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Menkes Disease

– An Autopsy Case with Metal Analysis of Hair –

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We report the first case of Menkes' disease in Korea, occurring in a 1½ year old boy with characteristic clinical, arteriographic and pathologic features.
Postmortem examination revealed widespread neuronal destruction and abnormally tortuous and elongated large arteries including cerebral, visceral and limb vessels. Microscopically, many of the hairs formed were twisted (pili torti), of varying caliber (monilethrix), and fractured (trichorrhexis nodosa). In the radioactivated analysis of scalp hair, copper elements was not found. The abnormal vessels were characterized by fragmentation and disruption of the internal elastic lamina with intimal proliferation.
The neuronal destruction was widespread in the cerebral gray matter and in the cerebellum, and there was associated gliosis. The changes in the cerebellum were particularly severe, with neuronal loss in the internal granular cell layer. Many Purkinje cells were lost, and the remainder showed unusual dendritic sprouts from the cell body and grotesque proliferation of dendritic tree. In other organs, mild chronic peribronchitis, and scattered foci of immature glomeruli in renal cortex were noted.

Key Words: *Menkes disease, kinky hair syndrome, Copper, Hair anomaly*

INTRODUCTION

In 1962 Menkes and associates (Menkes et al., 1962) described a new neurodegenerative disorder of infancy affecting five boys of a related pedigree. Its clinical features were characterized by peculiar white stubby hair, major motor seizure, early severe mental retardation, failure to thrive and cerebral and cerebellar degeneration. This disorder is also known as the kinky hair syndrome (Billings et al., 1971) because of the typical appearance of the hair. Microscopic examination of the hair reveals pili torti, trichorrhexis nodosa, and monilethrix. Today the disease is called either Menkes' syndrome or Menkes' kinky hair disease (Danks et al., 1972a; Danks et al., 1972b). Its occurrence may be as rare as 1 in 35,000 live birth, and it has been reported less than 50 cases in the world literature.

Recently we had a chance to examine a case of Menkes' disease which showed the characteristic clinico-pathologic features. We report this case together with postmortem angiographic findings of the vessels and scanning electron microscopic findings of the hair abnormalities.

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CASE REPORT

A 15 month old male was admitted to the Pediatric Department of Seoul National University Hospital for an evaluation of his growth and developmental

retardation on October 2, 1985. He was born at term via Cesarian section, weighing 3.0 kg, following a pregnancy complicated by placenta previa. The baby was the second child. His immediate neonatal period was uneventful. He smiled and was growing well until 2 months of age, but he had lost much of his scalp hair and the newly sprouted hair appeared sparse, coarse, dry and easily broken. At 3 months of age, he lost his smile and looked dull, lethargic and could not control his head. He had suffered from repeated respiratory infections and recurrent eczema until the time of admission. He ate well, but weight gain was poor.

Physical examination at admission revealed an extremely undernourished boy with pectus excavatum and decerebrate posture (Fig. 1). He weighed 6 kg and was 82cm in height. The palate was slightly high-arched, and upper and lower two incisors erupted. Cheeks were pudgy. His scalp hair was sparse, steely and brittle (Fig. 2). He did not smile, nor follow light, and there was complete head lag on pull to sitting position. He failed to lift his head on prone position. Laboratory findings included normal blood cell counts, urinalysis, and chemical constituents of blood. Serum copper and ceruloplasmin levels were 19–39.1 μg/100ml (Normal: 70–155 μg/100ml) and 7–8.1 mg/100ml (Normal: 23.3–40,2 mg/100ml), respectively. In skull X-ray multiple wormian bone was noted in the occipital area and brain CT showed diffuse parenchymal atrophy with minimal dilatation of ventricular system and subdural fluid collection. During his admission, biopsy of scalp hair and carotid angiography were performed. Microscopic examination of scalp hair showed of pili torti and trichorrhexis nodosa. Carotid angiography showed diffuse elongation, tortuosity and abnormal dilatation of arteries. He underwent progressively downhill course and died at 18 months of age.

POSTMORTEM FINDINGS

The body was that of a marasmic baby weighing 6 kg and measuring 72cm in length. The head was small and measured 40cm in circumference. The occiput was flat and forehead was wide. The scalp hair was sparse, short, dry, and stubby. His face was characterized by pudgy cheeks and slightly depigmented eye brows and eyelashes.

Steroscopic examination of scalp hair revealed portions of winding up around their own axis (pili torti) at irregular interval, of scattered nodules (trichorrhexis nodosa) and of varying caliber (monilethrix) (Fig. 3). Under the scanning electron microscope well-organized hair cuticles covered the hair surface even on the twisted portion, and the node was characterized by smaller degree of splayed out cortical fibers resembling a paint trush (Fig. 4 and 5). Determination of microquantity of elements in the patient's hair was performed by the Radioactive Measurement Association of Japan, Foundation, using the Ge3-solid-state detector (γ-ray spectrometer). The sample was analyzed by the comparison method with the standard sample and the sample which are activated by thermal neutron. In radioactivated analysis of the hair, 10 elements including Cl, Na, Mn, Zn etc were found and their density were measured. But copper element (Normal: 6. 39 ppm ±%) was not detected.

Postmortem arteriography demonstrated elongation, tortuosity and varying caliber of major arteries throughout the brain, viscera and limbs, with numerous collateral branches. These vascular changes were more prominent in the branches of mesenteric, renal and cerebral arteries, demonstrating corkscrew windings. The external iliac artery showed multiple segmental stenosis associated with portions of aneurysmal dilatation (Fig. 6). The aorta, pulmonary artery and heart were unremarkable. The microscopic findings of the abnormal vessels revealed marked loss of internal elastic and external elastic laminas with fragmentation, disruption and duplication, being associated with irregular proliferation of intimal cells. These vascular abnormalities were conspicuous in the elastic stain (Fig. 7).

Central nervous system: The brain was small and weighed 540 g. The anterior-posterior diameter was 11.3cm and biparietal diameter 12cm, the height 7.2cm. The meningeal surface of the brain was generally opaque and thickened. There were many tortuous and abnormally elongated blood vessels which were particularly prominent in the medium sized vessels. Also, aberrantly located or supernumerary vessels in the brain base were seen. The cerebral hemispheres showed no external abnormality, except for a global gyral atrophy in the frontal lobe (Fig. 8). Serial coronal sections were made for the cerebral hemisphere and horizontal sections for the branistem and sagittal sections for the cerebellum. The coronal sections of cerebrum disclosed generally preserved cortical bands with relatively distinct gray white junction. The white matter was diffusely reduced in volume, particularly in

Table 1. Role of copper enzymes known in human beings

Common name	Functional role	Consequence of deficiency
Tyrosinase	Melanin production	Failure of pigmentation
Dopamine B-hydroxylase	Catecholamine productions	Neurologic effects type uncertain
Lysyl oxidase	Cross-linking of collagen and elastin	Vascular rupture
Ceruloplasmin	Ferroxidase?	Anemia
Enzyme not known	Cross-linking of keratin (disulphide bonds)	Pili torti

the gyri of frontal lobe and less in the central white matter. The brain was generally firm and pale. Some of the cortical bands in medial portion of the temporal lobes were definitely thinned. The ventricular system was slightly prominent but no evidence of gross hydrocephalus was seen. The cavum septum pellucidum was prominent. The cerebellum measuring 6.4cm in width, 3.3cm in antero-posterior diameter, and 3.1cm in height, showed diffuse atrophy of folia. On section the folia were narrowed and gray white junction was indistinct (Fig. 9), these changes being more marked in the vermis. The central white matter was slightly reduced in volume and was firm in consistency. The brainstem was particularly firm and the cut surface showed pearly white appearance with poor distinction of gray matter.

Microscopically, the leptomeninges revealed abnormal proliferation of small arteries and arterioles with fibrosis. There was no evidence of meningitis. The cerebrum showed widespread degeneration of the cells in the cortex and white matter. In these areas there were a varying degree of nerve cell loss, ntense microglial proliferation and hypertrophy of astrocytes and breakdown of myelin. A marked loss of neurons and gliosis were more prominent in the frontal and temporal lobes. The cerebellum showed extensive neuronal loss in the internal granule cell layer (Fig. 10). Many Purkinje cells were lost, and the remaining cells were irregularly aligned, some lying in the internal granular cell layer. Some of Purkinje cells showed unusual dendritic sprout from the cell body and grotesque proliferation of dendritic trees. The dendrites were enormously swollen and appeared as cylindrical or stellate, eosinophilic homogeneous bodies in hematoxylin-eosin preparation (Fig. 11). The axons of Purkinje cells frequently showed a round and fusiform focal swellings in the internal granular layer. There was mild proliferation of Bergmann astrocytes in some folia. The white matter in the folia was rarefied and showed a mild proliferation of microglial cells and hypertrophied astrocytes. In the central and folial white matters myelin loss and gliosis were evident in Luxol-Fast-Blue preparation. In midbrain, pons, medulla and spinal cord, there were no significant findings except for poor staining of myelin in the posterior spinocerebellar tract of spinal cord.

The remaining organs were not remarkable. The lungs showed patchy atelectasis, emphysema and focal peribronchial collections of lymphohistiocytes. In the kidney, many of the glomeruli in the superficial portion of cortex were abnormally immature for the age of the patient.

DISCUSSION

The characteristic clinical and neuropathological features and X-linked inheritance of this condition were clearly described by Menkes et al. in 1962. In 1972, hypothermia, seborrheic rash and widespread arterial tortuosity were added to previous Menkes description by Danks et al. They had demonstrated copper deficiency in seven babies with Menkes' disease and submitted evidence for a defect in the intestinal absorption of copper by studying with labelled copper (Danks et al., 1973; Danks et al., 1974). In this case serum copper and ceruloplasmin level were much lower than those found in nutritional copper deficiency, and copper element of hair was undetectable. Danish group and Williams demonstrated tissue copper concentrations in patients with Menkes kinky hair disease; copper level

is elevated in kidney and duodenum, and is decreased in brain and liver. Recently, it has been suggested that the basic defect of this disorder is a generalized maldistribution of copper rather than just malabsorption and deficidency of copper (William, 1981). The basic pathogenesis of Menkes' disease is not fully defined, but copper dependent enzymes are supposed to play a role in the clinical manifestation in Menkes' syndrome.

The role of the copper enzymes known in human beings are summarized in table 1. The structural changes in the hair are due to defective disulphide bonding in keratin, as seen in copper deficient sheep (Billings, Degnan, 1971). Depigmentation of hair is presumably due to tyrosine deficiency (Holstein et al., 1979). The arterial disease is principally the result of defective elastin formation secondary to lysyl oxidase deficiency. Neuropathological changes of the brain are attributed to catecholamine deficiency secondary to dopamine hyroxylase and of superoxide dismutase deficiency (Hunt, 1977). Scorbutic bone changes had been described in copper deficient infants and explained by copper requirement of ascorbic acid oxidase. The hypothermia associated with Menkes' disease may be the result of defective cytochrome oxidase, which is an important copper containing enzyme for the function of basic energy chain (Danks, 1972).

The pathological changes seen in the cerebrum and cerebellum in this case were fairly similar to those reported in Menkes' original description, the only difference being in the number of Purkinje cells and the degree of degenerative changes of the cerebrum. In our patient the Purkinje cells of the cerebellar cortex were markedly decreased in number and the cerebral degeneration was relatively mild. The number of Purkinje cells was not diminished and degenerative changes in the cerebrum was more prominent and extensive in cases reported by Menkes et al. (1962). Some authors had reported diffuse progressive degeneration of the cerebral gray matter in infancy and childhood, but the involved cerebellum did not show any of peculiar morphologic changes noted in Menkes' disease. Therefore, such difference observed in Purkinje cells is considered unique to this disease.

Similar morphological changes in the Purkinje cells have been described for a number of conditions. They were induced experimentally by Cajal (1959) by acute trauma to the cerebellum in young animals. Norman (1940) and Jervis (1950) have observed them in cases of early familial cerebellar degeneration. In these patients, however, the degenerative changes did not involve the cerebral gray and white matter as was usually noted in Menkes' disease. The combination of focal cerebral degeneration and Purkinje cell alterations have also been described by Hunter (Hunter et al., 1954) and Russel in a man who suffered from severe neurological disturbance for 15 years following prolonged exposure to a methyl mercury compound. It has been commonly held that the toxic action of organic mercurial compounds involves in part an interaction with enzymes that have an SH or SS group in their action site. The central nervous system is one of the target organs, in which inumerable enzymes may be inhibited by organic mercury compounds.

The arteriographic changes seemed to be pathognomomic for this disease and findings were identical with the descriptions in the various reports of Menkes disease. The brain damage may all be secondary to arterial disease or may be partly the direct result of copper deficiency. The neurological effects of copper deficiency in animals have generally been attributed to cytochrome-oxidase deficiency.

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REFERENCES

Aguilar MJ et al.: *Kinky hair disease I. clinical and pathological features. J Neuropath exp Neurol 25:507-522, 1966.*

Ahlgren P, Vestermark S: *Menkes' kinky hair disease. Neuroradiology 13:159-163, 1977.*

Billings DM, Degnan M: *Kinky hair syndrome. Amer J Dis Child 121:447-449, 1971.*

Cajal RY: *Degeneration and regeneration of the nervous system, Vol II, translated and edited by R M. May. New York Hafner, 1959.*

Danks DM et al.: *Menkes' kinky-hair syndrome. Lancet 1:1100-1103, 1972a.*

Danks MDM et al.: *menkes' kinky hair syndrome. Pediatrics 50:188-201, 1972b.*

Danks DM et al.: *Menkes' kinky hair syndrome. An infinition of the defect in copper transfort; Science 179: 1140-1141, 1973.*

Danks DM et al.: *Menkes' kinky hair syndrome. An inherited defect in the intestinal absorption of copper with widespread effects. Birth defects 10:132-137, 1974.*

Holstein TJ, Fung RQ, Quevedo WC, et al.: *Effect of altered copper metabolism induced by mottled alleles and diet on mouse tyrosinase. Pro Soc Exp Biol Med 162:264, 1979.*

Hunt DM: *Catecholamine biosynthesis and activity of a number of copper-dependent enzymes in the copper-deficient mottled mouse mutants. Comp Biochem Physiol 57:79, 1977.*

Hunter D, Russell DS: *Focal cerebral and cerebellar atrophy in a human subject due to organic mercury compounds. J Neurol Neurosurg Psychiat 17:235, 1954.*

Jervis GA: *Early familial cerebellar degeneration. J Nerv Ment Dis 111:398, 1950.*

Menkes JH, Alter M, Steigleder GK, et al.: *A sex-linked recessive disorder with retardation of growth, peculiar hair and focal cerebral and cerebellar degeneration. Pediatrics 29:764-779, 1962.*

Norman RM: *Primary degeneration of the granular layer of the cerebellum; an unusual form of familial cerebellar atrophy occurring in early life. Brain 63:365, 1940.*

William DM: *Tissue copper concentrations of Patients with Menkes' kinky hair disease. Am J. Dis child 135:375-376, 1981.*

Figure Legends

Fig. 1. The undernourished body with pectus excavatum and decerebrate posture.

Fig. 2. Scantly and sparse scalp hair with grayish white and steely appearance.

Fig. 3. Stereoscopic photograph of the hair (x 40). Pili torti (A) and trichorrhexis nodosa (B)

Fig. 4. SEM photograph of pili tori (A, x 150) showing imbricated scales of the hair cuticle covering the twisted parts in normal arrangement (B, x 1200).

Fig. 5. SEM photograph of trichorrhexis nodosa (A, x 30) showing small number of splayed out cortical fibers, resembling a paintbrush (B, 300).

Fig. 6. Postmortem angiogram showing elongation of renal artery (arrowhead), tortuosity of the mesenteric arterial branches and segmental stenosis of external iliac artery (double arrowhead).

Fig. 7. Light microphotograph of renal artery showing loss of internal and external elastic laminas with fragmentation and intimal thickening (elastic stain, x 40).

Fig. 8. The cerebral hemisphere showing global gyral atrophy in the frontal lobe.

Fig. 9. Sagittal section view of cerebellum showing extensive atrophy of folia with indistinct corticomedually junction.

Fig. 10. Marked neuronal loss of the internal granule cell layer of cerebellum (H & E, x 40).

Fig. 11. Note the abnormal Purkinje cells with marked swollen and grotesque dendrites (Bodiam stain, x 400).

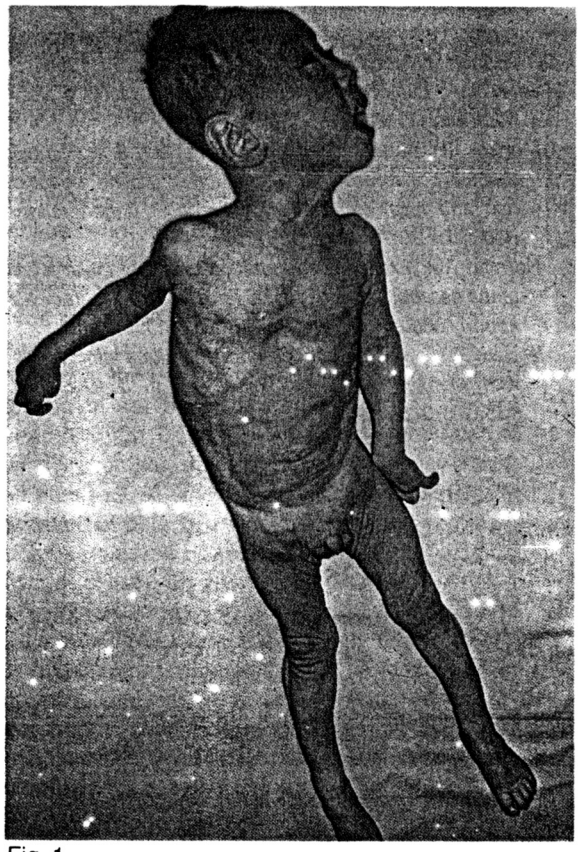


Fig. 1

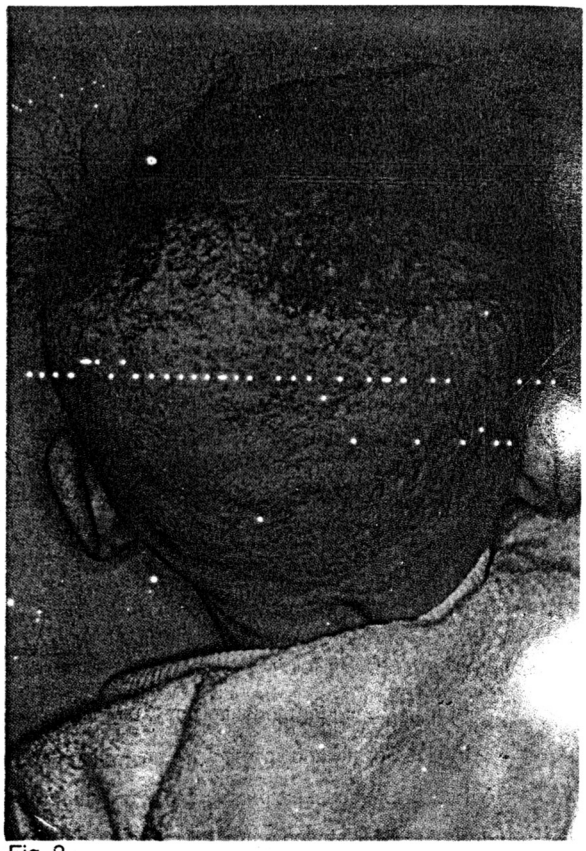
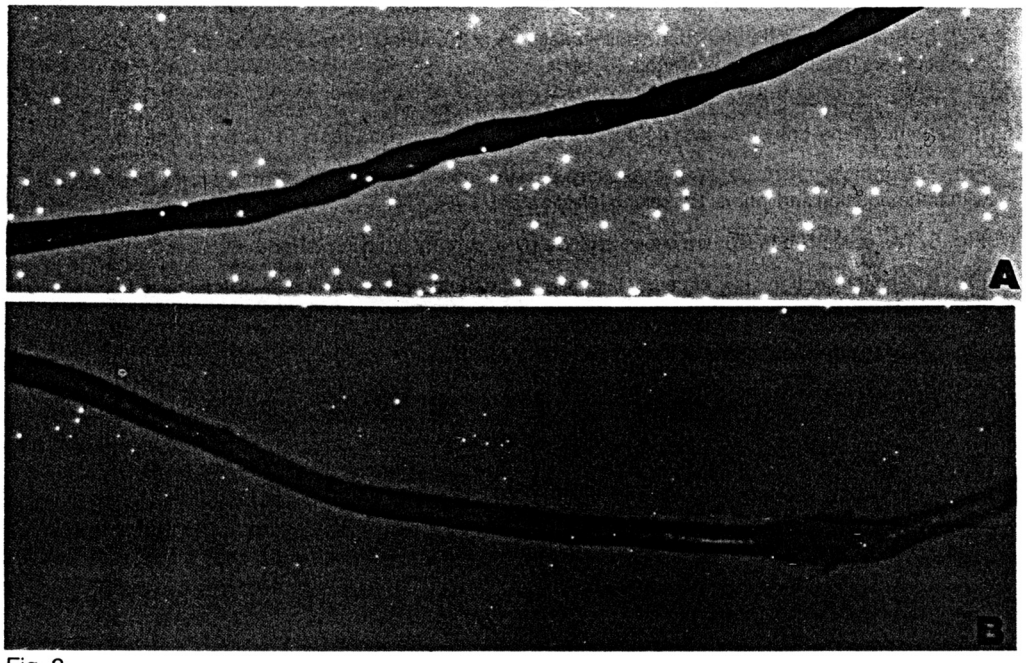


Fig. 2



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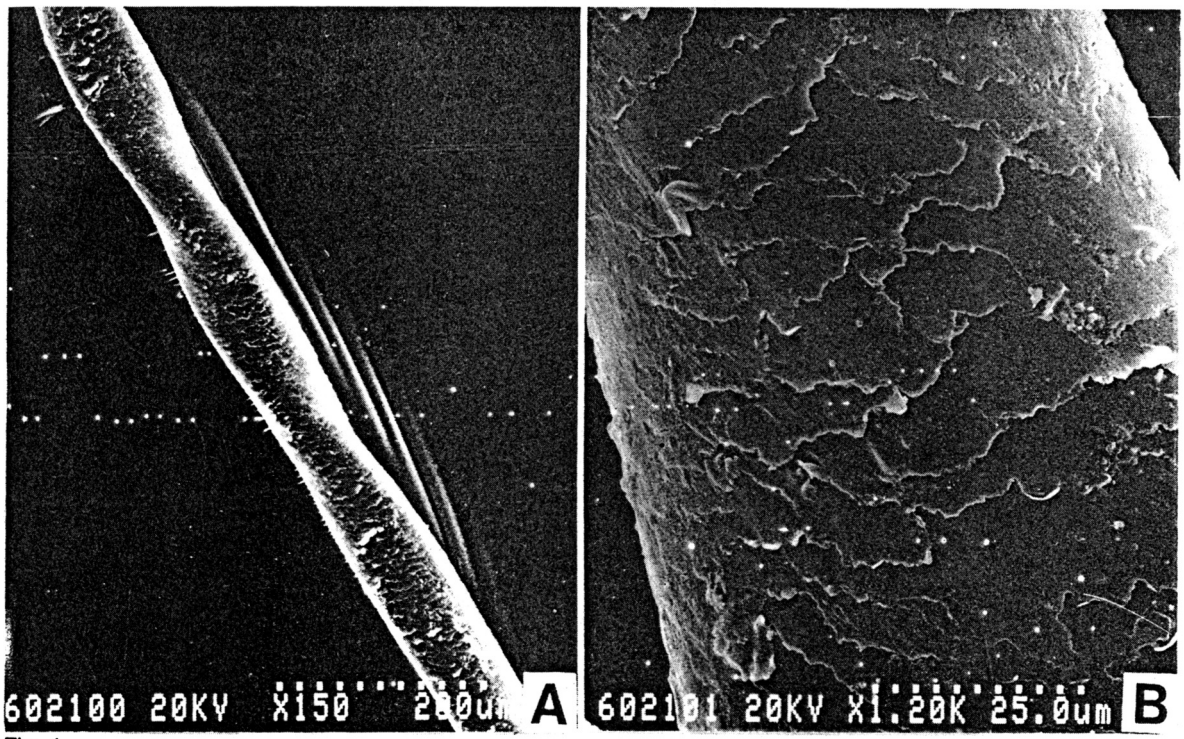
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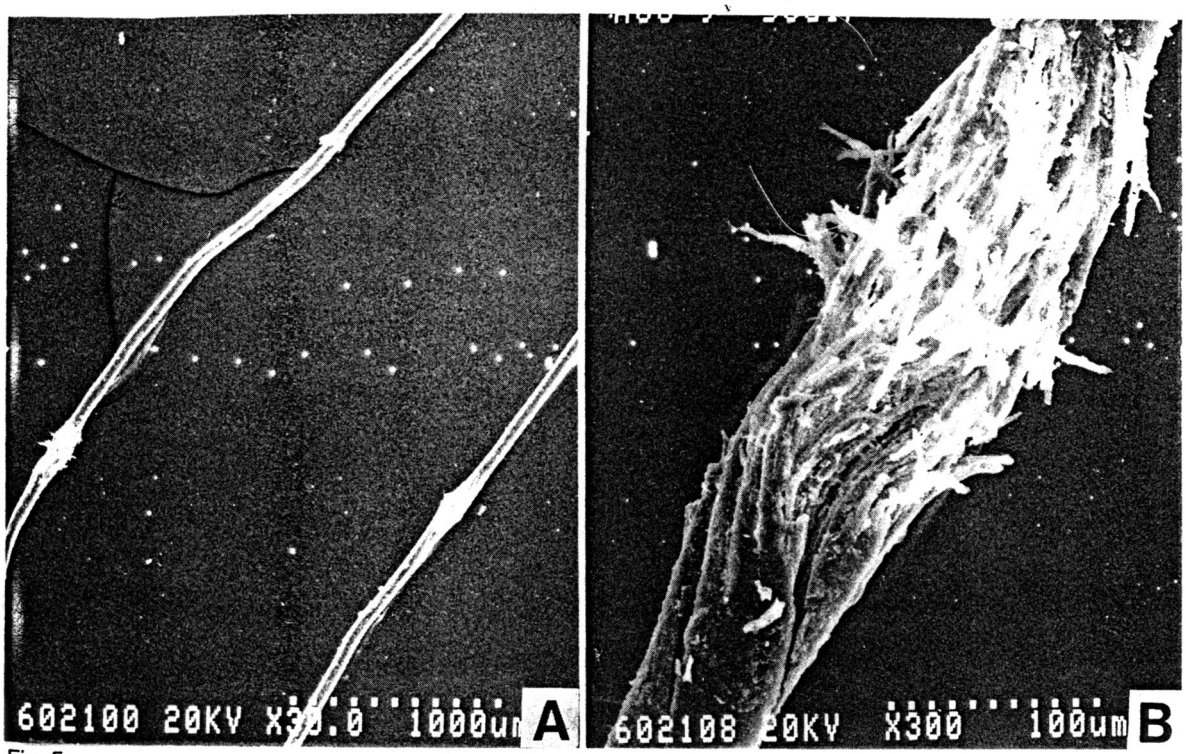
A
602101 20KV X1.20K 25.0um
B

Fig. 4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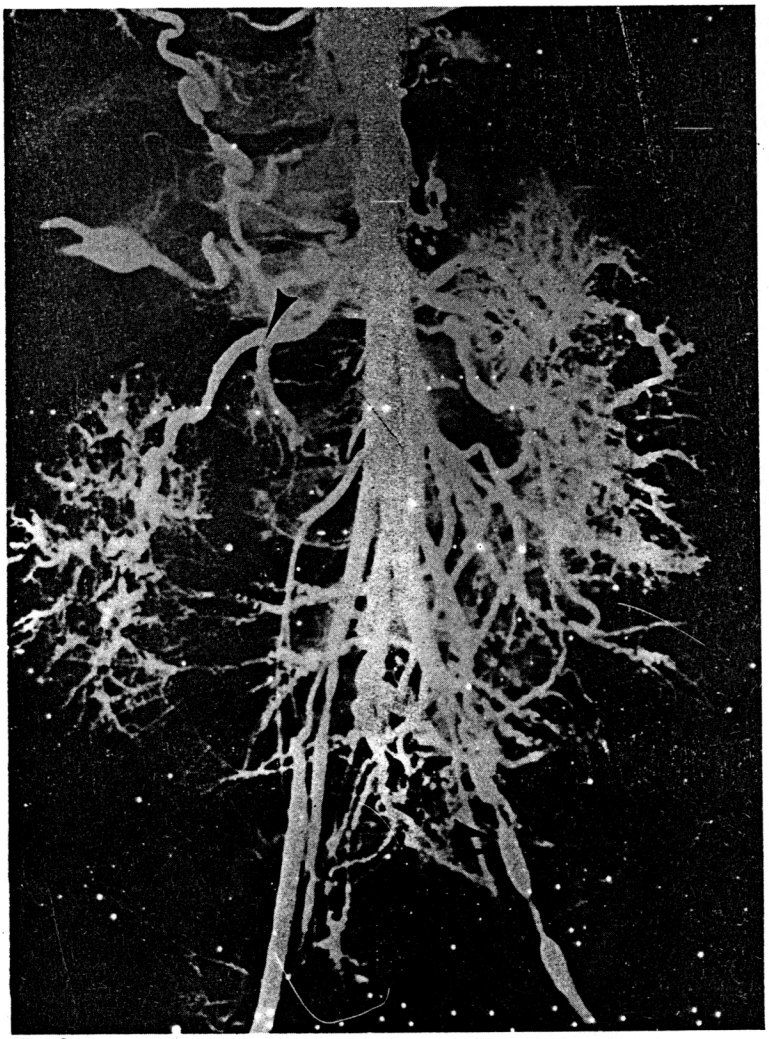
A
602108 20KV X300 100um
B

Fig. 5



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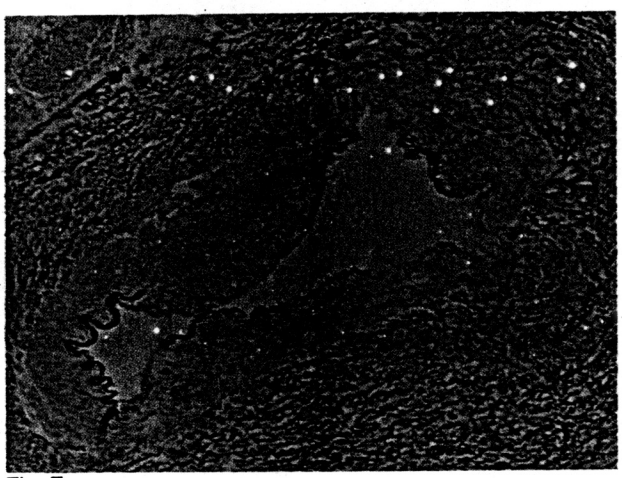

Fig. 7

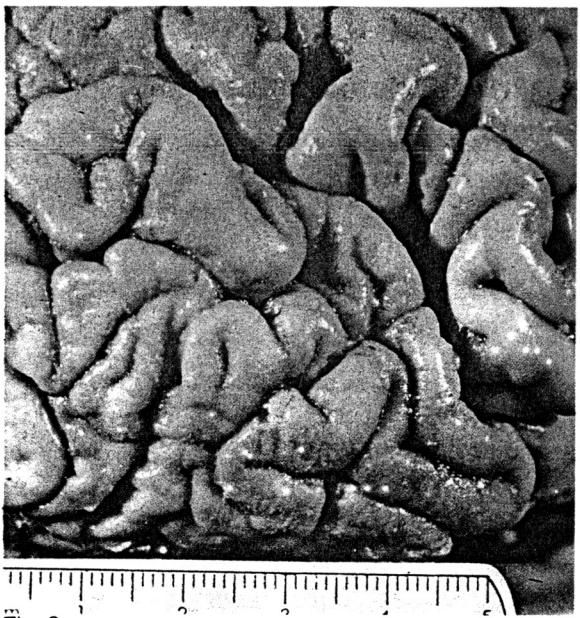

Fig. 8

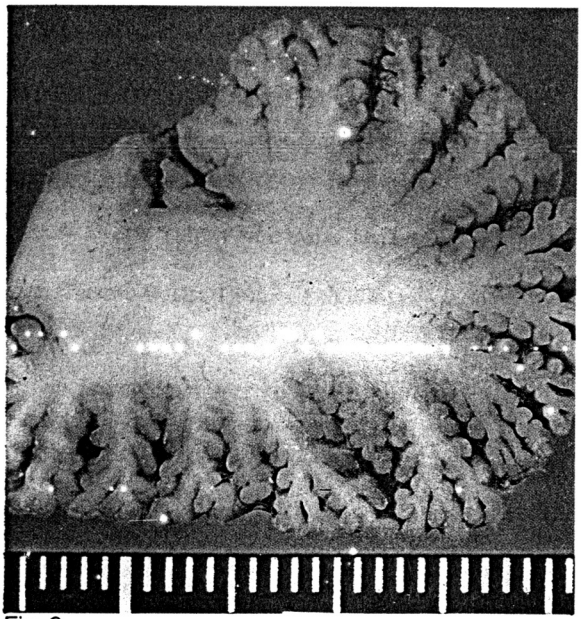

Fig. 9

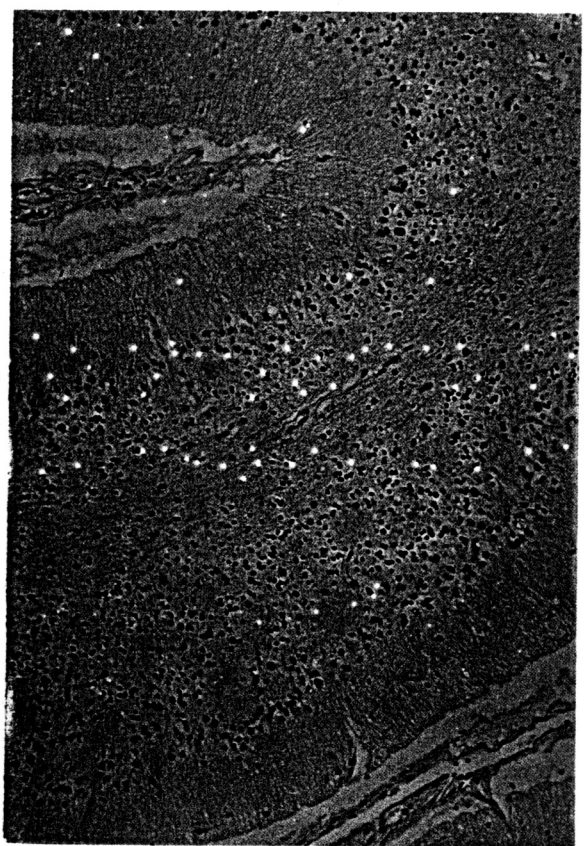

Fig. 10

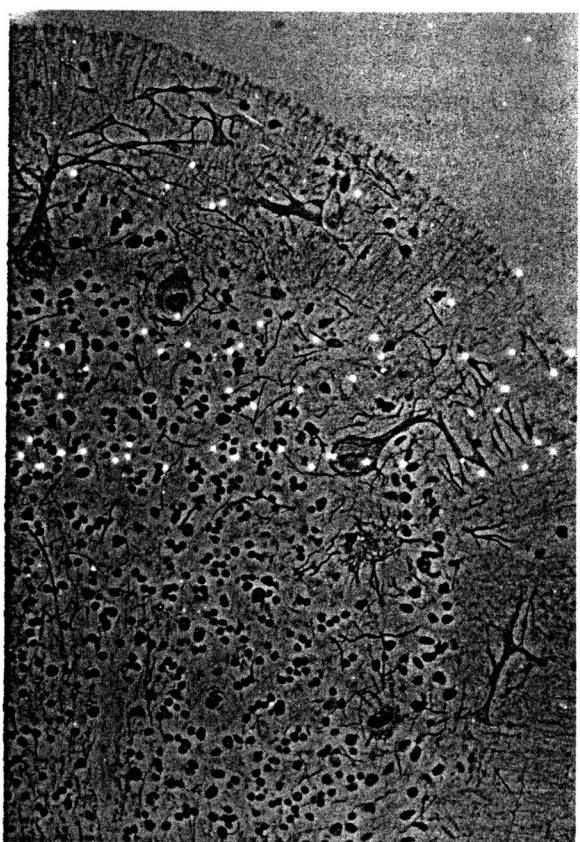

Fig. 11