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PITUITARY FIBROSIS WITH MYXEDEMA

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In 1914 Simmonds [1] described a syndrome of severe cachexia, premature senility, loss of hair, pigmentation of the skin, amenorrhea and weakness. Patients with this syndrome showed destruction of the anterior lobe of the pituitary, fibrosis of the thyroid and ovaries, atrophy of the adrenals, parathyroids and endometrium, and microsplanchia. About 75 cases of this syndrome have been reported. Silver's [2] recent article on the subject is an excellent review. One of the most striking features of the syndrome is the extreme grade of cachexia, without which the condition is not diagnosed.

We have recently studied a case that was believed clinically to be one of myxedema but which showed pathologically all the findings seen in Simmonds' disease except the cachexia.

REPORT OF CASE

A 48 year old Italian housewife entered the hospital Dec. 1, 1936, complaining of pain in the legs and left wrist of two months' duration.

Ten years before admission, when she was 38 years old, she had a miscarriage at five months in her first pregnancy. Within the next year she had a sudden onset of amenorrhea without attendant symptoms. Prior to this time she had had normal, regular catamenia. After this time she had no bleeding. During the ten years prior to her admission to the hospital she failed in general health, and there was vague gradual development of the symptom complex to be described. She stated that her skin grew progressively drier and coarser over a period of nearly ten years and that over a period of about two years it had shown scaling. For about five years she noted slow gradual loss of strength and enterprise, development of a placid disposition and rare bouts of nervousness and irritability. Four years before she entered the hospital she first noted severe headache, most marked on the left side of her head, which had no definite relation to eyestrain, food or other factor. During the past year she noticed loss of appetite and restricted her diet largely to carbohydrates. She also noticed that the constipation with which she had been troubled for years was becoming more marked. Two months before examination she first noticed definite pain in the bones, joints and muscles

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1. Simmonds, M.: Deutsche med. Wchnschr. **40**:322, 1914.
2. Silver, S.: Arch. Int. Med. **51**:175, 1933.

of her left arm and legs. For many years she had had bouts of pain in the spine, arms and legs, apparently mild. She did not describe these attacks accurately but attributed them to her insomnia and loss of strength.

"Rheumatism" had been present intermittently since the age of 15.

She was well developed, well nourished and in no discomfort. The skin over all the extremities was atrophic, dry and scaly; also, to a less degree, that over the trunk. The hair was dry and coarse. The gums were inflamed. There was questionable lichen planus of the mouth. The heart sounds were of only fair quality. The cardiac rate varied from 54 to 58 beats per minute. The blood pressure was 160 systolic and 100 diastolic. Pelvic examination showed an atrophic cervix.

The urine was normal. The blood showed 4,500,000 red cells and 5,500 white cells per cubic millimeter. The hemoglobin content was 85 per cent. The differential white cell count showed 67 per cent polymorphonuclears. The Hinton test was negative. The basal metabolic rate was —28 per cent. The blood showed cholesterol 374, calcium 9.85 and phosphorus 4.2 mg. per hundred cubic centimeters, and phosphatase 6.44 Bodansky units. Analysis of the gastric content showed free hydrochloric acid. The nonprotein nitrogen of the blood serum was 18 mg. per hundred cubic centimeters. A lumbar puncture gave negative results. An electrocardiogram showed normal rhythm, a rate of 72 and tracings consistent with myxedema.

The patient was believed to have myxedema, and thyroid extract was administered by mouth. She became nauseated and vomited. On the fourteenth day she was given thyroxin U. S. P. intravenously. Her drowsiness increased, and on the nineteenth day a psychosis developed. All the extremities were pseudospastic, although no other neurologic signs were present. The reflexes were active. The following day she had a convulsion, which lasted about four minutes. She refused to speak, move or eat, and on the twenty-second day her temperature became elevated. During this period the signs of myxedema disappeared, the temperature remained elevated between 102 and 105 F., rales developed in both lungs, and death occurred on the thirtieth day.

Autopsy.—The pertinent gross observations were as follows:

The body was that of a small, well developed and well nourished 48 year old woman weighing approximately 115 pounds (52.1 Kg.). The skin was only slightly roughened, especially over the arms, and was not darkened or pigmented. The mucous membrane on the inner aspects of the cheeks was grayish white, glistening and smooth. The abdominal subcutaneous fat was bright yellow and measured 4 cm. in thickness. The muscles appeared normal. The thyroid was small, weighing 4.8 Gm. The surface was grayish pink and smooth. The tissue cut with increased resistance, and the cut surface was pinkish gray and fibrous, with no colloid definitely discerned. Each lobe measured approximately 3 by 2 by 0.7 cm. Three normal-sized parathyroid glands were found. The lungs showed numerous foci of bronchopneumonia. The heart was small, weighing 175 Gm. The spleen weighed 125 Gm. The adrenals were very small, together weighing 5 Gm. On section there was marked narrowing of the cortex and medulla, the former measuring approximately 1 mm. The kidneys weighed 150 Gm. and were normal. The uterus was small and atrophic. The myometrium was narrow, measuring from 6 to 7 mm. in thickness. The endometrium was grayish white, smooth and very thin. Both ovaries were atrophic, together weighing 4 Gm.; on section no follicles were visible. The brain weighed 1,200 Gm. and showed normal convolutional markings. The stalk of the pituitary was normal. The whole gland, however, which was removed with the surrounding dura, was

markedly atrophic. The gland, excluding the stalk, measured approximately 5 by 5 by 2 mm. A definite division into lobes could not be made out. The sella turcica appeared slightly shallow.

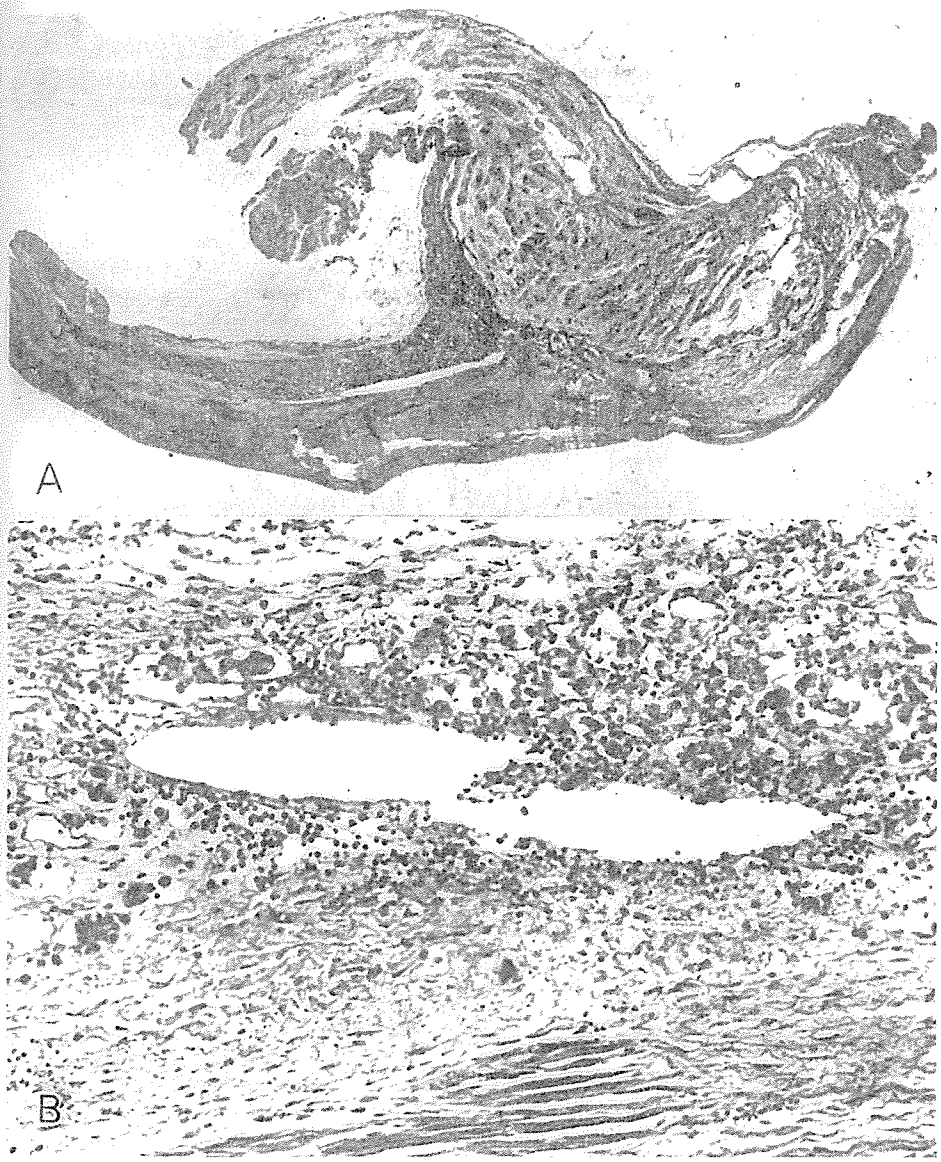

Fig. 1.—*A*, cross section of the whole pituitary, showing the extreme fibrosis of the anterior lobe. *B*, higher magnification of a portion of the anterior lobe, showing the lymphocytic infiltration around some of the epithelial cells.

Microscopic Examination.—Serial sections of the whole pituitary gland were made and stained in two ways: (1) with hematoxylin and eosin and (2) by a modification of the Mallory aniline blue stain for connective tissue which consisted in using hematoxylin before the regular staining process. The sections (fig. 1) showed that almost all of the anterior lobe had been replaced by dense fibrous tissue in which were scattered a few remaining isolated groups of small epithelial cells, often surrounded by a lymphocytic infiltration. The posterior lobe was possibly smaller than normal but showed no evidence of fibrosis. The vessels disclosed no diagnostic abnormality.

Several sections through various parts of both lobes of the thyroid (fig. 2) showed a similar process. There were broad interlacing bands of fibrous con-

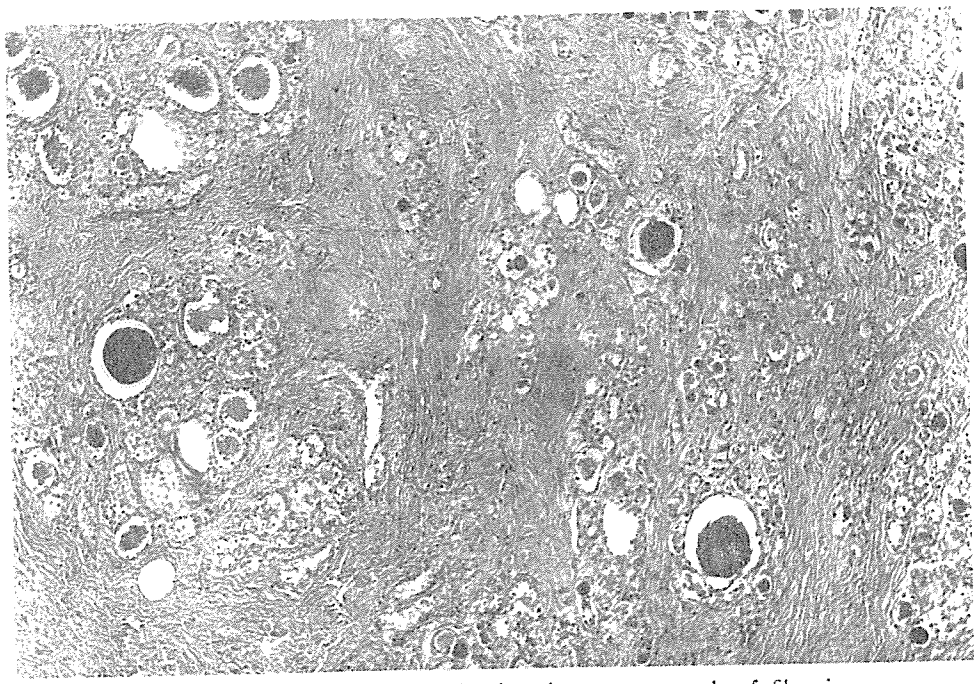

Fig. 2.—A section of thyroid showing the extreme grade of fibrosis.

nective tissue, in between which were very small thyroid follicles, some empty and others filled with colloid. There was no cellular infiltration or any evidence of acute or chronic infection. The striking feature was the extensive fibrous stroma. The larger vessels showed fibrous intimal thickening but no thrombosis.

Except for its small size, the adrenal was normal. The cells in both the cortex and the medulla were normal. In the center of the medulla, in one small area there was a slight lymphocytic infiltration with fibrosis.

The pancreas was normal. Both ovaries showed complete atrophy; there was no evidence of activity. Numerous corpora albicantia were found.

The uterus had a completely atrophic endometrium. Only an occasional gland was seen, and these were very small and showed no evidence of activity.

Approximately nine tenths of the parathyroid glands was composed of fat cells (fig. 3). The remaining parathyroid cells were normal chief cells with only an

occasional oxyphilic cell. This extreme fat replacement certainly evidenced atrophy. There was no cellular reaction or fibrosis.

Except for slight bronchopneumonia and lichen planus of the mouth, the other organs were normal.

REVIEW OF THE LITERATURE

In the literature we have been able to find records of only 6 cases similar to the case reported here. Some of these have been included in

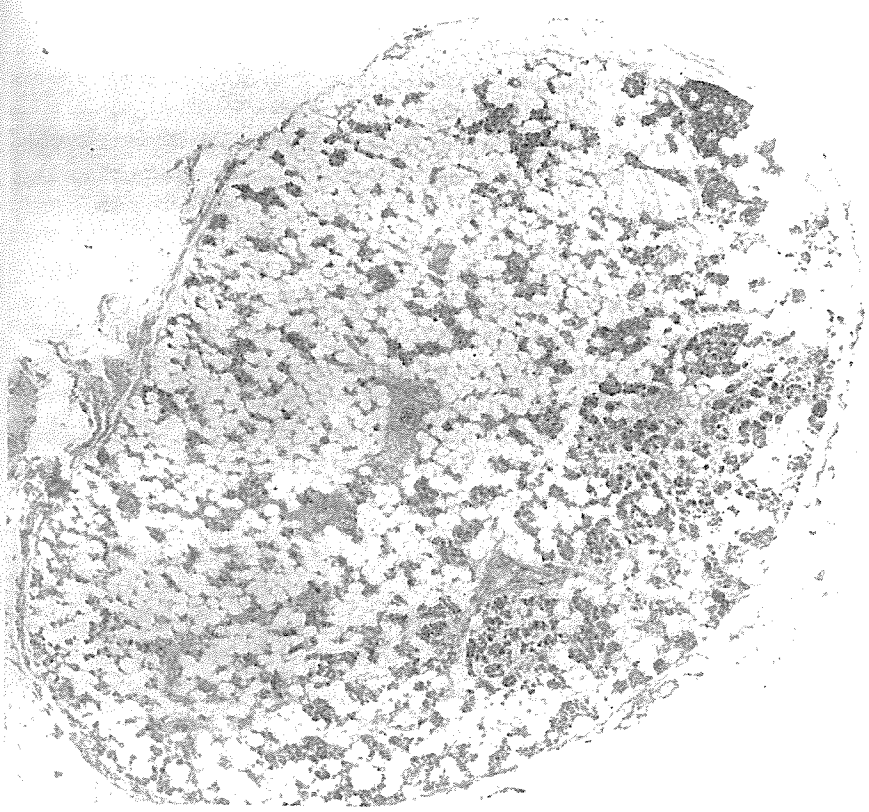

Fig. 3.—A cross section of a whole parathyroid, showing marked fatty changes as evidence of extreme atrophy.

previous reviews of cases of Simmonds' disease, but if cachexia is the sine qua non of this syndrome they should have been omitted.

Sainton and Rathery [3] reported the case of a 32 year old syphilitic woman who was believed clinically to have myxedema. She had no axillary or pubic hair and complained of headaches but had not lost

3. Sainton, P., and Rathery, F.: Bull. et mém. Soc. méd. d. hôp. de Paris **25**:647, 1908.

weight. Autopsy showed a sclerotic thyroid, which weighed only 12 Gm. There was also atrophy of the adrenals and genitals. The pituitary was replaced by a "mandarin"-sized cyst.

Fahr [4] reported the case of a 50 year old woman who had a spontaneous menopause following pneumonia at the age of 24. She had never been well since then and died after a three weeks' stay in a hospital, which she had entered because of abdominal symptoms. The clinical diagnosis was Addison's disease, based on the brown pigmentation of the skin. Autopsy showed atrophy of the adrenal cortex, the weight of the combined adrenals being only 3 Gm. There was no cachexia. The pituitary, although normal grossly, showed microscopically fibrosis of the anterior lobe.

Lindemann's [5] case is almost identical with ours. His patient was a 34 year old woman who married at the age of 20, contracted syphilis soon afterward and had a spontaneous menopause three years later. This was followed by a falling-out of axillary and pubic hair and of the hair of the eyebrows. In the year prior to examination she had dyspnea and asthma. Physical examination showed a woman who was small and pale but well nourished. The genitalia were infantile. Her temperature was elevated, and she died of bronchopneumonia after having become psychotic. Autopsy showed a sunken sella turcica, in which a completely atrophic pituitary was enclosed. Microscopically, the cells in the anterior lobe were markedly atrophic. The posterior lobe was not well visualized. The thyroid weighed 6.6 Gm. and was fibrotic. Two out of the three parathyroids found were small and atrophic. The adrenals together weighed 2.8 Gm. and showed atrophy but no fibrosis. The pancreas showed generalized atrophy of the chief cells but not of the islets of Langerhans. The endometrium and ovaries were also atrophic.

Jakob [6] reported 2 cases. One was a true case of Simmonds' disease, including cachexia. The other case was that of a woman 45 years of age in whom since her last pregnancy, ten years previously, symptoms had gradually developed. Her skin was dry, and the pubic and axillary hair was falling out. She died of tuberculous meningitis. Autopsy showed her to be fairly well nourished. The pituitary weighed 0.585 Gm., and the anterior lobe was fibrotic. The thyroid was normal in size but showed fibrosis. The adrenals weighed 6 Gm. The uterus was small, and the ovaries were atrophic. The abdominal organs showed microsplanchia.

Muller's [7] case was that of a 59 year old woman who died suddenly of apoplexy. There were no symptoms. Autopsy showed dry skin,

4. Fahr, T.: Deutsche med. Wchnschr. **44**:206, 1918.
5. Lindemann, E.: Virchows Arch. f. path. Anat. **240**:11, 1923.
6. Jakob, A.: Virchows Arch. f. path. Anat. **246**:151, 1923.
7. Muller, E.: Klin. Wchnschr. **2**:1576, 1923.

sparse axillary and pubic hair, a bloated appearance and an increased amount of subcutaneous fat. The pituitary weighed 0.13 Gm., and the anterior lobe contained only a few cells. The thyroid measured 4 by 2 by 1.8 cm. and contained very small follicles. No other observations were given.

Hirsch and Berberich [8] reported the case of a 57 year old woman with syphilis who at 40 lost her libido, at 52 had her menopause and at 53 lost the hair from her eyebrows and the axillary and pubic hair. She began to experience slow, difficult speech, weakness, fainting spells and chilly sensations. There was no emaciation, but there was some brown pigmentation of the face. The basal metabolic rate was — 17 per cent. Terminally a depressive psychosis developed. At autopsy the pituitary weighed 0.6 Gm., and microscopically the anterior lobe was composed predominantly of cholesterol crystals and hemosiderin. In one corner there was an area of normal anterior lobe. The thyroid was fibrous and atrophic and weighed 11 Gm. The adrenals were normal and the ovaries small and atrophic.

Falta [9] described a syndrome which he called *die multiple Blutdrüsensklerose* and reported 2 clinical cases without pathologic corroboration.

COMMENT

Given the microscopic observations alone in this case, one would have to call it a case of Simmonds' disease, but the absence of cachexia raises the question whether the small group of cases in which cachexia is not present should be singled out from the rest. Without cachexia a clinical diagnosis of Simmonds' disease is usually not considered, and for that reason alone this syndrome of pluriglandular insufficiency should be considered in the differential diagnosis in cases that to all intents and purposes are instances of myxedema, Addison's disease or some other endocrine insufficiency. Falta's 2 cases might well fit into this group, in which theoretically the patients should be treated with extracts of the anterior lobe of the pituitary. Falta, however, had no right to assume in his cases that all the endocrine glands would show sclerosis. Atrophy alone, without sclerosis, might well account for the insufficiency.

This distinction between sclerosis and atrophy brings up the subject of the causes and primary origin of the disease. If one assumes, as Falta did, that all the endocrine glands are sclerotic, this would be strong evidence that the disease did not begin in one gland but that the same injurious agent affected all the endocrine glands. On the other hand, if some of the endocrine glands are sclerotic and others only

8. Hirsch, S., and Berberich, J.: Klin. Wchnschr. **3**:483, 1924.

9. Falta, W.: Die Erkrankungen der Blutdrüsen, Berlin, Julius Springer, 1913, pp. 363-373.

atrophied, one might assume a primary lesion in one of the sclerotic glands and secondary atrophy of the others. It is only reasonable to suppose that the same injurious agent that produced sclerosis in one gland would affect the other glands in the same way. We have not been able to find record of any case in which all the endocrine glands showed sclerosis, and since in Falta's cases there were no autopsies there is no evidence to support the concept of a disease entity characterized by sclerosis of all the endocrine glands. In our case and in some of the others reported the only glands that showed sclerosis were the pituitary and possibly the thyroid. The parathyroids, adrenals and ovaries were only atrophic and showed no evidence of the cellular infiltration and fibrosis that one ordinarily sees following an injurious agent. We are forced to propose, therefore, that the disease originated in either the thyroid or the pituitary or in both and that the other glands were affected secondarily.

If we could show still further that either the thyroid or the pituitary was not primarily sclerotic but involved in fibrosis secondary to atrophy, our problem as to the original focus of the disease would be solved. Regarding the pituitary, there can be no doubt that the destruction of most of the cells of the anterior lobe, the fibrosis and especially the lymphocytic infiltration point to the previous presence of an injurious agent, infectious or chemical. The cellular reaction is the important factor. The lesion in the thyroid, however, is different. Here there is no cellular reaction. It is well known that normally the thyroid contains a goodly amount of fibrous stroma. When atrophy of the thyroid occurs, it of course concerns the epithelial elements; the more severe the atrophy, the more prominent is the fibrous stroma. When complete atrophy with focal disappearance of follicles occurs, the fibrous stroma assumes greater prominence and strongly resembles postinfectious sclerosis. In his monograph on the thyroid Wegelin [10] went so far as to say that often no sharp line can be drawn between atrophy and sclerosis. Although it was not definitely proved that the thyroid in our case was atrophied, the burden of proof rests with those who say that it was not. We feel, therefore, that the primary disease in our case was in the pituitary and that all the other endocrine glands were atrophied secondarily. The same reasoning probably applies to the cases in the literature, but without having seen the microscopic sections we can form no definite opinion.

Experimental evidence of the primacy of the pituitary in the clinicopathologic syndrome which we have described here has several angles.

10. Wegelin, C.: Schildrüse, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 8, p. 86.

When the thyroid gland is the primary site of destruction, as in spontaneous myxedema and cretinism, the anterior lobe of the pituitary is often hypertrophied (Rogowitch[11]). If the thyroid is removed in animals, a similar enlargement of the glandular portion of the pituitary occurs (Rogowitch). That this increase in the pituitary functional activity is more than a histologic one was shown by Hertz and Oastler,[12] who found increases in the thyrotropic hormone of the blood and urine of patients with myxedema. In sharp contrast to this, the assay on the urine of our patient as performed by the method of Hertz and Oastler was negative for thyrotropic hormone. The method of Hertz and Oastler makes use of hypophysectomized animals as test objects in a replacement type of experiment.

In rats, following hypophysectomy the thyroid, parathyroid, ovary and adrenal undergo atrophy. This is in complete harmony with the primary lesion in the pituitary, the secondary atrophy of the remainder of the endocrine system and the development of incomplete myxedema, hypofunction of the adrenal cortex and cessation of ovarian function (amenorrhea) in our patient. Hypophysectomized animals live for many months after operation, and following the atrophy of their endocrine glands they enjoy comparative health for many weeks, although growth ceases. Their metabolism drops; they become inactive, acyclic and hypoglycemic, and die in a condition of marked asthenia and stupor but in good nutrition. Hence, the analogy between the clinical course of our patient and the clinical course of animals suffering from pituitary insufficiency is striking. Considering the span of life of the rat as compared with that of our patient, the removal of the pituitary in a rat can be regarded as providing an approximately equal chronicity of pituitary insufficiency as that which must have existed in our patient, sufficient amounts of the hormones of the anterior lobe of the pituitary having been already secreted to "carry on" in the rat for a time after hypophysectomy.

Clinically the syndrome which we have described is to be distinguished from congenital pituitary aplasia, since growth, menstruation and pregnancy ensued in this patient in a normal fashion. The miscarriage which preceded the onset of amenorrhea may be interpreted as a part of the insidious onset of chronic pituitary failure, or it may have stood in some etiologic relation to the "secretory exhaustion" of the pituitary which is often suspected in true Simmonds' cachexia.

The absence of cachexia in our case was striking both during life and at the time of postmortem examination and deserves special mention. The patient was moderately obese. The obesity had no special distribu-

11. Rogowitch, N.: Beitr. z. path. Anat. u. allg. Path. **4**:453, 1888-1889.

12. Hertz, S., and Oastler, E. G.: Endocrinology **20**:520, 1936.

tion and was fairly generalized. The preservation of such excellent nutrition despite chronic failing health over a period of ten years is in sharp contrast with the rapid wasting which occcurs in Simmonds' cachexia following acute damage to the anterior lobe of the pituitary (infarct, hemorrhage or syphilis). Anorexia was prominent, and her restriction of her diet to carbohydrates is of considerable interest in view of what is known of the role of the pituitary in fat and carbohydrate metabolism. Chronic hypoglycemia may well have been the stimulus for such a change in appetite and may in part have explained her excellent nutrition at death. The aches in the bones and joints of which she complained so prominently may have been on a hypothyroid basis. No disturbance in bone metabolism was found which was sufficient to explain the aching. The high blood cholesterol, the characteristic findings in the electrocardiogram and the clinical appearance of the patient confirmed the diagnosis of myxedema and fitted with a basal metabolic rate of —28 per cent.

The results of the attempted thyroid therapy are worthy of special discussion. Dr. John H. Talbott and one of us (S. H.) have been struck by the sensitivity of patients with adrenal insufficiency to thyroid extract. In two definite instances we have reliable evidence of a precipitation of crises of adrenal insufficiency, which may be accompanied by nausea, vomiting, a high temperature, psychosis, coma and convulsive manifestations without a definite lesion of the brain. It is therefore quite likely that our patient died of adrenal insufficiency after the attempt to relieve her thyroid deficiency. Chemical evidence of this would have been available in determinations of the blood sodium if these determinations had not been vitiated by the administration of saline solution. The diagnosis of adrenal insufficiency could not otherwise have been made during life, although there was slight malar pigmentation.

It is important to recognize that this interesting possibility of chronic pituitary insufficiency may exist. Future research may give adequate pituitary fractions for complete replacement therapy. Such a condition should be suspected in all cases of typical myxedema or in cases of myxedema in which earmarks of other endocrine deficiencies are present, such as onset of early amenorrhea (myxedema is usually characterized by metrorrhagia) or signs or symptoms of adrenal insufficiency, and finally a negative thyrotropic assay of blood or urine in the untreated state of myxedema should point to a primary deficiency of the pituitary.

SUMMARY

A case of pluriglandular insufficiency without cachexia, clinically believed to be a case of myxedema, is described. Except for the absence

of cachexia, all the postmortem observations (fibrosis of the anterior lobe of the pituitary and atrophy of the thyroid, parathyroid, adrenal, ovary and uterus) are characteristic of Simmonds' disease. Pathologic and experimental evidence is presented to establish the primacy of the anterior lobe of the pituitary in the pathogenesis of the disease. The importance of recognizing this condition clinically and differentiating it from myxedema or any other primary endocrine insufficiency is emphasized. Only 6 other similar cases were found recorded in the literature, the most typical being that reported by Lindemann.

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