PSEUDOHERMAPHRODITISM, ADIPOSITY, POLYURIA, AND HYPERGLYCÆMIA. AN INFUNDIBULO- TUBERIAN SYNDROME

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ALTHOUGH the literature contains numerous reports of adiposo-genital dystrophy, the number of cases in which it has been possible to investigate the tissues after death is comparatively small. For this reason, it may be of some interest to place on record the clinical history of an instance of this kind, together with the results of a complete post-mortem examination, including the microscopic investigation of the central nervous system.

Case Report

M.C., a boy aged 16 years, was admitted to the Leavesden Hospital on 4th May, 1932. His mother was an unmarried Swiss girl who came to this country in her twenty-fifth year. Nothing was known of the father save that he was of the same nationality. The patient was born in Queen Charlotte's Hospital on 18th June, 1915, and remained in the care of his mother until her return to Switzerland in 1920; subsequently a great-aunt took charge of the defective until his admission to hospital. During pregnancy the mother enjoyed good health, but is said to have resorted to tight-lacing in order to conceal her condition. Born at term, the child was of normal proportions and was breast fed for a year. He was a feeble infant, neglected and undernourished. At the end of twelve months he could neither stand nor walk, and he made no attempt to speak until he was eighteen months old. Signs indicating mental deficiency were noted at an early age; by his third year he had learnt to walk, but the ordinary language of infancy was not acquired until two years later. Habits of cleanliness were not established until his twelfth year. He learnt to dress himself, but always required assistance in washing. When six years old he was rejected as not educable at an ordinary elementary school, and subsequent efforts to teach him to read and write by private tuition proved fruitless. In his early years he enjoyed good health and was described as being a lively and sociable child.

The genital defect was noted at birth, but obesity was not a noticeable feature until his third year. The increase in weight was progressive and when five years old his appearance was grotesque, the excessive obesity and the dwarfism making him "as broad as he was long." At this age, too, a new symptom, excessive thirst, developed, and he drank enormous quantities of milk, water, and eau sucré. Micturition became correspondingly frequent, and in the words of his foster-mother "one saw him nearly always in this action."

In 1925, when he was nine years of age, he began to show marked somnolence,

which gradually increased until ultimately it became so pronounced that he went to sleep as soon as he sat down, no matter what hour of the day. It was this symptom and his excessive obesity for which advice was sought at the French Hospital in 1926. On examination in this hospital on 30th January, 1926, he was noted to show generalized adiposity, his weight being 9 st. 3 lb. and his height 4 ft. 2 in. The tissues were firm, well coloured and the abdomen protuberant. The penis and scrotum were very small and hidden in folds of fat, giving at first glance the impression of female organs. Umbilicus-soles measurement, 65 cm. ; umbilicus-vertex, 69 cm. Micturition was frequent and urgent and he had little control over the movement of his bowels. Mentally he was alert when moving about, but was overcome by sleep as soon as he sat down. He understood simple phrases and repeated spoken words in a low voice but with faulty articulation. He could neither read nor count, but recognized his friends, for whom he showed affection. When asleep in bed he snored loudly and became a little cyanosed. The clinical notes do not refer to the urinary output, but the urine was noted to be free from sugar and there was no glycosuria after the oral administration of 80 gm. of glucose. A second examination made fifteen days later still showed an absence of sugar, but the urine now contained albumen, 0.4 gm. per litre. The patient remained in hospital for four weeks and on nineteen occasions an evening rise of temperature to 99° F. was recorded ; the pulse rate varied between 80 and 92.

Re-examined on 18th February, 1929, the patient was noted to have gained 2 in. in height and to be 1 st. lighter in weight. The skin was smooth, the hair on the scalp abundant, the muscles hypotonic, and the genital organs undeveloped and showing the features of external hermaphroditism. The systolic blood pressure was 98 and the diastolic 58 mm. Hg. Marked polydipsia and polyuria were present. Blood : red blood corpuscles, 4,600,000 ; white blood corpuscles, 9,000 ; hæmoglobin, 86 per cent. Colour index, 0.9. Polymorphs, 4,860 ; eosinophils, 0 ; basophils, 180 ; lymphocytes, 3,600 ; monocytes, 360. The blood Wassermann reaction was negative. The specific gravity of the urine was 1.025, and sugar was present, but no acetone bodies, nor albumen. The fasting blood sugar was 135 mg. per cent. After ingestion of glucose the following curve was obtained : $\frac{1}{2}$ hr., 181 mg. ; 1 hr., 287 mg. ; $1\frac{1}{2}$ hrs., 225 mg. ; 2 hrs., 129 mg. per cent. X-ray examination of the skull showed a pituitary fossa much smaller than normal.

He was admitted to hospital on 4th May, 1932, when the following observations were made.

The patient was an imbecile boy, aged $16\frac{1}{2}$ years ; height 4 ft. 5 in., weight 8 stone $6\frac{3}{4}$ lb. Circumference of head, 52.7 cm. ; breadth, 14.9 cm. ; length, 18.1 cm. ; cephalic index, 83. He was remarkably stunted in growth, with a brachycephalic head, long face, short, thick neck, and rather slender limbs. His appearance was that of a eunuchoid with pronounced feminine characteristics (Fig. 2). On the scalp there was an abundant growth of dark curly hair, but on the face there were only fine lanugo hairs ; the axillæ were hairless. The skin, smooth, soft, and velvety, was of a reddish hue on the face and pale elsewhere. The face was large, the eyes rather close together, the nose long and straight, the cheeks fat, the lower jaw large and with a slight double chin. The upper teeth were crowded together, the palate high, the tonsils enlarged, and the tongue dry and coated. The pomum adami was not visible on the short, fat neck. The voice was high-pitched and feminine in character. The contour of the body was most unusual, the shoulders being broad and square, the thorax wide, and the abdominal wall covered with a heavy mantle of fat which dragged the skin downwards so that it hung in a heavy apron concealing the pubes and upper thirds of his thighs. There was slight development of the breasts, and, as may be seen from the accompanying illustration, the weight of subcutaneous fat had displaced downwards the nipples and umbilicus. The upper limbs were slender, feminine in contour, and the hands relatively small. The lower limbs were also somewhat slender and free from excess of subcutaneous tissue. There was considerable deformity and eversion of the

left leg, due partly to an old-standing fracture at the hip joint and partly to a chronic enlargement of the knee-joint. There was a moderate degree of genu valgum and pes planus. The feet and toes were broad. The symphysis-vertex measurement exceeded the symphysis-soles height by 3 in.

There was a well-marked mons veneris covered with thick hair of feminine distribution. The penis measured 2 cm. from symphysis to meatus and had a fully formed glans. About 3.5 cm. behind the penis there was a small rounded eminence with a centrally placed orifice which admitted the tip of the little finger. A nodule the size of a small bean which was felt lying deeply behind the eminence was probably a testicle; the other testicle could not be felt. Examination of the thoracic and abdominal viscera revealed no abnormality.

X-ray films of the cranium showed bones of normal density with normal coronal and lambdoid sutures; the sella turcica was, however, small. The bones of the forearms and hands were rather long and slender and the terminal phalanges pointed with feebly developed tufts. The arrangement of the epiphysis of the radius, ulna, and bones of the hand was normal and all were ununited. There was a deformity at the upper end of the left femur owing to the presence of an old fracture through its neck. The subpubic angle was wide, resembling that of a female pelvis.

The patient was a low-grade imbecile, his mental age, estimated by Burt's modification of the Binet-Simon scale, being two and a half years. He was shy, retiring, stubborn, and at times destructive. All his actions were slowly performed and he needed encouragement before he would answer questions. He knew no letters of the alphabet, but could give his name. He fed and dressed himself but needed assistance in washing. At times he was faulty in habits. He was quite alert and showed no drowsiness or tendency to fall asleep during the daytime. He asked frequently for drinks.

Blood examination gave the following: Hæmoglobin, 100 per cent. Red blood corpuscles, 5,300,000. Colour index, 0.94. White blood corpuscles, 12,400. Polymorphs, 7,320. Eosinophils, 125. Lymphocytes, 4,210. Monocytes, 745. He passed large quantities of pale urine. An attempt was made to estimate the fluid intake and the output volume of urine, but owing to his habits and lack of co-operation no accurate figures could be obtained. Over a period of eight days the patient's daily excretion of urine varied between 1,900 c.c. and 3,200 c.c., the average excretion in 24 hours being 2,330 c.c. The urine contained 540 mg. of sugar per 100 c.c. Blood sugar curves after the oral administration of 50 gm. glucose yielded the following graphs.

The cerebrospinal fluid was examined on 17th September, 1932. It contained 240 mg. of sugar per 100 c.c. ; no other abnormality was present.

The patient was put on an ordinary mince diet, which included bread and milk, and no medicinal treatment was prescribed. He continued to drink large quantities of water and on one occasion when he could not get access to a tap was found drinking the contents of a urine bottle. He remained active and alert with no evidence of drowsiness until 2nd February, 1933, when he developed a quinsy. His temperature rose to 103° F. and five days later he succumbed to broncho-pneumonia.

Pathological Findings

A necropsy was carried out 20 hours after death. The body, which was extremely obese, showed a deposit of fat 1 in. in thickness on the anterior abdominal wall. The mammae were represented by discs of areolar tissue and fat $2\frac{1}{2}$ in. in diameter. A small left testicle (weight 3 gm.) was found lying in the tissues behind the perineal eminence ; the latter appeared to be a rudimentary scrotum and the small orifice seen on it proved to be nothing more than a rather marked dimpling or infolding of its cutaneous surface ; the right testicle (weight 2.40 gm.) lay in the inguinal canal.

The brain weighed 1,380 gm. ; there was slight thickening of the pia arachnoid of the frontal poles ; and the convolutions were large and simple. The base of brain was normal, there being no evidence of tumour or meningitis ; the infundibulum and tuber cinereum were rather small in proportion to the rest of the brain. The pituitary gland was rather small, especially its anterior lobe ; it weighed 0.40 gm. The thyroid and parathyroid glands were normal in appearance. A large thymus gland was present. Both lungs showed a condition of broncho-pneumonia. The heart was normal in size and weighed 270 gm. The myocardium was soft and slightly fatty ; the valves were normal. The large arteries were hypoplastic. The liver, weighing 1,590 gm., was moderately enlarged, congested, and slightly fatty. The kidneys weighed : the right, 1,259 gm., and the left, 1,309 gm. Foetal lobulation present, otherwise there was no abnormality. The pancreas weighed 65 gm. and had a normal appearance. The suprarenals weighed : the right, 5 gm., and the left, 6.5 gm. The cortex and medulla were well defined. The bladder was unusually large and thick-walled, the prostate rudimentary and the seminal vesicles each about 2.5 cm. in length.

Microscopical Appearances.—The pineal gland was rather cellular, there being less neuroglial fibres and supporting tissue than in the normal adult gland.

The pituitary gland on examination showed an excess of eosinophile and chromophile cells in the anterior lobe. The basophil cells occupied principally the periphery of the gland. Chromophobe cells were relatively few in number. In the pars intermedia, the basophil cells were the seat of a small-celled infiltration. A number of vesicles were present, containing colloid which stained pink with eosin. The pars nervosa (Fig. 3) was nearly as large as the anterior, but showed no structural abnormality.

The thyroid gland had a cubical type of epithelium lining the vesicles and there was a marked degree of colloid storage. There was no fibrosis or evidence

of lymphocytic infiltration. The parathyroid glands were normal in structure. The thymus gland was very vascular and lymphocytes appeared to be increased in number. No Hassall's corpuscles were seen.

Sections of the body of the pancreas showed a slight degree of fatty infiltration lying between normal cell columns. No islets of Langerhans could be identified; in several sections of the whole block of tissue of more than $\frac{1}{2}$ cm. in thickness not a single islet could be seen. There was no interlobar fibrosis, but an unusual feature was the presence of numerous thick-walled channels completely filled with cells containing dark, oval-shaped nuclei. Tall columnar cells were also present in them lining the vessel walls, which were made up of plain muscle fibres. These channels appeared to be pancreatic ducts, the lining cells of which had proliferated to such a degree as to block completely the lumen.

In the adrenals, the cortex was slightly thicker than normal, but no departure from the normal could be seen in its cell columns. Frozen sections examined by polarized light showed the presence of lipid substances in the cells of the zona fasciculata. Broster and Vine's stain gave no selective staining.

Both testicles consisted of numerous tubules in none of which was there evidence either of cell differentiation or of spermatogenesis. The cells lining the tubules all possessed relatively large oval or rounded nuclei containing well-marked chromatin granules but no evidence of mitosis. The basement membrane of the tubules were slightly thickened. Between the tubules it was possible to find isolated interstitial cells of Leydig, polygonal in shape, the cytoplasm staining with eosin and their oval nuclei staining darkly by the basophil dye. These interstitial cells were not found in groups, and a comparison with the normal suggested that they were definitely deficient in number. Apart from slight evidence of fibrosis this epididymus was normal. In the prostate many of the tubular alveoli were filled with spindle-shaped cells, apparently derived by proliferation of their lining columnar epithelium.

The liver, kidneys, and spleen were normal in structure; sections of lung showed changes typical of broncho-pneumonia; and the heart was in a rather early stage of fatty degeneration.

A more detailed study of the nervous system was carried out. Sections of the frontal grey matter (Economo's area Fe) stained by cresyl violet showed changes which are not unusual in low-grade imbecility—a numerical deficiency of nerve cells with poorly developed processes and irregular alignment; in addition, there was present a fairly marked degree of subpial gliosis, but the underlying white matter showed no glial proliferation.

In the hypothalamus a study of the various hypothalamic nuclei was made in vertical coronal sections cut in three planes—through the anterior end of the tuber cinereum, through the oral halves of the mammillary bodies, and in a plane immediately posterior to the middle commissure. A comparison of sections with normal control tissue indicated that certain nuclei had suffered a definite reduction of nerve cells and that those cells which had survived in such nuclei exhibited degenerative changes of a chronic character. Furthermore, Holzer preparations showed the presence of a fibrous gliosis involving nearly

the whole region of tuber cinereum and certain adjacent nuclei. Those most affected were the nucleus supra opticus (of Greving), the three divisions of the nucleus tuberis lateralis, the nucleus tubero-mammillaris, the nucleus paraventricularis, and the substantia grisea of the third ventricle. Not all of these cell groups were equally affected. Thus, evidence of cell loss was not marked in the tuberal and paraventricular nuclei. In the nucleus tubero-mammillaris the loss of cells was much less, but pathological changes were pronounced. Even under normal conditions the appearance of these cells is peculiar—large cell bodies with substance aggregated round the periphery and comparatively small nuclei with indistinct nuclear membranes ; but here the morphological appearances were of a most unusual character (Fig. 4), the large nerve cells possessing extremely irregular cell bodies, with ill-defined nuclei, often displaced to the periphery, and in some instances discernible only through the survival of their conspicuous nucleoli. Attached to the margins of the cells were numerous dark-staining processes, some club-shaped and others bead-like or granular in outline, the general appearance being rather as if they were cytoplasmic extrusions. These unusual changes were not present in other nuclei, nor were they found in the small nerve cells of this region, the latter for the most part exhibiting the “ severe cell change ” of Nissl.

It may be recalled that Roussy and Mosinger (1934) have suggested that in at least four nuclei of the hypothalamus the nerve cells have a secretory function in some ways analogous to that possessed by the chromaffin cells of the adrenal gland, and they claim that it is possible to trace the gradual accumulation of droplets within these cells and their final extrusion into the surrounding nervous tissue. It is possible that the peculiar appearance of the nerve cells described above marked a final stage of a process such as is envisaged by Roussy and Mosinger, but the absence of vacuoles or droplets in these cells and the limitation of the changes to the nucleus tubero-mammillaris militates against the acceptance of such a view, and it would perhaps seem wiser to offer no pronouncement on their pathological significance.

The large nerve cells of the basal optic ganglion exhibited changes in much less degree, some of them having surprisingly little evidence of degeneration. The gliosis likewise showed a remarkable unevenness in extent and intensity. Beneath the ependymal lining of the ventricle there was a moderate degree of gliosis ; in the tuber cinereum the gliosis consisted of a delicate felt-work of glial fibres, nowhere very marked, but on the other hand the basal optic ganglion and the paraventricular nucleus exhibited a gliosis so intense as to be easily discernible with the naked eye in stained sections, the sharply defined dark-staining patches contrasting with the surrounding paler areas (Fig. 5). Under a high magnification, the appearance of these nuclei was very striking, the nerve cells lying in dense baskets of glial fibres (Fig. 6). The glial fibres seemed to have a special relationship to the blood vessels which they encircled, so as to form very condensed interlacings. The vessels, though dilated, showed no structural abnormalities. It was important to note how selective this gliosis was, one nucleus being heavily involved while its neighbour escaped. Thus Meynert's ganglion was free from glial increase, while, as described above, the

supra optic nucleus lying ventro-medial to it was the seat of a gliosis of intense degree.

In addition to the cell degeneration seen in the hypothalamic nucleus, chronic chromatolytic changes were also found in the subthalamus : several of the cells of this nucleus were binucleated. There was, however, no accompanying gliosis. The nerve cells of the various thalamic nuclei and in the globus pallidus and putamen were much better preserved. Sections stained by the method of Loyez showed a general thinning of myelin sheaths of the nature of a primary degeneration, which was very evident when comparison was made with normal control tissue.

Discussion

It is instructive to trace the sequence of events in this case. A male child, normal at birth except for the presence of a deformity of the external genital organs, developed in his third year an obesity typical of adiposo-genital dystrophy together with a retardation of growth and intelligence. To this picture, at the age of 5 years, there was added a disturbance of water metabolism, the patient exhibiting a very marked degree of polydipsia and polyuria. Later, somnolence appeared, and finally in his thirteenth year a very marked hyperglycæmia and glycosuria were established. In the last year of his life the excessive need for sleep disappeared. The diminutive size of the sella turcica noted radiographically on two occasions, the smallness of the anterior lobe of the pituitary established at autopsy, together with the anomalies of growth and metabolism in this case speak in favour of a diagnosis of pituitary ateleiosis, and it seems likely from the pathological changes encountered in the nervous system that the entire clinical picture was conditioned not by structural alterations limited to the pituitary but by a disturbance of the reciprocal interactions between this gland and the hypothalamic nuclei which regulate its activities. For the view that this disturbance was the outcome of the chronic degenerative changes found in certain of the diencephalic nuclei, there is support in the now extensive literature devoted to the hypothalamus and to the clinical disorders which have been ascribed to lesions confined to its nuclei.

It may be recalled that around the walls of the third ventricle are found a number of nerve cell groups for some of which important vegetative functions have been definitely established ; of these the most important are the substantia grisea centralis, the nucleus supra opticus (of Greving), the nucleus tuberis lateralis, the nucleus tubero-mammillaris, and the nucleus paraventricularis. Furthermore, there is experimental and clinical evidence in support of the view that it is the nuclei of the tuber cinereum—probably the three cell groups of the nucleus tuberis lateralis—which exert a definite influence on the unstriped muscle of the bladder, on the cardiovascular system, on the alimentary canal, on heat regulation, and on carbohydrate, protein, and water metabolism.

On the experimental side, Bailey and Bremer (1921) have shown that, in dogs, puncture of the tuber cinereum can produce polyuria and in some cases adiposo-genital dystrophy. In addition, Houssay (1923) likewise succeeded in producing polyuria by lesions of the tuber in animals with denervated kidneys.

Very similar results were obtained by Camus and Roussy (1920), while Sachs and MacDonald (1925) succeeded in causing polyuria in dogs in some cases by injury to the tuber cinereum and in others by injury to other areas.

Glycosuria, though usually transient and rather difficult to produce experimentally, has been found to follow hypothalamic puncture by Camus, Gournay, and Le Grand (1923), Sachs and MacDonald (1925).

During the past few years the occurrence of polyuria, glycosuria, and adiposo-genital dystrophy following tumours, lesions, and injuries of the hypothalamus has been recorded in papers too numerous to be reviewed here ; the clinical evidence of the important part played by the hypothalamus in the production of disturbances of the vegetative functions of the body seems, indeed, well-nigh incontestible. Unfortunately, in pathological material obtained from the human subject the size or diffuseness of the hypothalamic lesions usually found after death makes the task of determining the exact location of the structures responsible for the symptoms observed during life one of great difficulty, and in the case now reported this difficulty was present ; though three hypothalamic nuclei—the nucleus tuberis lateralis, the nucleus supra opticus, and the nucleus paraventricularis—showed degenerative changes of their ganglion cells, it was quite impossible to determine the order in which they became involved, if indeed they were not all three simultaneously affected. Similarly, with regard to the glial overgrowth, though the paraventricular nucleus and the basal optic ganglion showed a very marked fibrillary gliosis, it was impossible to state whether this morbid process affected first one nucleus and then another, or whether the degeneration commenced at the same period of time in each nucleus.

The significance of the neuroglial proliferation is by no means clear. It has, of course, long been known that nerve cells when attacked by noxious agents undergo a regressive transformation and the neighbouring neuroglial cells a progressive transformation, but it would also appear from recent research that under certain circumstances, at present little understood, a fibrous gliosis of the tissues may be primary. In certain of the hypothalamic nuclei in this case the gliosis was clearly a substitution for destroyed parenchymatous tissue, while in others it appeared to be out of all proportion to the amount of damage sustained by the nerve cells ; that it was the consequence of some form of physico-chemical change can hardly be doubted, though whether the change was the expression of an inherent vulnerability, such as was postulated by Gowers, or whether it was due to some vascular disturbance in this region cannot be determined. The character of the changes in the affected nuclei did, however, suggest a degenerative process of very long standing, and it seems permissible to conclude that the unusual clinical picture presented by this patient was that of an infundibulo-tuberian syndrome.

Summary

A male child, normal at birth save for the presence of external pseudo-hermaphroditism, acquired in his third year a marked degree of obesity which

was followed later by polyuria, polydipsia, excessive somnolence, and finally a very marked degree of hyperglycæmia.

In the nervous system degenerative changes of a chronic character were found in the nerve cells of certain of the hypothalamic nuclei together with a marked degree of fibrillary gliosis.

For the notes relating to the patient's clinical history during the years 1925 and 1929 I am indebted to the Secretary of the French Hospital, W.C.2.

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Fig. 1.—Patient, aged 7 years. Note stunted growth and obesity.

Fig. 2.—The patient, aged 16 years, showing obesity largely confined to the thorax and abdomen.

Fig. 3.—Section through the pituitary to show the relative enlargement of the posterior lobe : $\times 10$.

Fig 4.—Nerve cells of the nucleus tubero-mammillaris. Note irregular contour with stumpy processes and lack of definition of the nucleus. Cresyl violet stain ; $\times 550$.

Fig. 5.—Vertical coronal section through the walls of the third ventricle in a plane posterior to the middle commissure. V, III, third ventricle ; p.n., the two paraventricular nuclei sharply delineated by the fibrous gliosis. Holzer's stain ; $\times 15$.

Fig. 6.—Nucleus supra opticus. The surviving nerve cells are seen lying in a dense entanglement of fibrous glia. Holzer's stain, counterstained with ponceau fuchsin ; $\times 410$.