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Cockayne's Syndrome

Report of Case with Necropsy Findings

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Summary. The clinical and necropsy findings have been described in an 11 year old girl with classical Cockayne's syndrome which consists of microcephaly, dwarfism, bird facies, mental deficiency, retinal pigmentation, deafness, large hands and feet, and a thick skull with a small pituitary fossa. The disease, as is usual, appeared after a normal first year of life and was characterized by initial mental and physical retardation followed by progressive deterioration. The most striking neuropathological findings were marked atrophy of white matter, patchy demyelination of residual fibres in cerebrum, cerebellum, brain stem and spinal cord, fine deposition of calcium in the cerebral and cerebellar cortical ribbon and coarse focal calcification of the basal ganglia. The most likely cause of this rare condition is probably an inherited genetic defect involving several germ layers.

Zusammenfassung. Klinisch-autoptischer Fallbericht eines 11jährigen Mädchens mit klassischem Cockayne-Syndrom, bestehend aus Mikrocephalie, Zwergwuchs, Vogelgesicht, psychischer Retardierung, Retinitis pigmentosa, Taubheit, großen Händen und Füßen sowie dickem Schädel mit kleiner Fossa hypophyseos. Wie üblich, setzte die Erkrankung nach regelrechter Frühentwicklung ein. Sie war durch initiale psychische und physische Retardierung mit späterer progressiver Demenz gekennzeichnet. Die wesentlichen neuropathologischen Befunde waren deutliche Atrophie des Markes, fleckige Entmarkung der verbliebenen Fasern in Groß- und Kleinhirn, Hirnstamm und Rückenmark, zarte Kalkablagerungen im Rindenband des Groß- und Kleinhirns sowie grobe fokale Verkalkungen in den Stammganglien. Die wahrscheinlichste Ursache dieser seltenen Erkrankung ist ein angeborener genetischer Defekt, der verschiedene Keimblätter betrifft.

Key-Words: Cockayne's Disease — Dwarfism — Pelizaeus-Merzbacher Disease — Calcium Deposition — Microcephaly.

COCKAYNE (1936, 1946) described a syndrome in two siblings "characterized by dwarfism with prognathism, thickening of the skull bones and other skeletal changes, a peculiar form of retinal pigmentation, optic atrophy, and cataract, deafness, and mental deficiency. The extremities are cold and blue".

Twenty-six further cases have been reported since 1946 (CIVANTOS; CULLEN and MORA; LIEBERMAN *et al.*; MACDONALD *et al.*; MARIE *et al.*; MCINTYRE and BROWN; MOOSSY; NEILL and DINGWALL; OHNO and HIROOKA; PADDISON *et al.*; SPARK; SUWA; UESUGI *et al.*; UPJOHN; WILKINS; WINDMILLER *et al.*). A few additional features have been identified as belonging to the syndrome. The skin of the face and hands is dry, rough and very sensitive to sunlight as was seen in an extreme form in the children from West Australia (MACDONALD *et al.*) where cloud cover is slight and average temperatures high. Anhidrosis is common. Facial subcutaneous fat is often scanty with accentuation of the large, sunken eyes, prominent beak-like nose and projecting jaw. Dental caries, often advanced, is common. A small pituitary fossa, disproportionately large hands and feet, kyphosis and flexion deformities of the limbs associated with ataxia and tremor are common findings.

Intracranial calcification of the frontal lobes and basal ganglia can sometimes be seen in a skull radiograph.

The syndrome has been described five times in siblings and once in a pair of twins; in all six families, other siblings were normal. Twenty-one of the patients were male, 7 were female. With the exception of the complicated family relationships of the patients described by PADDISON *et al.* and MOOSSY and the three unrelated Japanese children described by OHNO and HIROOKA, there have been no instances of parental consanguinity.

Typically, an affected infant is normal at birth and grows well for the first year of life. Thereafter, development ceases and the characteristic stigmata become apparent. At first, the child is lively and cheerful, though excitable. Standard intelligence tests show a low I. Q. but the Rorschach findings are more those of a normal though chronologically much younger child. The inference is that mental retardation at this stage is a result of arrested development rather than maldevelopment from birth (MACDONALD *et al.*). Definite mental deterioration becomes apparent in the early teenage period and performance is impeded by increasing blindness and deafness. Crippling from flexion deformities and kyphosis becomes more marked and death usually takes place by the fourth decade, from inanition and secondary infection.

A normal chromosome number and a normal karyotype has been found in four out of the five patients that have been examined in this way. CIVANTOS found 47 chromosomes in his patient, with trisomy in Group 19—20. WINDMILLER *et al.* believe that this finding is either due to mosaicism or to coincidence in that trisomy for Group 19 has been described in a normal male with 47 chromosomes.

Cockayne dwarfs bear a superficial resemblance to children with progeria in that both are thin-faced, rather old-looking dwarfs with joint deformities. The terms "progeria-like" and "progeroid", with respect to Cockayne dwarfs, are probably misleading in that abnormal lipid metabolism and premature atherosclerosis have been described in progeria (KEAY *et al.*) but no consistent metabolic disorder has been found in Cockayne's syndrome (MACDONALD *et al.*). The bird-headed dwarfs described by SECKEL are microcephalic and mentally retarded and have a prominent nose, large eyes and a narrow face but lack retinal or auditory disturbances or distal skeletal disproportion. Possibly the "microcephalic midget of extreme type" reported by MANN and RUSSELL should be accepted as a Cockayne dwarf but there were some abnormal biochemical findings and the hands and feet were in proportion to the rest of the body.

Of the 28 Cockayne dwarfs in the clinical literature, 5 are known to be dead. PADDISON *et al.*, MOOSSY and MACDONALD (see GELLIS) described changes in the central nervous system in one of their cases but beyond this and the findings in two patients reported briefly by NORMAN (1963a) the morbid anatomy of the syndrome has not been described. It is for this reason that the present classical case of Cockayne's syndrome is being reported in detail.

Case Report

M. B. was born, weighing 6 lb. 8 oz., after a full-term pregnancy and normal delivery. No abnormalities were noted at birth. She was breast-fed for 8 months during which period no peculiarities were observed but progress was noticeably slow after the first year. The

child first began to sit up at about 12 months; crawling started at 22 months, standing with support at $2^1/_2$ years and walking, with assistance, at 4 years.

She is said to have had a vocabulary of 30 words at 3 years. On the Revised Standard Binet Test, Form L, her mental age was 22 months at $4^3/_4$ years (I.Q. = 39) and about the same at $5^3/_4$ years (I.Q. = 32). She was said to have been happy, affectionate and interested in her toys. At 10 years she gave an age equivalent score of 16 months on the Vineland Social Maturity Scale and a mental age of 15 months on the Griffiths Mental Development Scale (I.Q. = approximately 13). At this stage, she had to be fed, dressed and undressed and was doubly incontinent. She sat motionless for most of the day, with her knees drawn up to her chin. She knew the meaning of about 10 words and occasionally repeated others.

Clinical Findings and Special Investigations

She was often described as dwarfed and microcephalic. Unfortunately, there is no record of the time of closure of the cerebral sutures. At 11 years of age, the length, breadth and height of her head was 153 mm, 109 mm and 103 mm respectively and the cranial capacity, calculated from Lee's formula, was 729 ml (respective norms approximately 178 mm, 140 mm, 126 mm and 1198 ml). Her facial appearance at 11 years is shown in Fig. 1.

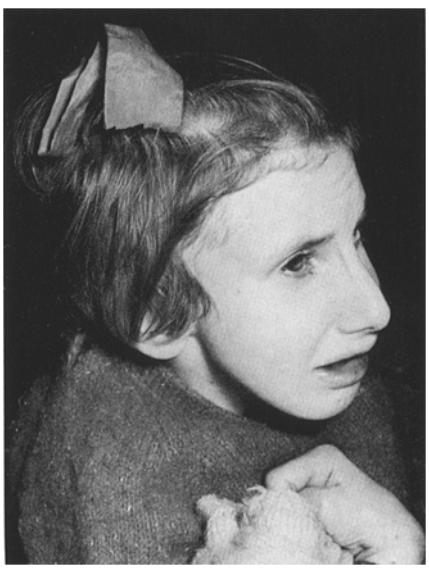

Fig. 1. Close-up view of face to show prominent beak-like nose, prognathism and lack of facial subcutaneous fat

Hearing seemed to be impaired but is was not found possible to test for specific auditory defects. Vision also was thought to be poor. The pupils were equal and reacted to light; ocular movements were normal and there was no nystagmus or strabismus. Ophthalmoscopic abnormality was first recorded at 3 years when the retinae were described as having a diffuse, motled "pepper and salt" appearance. These changes were noted on several occasions in subsequent years. The eyes were examined by Prof. A. SORSBY (who had also seen Cockayne's cases), who made the following observations: "Fundi: disc dead white with well-defined margins. Retineal vessels markedly narrowed. Fundal background: uniformly greyish suggestive of extensive gliosis. No obvious pigmentation but the background is rather broken up. The findings suggest an extensive retinal atrophy or perhaps, incomplete development." The teeth were carious since early childhood. There was congenital absence of several molars and the remaining anterior teeth were hypoplastic. The limbs were hypertonic with brisk reflexes for most of the child's life. In the last few years, she displayed spastic quadriparesis and extensor plantar responses. Variable intention tremor in the arms was noted from time to time. Fits never occurred. Contractures of the Achilles' tendons were marked by the age of 4 years.

No biochemical abnormality was detected but at $8^1/_2$ years, the child began to menstruate. The first period lasted 2 weeks and another occurred 14 days later. Thereafter, periods were fairly regular at 5—6 week intervals, each lasting about 5 days, until an artifical menopause was successfully induced by radiotherapy at $9^1/_4$ years.

The child's general health was poor for the last 2 years of her life with marked weight loss and she died of bronchopneumonia aged 11 years.

Family History

The mother was 29 years and the father 28 years of age when the patient was born; there was no consanguinity. An older brother had been delivered normally weighing 6 lb. 5 oz.

His feet were said to have been deformed at birth, mental deficiency was noticed at about 6 months of age and bilateral cataracts at 1 year. Growth was always slow. He was admitted to Cell Barnes Hospital aged 5 years and was at that time thought to be an atypical microcephalic dwarf weighing $25^1/_2$ lb. and measuring $33^1/_2$ in. His condition deteriorated gradually and he died at the age of $7^1/_2$ years from bronchopneumonia. No autopsy was performed.

The mother's next pregnancy ended in a miscarriage at $2^1/_2$ months. The present patient was born one year later and a second boy 3 years after that. This youngest child has developed normally and is doing reasonably well at school.

A paternal second cousin was an epileptic and was said to be "simple" and another paternal cousin had congenital cataract. There were no other dwarfs in the family.

Necropsy Findings

External Examination. The body was that of an emaciated white female child measuring 92.0 cm from crown to foot, 45.0 cm from crown to pubis, leg 53.0 cm, arm (fingers extended) 45.0 cm. The head measured 15.3 cm anteroposteriorly, 10.9 cm biparietally and 10.3 cm in height. The eyes were normal in size but sunken, the nose prominent and bony, the teeth carious and broken. There were flexion deformities of both legs.

Internal Examination (excluding brain). The *skull* was remarkably thick, the parietal bones measuring 0.5 cm and the frontal bones 1.3 cm. The pituitary fossa was shallow and narrow in the anteroposterior plane with flattening of the pituitary gland. Cisternal cerebrospinal fluid was copious, clear and just faintly yellow.

The *trachea*, *bronchi* and *pulmonary vascular tree* were normal. There was a little fibrinopurulent exudate in the *pleural* cavities. In the *lungs*, there was patchy consolidation of the whole of the left lung, the right lower lobe and the basal part of the right upper lobe. The *heart*, *stomach*, *intestine*, *liver*, *gall bladder*, *pancres*, *kidneys*, *bladder*, *uterus* and *adnexa*, *spleen*, *salivary glands*, *thyroid*, *adrenals* and *lymph nodes* were normal. The thymus was not identified. The *parathyroids* were not examined specifically at the time of autopsy but none was found on the back of the thyroid which had been removed whole for histological examination.

Histology. Patchy fibrinopurulent bronchopneumonia was present in both *lungs* with areas of compensatory overdistension in the intervening lung. In the *kidney*, there was thickening of the basement membrane of the glomerular tuft and Bowman's capsule, slight hyaline arteriolosclerosis and calcium deposits in the tubules. There was diffuse fibrous thickening of the walls of the sinusoids of the *spleen* with haemosiderin deposits in the reticuloendothelial cells. The *endometrium* was atrophic as were the *ovaries*. The anterior lobe of the *pituitary* was small but its component cells were normal. Muscle fibres in *limb muscle* and *diaphragm* were wasted and striations were lost in places, the appearances being those of chronic wasting.

Examination of the Central Nervous System

Macroscopic Findings. The formalin fixed brain weighed 528 g (normal at 11 years = 1300 g). The *leptomeninges* were somewhat thickened on either side of the longitudinal fissure, over the inferior temporal sulcus and at the medial end of the Sylvian fissure on both sides. The basal meninges were thickened and adherent arount the circle of Willis, pituitary stalk and third nerves. The *cisterna magna*, which communicated freely with the fourth ventricle, was greatly enlarged measuring $4.5 \times 2.5 \times 2.5$ cm, the largest dimension being from side to side. The *optic nerves* were thin (0.25 cm in diameter). The *tuber cinereum* bulged but there were no internal herniae. The basal vessels were slightly thickened.

Coronal sections of the *cerebrum* showed some widening of the sulci, reduction in width of the cortical ribbon (bearing in mind the small size of the brain) and marked atrophy of the central white matter, corpus callosum and fornix, internal and external capsules. The white matter was white and firm in some areas, translucent and greyish in others. This stippled pattern was seen best in the frontal lobes (Fig. 2). The knife passed easily through the cortex but ground against a hard mineral deposit in the basal ganglia. These "brain stones" were most marked in the *putamen* and were symmetrical. The *thalamus* and *cerebral peduncles* were shrunken (Fig. 3).

The *cerebellum* was small and there was distortion and flattening of the posterior vermis and undersurface of the lateral hemispheres. The *brain stem* and *spinal cord* were shrunken and hard. There was generalised moderate dilatation of the *ventricular system* with early ependymal ridging. There was no internal obstruction.

Microscopic Findings. Representative blocks from cerebrum, basal ganglia, cerebellum, brain stem and spinal cord were embedded in celloidin or paraffin wax, stained with haema-

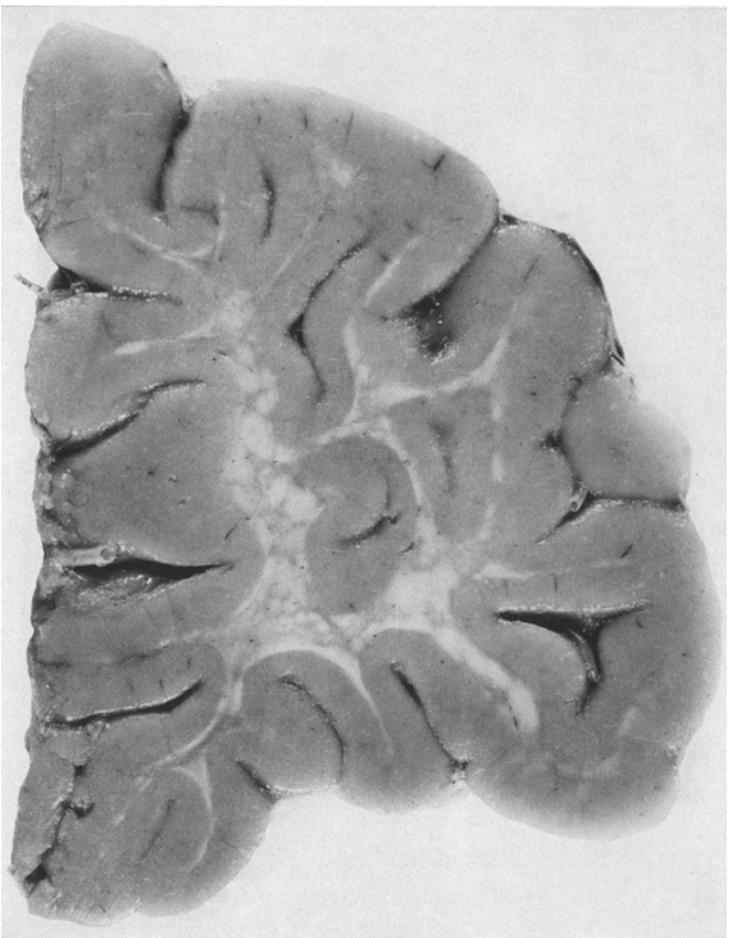

Fig. 2. Coronal section through frontal lobe to show leopard-skin patchy demyelination of white matter. × 2.5

toxylin and eosin, van Gieson's stain, Luxol-fast-blue for myelin sheaths and Nissl's stain for nerve cells. Von Kossa and purpurin stains were used to demonstrate calcium, the periodic acid Schiff stain (PAS) for mucopolysaccharide, the Prussian blue reaction for iron, Mallory's phosphotungstic acid haematoxylin and Holzer's method for glial fibres, Glees-Marsland and Palmgren stains for axon cylinders and Gallyas stain for microglia. Frozen sections were examined for fat using oil-red-O and for microglia using Weil and Davenport's method. One eye was embedded in celloidin and stained with haematoxylin and eosin, van Gieson's stain, Luxol fast blue and Mallory's stain.

Cerebrum. The meninges were thickened and fibrotic especially over the mouth of sulci and around the basal vessels. Macrophages and a few chronic inflammatory cells were present

among the collagen strands. There was focal calcification in the media of arteries near areas of cortical calcification. Neither here nor elsewhere was there an endarteritis or other obstructive lesion.

The most outstanding change in *grey matter* was the presence of bizarre foreign bodies in the subsulcine cortex in widely separated parts of the brain (Fig. 4). These bodies were globoid or star-shaped with laminated swellings at the end of prong-like radiations. Von Kossa's stain for calcium as phosphate or amorphous carbonate was negative but purpurin stain was positive. A strongly positive PAS matrix was left behind after decalcification. Some of this foreign substance was extracellular but most was plastered on pre-existing cells in some of which a central nucleus could be seen. Small pericapillary deposits arranged in

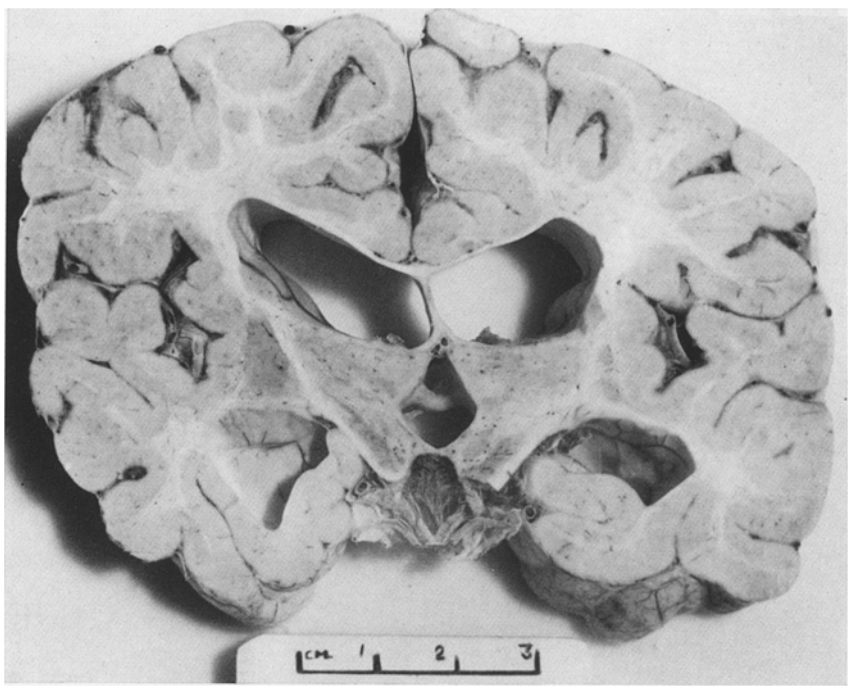

Fig. 3. Coronal section through cerebrum at the level of the thalamus to show widening of cortical sulci, marked wasting of central white matter and of corticospinal tracts and generalized ventricular dilatation. × 1

rows along the vessel wall were present in all areas of calcification but were less conspicuous than the larger irregular deposits. The cortical ribbon was reduced in thickness when compared with the normal for this age and in places clearly underpopulated by nerve cells. No cortical layer and no part of the cerebrum was affected in particular, the depletion being widespread and patchy. No specific abnormality of the remaining nerve cells was noted. Microglia and astrocytes, some of which were arranged in pairs, were increased.

The *white matter* was largely atrophic, the residual fibres being patchily and symmetrically demyelinated with preservation of islands of myelinated fibres. Axon cylinders were intact in the abnormal areas. Fatty breakdown products of myelin were absent from white matter or perivascular spaces. Glial cells were present in normal quantity in the demyelinated patches but were increased in the myelinated areas and at the margin of the patches. Many of these glial cells were clumped together in groups of about six to eight cells. There was definite but slight subependymal gliosis. Calcium deposits were found occasionally in the white matter as granules without the distinctive shape of the cortical bodies.

Basal Ganglia. Calcium was present as coarse granules in large quantity in the putamen and outer part of the globus pallidus on both sides. Pericapillary and medial calcification of large vessels was found in relation to the parenchymal deposits. Similar but less marked changes were present in the lateral part of the thalamus. Apart from compression by third ventricular dilatation, the hypothalamus was unremarkable.

Cerebellum. The meninges were thickened and fibrotic; a little iron pigment was present on the superior aspect of the lateral lobes near the midline. There was some reduction in the number of Purkinje cells and the molecular layer was thin. Calcium deposits were found on the branching dendrites and sometimes on the body of Purkinje cells at the bottom of major sulci forming spindly, arborizing foreign bodies quite unlike those in the cerebrum (Fig. 5). Glial cells were present in excess of normal in grey and white matter. There was patchy

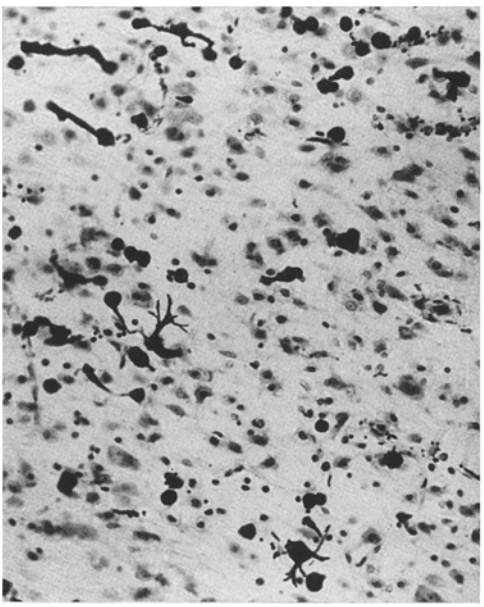

Fig. 4

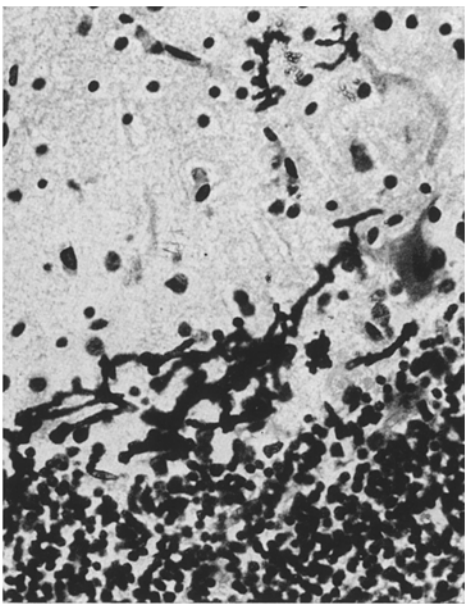

Fig. 5

Fig. 4. Calcium encrustation of cortical cells. Haematoxylin and eosin stain. × 90

Fig. 5. Calcium deposits on the arborizations of Purkinje cells. Haematoxylin and eosin stain. × 180

demyelination, as in the cerebrum, in the folial white matter and around the dentate nucleus. Several glial stars and an occasional granular calcium deposit were seen in the central white matter. The dentate nucleus was free from calcium deposits.

Brain Stem and Spinal Cord. Meningeal thickening, generalized nerve cell loss and patchy demyelination of fibre tracts were present as in the rest of the brain. There was no calcification of olive, pontine or cranial nerve nuclei or spinal grey matter. Demyelinated areas were gliotic. There was no long tract degeneration of the secondary, Wallerian type.

Ventricular System. The ependyma was flattened or absent. Granular ependymitis was present in the dilated aqueduct and fourth ventricle. The chloroid plexuses were shrunken due to stromal fibrosis. There was medial arterial calcification at the base of the plexus of one lateral ventricle.

Eye. The inner layers of the retina were gliotic, the outer relatively spared. The choroidal pigment layer was thicker than normal but was broken up into islands and irregularly distributed. In places, pigment extended into the sclera to varying depths. There was dense gliosis

at the optic disc and thickening of the retinal arteries. The optic nerve was gliotic and fibrotic. These changes are a combination of longstanding optic atrophy and abnormal retinal pigmentation.

Discussion

There seems little doubt that this patient is a microcephalic dwarf of the Cockayne type. Her appearance and the clinical history of a normal birth and early development followed by advancing blindness, deafness, mental deficiency and physical handicap are characteristic of the syndrome. The normal chromosome pattern and lack of obvious metabolic disorder are in agreement with the findings of others.

At necropsy, the most striking changes in the central nervous system were marked atrophy of white matter, patchy demyelination of residual fibres in cerebrum, cerebellum, brain stem and spinal cord, fine deposition of calcium in the cerebral and cerebellar cortical ribbon and coarse focal calcification of the basal ganglia. Axon cylinders were preserved in the demyelinated areas, gliosis was present but not marked and fatty breakdown products were absent. The lesions were not related to blood vessels. Islands of normal myelination were found among the lesions. The presence of groups of glial cells in the cerebrum and glial stars in the cerebellum suggest that the process was still progressing slowly. However, the overall appearance was not one of inflammation. Similar changes have been observed in Cockayne's syndrome by PADDISON *et al.*, MOOSSY, MACDONALD (see GELLIS, 1961—1962) and NORMAN (1963a). PADDISON *et al.* believed that the primary change is neuronal destruction with secondary (Wallerian) degeneration of nerve fibres. In the present case, patchy lesions rather than tract degeneration were found in the brain stem and spinal cord and axon cylinders were intact.

The time and mode of onset of the disease, the slowly progressive deterioration and the possibility that a sibling may be affected suggest that Cockayne dwarfism is related to the familial sudanophilic leucodystrophies. This group of disorders has been reviewed by NORMAN and TINGEY (1963) and by NORMAN (1963b). The process most closely resembles Pelizaeus-Merzbacher's disease in that the lesions are symmetrical, patchy, with leopard-skin stippling of the central white matter, but it is not sex-linked and the scanty sudanophilic products of myelin breakdown found in Pelizaeus-Merzbacher disease are absent. Cockayne dwarfism has patchy demyelination of the central white matter and calcification of basal ganglia and cerebellum in common with the microcephalic patients described by JERVIS and HORANYI-HECKST and MEYER but differs in that it involves other parts of the body as well as the nervous system.

The deposition of calcium in cerebrum and cerebellum as grotesque encrustations on pre-existing cells is a striking finding in this and previously reported necropsied cases. PADDISON *et al.* believed that encrusted cells were nerve cells; NORMAN felt that they were microglia. In the present case, the appearance of some of the less severely obscured cells is remarkably like that of a neurone and in the cerebellum the encrustations clearly follow the branches of Purkinje cells. Although the morphology of these deposits is spectacular, calcification is common in neurological disease, particularly in childhood, whatever the cause. The mechanism of calcium deposition is complex but may be, in part, related to vascular factors (NORMAN and URICH). Cerebral and cerebellar lesions are found in our case

in the depths of sulci rather than elsewhere in the cortical ribbon. There is no evidence that calcification is related to hypoparathyroidism in this instance as in some cases of Fahr's disease. Tetany and convulsions are not part of the clinical picture of Cockayne's syndrome nor have abnormal levels of calcium, phosphorus or alkaline phosphatase been recorded in the blood in cases in the literature.

Pituitary gland dysfunction, other than abnormality of growth, is not usually found in Cockayne dwarfs; the present patient is exceptional in showing sexual precocity as judged by an early menarche. In general, dwarfism with skeletal disproportion is considered to be due to congenital or acquired skeletal disease and is onyl rarely endocrine in origin (DAUGHADAY and PARKER).

It has been suggested that Cockayne's syndrome is caused by a multiple germ plasm defect depending on a recessive non-sex-linked gene (NEILL and DINGWALL). This seems the most likely interpretation of a disease process involving skin, skeleton and central nervous system. Recently, OHNO and HIROOKA have drawn attention to kidney abnormalities in three unrelated children with Cockayne's syndrome, in two of whom renal biopsy was performed. They described thickening of the glomerular basal membrane, poor vascularization and hyalinization of glomeruli, atropic lesions in some tubules and interstitial fibrosis. The lesions were unlike those of glomerulonephritis, pyelonephritis or nephrosclerosis. Similar changes were found in the present patient.

If the fundamental abnormality is occurring synchronously in several parts of the body, the final pathological appearance may be in part due to the sum of each tissue abnormality and in part due to the effect of one developing abnormal tissue on another. Thus, the affected individuals should resemble each other closely, as is certainly the case in Cockayne's syndrome, and differ in a constant manner from the normal.

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