

inflammatory closure of the foramen of Monro; in the other case only the posterior horn of the lateral ventricle was distended, and very greatly, from unknown cause. In this case the occipital lobe of the affected side was a mere sac. He also refers to a case of Bourneville and Noir,<sup>12</sup> in which the aqueduct was entirely occluded, but there was no microscopic study of the tissues. In this same paper he (Spiller) speaks of Touche's case,<sup>13</sup> in which there was occlusion of the aqueduct.

Our first case was reported by one of us (Spiller) without microscopic study.<sup>14</sup> The history as obtained from the Pennsylvania Training School for Feeble-minded Children is as follows:

*Patient.*—Sally H., age 62 at time of death; American.

*History.*—Father died of consumption, aged 39; mother died aged 63, cause unknown; two brothers and two sisters died of consumption. One sister (the first born) died in early infancy, cause unknown; two brothers are living in good physical and mental condition. Of the details of the patient's birth nothing is known. She was supposed to have been born hydrocephalic and was weak and sickly as a baby. Sight, hearing and speech were good. She had epilepsy for years and during her seizures would froth at the mouth and purge. She suffered frequently from vomiting without assignable cause, and had occasional attacks of vertigo. She was said to have chronic kidney disease six years prior to her death. There was no paralysis at any time, and although no joint complication was present she always walked as though lame. She was said by Dr. Llewellyn, who had known her for years, to have been fairly well developed mentally. Her advanced age and her mental condition are remarkable in view of the extensive hydrocephalus.

*Macroscopic Examination.*—The third and lateral ventricles of the brain were greatly dilated and the white matter surrounding them was intensely atrophied. The whole cerebrum appeared as a greatly distended sac. The lateral ventricles freely communicated with one another, and the walls of the third ventricle were so pushed apart that the floor of this ventricle was on a level with the upper part of the basal ganglia.

*Microscopic Examination.*—Left Optic Thalamus: The blood vessels were thickened and there were some recent hemorrhages within the substance of the thalamus. All the vessels were distinctly congested. There was little vacuolation of the cells of the choroid plexus such as described by Raubitschek.<sup>15</sup>

*Corpus Callosum:* A section from the median portion of this structure was not more than 1 mm. in thickness; it stained normally and contained numerous amyloid bodies.

*Left Occipital Lobe:* In places the cortex and white matter were not more than 2 mm. in thickness; in other places the thickness was 6 mm. The atrophy was relatively much greater in the white substance than in the cortex. Where the width of the section was the least, more than half was occupied by the cortex. The cells were much diminished in number as shown by the thionin method.

*The Fornix:* This was much atrophied and the blood vessels within it were greatly thickened.

The aqueduct was almost occluded, this occlusion being probably a congenital malformation because the cavity was well lined throughout by a layer of ependymal cells, which would hardly be the case if the occlusion were caused by proliferation of the neuroglia. The neuroglia tissue immediately adjoining the ependymal lining was a little proliferated, and the aqueduct was filled with red blood corpuscles which were unaltered in shape, and probably were deposited there shortly before death. To the naked eye the aqueduct seemed to be entirely occluded. In a microscopic section the aqueduct to the naked eye was hardly as large as the point of an ordinary pin.

The second case is reported as one of intense congenital hydrocephalus without occlusion of the aqueduct.

The pathologic material was received from Dr. Thompson S. Westcott, to whom the case belongs. The patient lived to be a year and a half old. The skull was excessively large. It is difficult to describe the gross appearance of the brain other than to say that it was a large thin bag of nerve tissue so attenuated in many places as to be translucent, and the mere handling of it caused numerous tears in its substance.

*Microscopic Examination.*—The corpus callosum was not more than 0.5 mm. thick.

*Left Occipital Lobe:* Sections in places were not more than 1 mm. thick. Here, as in the other case, the atrophy was much more pronounced in the white matter than in the cortex.

*Left Motor Area, Median Side:* The white matter was most affected. There was great diminution in the number of cells and the pericellular spaces were all distended. The cells appeared all decidedly smaller than normal. The pia was not thickened and the cortex and white matter were 4 mm. thick.

In contrast to the other case the fourth ventricle was greatly dilated as the result of the dilatation of the aqueduct of Sylvius. The cause of the hydrocephalus in this case could not be determined, but the condition seemed to have been a congenital malformation.

The two cases show very clearly that the distension of the fourth ventricle may depend on the patency of the aqueduct of Sylvius.

## MYXEDEMA: A STUDY.\*

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### INTRODUCTION.

#### HISTORICAL NOTE.

In 1873, in a paper entitled "A Cretinoid State Supervening in Adult Life in Women," Sir William Gull<sup>1</sup> first described the disease known later as myxedema. This name was suggested by Ord,<sup>2</sup> in 1877, as he said, "To be applied to an essential condition in the cretinoid affection occasionally observed in middle-aged women." He also wrote:

The whole collection of symptoms are related as effects to jelly-like swellings of the connective tissue, chiefly, if not entirely, consisting in an overgrowth of the mucous-yielding cement by which the fibrils of the white element are held together. Accordingly, I propose to give the name of "myxedema" to the affection.

He further emphasized the similarity of myxedema and cretinism and among other things pointed out that in one of his cases (as in one of the cretins reported by Curling), there was diminution in size and almost complete annihilation of the thyroid gland. Charcot<sup>3</sup> in 1880 proposed the name "cachexie pachydermique." He writes:

L'expression pachydermique nous paraît bien rendre compte des traits dominants du tableau clinique et qu'elle en donne une idée, sinon plus exacte, tout au moins plus vivante que la dénomination des auteurs anglais.

J. L. Reverdin<sup>4</sup> in a paper before the Medical Society of Geneva in 1882, called attention to a train of symptoms following the total extirpation of goitrous thyroid glands. The symptoms which he enumerated were

\* From the Medical Clinic of the Johns Hopkins Hospital, Baltimore.

1. Trans. Clin. Soc., London, 1874, vii.

2. Med. Chir. Trans., 1878, lxi.

3. Le Progrès Médical, 1880, viii.

4. Rev. Med. de la Suisse romande, 1882, ii.

12. Le Progrès Méd., July 14, 1900, 17.

13. Bull. et Mémoires de la Soc. Méd. d. Hôp. de Paris, 1902, vii, 141.

14. Jour. of Nervous and Mental Dis., 1900, 559.

15. Ztschr. f. Heilkun., 1905, p. 219.

weakness, languor, hebetude, pallor and edema of the face and hands, without albuminuria. One case he states "was very analogous to a cretin." A year later (1883) the same author<sup>5</sup> pointed out the similarity of the group of symptoms to the myxedema of the English writers and named the condition "myxedema postopérative." He rightly attributed it to a loss of the thyroid gland. At the twelfth congress of the German Surgical Association in 1883, Kocher<sup>6</sup> described a similar train of symptoms following total thyroidectomy to which he gave the name, "cachexia strumipriva." He, however, thought the condition was due to a mechanical injury to the structures of the neck, resulting in a chronic asphyxia. Later Kocher acknowledged his mistake and accepted the view of Reverdin and Semon.

Sir Felix Semon,<sup>7</sup> of London, next pointed out the correlation of myxedema and cachexia strumipriva and suggested a common causative factor, namely, a loss of function of the thyroid gland. Paul Bruns, in 1884, reported the case of a boy, aged 10, in whom extirpation of the thyroid gland was followed by the condition known as sporadic cretinism.

These observations led the Clinical Society of London to appoint on Dec. 14, 1883, a special committee to investigate this subject. The members of this committee immediately set about their researches and in 1888 published their monumental report<sup>8</sup> which has formed the groundwork for all later investigation of the subject. The committee comprised such men as Victor Horsley, who directed the experimental work, William Ord, who collected the clinical data, and Halliburton who investigated the chemistry of the tissues. In 1887, Virchow contributed some data to our knowledge of the pathology of the disease. More recently many valuable contributions have been published, which will be discussed later.

In America the first case of myxedema was reported in 1881 by W. A. Hammond.<sup>9</sup> In 1888 Hun and Prudden<sup>10</sup> described in detail 4 cases of their own and reviewed the literature up to the date of publication.

#### DEFINITION.

In his monograph, Murray<sup>11</sup> defines myxedema as follows:

It is an affection characterized by widespread changes in nutrition as shown by the appearance of solid edematous swelling of the subcutaneous tissues, dryness of the skin and arrest of development of its appendages, subnormal temperature, slowness in the mental processes and in the execution of voluntary movements.

#### CLINICAL VARIETIES.

Under the general term myxedema are included three groups of cases: 1, cretinism; 2, myxedema proper; 3, operative myxedema.

1. Cretinism.—This is a chronic affection, either congenital or appearing at any time before puberty. Osler<sup>12</sup> says:

It is characterized by disturbance of the growth of the skeleton and soft parts, a remarkable retardation of development, an extraordinary disproportion between the different parts of the body, and a retention of the infantile state with a corresponding lack of mental progress.

Three sub-varieties of cretinism are now recognized:

a. Endemic cretinism which develops in certain localities of Italy, France and Switzerland, in association

with goiter under local conditions of an obscure toxic nature. No cases of this variety have occurred in America.

b. Sporadic cretinism in which the thyroid gland may be congenitally absent or atrophied after one of the specific fevers or in association with goiter. In 1897 Osler<sup>13</sup> collected 60 cases of this type in America. Many more cases have since been reported.

c. Juvenile myxedema is a term suggested by Parker for a small group of cases occurring in children who have developed physically and mentally until their fourth or fifth year at least, at which time the symptoms occur in consequence of atrophy of the thyroid gland following in all probability an acute thyroiditis in the course of an infectious fever, as typhoid, scarlatina, etc. In this group there are the usual symptoms of the adult form, but there is also an arrest of development at that stage of a child's growth when the disease set in. Osler and others in America have reported a few instances of this variety.

Pineless<sup>14</sup> in a very excellent paper has recently drawn sharp lines of demarcation between three types of cretinism, which are practically identical with the foregoing. His varieties are: a, Thyroaplasie or congenital myxedema; b, infantile myxedema; c, endemic cretinism. The first type, though rare, includes some of the sporadic cases. The second comprises those cases in which atrophy of the gland occurs in association with goiter or follows one of the specific fevers; the third is identical with endemic cretinism above described.

A remarkably elaborate monograph on "Cretinism" by Wilhelm Scholz,<sup>15</sup> of Graz, has recently appeared, and is well worth a careful perusal. His clinical material is particularly rich, and some of his conclusions are both interesting and original.

2. *Myxedema Proper*.—This includes those cases in which the symptoms develop in an adult at any age after puberty.

3. *Operative Myxedema or Cachexia Strumipriva*.—This is the variety in which the symptoms of myxedema develop after a total thyroidectomy for goiter or other disease of the thyroid gland. Of this variety there are two different types, the cretinous and the adult myxedematous, according to the age of the patient at which the gland was removed.

In the American literature prior to July 1, 1905, I find but two cases of operative myxedema. The first, Dr. McGraw's case, which is briefly referred to by Osler,<sup>12</sup> occurred in a young man in whom a complete thyroidectomy for goiter at the age of 12 was followed six years later by the gradual development of the typical myxedematous features which persisted for 12 years. A second case was mentioned by Huntington<sup>16</sup> at a meeting of the California Academy of Medicine, Nov. 27, 1900. This patient was also a male in whom myxedema followed one year after complete thyroidectomy. More recently Moffit<sup>17</sup> states that two cases of postoperative myxedema have occurred in California, one of which was in all probability Huntington's case. I have not included any of these cases in my series which is restricted to myxedema proper.

Abortive forms occur in myxedema just as in exophthalmic goiter. The French have suggested the term

5. *Ibid.*, 1883, iii.

6. *Verh. d. Deutsch. Gesellsch. f. Chir.*, 1883, ii.

7. *Brit. Med. Jour.*, 1883, ii.

8. *Clinic. Soc. Trans.* (London), 1888, supplement vol., xxi.

9. "Neurological Contribution" (New York), 1881, i.

10. *Am. Jour. Med. Sci.*, 1888, xcvi.

11. *Twentieth Cent. Practice*, 1895, iv.

12. *Am. Jour. Med. Sci.*, 1893, cvi.

13. *Trans. Cong. A. M. Physicians and Surgeons*, 1897, 12.

14. *Wien. klin. Wochschr.*, 1902, xv.

15. "Klin. und anatom. Untersuch. über Cretinismus," Berlin, 1906.

16. *THE JOURNAL A. M. A.*, 1901, xxxvi.

17. *Ibid.*, 1905, xlv.

"myxedemie fuste." J. L. Reverdin<sup>18</sup> in 1886 first noted this form in cases following partial thyroidectomy in which there was subsequent atrophy of the remainder of the gland. In these cases there may be no mucinoid infiltration of the skin but there is a liability to swelling and localized hypertrophy of the mucous membranes of the nose, throat, etc., as well as a predisposition to tonsillar enlargement and adenoid formation. Further, the teeth may decay early and the hair fall out prematurely. The French consider loss of the outer half of the eyebrow as almost pathognomonic of this type of the disease. In women there is also a tendency to circulatory disturbances of the mucous membranes at the menstrual period or a hyper-sensitiveness of the nose, throat or even of the vaginal mucous membrane. Chronic constipation, painful joints, vague pains between the shoulders, paresthesiæ and an occasional giving way of the legs, are other obscure manifestations of the disease. Moffitt<sup>17</sup> has reported 11 cases of this type, in all of which definite improvement followed thyroid medication.

#### CASE REPORTS.

The following 10 cases occurred in the practice of Dr. William Osler, either in private or in the wards of the Johns Hopkins Hospital.

**CASE 1.**—*White female; aged 37; quintipara; sister of patient in Case 2; a second sister with exophthalmic goiter; a third sister with Raynaud's disease; three years' duration; thyroid therapy; loss of 54 pounds; recovery. (Previously reported by A. R. Oppenheimer.)*

**Patient.**—M. D., American, housewife, of Virginia, was admitted Jan. 26, 1894, to the Johns Hopkins Hospital complaining of "swelling of the body."

**History.**—The parents were not blood relatives; of two brothers one had "renal trouble." There were three sisters, one of whom is the patient in Case 2 of this series; another had exophthalmic goiter and died from "peritonitis," and a third later consulted Dr. Thayer (October, 1905) for Raynaud's disease. Patient had always been healthy and had borne five children.

**Present Illness.**—This dated back three years (1891), when at the age of 34, while pregnant, she underwent a prolonged physical and mental strain. Subsequently she gave birth to a child, which lived only three months. About three months after delivery and about ten days before her menstrual period, she first noticed that her entire body became more or less swollen, but did not pit on pressure. This swelling was repeated before subsequent "periods," but would disappear temporarily with the onset of the flow. A year before admission (1893) the menses became less frequent, being at intervals of from six to eight weeks. The swelling also became more or less constant, though it was more pronounced at certain times. The tongue began to feel stiff and swollen. Later the skin became dry, harsh and rough; there was some loss of hair and a constant chilly sensation. The bowels were constipated. The appetite was good. Micturition was free, but never excessive. There was no loss of memory or difficulty of speech.

**Physical Examination.**—On Feb. 26, 1894, examination revealed a very large woman of medium height, weighing 189 pounds. She was very garrulous. The face was heavy, rather dull and expressionless. The cheeks and neck were very full and with an almost edematous appearance. The complexion was doughy, without any marked hectic flush. The supraclavicular regions were moderately full. The arms and legs were decidedly swollen. The dorsal surfaces of the hands and feet were very puffy and edematous looking, but nowhere pitted on pressure. The skin had a resistant feel, very dry and in some places showed a little scaling. The hair was rather dry and coarse. The finger nails were thin, with marked longitudinal striations, and a slightly everted and very irreg-

ular free edge. The thyroid gland could not be felt, though, owing to the thickness of the neck, it was impossible to determine any diminution in its size.

The abdominal and thoracic viscera were normal. The pulse ranged between 60 and 68 to the minute. The temperature in the mouth ranged between 97.6 and 98.4 degrees. The urine had a specific gravity of 1020; and on two examinations contained neither albumin nor casts.

**Clinical History.**—Jan. 27, 1894: Five grains of desiccated sheep thyroid were given three times a day.

January 31: In the evening there was a very striking fullness over both clavicles, and a mass the size of a hen's egg was present in each fossa. These disappeared by next morning.

February 2: For the first time she complained of weakness, headache and pain in the back. The pulse had become more rapid, ranging from 80 to 90 to the minute. There was sweating and some nausea. She had taken but 65 grains in the five days, and had lost 8 pounds. The dose was reduced to 5 grains twice a day.

February 9: She had then taken 160 grains of thyroid. The temperature and pulse range since February 2 was 98.4 to 99.5 degrees and 84 to 108, respectively. There was a loss of 10½ pounds during twelve days' treatment.

She was discharged from the hospital much improved, with directions to continue the treatment at home.

**Further History.**—A letter from her physician, Dr. H. B. Melvin, stated that her improvement continued. During the first twenty-five days of treatment she had lost 25 pounds, and the loss continued until she then was very nearly her normal weight.

November, 1894: She was then taking only 3 grains every second day, and though eight months' pregnant, was very well.

Sept. 30, 1896: The patient was readmitted to the hospital for observation. "Her condition beyond being nervous was very good." The skin was soft and natural and there was no edema.

October 1: Her weight was 135 pounds, i. e., a loss of 54 pounds since admission in 1894.

October 9: After a few days' rest in the hospital she was discharged.

Oct. 21, 1905: The patient consulted Dr. Thayer, who kindly gave me the following notes: "She has regarded herself as well since leaving the hospital. She has, however, taken the thyroid intermittently. Her ordinary course has been to take 5 grains of Armour's extract in capsules three times a day for four or five days, then to stop taking anything for two or three weeks, at the end of which time she begins 'to feel slow and tired and to swell.' This swelling consists of a puffiness of her hands and shoulders. The ankles are continually puffy. Her pulse is always slow, and she is always rather susceptible to cold, a susceptibility which is much more marked after she has stopped taking the thyroid for a considerable length of time."

On examination, "she looked well and bright. The face, however, was a little heavy and above the clavicles there was rather a marked fullness. The hands were chubby, but nothing more. About both ankles there was a marked elastic puffiness. Between the sternomastoids in the region of the thyroid there was a distinct hollow; the thyroid was not to be felt. The pulse was 68."

**CASE 2.**—*White, female, aged 19; nullipara; sister of patient in Case 1; exophthalmic goiter (previously reported by A. R. Oppenheimer); readmitted at 22 with myxedema; no trace of goiter; thyroid therapy; recovery.*

**Patient.**—S. E., American, of Virginia, was admitted Jan. 26, 1894, to the Johns Hopkins Hospital, complaining of "enlargement of thyroid gland" and "great nervousness."

**History.**—Her family history was the same as that of her sister, the patient in Case 1. Patient had measles and scarlatina in childhood. Menses had always been irregular, appearing only once in the previous year. Patient was single and had borne no children.

**Present Illness.**—This began in 1891, three years before admission, when after a severe fright she became very nervous, excitable and restless. There were frequent palpitations of the heart. The thyroid gland became enlarged in 1893 and re-

18. Congrès franc. de Chir., 1886, II.

mained so. There were attacks of dyspnea due, the patient thought, to pressure on the trachea by the goiter. There was also tremor of the hands following any excitement. The voice became husky; the eyes became a little more prominent. The appetite was good; there was no nausea and no vomiting. Bowels were regular; there was no cough.

*Physical Examination.*—Examination on Sept. 26, 1894, revealed a slight though well nourished girl, of very neurotic temperament. The face was flushed and there were numerous areas of transient flushing of the skin over the body. There was a decided double exophthalmos, but von Graefe's sign was absent. There was marked symmetrical enlargement of the thyroid gland. The apex beat of the heart was in the sixth interspace; the impulse was powerful and heaving; first sound markedly booming. The lungs and abdominal viscera were negative. The urinalysis showed a specific gravity of 1012, with a slight trace of albumin, but no casts. The pulse was rapid, from 110 to 120 to the minute. Temperature was 99 to 99.5 degrees. Weight was 137 pounds.

*Clinical History.*—January 27: A diagnosis of exophthalmic goiter was made and the patient was given thyroid extract gr. v, t.i.d.

February 2: A very definite fine tremor of the hands was noted.

February 9: She was discharged after having taken 200 grains of thyroid extract and having lost 2½ pounds (134½ pounds).

*Subsequent History.*—November 22: After her discharge from the hospital, she was given tincture belladonnæ, gr. xv, t.i.d. for two months, which resulted in some diminution in the size of the goiter and in the degree of exophthalmos.

May 7, 1897: Patient was readmitted. She was then aged 22 and single. She complained of "general swelling" and "soreness."

After leaving the hospital in 1894 she had not felt very strong and was unable to take any active exercise. In January, 1896, her friends noticed that she was becoming stout, and the patient found that her collar was getting tight and that her shoes would not button. The swelling was general, including the supraclavicular regions. It was more pronounced after exercise and in the afternoon. She felt very drowsy and "not up to anything." Her speech became slow. Occasionally the skin of the hands and face around the mouth would turn purple. She suffered from the cold, especially in the evenings, and she became very nervous. Bowels were regular. There was no increase in the amount of urine. She was given thyroid extract three times a day by her physician, and at first improved, but later became so weak that she was unable to sit up, and the dose was reduced.

*Second Physical Examination.*—Examination on May 7, 1897, revealed a paler and little fuller facies than on previous admission. There was no puffiness above the clavicles. The goiter had entirely disappeared. The tongue was rather large, dryish and indented. The hands were a little full. The feet and legs above the ankle joints were swollen, but did not pit. The skin was harsh. Over the face was a marked vasomotor disturbance. There was marked dermatographia. Superficial reflexes were active. Except for a palpable right kidney the examination was negative.

Urine had a specific gravity of 1010, and contained neither albumin nor casts. The amount in twenty-four hours was 340 to 800 c.c.. Temperature was from 99.4 to 98.2 degrees; pulse, 60 to 98; weight, 122 pounds (i. e., 12½ pounds less than on discharge, February, 1894).

*Further Clinical History.*—May 12, 1897: She was given thyroid extract, gr. ii, t.i.d., which, on May 23, was increased to gr. iv.

May 31: Dr. Osler noted that "the joints of the feet were painful, but not swollen or infiltrated. There was some puffiness of the wrist and face. The legs were much smaller and more natural. There was slight tremor. There was no enlargement of the thyroid gland, but the lobes could be felt. There was instability of the vasomotors of the skin, and a patchy chloasma over forehead, chin and neck." Patient was discharged "much improved," having taken 186 grains of thyroid extract and having lost 4 pounds in weight (118 pounds).

Her temperature after beginning treatment was practically unaffected, being still always above normal, but the pulse ranged a little higher (70 to 112). The quantity of urine also showed some increase, sometimes reaching to 800 and once to 950 c.c. in the twenty-four hours.

Oct. 21, 1905: Dr. Thayer learned from the sister (Case 1) that the patient "has grown rather worse. From time to time she has had definite mental symptoms, being 'flighty.' She feels that she is sick and that her presence in the house makes others sick and she tries at times to get away." At other times she is perfectly well except for "nervousness." There was no statement as to the use of the thyroid tablets.

*CASE 3.*—White, female, aged 23; nullipara; consanguinity of grandparents and parents; duration four months; marked delusions and hallucinations; thyroid therapy; loss of 3½ pounds in two weeks; recovery.

*Patient.*—E. T., German; tobacco factory girl of Baltimore, was admitted to the Johns Hopkins Hospital June 26, 1894.

*History.*—Her paternal grandparents were first cousins. Her father and mother were healthy, but were second cousins. There was a history of tuberculosis in mother's family. There was no history of goiter, myxedema or neurosis in the family. Patient was born in Germany, in the district of Westphalia, but came to America at 16. She did not remember having seen any cases of goiter, etc., in her native village. Except for the diseases of childhood she had always been well and strong. The menses began at her fifteenth year and were regular until after her arrival in America, when she had amenorrhea for three months. They returned and were regular until May, 1891. She came to the Johns Hopkins Hospital Dispensary on June 6, 1891, complaining of pallor, constipation, fulness after eating and loss of weight. Physical examination was practically negative except for slight chlorosis.

She occasionally attended the dispensary during the following year. The general condition improved markedly, though the catamenia did not return. Between April 9, 1892, and June 25, 1894, the patient was lost sight of. When last seen she was a rather delicately formed, well-nourished girl with good color and delicate attractive features. On June 26, 1894, she applied to the hospital for treatment and was admitted. The following additional facts were obtained: On July 15, 1893, she went to the country as chambermaid. While there her general condition improved greatly. The catamenia reappeared for the first time since 1891, and became regular, lasting three days without pain. She returned from the country Oct. 1, 1893, and went to work in a tobacco factory.

*Present Illness.*—In February or March, 1894, her health began to fail. In April, 1894, her family began to notice that her eyes appeared swollen. She herself observed loss of appetite, dryness of the throat and also a general dryness of the skin, with absence of sweating. The swelling increased and appeared also in the hands and arms. Her friends noticed that her voice became changed, being deeper and harsher, while she spoke in a distinctly slower, more expressionless manner. There was an unnatural thirst. She became very susceptible to cold and wore heavier clothes than formerly. She was very irritable and nervous and her ordinarily placid disposition entirely changed. Her sleep, however, was always good. In fact, there was a certain tendency to drowsiness and she was easily fatigued. The bowels were constipated. There was no cough, but she complained of a heavy feeling in her chest. Several weeks before entry she began to have delusions. She fancied that certain members of her family were going to poison her. She also believed that she was pregnant, and insisted that she felt something moving in her abdomen. She declined to stay at home, and went to the house of a companion, who brought her to the hospital. She had gained slightly in weight.

*Physical Examination.*—Examination by Dr. Thayer June 26, 1894, revealed a most extraordinary change in her general appearance. There was marked puffy edematous condition of the face, hands and arms, which did not, however, pit on pressure. She had a peculiar muddy complexion. The puffiness was particularly marked about the eyes, the bridge of the nose and chin. There was a fulness over the clavicles, but no marked edema. The hands and arms showed the same puffy appearance, without any pitting. She had an expressionless,

dull manner, talked slowly, appeared suspicious and was distinctly irritable. She was reticent about stating her delusions and was unwilling at first to allow a physical examination. The urine was free from albumin. The thyroid gland could not be distinctly felt. A diagnosis of myxedema was made, and she was admitted to the hospital for observation. During the first four days there was little change.

**Clinical History.**—June 30, 1894: Dr. Thayer noted that the skin, particularly that of face and hands, was rather dry, harsh and resistant. The lips seemed thick. The general expression was dull and heavy, very similar to that in acute nephritis. The cheeks were pink in rather sharp contradistinction to the white areas elsewhere. The hair was dry, but the nails were well formed. The pulse was slow, 50 to the minute, regular and full. The thyroid gland appeared extremely small, being scarcely distinguishable on palpation. The heart, lungs and abdominal viscera seemed normal. The deep reflexes were not increased. There was no edema of the legs. She was placed on desiccated thyroid, gr. iii, t.i.d.

July 1, 2 and 3: The urine showed no albumin and no casts and a normal specific gravity (1020 to 1022).

July 4: There was a trace of albumin, but no casts.

July 5: Blood examination revealed: Hb = 59 per cent.; red blood corpuscles, 3,532,000; white blood corpuscles, 6,000. A differential count of 500 leucocytes gave:

	Per cent.
Polymorphonuclear neutrophils .....	77.4
Small mononuclears .....	17.1
Large mononuclears .....	4.2
Eosinophiles .....	1.3

There was no poikilocytosis.

July 9: The condition had changed materially since beginning the thyroid treatment 9 days before. The puffiness about the face had diminished, but scarcely as much as that about the hands and arms, which had disappeared in a most remarkable manner. The mental condition had entirely cleared up and she was then bright and cheerful. Pulse was 104.

July 14: A further change in her condition was noted. While the face was still a little full, the edematous appearance about the eyes was almost entirely gone. The change in the hands and arms was almost more remarkable. The skin was no longer dry, but moist and warm, and she stated that there was a good deal of sweating. She was placid and cheerful. The blood count revealed Hb. 69 per cent.; red blood corpuscles, 6,124,000; white blood corpuscles, 8,500.

She was discharged on the fourteenth day much improved, having taken 270 grains of thyroid extract and having lost 3½ pounds.

The temperature, which was usually normal or slightly above, showed later a tendency to be subnormal. The pulse which formerly ranged between 72 and 86 became more rapid with the thyroid treatment and varied from 80 to 105. She was directed to continue the thyroid extract, but to increase the dose to gr. vii, t.i.d.

**Subsequent History.**—July 28, 1894: She returned to report herself as feeling perfectly well. The change in her physical condition was most extraordinary. All signs of puffiness were gone, her color was natural, her voice and manner as they used to be.

Sept. 4, 1894: She again reported; she had gained materially in weight, and looked stronger and better. There was no sign of puffiness in the face or hands. She was then taking the glycerin extract, instead of the desiccated powder, every other day.

Dec. 14, 1894: She was not feeling as well, as she had been more irregular in the use of the thyroid extract. The face was a little swollen and the skin dry. There was a tenseness about the skin of both hands and feet, but no swelling of the legs.

At intervals during the subsequent ten years Dr. Thayer saw the patient, who remained free from symptoms as soon as she recognized the absolute necessity of taking small doses of the thyroid gland.

Oct. 20, 1905: The patient reported again at Dr. Thayer's request. She stated that she still took a 5-grain tablet every day. If she omitted it for more than forty-eight hours she felt the bad effects. The general health was excellent. Men-

struation was regular. On examination she looked well. There was still a little roundness about the face and a peculiar expression about the eyes due to a little fullness of the lids, but so slight as to be overlooked by the casual observer. Her skin felt natural. There was, however, a striking depression over the thyroid cartilage and no trace of the gland could be felt.

(To be continued.)

## PATHOLOGY OF PARALYSIS AGITANS.\*

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The subject of the pathology of paralysis agitans is one on which few physicians have definite ideas, and those who have differ widely from each other. It is obvious that so long as the nature of this disease is in controversy and obscurity the treatment must be imperfect, changeable and unfortunately inefficient. Numerous investigations with the idea of clearing up this problem have but added to its complexity by suggesting new hypotheses and unexplored fields for research.

The clinical picture of paralysis agitans is so clear cut and typical, the course of the disease so unchangeable and progressive that it certainly suggests an organic basis. To classify it as a neurosis is begging the question and explains nothing, while it would be distinctly harmful if it hindered further search for the real pathology.

### SUMMARY OF LITERATURE.

In order to define the present status of our knowledge of the subject, it will be necessary to review briefly the findings and opinions recorded by numerous observers since Parkinson wrote his classical paper in 1817. For the sake of convenience these findings may be classified according to their location into: 1. Those in the nervous system, the brain, spinal cord and peripheral nerves. 2. Those in the muscles. 3. Those in the ductless glands.

The gross lesions in the central nervous system found by some of the earlier writers which were regarded by them as the cause of paralysis agitans are not now credited with such a relationship. It must be remembered that at that time the difference between multiple sclerosis and paralysis agitans was not well understood; consequently, in the opinion of Wollenberg,<sup>1</sup> one of the cases which Parkinson himself described was probably a case of multiple sclerosis and, according to the same authority, similar cases have been reported by Oppolzer,<sup>2</sup> Marshall-Hall,<sup>3</sup> Skoda,<sup>4</sup> Lebert<sup>5</sup> and others.

Confusion has arisen, also, from the fact that cases are reported in which paralysis agitans was combined

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\* Read in the Section on Nervous and Mental Diseases of the American Medical Association, at the Fifty-seventh Annual Session, June, 1906. This paper was accompanied with a detailed report of fourteen cases, for which THE JOURNAL could not give space. The author offers to send a reprint of the complete article, including the case reports, to anyone who requests it and sends a two-cent stamp for postage. The entire article will also appear in the volume of Transactions of the Section on Nervous and Mental Diseases of the American Medical Association, 1906, and in the volume of Contributions of the Laboratory of Neuropathology of the University of Pennsylvania, 1907.

1. Nothnagel: spec. Path. u. Therap., xii.  
2. Wien. med. Wochschr., 1861, Nos. 36-38. Quoted by Wollenberg, reference 1.  
3. "Traité des Maladies du Systeme Nerveux," 1841.  
4. Wien. med. Halle, 1862, No. 13.  
5. "Handb. d. prakt. Med.," 1871, II, p. 632.