol oxalosis (Fonck-Cussac et al., 1971). The finely refractile amorphous perinuclear material shown in Fig. 4 and the lamellar bodies of Figs. 8 and 9 are perhaps nonspecific degenerative changes of the Schwann cells. They resemble the structures shown by Tomonaga and Sluga (1970) as Reich's π granules.

It has been established that hemodialysis is not capable of removing adequate amounts of oxalate from the body (Walls et al., 1969; Zarembski et al., 1969; Mahoney et al., 1972; and Boquist et al., 1973). Hence, it is possible that a neuropathy developed in this patient after the hemodialysis because of the increase in the body pool of oxalic acid. This is a highly toxic substance which may conceivably lead to segmental demyelination and axonal damage.

Approximately two-thirds of patients on hemodialysis have mild peripheral neuropathy as shown by neurophysiologic and morphometric methods (Dyck et al., 1975). Severe peripheral neuropathy may also develop in patients on dialysis (Tenckhoff, 1965). Intensification of the dialysis may bring about an arrest in the progression of uremic neuropathy or even an improvement (Jebsen et al., 1967). The mechanism by which hemodialysis affects the course of a neuropathy remains undetermined. It may then be argued that in our patient the peripheral neuropathy was associated with renal failure (Dinn, 1970; and Dyck, 1971) and inadequate hemodialysis, and so incidental to the basic metabolic disease, primary hyperoxaluria. However, the presence of crystals of calcium oxalate in peripheral nerves, within myelinated fibers and endoneurium provides indirect evidence that oxalic acid may be responsible for the development of a polyneuropathy in patients with primary hyperoxaluria on chronic hemodialysis. We suggest that the metabolism of oxalic acid by studied in all patients on chronic hemodialysis who develop peripheral neuropathy. It would appear that the development of peripheral neuropathy is an absolute contraindication for hemodialysis in renal failure due to primary hyperoxaluria.

ACKNOWLEDGEMENTS

The Authors appreciate the valuable advice of Dr. M. H. Finlayson, of the Montreal General Hospital, and the secretarial help of Mrs. Doreen Mead.

REFERENCES

BARBIZET, J., WORMS, R., BRION, S., MIKOL, J., DESCROIX, R., et GALIAN, A. (1971). Observation anatomo-clinique d'une oxalose generalisée associée à une sclerose du cervelet. Révue Neurologique, 125, 409-423.

BOQUIST, L., LINDQVIST, B., OESTBERG, Y. and STEEN, L. (1973). Primary oxalosis. The American Journal of Medicine, 54, 673-681.

DINN, J. J. and CRANE, D. L. (1970). Schwann cell dysfunction in uremia. Journal of Neurology Neurosurgery and Psychiatry, 33, 605-608.

DUNN, H. G. (1955). Oxalosis. Report of a case with review of the literature. The American Journal of Diseases of Children, 90, 58-80.

DYCK, P. J., JOHNSON, W. J., LAMBERT, E. H. and O'BRIEN, P. C. (1971). Segmental demyelination secondary to axonal degeneration in uremic neuropathy. Mayo Clinic Proceedings, 46, 400-436.

DYCK, P. J., JOHNSON, W. J., LAMBERT, E. H. BUSHEK, W. and POLLOCK, M. (1975) Detection and evaluation of uremic peripheral neuropathy in patients on hemodialysis. Kidney International 7, Supplement No. 2, 201-205.

FONCK-CUSSAC, Y., AUBLET-CUVELIER, J. L., FONCK, J. et DELAGE, J. (1971). Etude ultrastructural du rein dans l'oxalose experimentale par l'ethylene glycol. Annales d'anatomie Pathologique (Paris), 16, 153-158.

HALL, E. G., SCOWEN, E. F. and WATTS, R. W. E. (1960) Clinical manifestations of primary hyperoxaluria. Archives of Disease in Childhood, 35, 108-112.

HOCKADAY, T. D. R., CLAYTON, J. E., FREDERICK, E. W. and SMITH, L. H. Jr. (1964). Primary hyperoxaluria. Medicine, 43, 315-345.

HUGHES, D. T. (1959). The clinical and pathological background of two cases of oxalosis. Journal of Clinical Pathology, 12, 498-509.

JEBSEN, R. H., TENCKHOFF, H. and HONET, J. C. (1967). Natural history of uremic polyneuritis and effect of dialysis. New England Journal of Medicine, 277, 327-333.

JOHNSON, F. B. (1972). Crystals in pathology specimens. In Pathology Annual, edited by Sommers S. C. Vol. 7. Appleton-Century-Crofts, New York.

KATZUNI, E. and SANBANK, U. (1959). Oxalosis. Archives of Disease in Childhood, 34, 60-62.

KOTEN, J. W., VANGASTEL, C., DORHOUT MEES, E. J., HOLLEMAN, L. W. J. and SCHUILING, R. D. (1965). Two cases of primary oxalosis. Journal of Clinical Pathology, 18, 223-229.

MAHONEY, J. F., STOREY, B. G., McCARTHY, S. W. and STEWART, J. H. (1972). Treatment of oxaluric renal failure. New England Journal of Medicine, 287, 1252-1253.

NEUSTEIN, H. B., STEVENSON, S. S. and KRAINER, L. (1955). Oxalosis with renal calcinosis due to calcium oxalate. Journal of Pediatrics, 47, 624-633.

PONS, C. A. and CUSTER, R. P. (1946). Ethylene glycol poisoning. A clinicopathologic report of 18 cases. The American Journal of Medical Science, 211, 544-552.

ROSCHER, A. A. (1971). A new histochemical method for the demonstration of Ca oxalate in tissues following ethylene glycol poisoning. The American Journal of Clinical Pathology, 55, 99-104.

SCOWEN, E. F., STANSFIELD, A. G. and WATTS, R. W. E. (1959). Oxalosis and primary oxaluria. Journal of Pathology and Bacteriology, 77, 195-205.

TOMONAGA, M. and SLUGA, E. (1970). Zur ultrastruktur der π granula: Acta Neuropathologica (Berlin) 15, 56-69.

TENCKHOFF, H. A., BOEN, F. T., JEBSEN, R. H. and SPIEGLER, J. H. (1965). Polyneuropathy in chronic renal insufficiency. Journal of American Medical Association, 192, 91-94.

WALLS, J., MORLEY, A. and KERR, D. N. S. (1969). Primary hyperoxaluria in adult siblings. With some observations on the role of regular hemodialysis therapy. British Journal of Urology, 41, 546-553.

WILLIAMS, H. E. and SMITH, L. H. (1972). Primary hyperoxaluria. Stanbury, J. S. Editor. The metabolic basis of inherited disease. McGraw Hill Book Company, 196-219.

YING CHOU, L. and DONOHUE, W. L. (1952). Oxalosis: "inborn error of metabolism" with nephrolithiasis and nephrocalcinosis due to calcium oxalate as predominating features. Journal of Pediatrics, 10, 660-666.

ZAREMBSKI, P. M., ROSEN, S. M. and HODGKINSON, A. (1969). Dialysis in the treatment of primary hyperoxaluria. British Journal of Urology, 41, 530-533.

https://doi.org/10.1017/S0317167100026020 Published online by Cambridge University Press