DYSONTOGENETIC PITUITARY CYSTS

(PITUITARY CACHEXIA IN CHILDHOOD)

BY

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The confused classification of pituitary tumours was clarified at the beginning of this century by the work of Erdheim (1904, 1926). In a series of exemplary papers, he gave proofs that a variety of solid and cystic tumours of the pituitary gland and its stalk have a common origin in the displaced stratified squamous epithelium of the hypophyseal duct. This histogenesis is well expressed in the designation 'hypophyseal duct tumours' (Erdheim) or craniopharyngeomata. Recently Ingraham and Scott (1946) rightly objected to the term craniopharyngeoma, pointing out that the hypophyseal duct develops from the ectodermal stomodeum and not from the entodermal primitive pharynx. They suggested tentatively the term 'craniostomodeoma.' The designation 'craniopharyngeoma' however, being in common use, will be retained in this paper. While the experimental work on the pituitary has made spectacular progress, very little has been added since Erdheim's classical monograph (1926) to our knowledge of the morphogenesis of pituitary tumours. Unfortunately much confusion has been caused by the use of such names as 'tumours of Rathke's pouch,' 'cysts of Rathke's pouch,' 'adamantinomata of the pituitary,' etc. The use of the term 'tumour of Rathke's pouch' as synonymous with craniopharyngeoma is particularly deplorable, as will be obvious by reference to the developmental relationship of Rathke's pouch and its cavity to various parts of the pituitary gland. This shows that Rathke's pouch is at first a rather flat bag which, after frontal turning of the lateral and later cranial seams, resembles a basket. In the frontal wall of the basket a midsagittal crest is then formed, which in cross section appears as a solid process. By proliferation of the crest and of the lateral (frontally turned over) seams, a large number of solid glandular columns and narrow tubules are produced, which, with the invaded vascular connective tissue, form the main mass of the adenohypophysis. The upper seam with a few wider tubules probably gives rise to the pars tubularis and some of the cysts of the medullary zone

(Hochstetter, 1924; Benda, 1932; Guizzetti, 1933). After obliteration of the craniopharyngeal duct, the original cavity of Rathke's pouch is represented in embryonic life by the 'primary Rathke's cyst,' which in young infants still persists in the form of Rathke's cleft (Koelliker's space = Frazer's pituitary lake, Frazer, 1921). By progressive segregation from the cleft, which was originally single, small colloid cysts are formed in the medullary or intermediate zone of the pituitary; these Kraus (1926) calls 'secondary Rathke's cysts.' However, the cysts of the medullary zone, which latter is often erroneously called 'pars intermedia,' only in part originate from the segregation and partial obliteration of Rathke's cleft; some are the product of cellular degeneration, and others probably arise from hollow glandular buds of the cranial seam of the pituitary basket (Collin, 1923; Benda, 1932; Berblinger, 1932; Guizzetti, 1933; Selye, 1943). Usually the origin of the cysts is not recognizable from their morphology. Bailey (1932) says that cysts deriving from Rathke's cleft may be distinguished from other cavities in this region by their being lined by ciliated epithelium; this statement is misleading, because an intact Rathke's cleft is often seen in young infants, where ciliated epithelium is found only occasionally and in limited areas. Cysts lined by ciliated epithelium are, except for the suprasellar ones, certainly derived from the original Rathke's cyst, but the majority of colloid cysts, produced by the segregation of Rathke's cleft, are lined by cubical and not by ciliated epithelium.

The craniopharyngeal duct is pulled upwards anteriorly during the proliferation of the anterior wall of Rathke's pouch, and in the rare cases of persisting craniopharyngeal duct the cranial end of the intrasphenoid canal is situated in the anterior part of the sella, in front of the eminentia olivaris. 'The region of the insertion of the erstwhile hypophyseal duct is carried upwards, by the . . . rotation of the developing gland, to the anterior infundibular and upper pars anterior surfaces' (Duffy, 1920). How far upwards the insertion of

the craniopharyngeal duct, which is originally situated at the caudal end of the pouch, can be carried by the developing glandular mass is well seen in a figure of Hochstetter's, where a persisting rest of the hypophyseal duct is seen inserted high (i.e. cranially) on the ventral aspect of the adenohypophysis. This explains the main localization of displaced squamous epithelium on the anterior aspect of the pituitary, and especially of its stalk and the corresponding situations of craniopharyngeomata. Schematic drawings and reproductions of wax models illustrating the developmental anatomy of the pituitary may be found in papers of Miháľkovics (1875), Hochstetter (1924), Erdheim (1926) and Benda (1932). The whole anterior lobe of the pituitary being derived from the wall of Rathke's pouch, the designation 'tumours of Rathke's pouch' could, in fact, be applied with more justification to adenomata of the pituitary than to craniopharyngeomata, which are derived from displaced squamous epithelium of the craniopharyngeal duct, which in embryos of 12 to 16 mm. crown-rump length is already well differentiated from Rathke's pouch proper. If, on the other hand, the term 'Rathke's pouch' is used as synonymous with 'primary Rathke's cyst,' which is done by Worster-Drought et al. (1927) the designation 'cysts and tumours of Rathke's pouch' can be applied only to those arising from the pituitary cleft and its lining epithelium, and not to the vast majority of craniopharyngeomata. The term 'tumour of Rathke's pouch' thus leads to confusion of craniopharyngeomata with cysts (either colloid or ciliated epithelial) which develop from the primary or secondary Rathke's cysts and which have histogenetically nothing in common with the former. Frazier and Alpers (1934), who do not agree with the present classification of pituitary tumours, proposed a classification into (1) adenomata, (2) tumours of the pituitary stalk, and (3) tumours of Rathke's cleft. Except for the adenomata, this classification is purely topographical, makes no distinction between neoplastic and non-neoplastic cysts, and cannot be considered as satisfactory when a morphogenetic classification is possible.

It is hoped that the publication of the two following cases may contribute to a more satisfactory classification of pituitary cysts. Moreover the cases present several other points of interest. In the first place they are examples of the very rare pituitary cachexia in young children. The few cases of Simmonds' disease in childhood (Thomas, 1933; Goebel, 1932; Geldrich, 1939; and others) were almost all only clinically observed. Only one case (Simmonds, 1916) is mentioned in Graubner's

(1925) review and Escamillo and Lisser (1942), reviewing all cases of pituitary cachexia, found among 111 cases verified by autopsy, only one case under ten years. Secondly, it is exceptional for even large colloid cysts, such as those described in this paper, to cause clinical symptoms. Goldzieher (1913) described a large colloid cyst causing diabetes insipidus, and Kiyono (1926) a case of pituitary cachexia due to similar cyst.* Merz (1930) described a case of pituitary cachexia due to a pea-sized colloid cyst between the anterior and posterior lobes, but the presence of sclerotic changes at the insertion of the pituitary stalk makes the interpretation of his case somewhat uncertain. Finally, in one patient described in the present paper, the pituitary cyst was associated with syringomyelia, and in the other with fibrocystic dystrophy of the pancreas. While the first association can be regarded as a simultaneous occurrence of two developmental disturbances, the possibility of a causal connexion between pituitary and pancreatic disease cannot be ruled out and will be discussed below.

Case 1

After seven months' gestation, a boy was born on March 15, 1941; he was admitted to the Children's Hospital, Birmingham, on July 20, 1945. The child thrived normally until the age of eight months, when he developed pneumonia, for which he was in hospital for several months. Before this he could stand and walk with assistance. A few weeks after his discharge he showed so little improvement that he was readmitted. He remained in hospital until the age of two and a half years. He always had a cough, variable in severity, and a poor appetite. He had no difficulty in swallowing, but the act often produced coughing, which in its turn caused vomiting; he never vomited except after cough. He drank well. He could not sit up by himself, but was able to feed himself when he felt strong enough. He liked to play with an engine, and he would look at a picture book for hours and was not destructive. At the time of his discharge from hospital he was not able to talk much, but uttered words such as 'gee gee.' His sleep was restless. He had no fits. Bowel and urinary functions were good, but if he had been vomiting during the day he had nocturnal enuresis.

Findings on admission. He was an emaciated child who did not smile. He knew the names of a few common objects, but the speech was confined to single words. He seemed to want to rouse himself, but could not succeed. He kept his head on one side, being unable to hold it up, and he sat only with support. There was some nystagmus in all directions, and ? fibrillation of the tongue. There was frequent, unexplosive cough, the chest was full of bronchial sounds, the abdomen normal,

* The paper of Jedlička (*Sborn. lík.*, 1924, 25, 149) describing an apparently similar case was unfortunately not available.

all reflexes brisk, and the voice monotonous. On July 21, 1945, the tongue protruded with difficulty and there was fibrillation, though there was none in the hands, nor any wasting of small muscle groups. On July 22 he regurgitated through the nose, and the next day he was weaker and the temperature, pulse, and respiration rates were raised and the colour poor. He died on July 24, 1945, and necropsy was performed nine hours after death.

Post-mortem findings. The body was of an extremely emaciated, pale boy. It measured 87.5 cm. long (normal average, 102 cm.). The sitting height was 50 cm. (normal, 56 cm.), and the length of the leg from the anterior superior iliac spine to the internal malleolus was 42.5 cm. (normal, 47.5 cm.). (The normal figures for body length are taken from Kornfeld, 1929; and other measurements from Brock, 1932; and the weights of normal organs in childhood from Copolletta and Wolbach, 1933.)

The thyroid and parathyroid glands appeared normal to the naked eye. The thymus was grossly atrophic. There were extensive and firm adhesions between the pulmonary pleura over the right lung and the costal pleura, and some fibrinous exudate over the lower lobe of the left lung. Moderately dilated bronchi, filled with pus, were seen on the cut surface of both lungs. In the lower lobe of the left lung there were numerous areas of consolidation, brownish-red in colour; there were areas of collapse in the right lung. The tracheo-bronchial lymph nodes were markedly enlarged, soft and hyperaemic. The largest was at the bifurcation and was almost as large as a walnut. The pericardium was normal. The liver was moderately congested. The testicles, each about the size of a pea, were in the inguinal canals.

The sella turcica was normal in sagittal and frontal diameters. The pituitary appeared (on inspection after an incision into the diaphragm sellae) to be replaced by a large pea-sized, thin-walled cyst which apparently filled the whole sella. It was not dissected immediately, but the whole body of the sphenoid bone was removed, fixed in formol saline, decalcified, and dissected in the mid-sagittal plane, one half being embedded in paraffin and the other saved. The spinal cord was saved but not dissected immediately.

The costo-chondral junctions were normal on naked-eye examination. The bone marrow of the right femur was dark red throughout.

Histological findings

PITUITARY. There was considerable shrinkage of the pituitary affecting mainly the cyst, which had an antero-posterior diameter of 3 mm. The anterior lobe was reduced to a narrow band which on sagittal section had the shape of a sickle. The pointed end of the sickle was at the floor of the sella turcica, and the diameter increased gradually and reached its maximum of 1.2 mm. at the antero-superior aspect of the cyst. The posterior lobe had

a maximal diameter of 1.5 mm. The cyst was situated between the two lobes of the pituitary and extended downwards to the peristomium of the sella. (Fig. 1, and Plate Ia.) It was filled with a homogenous material, which appeared pale pink in

FIG. 1.—Schematic reconstruction of the immediate post-mortem findings on the pituitary in case 1. A.L.=anterior lobe; C.C.=colloid cyst; P.L.=posterior lobe; D.S.=dorsum sellae; S.T.=stalk.

haematoxyline-eosin-stained sections and pale bluish in trichrome stain, and which showed fuchsinophil, fuchsinophobe, and tannin-fast areas by Kraus' (1914) colloid stain. The lining of the cyst consisted of a single, in a few places double, layer of flat or cubical cells which did not show any granulation in their cytoplasm (Plate Ib). Their nuclei were dark, oval or spherical, their cytoplasm pale and amphophil. A few small colloid cysts were also seen along the anterior aspect of the posterior lobe. Here, and occasionally on the posterior aspect, several glands were seen which had the appearance of salivary glands. Such glands are not uncommon in pituitaries. Erdheim (1903) considered them as identical with salivary glands. The structure of the posterior lobe was normal. In the anterior lobe the cells were arranged in parallel, longitudinal strands, instead of the normal tortuous columns, as if compressed between the bone and the cyst. The sinusoids between the cellular strands, however, were wide and engorged, thus suggesting that the cellular disarrangement was due to a chronic pressure directing the growth of the gland and not to an immediate mechanical effect. The numerical relationship between the acidophil and basophil cells was approximately normal. The chromophobe cells were rather scanty. There was no follicle formation in the anterior lobe, and nowhere within this part was there any evidence of colloid degeneration.

THYROID. The vesicles of the thyroid were normal in size; they were lined by cuboid or columnar epithelium. Colloid, which was present in a few vesicles only, showed a pale eosin stain and had in some places a vacuolated appearance. Desquamated epithelial cells were seen in many vesicles.

PARATHYROID. Only one parathyroid gland was examined. It measured 1.7 by 0.7 mm. There

were fairly large areas of fat tissue between the cells, which had all the character of water-clear 'chief cells' (Plate Ic). Normally no fat cells are seen in the interstitial tissue of the parathyroids before the fifth year of life (Erdheim, 1903).

SUPRARENALS. When the suprarenal glands were examined, only the cells of the zona glomerulosa showed an approximately normal foamy appearance. The cells of the zona fasciculata and reticularis were swollen, their cytoplasm was slightly granular, and pale pinkish in haematoxylineosin stained sections.

The seminiferous tubules of the testis were narrow, lined by one to three layers of cubical or columnar cells with dark nuclei, and separated by broad strands of interstitial tissue. The latter was cellular with numerous fibroblasts in some areas, acellular with broad collagenous fibres in others. Interstitial cells of Leydig were seen only occasionally (Plate Id).

THE MEDULLA. This showed an increased amount of glia at the floor of the fourth ventricle, and specially in the region of the hypoglossal nuclei. There was marked rarefaction, chromatolysis of nerve cells, and 'fading away' of nerve cells with formation of ghost cells.

THE LUMBAR CORD. The lumbar cord showed the central canal replaced by a cavity $5\frac{1}{2}$ by 3 mm. in diameter in its widest part. The cavity contained some disintegrated nerve tissue. Small parts of its circumference were lined by a single layer of cuboid or columnar cells in epithelial arrangement, the cells with very few exceptions not being ciliated. There was a ring of fibrillary glia, about 0.3 mm. in diameter, surrounding the cavity (Plate Ie and f). The glia fibres were in loose arrangement, but here and there formed patches of dense network. The astrocytes were poorly impregnated by the Cajal method; their processes were irregular and occasionally fragmented. Except for a slight increase of the glia around the central canal, the dorsal and cervical cord showed no pathological changes.

RIBS. The proliferation zone proper of the cartilage was very poorly developed, in many places scarcely recognizable as such. The columnar zone was normal in width, but in numerous places whole columns had undergone severe degenerative changes and the cells had fused with the ground substance of the cartilage. The provisional zone of calcification was interrupted in a few places, and in these it consisted of small isolated patches of calcified ground substance. In several places the osteoid seams of the bone trabeculae were definitely broader than normal. (Completely decalcified ribs, and ribs partially decalcified by Mueller's solution, were examined.)

BONE MARROW. In the rib there was a very cellular bone marrow with numerous normoblasts and myelocytes. In the distal end of the femur there was fat marrow.

Summary of Findings. A four-year-old boy who suffered from his eighth month of life from indefinite

symptoms of retarded development, muscular weakness, loss of appetite, and wasting, died with symptoms suggestive of bulbar palsy. Necropsy revealed a large colloid cyst of the pituitary causing a severe atrophy of the anterior lobe. This was associated with syringomyelia of the lumbar cord and a mild gliosis and rarefaction in the region of the hypoglossal nuclei. At the time of death he was 14.5 cm. shorter than the average for his age. His body length was 86 per cent. and the length of the lower limbs 89 per cent. of the normal figure. He may, therefore, be considered as of normal proportion. There was a lipomatosis of a parathyroid, an incomplete descent of testicles with atrophy and interstitial fibrosis of the latter. In addition there was a chronic ulceronecrotic bronchitis, peribronchitis, bronchiectasis, and adhesive pleurisy.

Case 2

A girl of eight years of age was well until April, 1945, when she started to have eight or nine very offensive, loose, yellow stools daily. She lost her appetite. She had an attack of diarrhoea twelve months before admission, but recovered in three or four days. On admission on July 17, 1945, she was very emaciated, and talked with a slow, monotonous voice; her feet were pale and cold, and there was excessive muscular wasting in her legs. There was slight oedema, and a purpuric rash. On the knees were depressed scales about the size of the head of a pin, surrounded by narrow rings of erythema. There was latent tetany, but no other relevant findings. A five days' collection of stools showed a daily output of 18.4 g. of fat. The total fat was 43.2 per cent. of the dried faeces, and the neutral fat 15.8 per cent. The blood urea was 29 mg. per 100 c.cm., the albumin 1.77 g., and the globulin 1.15 g. There was 248 mg. sodium per 100 c.cm. serum, 477 mg. chlorine (calculated as sodium chloride), 1.0 mg. pyruvic acid, 6.0 mg. calcium, 4.4 mg. phosphorus, and 8.5 mg. inorganic phosphorus liberated in three hours, at 37° C. The water-elimination test for Addison's disease was inconclusive. The test of Robinson et al. (1941) was performed on Aug. 12 and 13, and the resulting quotient was 5.7 (normal more than 25). Another estimation of faecal fat in the period from Aug. 9 to 14 showed a daily output of 24.8 g., with the total fat forming 52.3 per cent. and the neutral fat 18.0 per cent. of the dried faeces.

The blood findings are shown in the table and in the Price Jones curve (fig. 2). The mean corpuscular volume was 81.6 to 85.2 μ^3 . The bleeding time was one and a half minutes and the clotting time three minutes (Aug. 17, 1945). An oral and an intravenous glucose tolerance curve showed no gross abnormality. Two units of insulin injected intravenously caused a depression of the blood-sugar level from the fasting level of 104 mg. per 100 c.cm. to 42 mg. per 100 c.cm. after twenty-three minutes. and after sixty-two minutes it was 62 mg. per

100 c.cm. The Mantoux test was negative with 0.1 and with 1 mg. tuberculin. The child was given plasma intravenously, calcium chloride by mouth, and, from Aug. 18, 5 mg. percartin daily. There was a transient improvement after the percartin treatment, but after this a rapid deterioration, and the child died on Sept. 20, 1945. Her weight was

FIG. 2.—Price Jones curve of case 2.

3 st. 11 lb. one week after the onset of the disease, and 1 st. 10 lb. 14 oz. two days before death.

Post-Mortem findings. The body, which was of an extremely emaciated girl, measured 116 cm. long (average, 123 cm.). The distance from the acromion to the tip of the middle fingers was 50 cm. (normal, 53.5 cm.); and from the spina iliaca anterior to the malleolus externus, 56.25 cm. (normal, 62.5 cm.). The skin was pale, with a greyish-yellow tinge. Ecchymoses, pin-head to millet-sized, occasionally lentil-sized, and not sharply demarcated, were situated mainly on the anterior aspect of the chest; but there were a few on the anterior abdominal wall and on the limbs, a single one 11 by 5 mm. in diameter on the interior aspect of the lower third of the left thigh, and another measuring 10 by 5 mm. on the radial side of the back of left hand, between the metacarpes of the thumb and the second finger. There were no pubic and axillary hairs. The subcutaneous fat tissue was almost absent, being reduced to small patches, saffron yellow in colour. The bone marrow of the sternum was a dark raspberry red. The tongue showed atrophy of the filiform papillae and several blackish-grey patches

approximately in the middle. The right lobe of the thyroid measured 30 by 12 by 9 mm., the left 28 by 9 by 6 mm., the cut surface being moist, granular, and lustrous yellowish pink.

The thymus was grossly atrophic. The heart measured 8.2 by 7.5 by 3.6 cm., and weighed 67 g. (empty) (normal, 80 to 130 g.). The wall of the left ventricle was 9 mm. and that of the right 2 mm. thick. The heart muscle was pale, flabby, and friable. The valves and the septa were normal. The ductus arteriosus was obliterated, and a shallow pit on the aortic side was noticeable.

There was one pinhead-sized subserous haemorrhage on the anterior aspect of the stomach near the greater curvature. Very little fat was present in the great omentum and in the appendices epiploicae. The anus was rather wide; the blood vessels of the mesentery somewhat distended and engorged. The stomach was distended and contained about a handful of a greyish material of the consistency of porridge. Its mucous membrane was normal. The contents of the duodenum were bile-stained, and bile was easily expressed from the gall bladder by manual pressure. The small intestine was collapsed, and the large intestine, especially the pelvic colon, considerably distended. The contents of the small intestine were green, liquid, and somewhat slimy. The large intestine contained watery-green faeces. The mucous membrane of the intestine was normal, and the lymphatic apparatus rather atrophic. The mesenteric lymph nodes were lentil to pea-sized, greyish-white, and normal in consistency.

The liver weighed 1 lb. and showed fatty changes and some congestion. The bile ducts were patent. The pancreas weighed 34 g. and was rather firm, its cut surface being normal in appearance. The spleen measured 6.5 by 4.5 by 1.5 cm. and weighed 27 g. (normal, 69 g.). The capsule was smooth, the colour pale salmon red, and the consistency normal. On the cut surface the Malpighian bodies were fairly large, and the pulp bright red and not diffuent. The right adrenal weighed 3.3 g., and the left 3.5.; their cortex was greyish and poor in lipoids. The left kidney measured 7 by 4.5 by 3 cm. and weighed 59 g. (normal, 75 g.); the right

TABLE

Date	Hb. g. per c.cm. of blood	Erythrocytes (million)	Colour Index	Reticulocytes %	Leucocytes	Platelets	Neutrophil		Eosinophils %	Monocytes %	Lymphocytes %
							band %	sgm. %			
July 23	9.3	2.36	0.88	1.8	6,250	290,000	2.0	44.5	0.0	6.0	47.5
Aug. 17	9.6	2.78	1.22	3.4	3,900	222,000	2.0	42.0	3.0	3.0	50.0
Aug. 23	9.8	2.98	1.18	6.6	6,000	307,000	1.0	57.0	1.0	5.0	36.0
Sept. 6	10.8	2.58	1.52	0.8	11,250	337,000	3.0	84.0	0.0	1.0	12.0

measured 8 by 4.5 by 3.5 cm., and weighed 61 g. (normal, 74 g.). Their capsules were easily stripped off, and the surface was smooth and pale yellowish-red. On the cut surface the medulla was dark red; the normal markings of the cortex were indistinct. The renal pelves appeared normal. The right ovary weighed 0.71 g., the left 0.66 g., and they appeared normal.

The vault of the skull showed on both sides of the sagittal suture, close to the coronary suture, triangle-shaped, thin, white, transparent, non-flexible areas. In other areas dark red bone marrow was visible in transmitted light. The thickness of the vault was between 1 and 2 mm. The appearance of the internal aspect was normal. The distance between the anterior clinoid processes was 24 mm., that between the posterior 16 mm. The pituitary appeared normal from above, but when it was removed from the sella a thin-walled cyst, 8 by 8 by 3 mm. with clear, yellowish, apparently gelatinous contents was found replacing a considerable part of its anterior lobe. The size of the whole pituitary was 11 by 8 by 3 mm., its weight being 0.341 g. The depth of the sella turcica was 7 mm. and its midsagittal diameter 9 mm.

The pineal gland measured 14 by 8 by 2 mm. and appeared normal. The labia majora were scarcely discernible, the clitoris rather small, and the vagina and uterus normal. On the sixth left rib the proliferation zone of the cartilage was 2 mm. in depth, and the provisional calcification zone was straight, sharply defined, and about 0.25 mm. in width.

The femur was easily sawn through. Its cortex and the trabeculae of the cancellous bone were thin. The epiphyses were ossified, leaving a narrow epiphyseal cartilage. The bone marrow of the proximal three quarters of the femur was raspberry-red and that of the distal quarter was pale, greyish-white, and gelatinous. The marrow of the proximal epiphysis was red, and that of the distal epiphysis pale greyish-white.

Histological findings

PITUITARY. The Rathke's cleft was very considerably dilated, and, on midsagittal section, triangle-shaped. It contained a large amount of fuchsinophobe colloid with a small admixture of fuchsinophil and tanninfast colloid. The wall of the cyst was ruptured and the cyst collapsed, and a considerable amount of colloid was seen outside the cyst. The lining epithelium of cyst was cubical, and the cells showed no granulation. There were a few small colloid cysts between the posterior wall of the main cyst and the posterior lobe of the pituitary (Plate I, g, h, Plate II, j, and fig. 3). The anterior lobe had a maximal antero-posterior diameter of 2.5 mm. Basophil cells were plentiful in all areas. In some areas the eosinophil cells were almost absent, while in other areas they were increased in number at the expense of chromophobe cells (compensatory hypertrophy: Berblinger, 1927).

THYMUS. There was atrophy of the thymus, with marked lipomatous metamorphosis.

THYROID. The vesicles were large and filled with a colloid which in some places showed a few large vacuoles, in other places numerous small vacuoles.

FIG. 3.—Schematic reconstruction of the immediate post-mortem findings on the pituitary in case 2. A.L. = anterior lobe; P.L. = posterior lobe; ST. = stalk; C.C. = colloid cyst; D.S. = dorsum sellae.

KIDNEY. The glomeruli showed a slight intracapillary hyalinization. The hyaline was present only in a few loops of the tuft, the majority of loops being widely patent. The first convoluted tubuli were markedly dilated and filled either with a pale, foamy material or with hyaline casts. The lining epithelium was cuboid or flat. Many of the epithelial cells showed large vacuoles (no fat stain made). A foamy material similar to that in the first convoluted tubuli was also seen in the Henle loops and in the collecting tubuli. The renal pelvis showed an epithelial proliferation, and in a few places a modified epithelium with the characters of a stratified squamous epithelium without cornification.

SPLEEN. The malpighian bodies were normal, the venous sinuses narrow, and Billroth's cords very cellular with numerous polymorphonuclear leucocytes.

PANCREAS. The interlobular connective tissue was considerably increased in amount. It consisted of fibroblasts, thick collagenous fibres, and numerous small round cells with an occasional polymorphonuclear leucocyte. This connective tissue invaded the individual lobules, which showed an advanced atrophy of the secretory tissue. They consisted of ducts, infundibuli, and small, usually crescent-shaped, groups of secretory cells attached to the tips of the infundibuli. The acinus cells were modified and more narrow than normal, and zymogen granules were absent. When they were isolated, it was often difficult to decide whether we had to deal with an acinus or a cross section of a duct. Between these parenchyma cells there was a large amount of loose connective tissue with patches of round-cell infiltration. Many of the inter- and intralobular ducts were markedly dilated and filled with an eosinophil homogenous or stratified material. In some places the latter showed a pale granular centre and a homogenous, intensely eosinophil

periphery; in other places the central part was homogenous and surrounded by several wavy layers of deeply eosinophil material, separated by almost colourless interspaces. In some of the larger dilated ducts, desquamated epithelial cells and a few inflammatory cells were enclosed in the eosinophil concretions. Some of the dilated ducts showed necrosis of the lining epithelium and were surrounded by connective tissue with dense cellular infiltration. The cellular infiltration was more marked in the head of the pancreas near to the duodenum than in the body and the tail. The main pancreatic duct was patent. Near to the papilla of Vater it was almost completely blocked by numerous eosinophil 'microliths,' fibrillary concretions, and desquamated epithelial cells. The islands of Langerhans were normal in number and appearance (Plate II, k and l).

DUODENUM. The duodenum showed a marked cellular infiltration of the mucosa which in a few places extended into the submucosa and which consisted of plasma cells, lymphocytes, and eosinophil leucocytes.

OVARY. There were several follicular cysts, 1.5 to 3 mm. in diameter, but otherwise nothing abnormal.

BONE MARROW. The bone marrow of the middle part of the femur consisted of fat tissue with islands of haematopoietic tissue. The latter showed numerous myelocytes, nucleated red blood corpuscles, and a few mature neutrophil leucocytes.

BONES. The rib and lower end of the femur were decalcified—the former completely, the latter partially. The proliferating zone proper of the cartilage and in a lesser degree the columnar zone were decreased in width. The provisional calcification zone was normal. In the zone of primary marrow formation, the longitudinal trabeculae of bone and calcified cartilage matrix were short and separated by wide and shallow bays. In some places there were, instead of the longitudinal, transverse bone trabeculae directly attached to the zone of provisional calcification. In the diaphysis the trabeculae were thin and widely separated, and showed osteoid seams which were, especially in the rib, markedly broader than normal. Fairly broad osteoid seams surrounded also the short trabeculae of calcified cartilage matrix. The bone marrow within the distal part of the femur was entirely fat marrow.

Summary of findings. A girl, eight years of age, died after five months' illness with severe wasting, muscular weakness, apathy, steatorrhoea, macrocytic hyperchromic anaemia, latent tetany, decrease of sodium and chlorides in the serum, and hypersensitiveness to insulin. The necropsy examination revealed a large colloid cyst of the pituitary, replacing Rathke's cleft, and a fibrocystic dystrophy of the pancreas. The child was 7 cm. shorter than the normal average, and the histological examination showed evidence of arrested growth (cf. Harris, 1933) associated with osteoporosis and mild rickets.

The kidneys showed histological evidence of early glomerulo-nephritis.

Discussion

The two cases reported in this paper presented symptoms of progressive cachexia associated with muscular weakness and an apathetic state of mind. In one case there was an obvious, in the other a slight, stunting of growth. These symptoms were associated in the first case with symptoms of a lower motor neuron lesion. In the second case there was steatorrhoea, macrocytic hyperchromic anaemia, and metabolic changes suggestive of Addison's disease. Percortin treatment was, however, ineffective and this, together with an increased insulin-sensitiveness, pointed to disease of the pituitary or hypothalamus.

Necropsy in each case showed a large colloid cyst replacing the cleft of Rathke and causing atrophy of the anterior lobe. The cysts were lined by flat or cubical epithelium; there was no evidence of neoplastic growth. The absence of inflammatory changes or fibrosis, and the presence of an almost intact epithelial lining and of colloid in the cysts ruled out the possibility of the cysts being the result of a previous necrosis. There could, therefore, be no doubt that the origin of the cysts was over-secretion and retention of colloid. In this respect they resembled the pancreatic cysts studied by Wegelin (1921) and his pupil Yamane (1921), which were due to a developmental error, grew very slowly as a result of secretion and retention, and have, therefore, been met with almost exclusively in adults. They have sometimes been associated with the Lindau syndrome. Wegelin (1921) introduced the designation 'dysontogenetic retention cysts' for this type of cyst formation. The application of such an interpretation to the pituitary cysts is closely related to the problem of pituitary colloid. The original conception of its being the internal secretion of the pituitary was rejected by Erdheim (1926) Kraus (1926) and others, who saw in the colloid a useless waste product. Erdheim regarded the production of hypophyseal colloid as an atavistic rudimentary external secretion, Kraus as a product of colloid degeneration of anterior lobe cells. More recent investigations give support to the idea that the formation of colloid is linked with a part of the internal pituitary secretion. Guizzetti (1933) stressed the similarity between the lining cells of colloid cysts of the medullary zone on one hand, and the basophil cells of the anterior lobe on the other. Migration of basophil cells into the posterior lobe, and presence of a material, indistinguishable from the colloid of the medullary zone (Hering's 'hyaline bodies') in the posterior lobe and all the way towards the

hypothalamus, has been demonstrated by several authors (Kraus, 1926; Cushing, 1933; Benda, 1942; Selye, 1943). The inundation of hypothalamic centres with colloid is very marked after removal of the upper cervical sympathetic ganglion (Popjak, 1940). Selye (1943) has shown that intravenous injections of hypertonic NaCl-solutions into rats caused swelling of basophil cells in the anterior lobe of the pituitary gland, eventually with degenerative changes and at the same time considerable distension of Rathke's cleft with colloid. On the other hand the presence of symptoms of pituitary cachexia, of arrested growth, of suprarenal, testicular, and parathyroid changes in our two cases and in the case of Kiyono (1926), where a large amount of colloid was present in the cystic dilatation of Rathke's cleft, are strong evidence that the main hormones of the anterior pituitary lobe are not present in the colloid secretion. It is also worthy of note that in the two cases presented in this paper there was no evidence of colloid degeneration in the anterior lobe, and the whole amount of colloid was apparently the product of the epithelial lining of the cysts. It appears, therefore, conclusive (1) that the colloid is formed by both apocrine secretion of the lining cells of Rathke's cleft and by holocrine (possibly also apocrine) secretion of basophil cells of the anterior lobe; and (2) that the colloid formation is linked with only a part of pituitary hormone production, probably that associated with the activity of posterior lobe and the hypothalamic centres. The problem of 'neurocrine' formation of colloid by pituitocytes and the hypothalamus (Scharrer's (1941) diencephalic gland) is for our problem irrelevant.

In the present two cases the cleft of Rathke did not undergo the normal segregation into a series of small cysts; but instead, as a result of a continuous, increased colloid secretion by its lining epithelium, it became transformed into a large retention cyst, thus causing atrophy and hypofunction of the anterior lobe and an accumulation of a secretion which may have an influence on the hypothalamic centres.

As mentioned in the introduction, even comparatively large colloid cysts do not usually cause symptoms of hypo- or apituitarism. Why they do so in rare cases is still a debatable problem. It has been repeatedly assumed (Kiyono, 1926; Merz, 1930) that a separation of the anterior lobe from the posterior has similar effects to disease of the anterior lobe. In the first of the two cases described in this paper there was complete separation, but in the second a strip of anterior lobe tissue was seen closely attached to the superior pole of the neurohypophysis. Possibly the presence of pharyngeal

hypophysis accounts for the fact that some large colloid cysts cause no clinical symptoms.

In the first case there was a marked atrophy of the testicles, morphological changes in the suprarenals, lipomatosis of at least one parathyroid, and syringomyelia of lumbar cord. The parathyroid changes are noteworthy because of the still contested formation of a parathyrotropic hormone by the anterior pituitary lobe (see Cameron, 1945; Perlman, 1944). The changes in the testicles, although very marked, occur also in other cases of undescended testicles (Kyrle, 1910). It is, however, possible, that these are also related to pituitary dysfunction, and according to Gruenwald (1946) they are less frequent than previously assumed and changes less marked than those found in the present case are considered by this author as evidence of underdevelopment. Syringomyelia is apparently an independent, associated condition. As syringomyelia is now considered by most authors to be a developmental error with persistence of primitive glia (Tamaki and Lubin, 1938), this association supports the interpretation of the pituitary cyst in the present case as 'dysontogenetic' in origin. The slight gliosis and rarefaction at the floor of the fourth ventricle is apparently of the same nature as the cavity formation in the lumbar cord. There is no reason to associate the changes in the spinal cord of this case with the condition described as 'pseudotabes pituitaria' (Otto, 1936; Snapper et al., 1937).

In the second case the colloid cyst of the pituitary was associated with atrophy and fibrocystic degeneration of the pancreas. The relationship of these two conditions can, in the present state of our knowledge, only be a matter of speculation. The possibility of a causal link between these diseases cannot, however, be disregarded. In a paper read before the Association of Clinical Pathologists it was pointed out (Baar, 1944) that what is now generally called 'fibrocystic disease of the pancreas' comprises two pathogenetically different conditions. In very rare cases there is histological evidence that the cysts are due to segregation of ducts, pathological proliferation of their epithelium, and retention of a thin, mucoid, secreted material. This has been considered as the infantile form of the condition described by Wegelin (1921) and Yamane (1921) as 'dysontogenetic pancreatic cystosis.' Wissler and Zollinger (1945) recently came to the same conclusion. For the common form of the infantile fibrocystic disease of the pancreas, histological evidence has been presented to support the opinion of Blackfan and Wolbach (1933) and Blackfan and May (1938) that a pathological change in the secretion leading to its inspissation is the primary

change, resulting in stagnation of the secretion, cystic dilatation of ducts, infundibuli and acini, their secondary segregation, occasionally necrosis of the epithelium and rupture of ducts, atrophy of secretory tissue with inter- and intracinous fibrosis, and secondary inflammatory cellular infiltration. The present case belongs to this second type, for which the designation 'fibrocystic dystrophy of the pancreas' was proposed. An attempt was made to explain these findings in a way which would do justice to the identical condition in the early neonatal period, which is invariably associated with either a meconium ileus or a congenital obliteration within the small intestine. A hypothesis was put forward that the primary cause is a disturbance in the balance between the autonomic and secretin stimuli in favour of the former. In the present case it is possible that the increased formation of pituitary colloid caused an increased stimulation of the posterior lobe and of the parasympathetic hypothalamic centres. It may be interesting in this connexion to observe that proliferative changes in the neurohypophysis have been actually described in Simmonds' disease (Jacob, 1923; Meng, 1928). The writer is fully aware of the hypothetical nature of the views presented but hopes that they may stimulate a more thorough investigation of faecal fats and of changes in the secretory pancreatic tissue in cases of pituitary disease.

The presence of a disturbance in the electrolytes resembling that in Addison's disease is of particular interest. Although hypophysectomy causes an atrophy of the suprarenal cortex, no change occurs in the blood sodium, chloride, or potassium levels (Swan, 1940). Cameron (1945) calls cases of Simmonds' disease with marked symptoms of hypocorticoadrenalism pituitary Addison's disease, but the writer is aware of only one case (Moss, 1942) in which changes in blood electrolytes similar to those in the present case were found.

The macrocytic hyperchromic anaemia in this case is probably due to the steatorrhoea and not directly to the pituitary disease. Snapper et al. described cases of hyperchromic anaemia and histamine-refractory achlorhydria in chronic pituitary insufficiency. They stress, however, the fact that the anaemia was a late symptom in the course of the disease and developed only after achlorhydria was present for a considerable period. The hypocalcaemia and latent tetany have also their reasonable explanation in the pancreatic steatorrhoea and formation of excess calcium soaps in the intestine. The blood was not examined in the first case, but the presence of haemosiderosis and extramedullary haematopoiesis are evidence of a haemolytic anaemia.

With regard to the histogenesis of the two pituitary cysts, there can be but little doubt that they are due to a developmental error. There is not the slightest evidence of neoplastic growth. Both cysts have developed in a position where in embryonic life there is a flat cavity, the 'primary Rathke's cyst.' Instead of becoming rudimentary, changing into the Rathke's cleft and finally segregating into a few small 'secondary Rathke's cysts,' in these cases the lining epithelium continued to grow as such, and to produce a colloid secretion which accumulated and caused the formation of a cyst gradually increasing in size. In analogy with the nomenclature of Wegelin mentioned above, the designation 'dysontogenetic pituitary cysts' for this type and the following classification of pituitary cysts is, therefore, suggested.

1. Neoplastic (cystic craniopharyngeoma, the most common form among the pathological cysts of the pituitary, and very occasionally adenoma with cystic degeneration).

2. Dysontogenetic (pathological colloid cysts and ciliated epithelial cysts, cases of Goldzieher, Kiyono, Frazier and Alpers and the present two cases, and ? Merz's first case).

3. Dystrophic (due to embolism or thrombosis followed by necrosis and cystic degeneration: Falta, 1913; Simmonds, 1919; ? Merz, 1930).

4. A combination of 2 and 3 (the only case of this type has been described by Priesel in 1920. In this case a developmental dystopy of the pituitary caused a defective nutrition with secondary cyst formation and symptoms of pituitary dwarfism).

5. Combination of 2 and 1 (this is represented by the remarkable case of Worster-Drought et al., 1927). In a girl aged nineteen with pituitary dwarfism, three ciliated epithelial cysts were found, and a neoplastic growth arising from the primitive epithelium of Rathke's cyst or from the ependyma of the third ventricle (? Duffy's fourth case).

Summary

Two cases of pituitary cachexia in childhood are described. Both were due to large colloid cysts of Rathke's cleft with pressure atrophy of the anterior lobe. The designation 'dysontogenetic pituitary cysts' for this type, and a classification of the various pituitary cysts are proposed. The reasons are pointed out why the designation 'tumours of Rathke's pouch' for craniopharyngeomata is considered to be a misnomer. The pituitary cachexia was associated with syringomyelia in one case and with fibrocystic dystrophy of the pancreas in the other. The possibility of a causal link between the latter and the pituitary disease is discussed.

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REFERENCES

- Baar, H. S. (1944). Meeting of the Association of Clinical Pathology. London. January.
- Bailey, P. (1928). *Cowdry's spec. Cytol.*, **2**, 484. New York.
- (1932). In 'Penfield's *Cytology and cellular Pathology of the nervous system*', **3**, 1133. New York.
- Benda, C. (1932). *Hirsch's Handb. inneren Sekr.*, **1**, part 6. Leipzig.
- Benda, C. E. (1942). *J. clin. Endocrinol.*, **2**, 737.
- Berblinger, W. (1932). *Hirsch's Handb. inneren Sekr.*, **1**, part 6. Leipzig.
- (1927). *Verhandl. Dtsch. path. Ges.*, **22**, 191.
- Blackfan, K. D. and Wolbach, S. B. (1933). *J. Pediat.*, **3**, 679.
- and May, C. D. (1938). *Ibid.*, **13**, 627.
- Brock, J. (1932). *Biol. Daten für den Kinderarzt.*, **1**, Springer. Berlin.
- Cameron, A. T. (1945). *Recent advances in Endocrinology*. London. Churchill.
- Collin, R. (1923). *C.R. Soc. Biol.*, **88**, 92.
- Coppoletta, J. M. and Wolbach, S. B. (1933). *Amer. J. Path.*, **9**, 55.
- Cushing, H. (1933). *Ibid.*, **9**, 539.
- Duffy, W. C. (1920). *Ann. Surg.*, **72**, 537, and 725.
- Erdheim, J. (1903). *Beitr. path. Anat. allg. Path.*, **33**, 158.
- (1904). *Sitzungsber. Kais. Akad. Wiss. Wien.*, **113**, 537.
- (1926). *Ergebn. allg. Path. path. Anat.*, **21**, 482.
- Escamilla, R. F. and Lissner, H. (1942). *J. clin. Endocrinol.*, **2**, 65.
- Falta, W. (1913). *Erkrankungen der Blutdruesen*. Berlin.
- Fraser, J. (1921). *Edinb. med. J.*, **27**, 136.
- Frazier, Ch. H. and Alpers, B. J. (1934). *Arch. Neurol. Psychiat.*, Chicago, **32**, 973.
- Geldrich, J. (1939). *Mtschr. Kinderheilk.*, **80**, 103.
- Goebel, F. (1932). *Z. Kinderheilk.*, **53**, 575.
- Goldzieher, M. (1913). *Verhandl. Dtsch. path. Ges.*, Sixteenth meeting, **281**.
- Graubner, W. (1925). *Z. klin. Med.*, **101**, 249.
- Gruenwald, P. (1946). *Arch. Pathol.*, **42**, 55.
- Guizzetti, P. (1933). *Pathologica.*, **25**, 1.
- Harris, H. A. (1933). *Bone growth in health and disease*. Oxford Medical Publications. London.
- Hertwig, W. A. O. (1906). *Lehrb. Entwicklungsgesch. Menschen Wirbeltiere*. Jena.
- Hochstetter, F. (1924). *Beitr. Entwicklungsgesch. mensch. Gehirnes*, **2**. Vienna. Leipzig. Deuticke.
- Ingraham, F. D. and Scott, H. W. (1946). *J. Pediat.*, **29**, 95.
- Jacob, A. (1923). *Virchows Arch.*, **246**, 151.
- Kiyono, H. (1926). *Ibid.*, **259**, 388.
- Kornfeld, W. (1929). *Z. Kinderheilk.*, **48**, 188.
- Kyrle, J. (1910). *Wien. klin. Wschr.*, **23**, 1583.
- Kraus, E. J. (1914). *Virchows Arch.*, **218**, 107.
- (1926). *Henke-Lubarsch's Handb. path. Anat. Histol.*, **8**. Berlin.
- Meng, H. (1928). *Frankf. Z. Pathol.*, **36**, 650.
- Merz, W. (1930). *Ibid.*, **40**, 452.
- Miháľkovics, V. v. (1875). *Arch. mikrisk. Anat.*, **11**, 439.
- Moss, R. E. (1942). *J. clin. Endocrinol.*, **2**, 395.
- Otto, H. (1936). *Dtsch. Arch. klin. Med.*, **178**, 453.
- Perlman, R. M. (1944). *Arch. Pathol.*, **38**, 20.
- Pietsch, K. (1930). *Z. mikrosk. anat. Forsch.*, **22**, 227.
- Popjak, G. (1940). *J. Path. Bact.*, **51**, 83.
- Priesel, A. (1920). *Beitr. path. Anat. allg. Path.*, **57**, 220.
- Robinson, F. J., Power, M. H. and Kepler, E. J. (1941). *Proc. Mayo Clin.*, **16**, 577.
- Scharrer, E. (1941). *J. comp. Neurol.*, **74**, 81 and 93.
- Selye, H. (1943). *Anat. Rec.*, **86**, 109.
- Simmonds, M. (1916). *Dtsch. med. Wschr.*, **42**, 190.
- (1919). *Ibid.*, **45**, 487.
- Snapper, I., Groen, J., Hunter, D. and Witts, L. J. (1937). *Quart. J. Med.*, N.S., **6**, 195.
- Swan, H. G. (1940). *Physiol. Rev.*, **20**, 493.
- Tamaki, K. and Lubin, A. J. (1938). *Arch. Neurol. Psychiat.*, Chicago, **40**, 748.
- Thomas, E. (1933). *Hirsch's Handb. inneren. Sekretion*, **2**, part 2. Leipzig.
- Wegelin, C. (1921). *Verhandl. Dtsch. pathol. Ges.*, **18**, 169.
- Wissler, H. and Zollinger, H. U. (1945). *Die familiäre kongenitale. cystische Pankreasfibrose*. Basel.
- Worster-Drought, C., Carnegie Dickson, W. E. and Crowhurst Archer, B. W. (1927). *Brain*, **50**, 704.
- Yamane, M. (1921). *Beitr. Kenntnis primären Leberrebes*, Berne.

PITUITARY CACHEXIA BY H. S. BAAR

(a). Midsagittal section of the sella turcica with the pituitary cyst in case 1. The cyst shows considerable shrinkage. Originally the cyst with the posterior and the atrophic anterior lobes filled the whole sella. A.L.=anterior lobe; C=colloid cyst; P.L.=posterior lobe. H.E., $\times 4$.

(b). Posterior wall of the cyst in case 1. H.E., $\times 670$.

(c). Part of the thyroid and a parathyroid in case 1, showing lipomatosis of the latter. H.E., $\times 65$.

(d). Testicle in case 1. H.E., $\times 65$.

PLATE I

(e). Cross section of the lumbar cord in case 1, showing the central cavity. H.E., $\times 4$.

(f). Part of the wall of the cavity in the lumbar cord of case 1. This part is lined by ependyma and surrounded by an area of dense gliosis. Mallory's phosphotungstic acid-haematoxylin. $\times 670$.

(g). Midsagittal section of the pituitary in case 2. The cyst is ruptured and collapsed, most of the colloid is outside the cavity of the cyst. A.L.=anterior lobe; P.L.=posterior lobe; Ar=artifact; c=colloid. H.E., $\times 4$.

(h). Upper part of Rathke's cleft in case 2. H.E., $\times 85$.

(j). Middle part of the cystically dilated Rathke's cleft in case 2, with colloid in the cavity, and two small colloid cysts on the anterior aspect of the posterior lobe (secondary Rathke's cysts). H.E., $\times 85$.

(k). Fibrocystic dystrophy of the pancreas in case 2. H.E., $\times 85$.

(l). Fibrocystic dystrophy of the pancreas in case 2. H.E., $\times 85$.