SUMMARY AND CONCLUSIONS
The present study was undertaken to compare the morphological features of skeletal muscle in infantile neuromuscular disorders with human foetuses at different gestational ages utilizing histological, histochemical and electron microscopic techniques. Skeletal muscle biopsies from 81 patients submitted for routine diagnosis and muscle from 18 foetuses of age group ranging from 9 to 36 weeks were studied.

In the development of normal human foetal skeletal muscle, it was noticed that during 9-10 weeks of foetal life, the myotubes predominated the picture. Migration of centrally located nuclei to the subsarcolemmal position occurred at 14th week of embryonic life. Histochemical differentiation into major fibre types (type-I and type-II) was noticed by the 24th week of gestation. At 28th week, distinct checkerboard pattern was observed. Electron microscopic investigations revealed mature myotubes predominantly at 14th - 15th weeks of gestation. Mature fibres were formed by the fusion of myotubes. Membrane densities present on the adjoining cells forming mature myotubes were considered as probable sites of fusion.

Of the total number of 81 biopsies studied, spinal muscular atrophies (SMA-1, SMA-2) constituted the major disease entity presenting as infantile neuromuscular disorder.
22 cases were diagnosed as having SMA-1 (27.16%) and 13 cases as SMA-2 (16.05%). Our observations suggest that denervation atrophy to be the basic pathogenetic mechanism rather than arrest of maturation in these two groups of SMA. This hypothesis was further supported by the changes seen in the spinal cord specimen of a 20-day-old infant from a case of Werdnig-Hoffmann disease such as marked fallout of anterior horn cells, chromatolysis of the surviving neurons and gliosis. In a comparison with the foetal muscle development it was found that SMA-1 was due to denervation occurring in the embryonic life possibly after differentiation into major histochemical fibre types. On the other hand, the pathogenesis in SMA-2 appeared to be due to denervation starting early in the postnatal life.

Although congenital muscular dystrophy is a relatively uncommon condition, this constituted 16.05% in our study. Based on histomorphology, CMD was found to be heterogeneous in nature and could be grouped into three distinct types: Group-1 resembled the classical form with marked fallout of myofibres and excessive endomysial fibrosis. In Group-2 the changes resembled those seen in limb girdle type dystrophy such as presence of hypertrophic fibres and fibre splitting. Group-3 showed myopathic features similar to those seen in Duchenne muscular dystrophy in the form of rounded hyalinised fibres and significant necrosis and myophagocytosis.
Myopathic changes starting in the foetal life was considered to be the basic underlying pathology while, increase in collagen could be secondary to degeneration and loss of myofibres.

Congenital myopathies are relatively non-progressive muscle disorders. They are characterised by a predominance of a particular identifying myopathological feature. This group constituted 18.62% of infantile neuromuscular disorders in our series. The congenital myopathies encountered in the present study are the central core disease, multicore disease, centronuclear myopathy and congenital fibre type disproportion, comprising - myopathy with type-II fibre hypoplasia and myopathy with type-I fibre predominance. Centronuclear myopathy was the commonest amongst the congenital myopathies (6 out of 22 cases). It was noticed that in most biopsies of congenital myopathies, type-I fibre predominance was a significant feature. Neither the pathogenesis nor the significance of fibre type predominance is fully understood. Our observations suggest that dysmaturation starting in the foetal life such as improper differentiation of type-I and type-II fibres and lack of peripheral migration of centrally placed nuclei appear to be the defects in congenital myopathies.

Patients who presented with hypotonia and delayed acquisition of motor milestones and with muscle biopsies
showing normal histological, histochemical and ultrastructural features were grouped under benign congenital hypotonia (7 out of 81 cases). Follow-up study in this group is essential to understand the cause of hypotonia.

Mitochondrial myopathies constituted an important group amongst the metabolic myopathies studied (6 out of 11 cases). Accumulation of oxidative enzyme reaction product in most fibres was the common finding seen in all the six cases. It was important to note that even though the presence of ragged red fibres is considered as the hallmark for the diagnosis of mitochondrial myopathies, the same was not true for all the cases. Two out of six cases in the present study did not reveal ragged red fibres. The diagnosis in these two cases was possible only by ultrastructural finding of subsarcolemmal accumulation of a large number of normal looking mitochondria. The other forms of metabolic myopathies included were the vacuolar myopathies, namely carnitine deficiency disorder, mitochondria-lipid-glycogen disease and the acid maltase deficiency (Pompe's disease). The diagnosis in all these cases was based on morphological findings of muscle biopsies such as demonstration of ragged red fibres, vacuoles containing neutral fats and presence of abnormal mitochondria in carnitine deficiency, and vacuoles containing PAS positive material and neutral fats in mitochondria-lipid-glycogen disease. Acid maltase deficiency was characterised by the presence of PAS positive material
digested by diastase within the vacuoles. Presence of glycogen particles within the membrane-bound vacuoles seen at electron microscopic level confirmed the diagnosis.

Thus, application of histological, histochemical and electron microscopic techniques on muscle biopsies formed an important approach in delineating the various forms of infantile neuromuscular disorders. A comparison of the morphological findings in these disorders with those of normal foetal muscle enabled us to understand that the pathology in ISMA, CMD and CM was due a defect occurring during the course of foetal development. The current approach for the management of the infantile neuromuscular disorders being genetic counseling, a proper diagnosis needs to be established. The concurrent application of the above mentioned techniques therefore helped us in providing an accurate diagnosis presented by us in this work.