myocardial ischemia is the first reported observation of hepatic ischemia during acute MI. This 60% reduction in liver blood flow could result in a marked reduction in oxygen availability to the liver and impaired liver function. Previously, it has been demonstrated that prolonged hypoxia or ischemia can result in a loss of liver cellular integrity[13]. In this regard, Dunn et al.[14] noted during congestive heart failure liver injury is often a complicating factor. However, animals experiencing a reduced liver blood flow may be able to compensate for the decreased oxygen delivery by increasing the extraction of oxygen from the blood. Such compensation could mask the effects of an acute reduction in liver blood flow. Furthermore, since the clearance of many substances by the liver is dependent on blood flow[15], a significant decreased flow could compromise the clearance capacity of the liver. In this regard, Lautt[12] has reported that a reduction in hepatic blood flow is accompanied by a decrease in the removal of substances from the blood. Thomson et al[16] reported that in clinical situations associated with reduced hepatic blood flow, the incidence of toxic reactions to lidocaine was increased.

In summary, myocardial ischemia results in a significant reduction in liver blood flow 2 h after coronary artery occlusion. This decrease progresses so that total liver blood flow is only 40% of initial values at 5 h. The resulting ischemia to the liver may contribute to the pathophysiology of myocardial ischemia.

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3 A.M. Lefer, in: Cardiovascular Clinics, p.25. Ed. A.N. Brest. F.A. Davis Co. Philadelphia 1975.
4 E. Braunwald, in: Pathophysiology and Therapeutics of Myocardial Ischemia, p.265. Ed. A.M. Lefer, G. Kelliher and M.J. Rovetto. Spectrum Publications, New York 1977.
5 A.G. Gornall, C.J. Bordowill, and M.M. David, J. biol. Chem. *177*, 751 (1949).
6 S.B. Rosalki, J. Lab. clin. Med. *69*, 676 (1967).
7 M.L. Ogletree and A.M. Lefer, Circulation Res. *42*, 218 (1978).
8 M.L. Ogletree, J.T. Flynn, M. Feola, and A.M. Lefer, Surgery Gynec. Obstet. *144*, 734 (1977).
9 J. Spath and A.M. Lefer, Am. Heart J. *90*, 50 (1975).
10 D.H. Johnson, J. Physiol. *126*, 413 (1954).
11 J.L. Nxumalo, M. Teranaka, and W.G. Schenk, Archs Surg. *113*, 169 (1978).
12 W.W. Lautt, Gen. Pharmac. *8*, 73 (1977).
13 M.J. Galvin and A.M. Lefer, Life Sci. *20*, 1969 (1977).
14 G.D. Dunn, P. Hayes, and K.J. Breen, Am. J. med. Sci. *265*, 174 (1973).
15 G. Biozzi and C. Stiffel, in: Progress in Liver Disease, p.11. Ed. H. Popper and F. Schaffner. Grune and Stratton, New York 1965.
16 P.D. Thomson, P.M. Rowland and M.L. Melmon, Am. Heart J. *82*, 417 (1971).

Fine structural correlations between the muscle pathology of amyotrophic lateral sclerosis (ALS) patients and experimental Ca-Mg deficient rats

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Summary. Nonspecific myofibrillar changes such as streaming of the Z-line, formation of rod-like structures, satellitosis, proliferation of sarcolemmal nuclei and papillary projection of the sarcolemma were recognized as a disorganization of the muscle itself. In addition, fine structural pathology in ALS specimens showed characteristically a pig-tail formation - 'Zopfformation'- which has been considered to have a neurogenic origin.

Although amyotrophic lateral sclerosis (ALS) is a systemic degenerative disease of unknown etiology, involving motor neurons selectively, the possible participation of Ca dysmetabolism in the pathogenetic process of ALS has recently been indicated[1,2]. In relation to this, experimental studies on rats fed a Ca-Mg-deficient diet have been done, with the interesting finding that there was muscle fibre atrophy in white muscle (type II fibre), and a decreased activity of the enzyme succinic dehydrogenase in the gastrocnemius muscle[3, 4]. In this study, myofibrillar changes found specifically in ALS patients and Ca-Mg-deficient rats are demonstrated.

Materials and methods. Human muscle specimens were obtained from biopsied gastrocnemius muscle from 3 cases of ALS. Muscle specimens from experimental animals were obtained from 4 Ca-Mg deficient rats and 5 control rats. 4 experimental rats were fed a Ca-Mg deficient diet for a period of 5-15 weeks. The body weight of the animals continuously decreased during the period of the experiment. Total body weight loss was about 47%. Human muscle specimens were fixed in 1% OsO_4 adjusted with 0.1 M cacodylate buffer (pH 7.4) for 2 h. Experimental animals were perfused with 4% paraformaldehyde-0.5% glutaraldehyde adjusted with 0.1 M cacodylate buffer (pH 7.4) and post-fixed in 1% OsO_4 adjusted with 0.1 M cacodylate buffer (pH 7.4). After fixation, muscle specimens were dehydrated with ethanol and embedded in epoxy resin. Ultrathin sections stained with uranyl acetate and lead citrate were examined under JEOL 100C and T7 model electron microscopes.

Results and discussion. In biopsied muscle specimens from ALS cases, strikingly abnormal features were demonstrated in the sarcolemma and sarcoplasm, as seen in figure 1, showing multiplicative sarcolemmal nuclei (figure 1, a) and papillary projection of the sarcolemma (figure 1, b). In addition, there was proliferation of the satellite cells, and cell wandering at the intermuscular space.

Experimental studies of muscle specimens of Ca-Mg deficient rats revealed papillary projection of the sarcolemma, satellitosis and proliferation of sarcolemmal nuclei, which are similar pathological changes to those observed in the ALS specimens. Besides, infolding or invagination appeared in the nuclear membranes of satellite cells and sarcolemmal nuclei.

Such changes; sarcolemmal papillary projection, and reactive satellite cells and sarcolemma, are commonly described as myopathic changes in skeletal muscle[5]. Satellite cell proliferation in denervated muscle has been frequently observed in hypertrophied muscles rather than in atro-

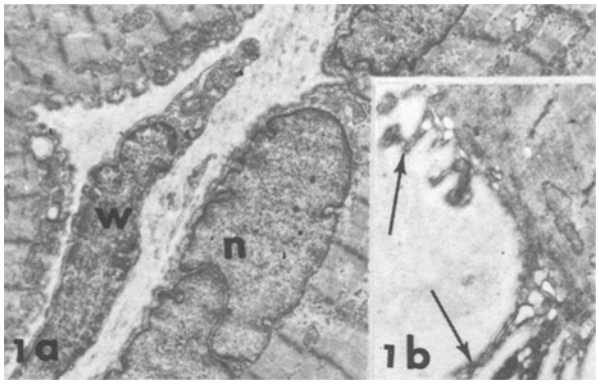

Fig. 1. Showing the multiplictive sarcolemmal nuclei (n) and the wandering cell (w) in (a), and sarcolemmal papillary projection (arrows) in (b). The type II muscle fibre of ALS. × 5800, × 10,000.

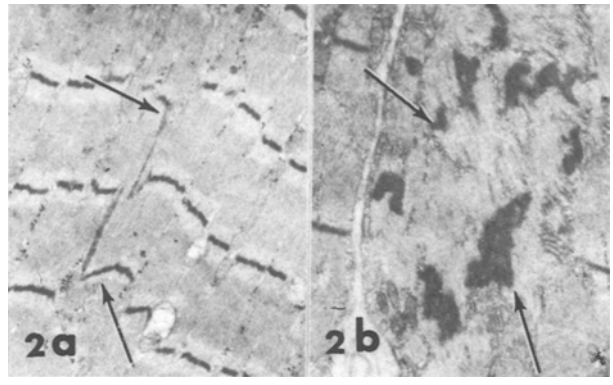

Fig. 2. Streaming of Z-line (arrow) in (a) and nemalin-like rod formation in the superficial zone gastrocnemius muscle (b), of the type II fibre of Ca-Mg deficient rat. × 6750, × 19,500.

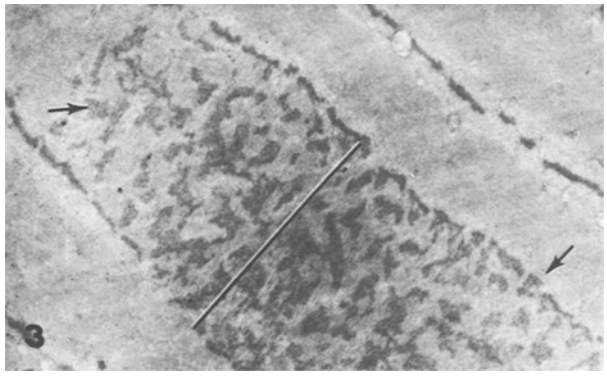

Fig. 3. Electron dense rods (arrows) arrangement between the Z-line (——) in the gastrocnemius muscle of the Ca-Mg deficient rat. × 9900.

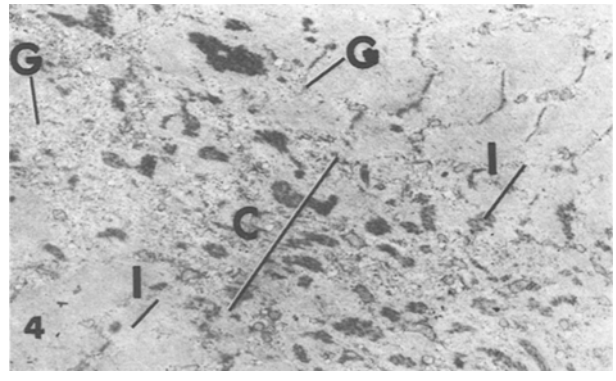

Fig. 4. 'Zopfformation' consists of normal, intermediate (1) and central (c) zones. Numerous glycogen are indicated by G. × 5350.

phied[6]. It is certain that the proliferation of satellite cells and sarcolemmal nuclei results from a nonspecific chronic dysfunction of muscle fibres as it is an early finding in myogenic and even in neurogenic disorders.

Myofibrillar changes during degenerative processesin Ca-Mg deficient rat muscle were identified with a streaming of the Z-line, which appeared in the peripheral zone of the type II fibre and was shown as connection between 2 different myofibrils forming a Z-shaped bridge. In other degenerating muscle fibres 2 kinds of nemalin-like rod structures appeared in the peripheral zone of the muscle fibre; irregular shaped rods (figure 2, b) and electron dense rods in parallel with 2 Z-lines (figure 3).

These myofibrillar changes may be explained as a reaction to such lesions of the muscle itself as denervation atrophy[7], toxic myopathy with late onset[8-11], hypothyroidism myopathy[12], Thomsen's disease[13], tenotomy[14], etc. Morton[14] also suggested that the Z-line streaming represents a normal adaptive response of muscle to workload stress.

In the ALS specimens, Z-line streaming, rod-like structure and 'Zopfformation' were recognized as abnormal structures of myofibrils in the degenerative type II fibre (figure 4). 'Zopfformation' is pig-tail in form and the 3 parts consists of normal sarcomere, an intermediate zone containing a small electron dense fragment, and a large electron dense irregular rod in the central zone. The fragments in the intermediate and the central zone are composed of Z-line material which appears to be surrounded by numerous glycogen particles.

It is, therefore, concluded that the rod-like structures and streaming of Z-line as well as 'unstructured cores'[16] may represent a nonspecific response of muscle fibre to a lesion of the muscle itself, while 'Zopfformation' may be found in neurogenic disorders[15, 17, 18].

1 Y. Yase. Lancet *2*, 292 (1972).
2 L.E. Mallette, B. Patten, T.D. Cook and W.K. Engel, Dis. Nerv. Syst. *6*, 457 (1977).
3 T. Kumamoto, S. Nakagawa, C. Suematsu, E. Shimizu, Y. Yata and T. Hirohata, Acta histochem. cytochem. *8*, 4 (1975).
4 S. Nakagawa, C. Suematsu, E. Shimizu, T. Hirohata, N. Ito, K. Matsumoto, T. Kasamatsu and T. Kumamoto, J. Wakayama Med. Soc. *26*, 281 (1975).
5 A.G. Engel and R.D. Macdonald, in: Muscle Diseases. p. 71. Ed. T.N. Walton, N. Canal and G. Scarlato. Excerpta Medica, Amsterdam 1970.
6 V. Hanzlikova, E.V. Macková and P. Hník, Cell Tissue Res. *160*, 411 (1975).
7 C.O. Pellegrino and C.O. Franzini, J. Cell Biol. *17*, 327 (1963).
8 N.B. Rewcastle and J.G. Humphrey, Archs Neurol. *12*, 570 (1965).
9 W.K. Engel and J.S. Resnick, Neurology *16*, 308 (1966).
10 A.G. Engel, May clin. Proc. *41*, 713 (1966).
11 L.P. Heffernan, N.B. Rewcastle and J.G. Humphrey, Archs Neurol. *18*, 529 (1968).
12 M. Fardeau, in: Muscle Diseases. p. 98. Ed. T.N. Walton, N. Canal and G. Scarlato. Excerpta Medica, Amsterdam 1970.
13 R. Garcin, A. Dubois-Poulsen, A. and M. Fardeau, Wien. Z. NervHeilk. *25*, 172 (1967).
14 D.J. Morton, in: Basic Research in Myology, p. 483. Ed. Kakulas. Excerpta Medica, Amsterdam 1973.
15 M. Tomonaga and E. Sluga, in: Muscle Diseases, p. 120. Ed. J.N. Walton, N. Canal and G. Scarlato. Exerpta Medica, Amsterdam 1970.
16 H.E. Neville and M.H. Brooke, in: Basic Research Myology, p. 497. Ed. B.A. Kakulas. Excerpta Medica, Amsterdam 1973.
17 W.K. Engel, Nature, Lond. *191*, 389 (1961).
18 J. Kovarsky, S.S. Schochet, Jr, and W.F. Mc Cornick, Am. J. clin. Path. *59*, 790 (1973).