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OF THE PITUITARY GLAND IN CHILDREN WITH
MALNUTRITION**

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A PRELIMINARY REPORT ON THE PATHOLOGY OF THE PITUITARY GLAND IN CHILDREN WITH MALNUTRITION

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There have been a number of reports on the general pathology of malnutrition, especially kwashiorkor, which have included careful studies of the exocrine glands (Davies, 1948; Jelliffe, Bras and Stuart, 1954; Tejada, 1955). However, little is known of the pathology of the endocrine glands in this condition. Clinical studies of malnourished adults show that they may have pigmentation of the skin, lowered metabolic rates, gynecomastia, asthenia and sexual disturbances (Jacobs, 1948; Klatskin, Salter and Humm, 1947; Zubirán and Gómez-Mont, 1953; Zubirán, Gómez-Mont and Laguna, 1955). Furthermore, there may be severe depletion of protein enzymes (Scrimshaw, Béhar, Pérez and Viteri, 1955; Véhelyi, 1948). Because of these facts, some authors have postulated that pituitary hypofunction comparable to 'panhypopituitarism' is characteristic of extreme malnutrition (González Valero, García Reyes and Gómez-Mont, 1950; Paullada, 1955; Zubirán and Gómez-Mont, 1953; Zubirán *et al.*, 1955). Pathological studies of the pituitary itself, however, are rare, and consist of observations on adults suffering from general malnutrition (Paullada, 1955, Zubirán and Gómez-Mont, 1953) or anorexia nervosa (Richardson, 1939; Siebenmann, 1955; Wilson, 1954). The purpose of this paper is to report the pathological anatomy of the pituitary in children with malnutrition.

Material

Nineteen children dying in the General Hospital of Guatemala were studied. Clinical data are summarized in Table 1. The children were classified in three groups, according to nutritional characteristics as previously described (Jelliffe, 1955; Scrimshaw, Béhar, Arroyave, Viteri and Tejada, 1956).

(1) **Kwashiorkor (Nine Cases).** This is a syndrome of severe malnutrition, characterized by growth retardation, apathy, anorexia, oedema, pellagroid dermatosis, changes in the character and colour of the hair and muscular wasting. Autret and Behar (1954) have reviewed this

syndrome in Central America, where it is named 'Síndrome pluricarenal de la infancia', and shown it to be identical in its major aspects with kwashiorkor as described elsewhere.

(2) **Pre-kwashiorkor (Síndrome de Pluricarenia Incipiente) (Four Cases).** This is a state of chronic malnutrition which is quickly followed by frank kwashiorkor after an episode of stress such as may result from infectious diarrhoea. The child shows retardation in growth and bone maturation. The hair is dull and brittle. The skin is usually dry and shows fine desquamation. Psychic changes such as moderate anorexia, apathy or irritability are usually present. In some cases there is also mild oedema.

(3) **Marasmus (Six Cases).** Marasmus is a state of infantile starvation, characterized by marked underweight, with atrophy of both muscles and subcutaneous fat. The face is monkey-like, due to the absence of fat pads in the cheeks. Neither hair and skin changes nor oedema are ordinarily observed.

Kwashiorkor and mild kwashiorkor are due primarily to a lack of protein in the diet; caloric intake may be adequate or somewhat diminished. Marasmus, on the other hand, is due primarily to a grossly inadequate caloric intake. As combinations of these two conditions may exist, a sharp division of cases is difficult to make. In fact, the element of marasmus is so common in the Central American form of the disease that it is often called marasmic kwashiorkor.

Methods

A complete necropsy was performed. The immediate cause of death for each case is listed in Table 1. Special attention was paid to the endocrine glands. The adrenals, thyroid and pancreas were carefully dissected and weighed immediately on a laboratory balance. These organs and the gonads were sectioned and stained with haematoxylin and eosin.

The pituitary glands were weighed on a torsion balance after fixation in formol-sublimite and serially sectioned in the horizontal plane. A differential count was performed on three sections of each gland stained by

TABLE 1
CLINICAL DATA ON 19 MALNOURISHED CHILDREN

Necropsy No.	Sex	Age	Weight (kg.)	Height (cm.)	Days in Hospital	Cause of Death
	<i>Marasmus</i>					
258	M.	13 mth.	4.99	65	2	Bronchopneumonia
249	M.	2 yr.	4.99	65	3	Bronchopneumonia
273	M.	3 yr.	6.98	85	19 hours	Bronchopneumonia
350	M.	4 yr.	6.08	80	8	Acute infectious colitis
268	M.	8 yr.	9.02	93	3	Bronchopneumonia
253	M.	1 yr.	5.90	67	6	Acute infectious colitis
						Lobar pneumonia
	<i>Pre-kwashiorkor</i>					
244	M.	16 mth.	9.07	70	1	Bronchopneumonia
293	M.	18 mth.	5.31	68	13	Bronchopneumonia
295	M.	4 yr.	9.07	88	4	Bronchopneumonia
251	F.	9 mth.	6.35	55	4	Acute infectious colitis
						Bronchopneumonia
	<i>Kwashiorkor</i>					
282	M.	15 mth.	5.40	70	6	Bronchopneumonia
331	M.	18 mth.	6.48	70	16	Bronchopneumonia
325	M.	3 yr.	7.66	84	15	Bronchopneumonia with abscess formation
298	M.	5 yr.	8.89	90	12	Bronchopneumonia
281	F.	15 mth.	6.71	74	12	Bronchopneumonia
307	F.	2 yr.	6.12	70	2	Bronchopneumonia
322	F.	3½ yr.	5.90	77	4	Pyelonephritis
278	F.	4 yr.	6.71	74	4	Unknown
292	F.	5 yr.	12.70	85	2	Bronchopneumonia

periodic-acid-Schiff-orange G, one through the centre of the gland, one some distance above, and one below the first cut. All the cells in every third oil-immersion field were examined.

The following cell types were classified:

(1) **Normal Basophils.** These were round or ovoid, intensely Schiff positive, densely granular cells which occur chiefly around the periphery of the anterior lobe in a normal hypophysis.

(2) **Amphophils.** Amphophils are round or polygonal cells which are frequently larger than the normal basophils and tend to have indistinct cell boundaries. They contain sparser and more weakly Schiff-positive granules, which are often irregularly distributed and may vary in size.

(3) **Hypertrophic Amphophils.** These cells are characterized by giant nuclei which may be of irregular shape and frequently contain a prominent nucleolus. They are derived from the sparsely granulated Schiff-positive cells through enlargement of the nucleus and degranulation of the cytoplasm.

(4) **Acidophils.** These are rounded, densely granular cells which are most abundant in the postero-lateral portions of the anterior lobe. The granules are Schiff-negative but stain with orange G.

(5) **Chromophobes.** These are apparently agranular cells which are usually much smaller than the cell types previously described. They are differentiated from the agranular hypertrophic amphophils by the size of the nucleus.

Results

The findings in the pituitary gland are shown in Table 2. The pituitary weight averaged 108 mg. in the children with marasmus, 138 mg. in pre-kwashiorkor and 154 mg. in frank kwashiorkor. It ranged from 60 mg. in a 13-month-old boy with marasmus to 210 mg. in a 45-month-old girl with kwashiorkor. No gross abnormality was found in any patient.

Normal basophils averaged approximately 8% in children with marasmus or pre-kwashiorkor, 11% in those with kwashiorkor. They ranged from 3.7 to 16.8% of the total differential count. Acidophils averaged approximately 14% in children with marasmus or kwashiorkor, 16% in those with pre-kwashiorkor. They were extremely variable, ranging from 1.7% to 33.8% of the total count. Chromophobes comprised the bulk of the cell population, averaging from 65 to 70% of the count.

The sparsely granulated amphophils, which previous studies have suggested may be the functionally active cells in the hypophysis (Russfield, 1957), were present in all cases, averaging about 8% in children with marasmus or kwashiorkor, and 5% in children with pre-kwashiorkor. They tended to be most numerous in children with very low percentages of well-granulated acidophils. In one gland from a patient with kwashiorkor (Case No. 325) in which only 1.7% acidophils were found, the amphophils were sufficiently numerous as to suggest adenomatous hyperplasia, and mitotic figures were present. The

TABLE 2
DIFFERENTIAL COUNTS ON PITUITARIES OF MALNOURISHED CHILDREN

Necropsy No.	Pituitary Weight (mg.)	Total Cells Counted	NB %	Ac %	Chr %	Amp %	HA %
	<i>Marasmus</i>						
258	60	6,123	3.7	26.0	63.6	5.1	1.6
249	80	4,883	5.1	5.2	86.7	2.6	0.4
273	160	7,077	11.3	2.4	69.4	14.6	2.3
350	70	7,145	14.3	17.8	57.5	9.2	1.2
268	150	5,650	9.9	5.5	73.9	9.8	0.9
253	125	4,093	4.8	26.2	63.8	3.9	1.3
Average	108		8.2	13.9	69.1	7.5	1.3
	<i>Pre-kwashiorkor</i>						
244	110	4,342	12.2	14.6	64.5	7.8	0.9
293	150	5,560	8.2	10.1	76.1	5.1	0.5
295	180	7,545	8.3	16.8	71.8	2.2	0.9
251	110	5,581	4.8	23.4	67.0	4.2	0.6
Average	138		8.4	16.2	69.9	4.8	0.7
	<i>Kwashiorkor</i>						
282	150	5,676	9.3	10.6	68.3	10.3	1.5
331	80	8,484	11.8	3.0	72.5	10.8	1.9
325	130	7,644	11.1	1.7	68.6	15.6*	3.0
298	180	7,327	9.1	15.9	63.9	9.9	1.2
281	100	5,951	9.5	18.8	64.5	4.4	2.8
307	200	7,335	11.2	10.1	74.5	2.3	1.9
322	150	5,645	7.8	10.2	70.1	10.8	1.1
278	210	7,560	10.6	17.3	64.8	6.1	1.2
292	190	6,819	16.8	33.8	40.7	7.5	1.2
Average	154		10.8	13.5	65.4	8.6	1.7

* Mitotic figures.

NB—normal basophils; Ac=acidophils; Chr=chromophobes; Amp=amphophils; HA=hypertrophic amphophils.

hypertrophic amphophils which are characteristic of every active pituitary (Mellgren, 1945; Russfield, 1957) were also present in all cases, averaging 1.3% in patients with marasmus, 0.7% in pre-kwashiorkor and 1.7% in marasmus. The range was 0.4 to 3.0%.

Because of the inherent variability of the material and the few cases available, the small differences observed among the various groups are not felt to be significant.

In all cases, the thyroid contained follicles of varying sizes. Seven glands contained colloid and 12 did not. The epithelium was usually cuboidal, although in two patients it was columnar. The testes showed only minimal signs of maturation, as would be expected in normal children of this age group. In three ovaries, however, developing follicles were present. The adrenals tended to be small. In eight cases the cortex had a linear pattern, the nuclei were pyknotic and abundant lipid was present in coarse droplets. In 11 cases, the nuclei were large and vesicular, there were varying degrees of lipid exhaustion, and the linear cortical pattern was obscured, although no frank nodularity was seen. The thymus was so small it was often difficult to find grossly. Microscopically it showed atrophy in all cases. Islets of Langerhans were abundant in all patients and appeared hyperplastic in nine.

Although no exact correlation between the differential counts in the pituitary and the histology of the end organs was apparent on preliminary survey, further studies are being carried out.

Discussion

Unfortunately, no necropsies on well-nourished Guatemalan children were available for comparison. The average numbers of basophils in the pituitaries described here were within the normal limits reported by Rasmussen (1950) for well-nourished children in the United States. Acidophils were usually, but not always, decreased. By the criteria of Mellgren (1945), who studied the pituitaries of Scandinavian infants, amphophils and hypertrophic amphophils were often significantly increased.

Previously descriptions of the adult human pituitary in malnutrition have varied widely. In patients dying of anorexia nervosa, both abundant normally granulated basophils and acidophils (Siebenmann, 1955) and decreased degranulated acidophils (Richardson, 1939; Wilson, 1954) have been reported. In one adult female with markedly decreased acidophils, there was hyperplasia of sparsely granulated cells staining with orange G (Wilson, 1954). Zubirán and Gómez-Mont (1953) have studied the pituitaries of 101 adults dying with chronic malnutrition. They report 'evidence of

atrophy' or 'degenerative lesions' in a high proportion of these, but no differential counts were performed. Paullada (1955), on the other hand, found no morphological alterations in the pituitaries of 30 undernourished adults. It is difficult to compare these reports with our findings because of differences in histological techniques and cell classifications used.

In adult pituitaries stained with P.A.S.-orange G, a hyperplasia of amphophils and a variable decrease in well granulated acidophils has been found to be characteristic of primary deficiency of the adrenals, thyroid or gonads, for which reason it has been postulated that the amphophils are the source of the trophic hormones in man (Russfield, 1957). It has also been found that an increase in the number of sparsely granulated Schiff-positive cells ('intermediate mucoid cells' or amphophils) relative to the number of fully granulated Schiff-positive cells ('maximal mucoid cells' or normal basophils) is the characteristic response of the human pituitary to stress (Currie and Symington, 1955).

The presence of unusually abundant amphophils in malnourished children would, therefore, suggest the production of trophic hormones in response to stress, although it is not possible to be sure of this point without biological analysis. The lipid depletion seen in many of the adrenals and the striking thymic atrophy in all our patients may well be indirect evidence of A.C.T.H. production. To some extent, these findings resemble those of Siebenmann (1955) in anorexia nervosa and of Uehlinger (1955) in malnourished inmates of concentration camps. We would, therefore, agree with those previous workers who feel that there is no primary pituitary deficiency in malnutrition and that there may, indeed, be some evidence for overproduction of adrenocorticotrophic hormones.

Further studies are being carried out to clarify the role of the pituitary in relation to the other target organs.

Summary

The pituitary glands of 19 Guatemalan children with malnutrition (kwashiorkor, pre-kwashiorkor and marasmus) were studied histopathologically, differential cell counts being performed. Relative percentages of basophils were usually within normal limits established by others. Acidophils were inconstantly decreased. Sparsely granulated amphophilic cells, thought to be the source of trophic hormones, were often unusually abundant. It was concluded that no morphological evidence for panhypopituitarism had been found.

REFERENCES

- Autret, M. and Behar, M. (1954). Síndrome policarencial infantil (Kwashiorkor) and its prevention in Central America (Food and Agriculture Organization of the United Nations), *FAO Nutritional Studies*, No. 13, Rome.
- Currie, A. R. and Symington, T. (1955). In *The Human Adrenal Cortex, Ciba Foundation Colloquia on Endocrinology*, 8, 396.
- Davies, J. N. P. (1948). *Lancet*, 1, 317.
- González Valero, E., García Reyes, J. and Gómez Mont, F. (1950). *Rev. Invest. clín.* 2, 179.
- Jacobs, E. C. (1948). *J. clin. Endocr.*, 8, 227.
- Jelliffe, D. B. (1955). *Infant Nutrition in the Subtropics and Tropics*. WHO Monogr. Ser. No. 29, Geneva.
- , Bras, G. and Stuart, K. L. (1954). *W. Indian med. J.*, 3, 43.
- Klatskin, G., Salter, W. T. and Humm, F. D. (1947). *Amer. J. med. Sci.*, 213, 19.
- Mellgren, J. (1945). *Acta path. microbiol. scand.*, Suppl. 60.
- Paullada, J. J. (1955). *Rev. Invest. clín.*, 7, 29.
- Rasmussen, A. T. (1950). *Amer. J. Anat.*, 86, 75.
- Richardson, H. B. (1939). *Arch. intern. Med.*, 63, 1.
- Russfield, A. B. (1957). *The Endocrine System: The Adenohypophysis*. In *Analytical Pathology*, pp. 293-360, ed. R. C. Mellors, New York.
- Scrimshaw, N. S., Behar, M., Pérez, C. and Viteri, F. (1955). *Pediatrics*, 16, 378.
- , —, Arroyave, G., Viteri, F. and Tejada, C. (1956). *Fed. Proc.*, 15, 977.
- Siebenmann, R. E. (1955). *Schweiz. med. Wschr.*, 85, 530.
- Tejada, C. (1955). *Rev. Col. Méd. Guatemala*, 6, 1.
- Uehlinger, E. (1955). In *The Human Adrenal Cortex, Ciba Foundation Colloquia on Endocrinology*, 8, 92.
- Véghelyi, P. V. (1948). *Acta paediat. (Uppsala)*, 36, 483.
- Wilson, R. R. (1954). *J. clin. Path.*, 7, 131.
- Zubirán, S. and Gómez-Mont, F. (1953). In *Vitam. and Horm.*, 11, 97.
- , — and Laguna, J. (1955). *Ann. intern. Med.*, 42, 1259.