

# CHILDHOOD MYXEDEMA OR SO-CALLED SPORADIC CRETINISM IN NORTH AMERICA.\*

MURRAY B. GORDON, M.D., F.A.C.P.

Assistant Clinical Professor of Pediatrics, Long Island College Hospital  
BROOKLYN, N. Y.

(From the Department of Pediatrics, Long Island College Hospital)

The object of this paper is to present a study of cretinism in the United States and Canada as to its prevalence, pathology, symptomatology and treatment. The first case was reported by Jacobi in 1879. The first attempt to collect all the available data on the subject was made by William Osler in 1893, covering but eleven cases in all. This was followed by a more extensive investigation in 1897 in which he presented sixty cases. In the following year McPhedran reported seventeen cases which had occurred in Ontario alone. In 1901 John McCrae added twenty-three more cases found in Canada. These writers were of the opinion, however, that the number of cases in existence was far in excess of those reported. Murdoch in 1900, as the result of a questionnaire sent to institutions for feeble-minded throughout the country, was able to obtain information on sixteen cases, two of which, however, had already been reported by Osler. Howard, in 1907, made a statistical study of myxedema in America and collected one hundred cases, but did not deal with cretinism or cases under puberty. The next investigation was by Anders in 1918 on myxedema and cretinism, covering the period from 1905 to 1918 under the misapprehension that Howard had covered all the cases of cretinism from 1897 to 1905. Anders found 28 cases in the literature and added 43 unpublished cases obtained from institutions and other sources, but he failed to include 16 cases reported by Sill in 1905 and 41 cases by Herrman in 1914. M. B. Gordon supplemented the literature by 21 cases in 1918. Prior to the publication of Anders' article in 1920, the writer undertook this study at the request of the editor of *ENDOCRINOLOGY* and found additional

---

\*Read before the Association for the Study of Internal Secretions, Boston, June 6, 1921.

## 236 CHILDHOOD MYXEDEMA IN NORTH AMERICA

case reports in the literature, which, with 5 personal unpublished cases, total 340 cases of so-called cretinism; these include the 60 of Osler. The prevalence of this disease is probably much greater than is indicated by the figures here given, as there are numerous references in the literature to cases which existed but had not been reported.

The data in this study will be primarily confined to the 280 cases reported subsequent to those by Osler.

### GEOGRAPHICAL DISTRIBUTION

The locations of the 280 cases included 27 states and Canada; when the residence of the patient was not given, it was assumed to be that of the doctor reporting it.

Canada .....	52	Oregon .....	3
New York.....	120	Rhode Island.....	3
Pennsylvania .....	25	Maine .....	2
Indiana .....	12	Missouri .....	2
Ohio .....	10	Nebraska .....	2
Massachusetts .....	6	Arkansas .....	1
Minnesota .....	6	North Dakota.....	1
Virginia .....	6	Montana .....	1
Kentucky .....	5	Washington .....	1
Iowa .....	5	Kansas .....	1
California .....	4	Colorado .....	1
Maryland .....	3	Louisiana .....	1
Illinois .....	3	District of Columbia.....	1
Wisconsin .....	3		

It is readily seen from these figures that geographical location has no bearing upon the prevalence of this disease. Even though goiter is endemic in Canada along the St. Lawrence, in the Allegheny Valley of Pennsylvania and along the Great Lakes, not a single case of endemic cretinism was found and the incidence of so-called sporadic cretinism was no greater than in other regions.

### NATIONALITY

It was very difficult to obtain statistics as to the nationality of the parents, in an endeavor to determine a foreign predominance, if any, because of the incompleteness of the data on all cases outside of New York State. Almost 50 per cent were reported from New York and Pennsylvania, two states with large foreign population. In New York City alone the cases of Herrman, Sill and Gordon, 84 in all, were known to consist of a predominating foreign element, Austrian, Russian and Italian. It is more than probable that the large foreign population in these two states accounts for the enormous excess over the other regions.

Munson studied the incidence of goiter and cretinism among the Indians of the United States and found that while goiter was of frequent occurrence among them, cretinism was rare. He states that 7 cases have been reported in which the mind was affected to a greater or less degree in persons with goiter and quotes Martin, who found a case of cretinism with a goiter in a girl of 12 years of age among the Indians of the Blackfoot Agency. He also states that Howard reported a case of an idiotic girl of about 19 years of age who had a goiter and whose mother was also goitrous.

#### CLASSIFICATION

Preparatory to undertaking such an investigation as this, it is necessary to have a working knowledge of some fundamentals of the underlying pathological processes existing in cretinism. Primarily, it was established by the committee of the Clinical Society of London in 1888 that in the conditions known as myxedema, sporadic cretinism, endemic cretinism, operative myxedema of animals and operative cretinism there is a pathological condition common to all, namely, the occurrence of morbid processes in the thyroid gland.

Since then very sharp controversies have raged as to the proper classification and terminology of the different forms of myxedema. Murray defines cretinism as "a condition which is due to diminished functional activity of the thyroid gland commencing before birth or in early life before 15." Osler amplifies this by calling it a "chronic condition characterized by disturbances 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."

Myxedema, so designated by Ord because of the collection of what was assumed to be mucin in the subcutaneous tissues, has been studied from every conceivable angle and viewpoint by numerous observers and as a result the classifications of the disturbances due to loss of, or diminution in, thyroid secretion have been many. It is, therefore, with trepidation that the present investigator offers a new classification based upon the present study of the condition as found in America. He feels that the condition in this country is not the condition which is recognized as cretinism in Europe, that the term "sporadic cretinism" should be dispensed with, in so far as it applies to the disease in America; that cretinism should be limited to the type occurring in Europe and Asia and that the disease which is met with in this country should be considered as a separate entity, a pathological condition resulting from diminution or absence of thyroid secretion. Based upon pathological and etiological grounds, it can well be termed "childhood myxedema." The cases published in this country were reported under various terms such as: congenital cretinism, congenital myxedema, myxedema in children, infantile myxedema, sporadic

cretinism, cretinism, etc. In this study, no specific attention was paid to the term used by the original observer.

The following classification is proposed:

*Myxedema—Types*

1. Cretinism (Endemic).
2. Childhood myxedema (formerly called sporadic cretinism).
  - a. Congenital myxedema.
  - b. Infantile myxedema.
  - c. Juvenile myxedema.
3. Adult myxedema.
4. Post-operative myxedema.

Congenital myxedema (also known as congenital cretinism, thyro-aplasie, angeborene myoxidiotie, myxedematous idiocy, athyreosis congenita, myxedema athyreosum) has as its fundamental basis the complete absence of the thyroid gland. Pineles insists that this term shall be limited to those cases in which there has never been the slightest vestige of a thyroid gland, and that it should be considered as an anomaly of embryological development. According to this investigator, the presence of a goiter at birth, even though this goiter be composed of nothing but inert connective tissue and the thyroid thus functionless, would be enough to prevent the case from being termed congenital myxedema. The general consensus of opinion accepts this dictum, Horsley, however, claiming that this type is rare and that the children as a rule die at birth. Their appearance is typical and the characteristic bone and cartilage changes with resulting deformities are already quite far advanced at birth.

Infantile myxedema includes those cases in which the pathological disturbances in the thyroid originated before birth, but enough thyroid tissue persists to enable the child to live. The symptoms are not present at birth, but develop within the first two to five years. The thyroid gland may be either atrophied or enlarged.

Juvenile myxedema is the term given by Parker to those cases which develop symptoms of myxedema as the result of some acute infectious disease or nutritional disturbance at any time during childhood. These children are born with a normal thyroid, are normal at birth and in their subsequent mental and physical development, but following an acute disease show symptoms due to a progressive atrophy of the thyroid gland.

Infantile and juvenile myxedema differ from congenital myxedema in that they are due to pathological processes in an already existing thyroid gland, whereas in the latter the gland has never been present.

McCarrison describes another type of cretinism which he terms nervous cretinism, characterized by idiocy associated with cerebral diplegia and tetany due to congenital fibrosis of the thyroid and parathyroid glands. No cases of this type have been encountered in American literature.

Endemic cretinism is characterized by similar clinical manifestations as sporadic, but occurs only in countries where goiter is endemic. It will be dealt with more fully later on in the paper. There has not been a single case of endemic cretinism reported in the United States or Canada, and Osler considers that it is not at all probable from what he can learn that it has ever existed here.

#### ETIOLOGY

A question that has not as yet been settled is whether or not cretinism is a congenital disease. McCarrison claims that cretinism is always congenital, whether endemic or sporadic, except in those cases that arise postnatally from nutritional or infectional conditions. Kocher feels that "where the children are not born cretins, the thyroid gland in the majority of cretins has been congenitally so influenced that as the child grows, the sleeping abnormality in the gland begins to develop and the process continues until cretinism has been established. As can be seen, this is not strictly congenital; that is, the condition does not appear at birth and yet it is congenital because during fetal life through the blood or nourishment or drinking water or the mother, who herself may not have been a cretin and may have possessed a normal gland, the injurious tendencies were implanted in the thyroid gland of the fetus."

G. E. Smith, as a result of extensive study of fetal and maternal athyreosis among animals in goiter districts, claims that when an individual affected with thyroid disturbance becomes pregnant, unless that disturbance is counterbalanced by exceptionally favorable conditions, there will be a very seriously arrested development of the fetus, resulting in a more or less severe form of fetal athyreosis and grave disturbances will be produced in the maternal organism also. In our series in which goiter in the parents was mentioned, 13 gave a history of a goitrous mother at the time of the birth of the myxedematous child, while in 2 others, the mother developed a goiter subsequent to the birth of the affected child. In one family in which there were 12 children, the mother developed goiter after the birth of the second child, bore normal children until the birth of the patient, who was the eleventh, and then had a normal child in the twelfth pregnancy. In this instance the thyroid condition in the mother could not have been of very much etiological importance. There was no history of goiter in the father. Hodgins of Canada called Smith's attention to cases in which the father had tetany and the children had developed myxedema. McCarrison also cites the prevalence of endemic tetany in India as a disease of child-bearing women and corresponding to the locality of endemic goiter.

There are probably many cases of so-called sporadic cretins who become impregnated, but the only case on record in the literature is that reported by Townsend in 1897 and mentioned by Osler in his series. This woman was 38 years old, a typical idiot with the characteristic appearance of a cretin. A Caesarian section was performed

and a male infant was delivered. This child, while very feeble, did not show any signs of myxedema. He died in four hours. No autopsy was performed. Of course, the absence of signs of myxedema at birth would preclude the diagnosis of congenital cretinism, to use Pineles' term, still we cannot state definitely whether or not that child would have developed the disease later.

Heredity is probably a factor in the development of thyroid derangement, but it is difficult to estimate the extent of its influence. We can, however, safely state that the occurrence of but 13 cases of goiter in the mother indicates that it is probably of slight significance as an etiological factor in the production of childhood myxedema.

Tuberculosis, neuropathy, alcoholism, insanity and other degenerative strains have not been considered of much etiological importance by such investigators as Pineles, Tredgold and Murray, while Crotti and others feel that they have some bearing. Their incidence in the parents and family was small in the cases reported in America. On the mother's side there was a history of alcoholism, 2; tuberculosis, 8; insanity, 1; epilepsy, 3. On the father's side, alcoholism, 4; tuberculosis, 4; neuropathy, 1; paralysis, 1. Epilepsy, mental deficiency and goiter were found in both cousins and maternal aunts in several instances, but not of such frequency as to make them of etiological import. There were two instances of feeble-mindedness not of thyroid origin in brothers and sisters.

The presence of childhood myxedema in more than one member of a family was met with several times. Sanderson and Sill each reported one instance of 3 cases in one family, and Herrman two. Manson, Niles, A. Gordon, Koplik, McPhedran, Stewart, M. B. Gordon and Murdoch all cite instances of two in a family. In all, there were 4 instances of 3 in one family and 14 of two in a family. Manson's cases were twins, while Herrman reported a case in a twin with the other child normal. In a case reported by Busey there was a marked incidence of goiter and childhood myxedema in the family; the mother, maternal grandmother, a sister and two brothers of the mother had goiter. McCrae reported a case of childhood myxedema with a goiter in which both of the patient's sisters had goiter but not myxedema.

So-called sporadic cretinism does not seem to have any special predilection for either the first born or last born in the family, for in 100 cases in which the incidence of birth was noted, it was shown that in the majority myxedema occurred in children who were both preceded and followed by normal children.

*Age at Time of Reporting, Where Given*

Under 1 year.....	9	6 years .....	11	12 years .....	4
1 to 2 years.....	16	7 years .....	8	12 to 15 years....	8
2 years .....	14	8 years .....	10	15 to 20 years....	11
3 years .....	10	9 years .....	10	20 to 30 years....	19
4 years .....	9	10 years .....	3	30 and over.....	13
5 years .....	13	11 years .....	3		

The sex of the cases where mentioned in this series, exclusive of Osler, shows the following: male, 78; female, 152—a female preponderance of 2 to 1 in keeping with the findings of Osler in America.

#### AGE OF INCIDENCE

The clinical manifestations of childhood myxedema depend primarily upon the amount of thyroid present and to a lesser extent upon the age of the child at the time of first appearance of the symptoms. Two, therefore, of the same physical age will present different stages of development if the disease appeared in one, say, at the age of 12 months and in the others at 8 years. Of 113 cases in which the date of first appearance of symptoms was noted the following distribution was found:

At or from birth.....	13	From 18 months to 24 months	25
From 6 weeks to 6 months...	10	From 2 years to 10 years....	16
From 6 months to 12 months	40	Over 10 years.....	2
From 12 months to 18 months	7		

There were 13 cases in which the symptoms were noted either at birth or the child appeared abnormal practically from birth. The incompleteness in the majority of cases of detailed symptomatology and the meagerness of description prevents us from considering all of these 13 cases as those of congenital myxedema. The presence of a goiter in one case automatically removes it from the congenital type to that of infantile myxedema, if we adhere to Pineles' classification. In three cases in our series, however, those of Sill, Herrman and Koplik, there seems to be no question that the condition at birth fulfilled the requirements of congenital myxedema. Osler includes one in his series, the case of Friend.

Herrman's case was that of a male whose parents were cousins. The delivery was normal. The symptoms were recognized at birth, but first observed by Herrman at 7 weeks of age. The length of the child was 50 cm., the trunk was large, the forehead low, hair dry and scanty, eyes small and placed far apart, the lips thick, nose broad and flat, cheeks soft and flabby, tongue large and thick, the neck short and thickened, thyroid not felt. The chest was well formed, the skin characteristic, the face of a stupid appearance. The temperature was 96° F.

Koplik's case was that of a female child who directly followed in birth a sister who was also myxedematous. As the first child was still under the doctor's care, he had an opportunity to observe the symptoms from birth. The delivery was normal. The child became jaundiced at four days of age and continued so for several weeks. She was short and thick set, the extremities short, but not deformed. The skin was cool to the touch but not myxedematous, the tongue large, lips puffed, neck short and thick, the head oxycephalic. The thyroid was not felt. The child had a stupid look, did not cry until teased, was apathetic and dull, even the clapping of hands failing to

attract her attention. The doctor made his diagnosis on reduced temperature, marked stupidity, peculiar conformity of the extremities as compared with the trunk, hypertrophied tongue, wrinkled skin, thick lips, coarse cry, and the improvement on thyroid medication as evidenced by the child's becoming brighter, noticing its surroundings, cooing, smiling, and by the thinning of the tongue and the normal appearance of the face. The hemoglobin at the beginning was higher than later, even though the child was placed on thyroid immediately. Koplik felt that this indicated that the anemia develops as the disease progresses, but is not present in the early stages.

The subject reported by Sill was small at birth, with short extremities, which were cold to the touch. The skin was yellow and wrinkled like an old man's and hung loosely upon the body. The nose was flat and stubbed, the eyes far apart, lips thick, tongue large. There was a fatty tumor in the supraclavicular space. The child never smiled and was very apathetic.

#### SYMPTOMATOLOGY

The symptomatology of a fully developed case of childhood myxedema or so-called sporadic cretinism, as evidenced by the increasing number of case reports in the literature, is well known. Once observed, the general appearance and facies will always be remembered.

*Head*—There is a lack of synthesis forcing the sutures and the fontanelles to remain open for a longer time than normal with a resulting larger head, and yet there is the same physiognomy as in endemic cretinism. In the latter type there is a premature synthesis of the skull with a production of a broad nose, prominent lower jaws, low forehead, prominent cheek bones and large alae nasi. Due to the early synchondrosis between the os basillare and the sphenoid bone, the basal ganglia of the brain cannot develop. The fontanelles close earlier in endemic cretinism. In keeping with the general observation, we found a late closure of the anterior fontanel in nearly every case, the latest age at closing being 10 years. In another instance, both fontanelles were still open at 5 years.

*Face*—There is a stupid, dull look. The shape is round, moon-shaped, with a low forehead and wrinkled skin. The nose is saddle shaped, wide at the base but short and retroussé, the alae nasi are dilated. The ears are thick and everted. The eyes are placed far apart with narrow slit-like apertures, the malar regions are prominent, cheeks flabby and hanging, the lips are thick and everted, the mouth is wide open and drooling with a protrusion of the tongue which is enlarged, but without muscular hypertrophy. The face may show eczema.

*Teeth*—Delay in the time of eruption of both the temporary and permanent teeth is almost general. It sometimes takes years before the first set has fully erupted and an additional longer time before the appearance of the second set. In one case the permanent teeth



did not erupt until the age of 17 and only 3 had appeared by 21. In another subject 30 years of age a few of the deciduous set were still present. The teeth in childhood myxedema are carious, brittle, short, irregular in their distribution and decay very easily.

*Neck*—The neck is short with lipomatous masses in the supra-clavicular space.

*Thorax*—Flatness of the thorax is characteristic.

*Abdomen*—Potbelly and umbilical hernia are seen.

*Extremities*—The arms, legs, hands and feet are very stocky; the fingers swollen; feet short and deformed, being too broad for their length; the toes are also swollen, producing an unsteady gait. The general appearance is that of a dwarf. The extremities are cold and blue at times. Muscular co-ordination is delayed. The most advanced age at which there was reported inability to sit was 3; inability to stand, 5; and backwardness in walking, 14. The gait as a rule is clumsy and unsteady.

*Skin*—The skin is sallow, semi-translucent as in phlegmasia albolens. There is edema and swelling of the subcutaneous connective tissue which is more marked in the face, tongue, lips and cheeks. This seems more pronounced in the child than in the adult and because of the softer tissues imparts a much more myxedematous appearance.

*Genitals*—There is lack of development of the genitals marked in both sexes with a delay in puberty. There may also be undescended testicles in the male. The oldest cases in which there were signs of delayed puberty was in a man of 30 who did not show any signs of a beard and in a woman of 20 who had not as yet menstruated. Precocious development in both the primary and secondary sex elements were noted in a few cases in both sexes.

*Skeleton*—The skeleton is smaller than normal, due to the persistence of the epiphyseal cartilage and retardation in the ossification along the epiphyseal line. The delay in ossification is seen in the skull, and pelvis as well as limbs. The spine generally shows lordosis, but at times kyphosis.

*Mentality*—This ranged from a mental deficiency in the congenital myxedematous type to a slight mental aberration in the other forms. In the congenital type, the children were dull, stupid, apathetic, leading a vegetative life of eating, breathing and sleeping. They could not attend to their wants, they would sit still with neither a smile nor a cry. Others showed no signs of defective mentality in the first months, but with time it was noticed that they neither cried or if so, very little, and paid no attention to other children. In the older children of the infantile and juvenile types, backwardness in school was a prominent feature. Delinquency in talking kept apace with mental deficiency. Some did not talk at all or else gave expression to their meager thoughts in monosyllables, but never advanced to the

phrase stage. The majority of advanced cases presented a guttural, harsh voice, giving vent to incoherent speech with a limited vocabulary.

Koplik and Lichtenstein described a prominence of the antithenar eminence over the situation of the os pisiformis which they consider a part of the symptomatology of so-called cretinism. They found it in all cases of this disease under their observation and also in other conditions like microcephalic idiocy and other degenerative states. The only mention of this sign in the literature is that of Engelmann, who mentions it as one of the symptoms of cretinism, but does not state whether or not it appears in her case. This prominence is immediately adjacent to the groove which separates the palm of the hand from the forearm. It is distinctly localized to this portion of the antithenar eminence and viewed from the side rises abruptly from the above groove, giving a bayonet-like appearance. It probably represents over-development of the small muscles of the inner border of the hand attached to the os pisiformis, as well as, perhaps, an enlarged condition of this bone itself. A similar condition is seen on the foot of the domestic cat. It might be caused by the act of crawling on the floor and supporting the weight on the inner border of the hands, but it was also observed in a myxedematous child only three months of age. The authors cited consider it a congenital anomaly in degenerative children and have not seen it perfectly developed in a normal child.

The onset of symptoms is early. At birth, the child appears normal, but with time it is noted that it does not act normally, does not take well to the breast, seldom cries, is more or less dull and apathetic, is backward in teething and perhaps in crawling and in the majority of instances in talking. When the child reaches a certain age, depending upon the amount of thyroid functioning, he stops growing or else slows down for a year or two and then ceases to develop. From then on, his mentality and physical development cease to progress and he either remains at that mental age or else advances very slowly. In some instances he may even retrogress and lose all the knowledge he had formerly acquired.

In another form of childhood myxedema, the so-called juvenile myxedema, the child is born normal and functionates normally until he is attacked by some acute infectious disease or some other acute pathological condition which produces acute thyroiditis and subsequent atrophy of the thyroid gland. It seems in these cases that during this acute attack there is a call for thyroid on the part of the body which is supplied but at the expense of a diminished reserve. There were 31 instances in this series in which the onset of the symptoms could be traced to a definite time following a definite acute attack. Of this number 1 followed diphtheria; 3, scarlet fever; 6, whooping cough; 1, "fever"; 3, pneumonia; 3, gastroenteritis; 4, jaundice; 1, vaccination; 1, acute thyroiditis; 2, cholera infantum; 1, sunstroke; and 4, weaning.

The manner of onset of the symptoms differs. One child at 2 years of age could talk, stand and crawl, but following an attack of whooping cough, it became dull, inactive, and constipated; the skin became dry and harsh; the hair, which was curly, became straight and dry, and the child quickly assumed the typical myxedematous appearance. Sometimes there is first a change in disposition, followed by gradual assumption of the other symptoms. In some instances, the changes are more gradual as in one case following diphtheria at 11 months of age. The change was not noted until six months later, when the first symptom to make its appearance was decaying of the teeth and a sudden swelling of the face and body. In another case, there was a history of a so-called "cold on the lungs" at 8 months, followed by very slow development until the age of 3, when there was a permanent cessation of growth. Koplik reported 3 cases following several weeks' attacks of icterus neonatorum. The patients developed signs of myxedema at 6, 12, and 15 months, respectively.

Shields describes a case in a girl who was normal until the age of 10 months, when she had an attack of acute thyroiditis accompanied by fever, swelling of the thyroid and pressure of the trachea, but with no signs in the throat. The symptoms subsided in a week. Immediately growth and development ceased. At the age of 7 she was a typical cretin of low mentality.

Four of the cases showed signs of myxedema upon being weaned. The face broadened, nose flattened, and the subcutaneous fat increased in amount. In another case, dentition ceased and the few teeth the child had already had begun to decay. She never developed any new teeth. This would apparently indicate that mother's milk contains thyroid substance. A study of our series, however, does not bear this out. Of 20 cases designating breast feeding, it was found that 8 were at the breast at the time of the appearance of symptoms, 4 showed signs at weaning and 8 gave a history of breast feeding for periods ranging from 9 months to two and a half years with no immediate symptoms following weaning. Both Gordon and Herrman found that breast feeding had apparently no influence on infantile myxedema, for a number of their cases developed the condition while at the breast. In their large series neither reported any cases of immediate onset after the discontinuance of breast feeding.

An unusual mode of onset is described by Manson in male twins, 23 years old at the time of reporting. They were both wet nursed until 16 months of age and were apparently normal until symptoms set in. At the age of 11 years, one of them was suddenly seized with an inability to walk, was put to bed, recovered and then had a second attack six months later, which was followed by ataxia and epilepsy. The second brother did not show anything abnormal until 14 years of age, when he also developed ataxia. Both ceased growing at the time of their respective attacks and at the time of reporting, their mentality was that of half their age, corresponding to the time at

which they stopped growing physically. The thyroid was non-palpable in both.

A. Gordon describes two cases of what is evidently juvenile myxedema complicated with diabetes mellitus. The children were brothers, aged 3 and 4½ years, respectively. Both complained of thirst, ravenous appetite and abundant, frequent urination with a gradual increase in mental dullness, apathy with outbreaks of excitement in the older, puffiness of the eyelids, edematous dry skin, dry hair, and in the younger the teeth were normal, but carious in the older. The thyroid seemed to be absent in both. The mother was obese and diabetic, while the father was neuropathic. While myxedema in adults attended with glycosuria is not rare, myxedema with true diabetes mellitus is.

The total energy requirements in cretins is 18 to 25 per cent below normal as shown independently by Du Bois and Talbot. With this decreased metabolism, it is to be expected that the mortality of these children would be high and their resistance low. Packard and Hand quote several instances of the lowered resisting power of myxedematous children. Still there were 13 subjects in this series over 30 years of age, one of them reaching the age of 64 after having shown symptoms when two years old.

#### PATHOLOGY

According to Rushton Parker, there are three groups of cases: (a) with absence of the gland; (b) with atrophy of the gland; (c) with enlargement of the gland. A diagnosis of complete absence of the thyroid cannot be made with certainty during life. The slightest strand of connective tissue may reveal its presence by means of the microscope. Excluding Osler's cases, there were 112 in which mention was made of the condition of the gland. The terms, "absent," "not palpable" and "not felt," were used interchangeably. It was noted either absent or not felt in 100 cases, atrophied in 2 and hypertrophied in 10. Complete absence is found only in congenital myxedema. Such a case was reported by Friend in Osler's series. In apparent absence of the thyroid careful microscopic examination of sections made through the usual site of the gland or neighboring structures may reveal rudimentary alveoli or anomalies as in MacCullum and Fabian's case in a 13 year old girl. There were no signs of either the superior or inferior thyroid artery. Two large parathyroid bodies lay on each side just at the lower limit of the larynx. Below and outside of the parathyroid, on each side were found small lobulated cystic structures. At one side of the cyst in each mass was a little glandular tissue formed into acini which had scarcely any lumen. It seems unquestionable that this was thyroid tissue, although it did not resemble the normal very closely. Dense fibrous tissue, in which there were occasionally very small alveoli, was found, probably representing scanty remains of the thyroid lobes. No trace of the thyroid could be found in small sections of tissues in front of the

larynx or hyoid bone. Sections through the root of the tongue showed thyroid tissue much better preserved than that in the neck, showing numerous alveoli containing colloid. The epithelial cells were cubical, some increased in size by the enlargement of the nuclei which took on a deep stain showing a functioning gland with compensatory hypertrophy. The parathyroids were normal.

Atrophy of the gland is generally found in that sub-group described as juvenile myxedema. Parker collected 10 such cases in England. Atrophy during childhood generally follows an acute infectious disease or disturbance. Osler gives a very excellent description of the gland in this type. Packard and Hand reported some unusual findings in a case of infantile myxedema. The child was breast fed until 20 months of age. When 4 months old she had an attack of apparent loss of consciousness. At the time of death she was 6 years of age and prior to that time could not walk or talk, was apathetic and fat. Thyroid had been administered with a rapid improvement in the symptoms, but she eventually died of typhoid fever after having been sick for 5 weeks. On autopsy the alveoli in the thyroid were found to be marked off by bands of white fibrous tissue, especially about the blood vessels. The cells varied in size, acini were small, many containing no colloid whatever, the total of the colloid material being smaller in amount than the normal. There were calcareous changes in the walls of the blood vessels, the media and at times the intima and adventitia showing a formation of cavities surrounded by calcareous deposits. There was found no other mention of this change in the literature. The hypophysis and thymus were both enlarged.

There were 10 cases in this series which presented a goiter. Of Osler's 60 cases goiter was present in 7, making a total of 17 goiters in 340 cases, an incidence of 5 per cent as compared with the 44 to 60 per cent found in true endemic cretinism. In one of the cases the thyroid enlargement was noted a few days after birth, from which time it became progressively larger. In another case there was a cyst about 2 inches in diameter in the right lobe of the thyroid, with a fibrosis of the left lobe.

The blood examinations reported show anemia with a hemoglobin range from 18 to 75 per cent. There was a decrease in red blood cells; in some cases a decrease in white blood cells, at other times an increase. The differential count was practically normal.

#### DIAGNOSIS

The diagnosis of childhood myxedema is comparatively simple. It must not be confused with minor types of hypothyroidism on the one hand or endemic cretinism and mongolian idiocy on the other.

*Differential Diagnosis*

*Mongolian Idiocy*  
 Oblique palpebral fissure and  
 superciliary margin.  
 Tongue is hacked, furrowed,  
 beef steak appearance.  
 Lips normal in size.  
 Complexion waxy and pale.  
 Skin not infiltrated.  
 Fingers thick but tapering at the  
 points with incurving of the  
 little finger.  
 Abdomen not protruding.  
 No pads of fat in supraclavicu-  
 lar region.  
 Thyroid gland can be felt.  
 Mobile.

*Childhood myxedema or So-Called  
 Sporadic Cretinism*  
 Lids swollen, almost closing eyes.  
 Tongue large and protruding,  
 but not furrowed and hacked.  
 Lips large and prominent.  
 Complexion muddy yellow.  
 Skin infiltrated and wrinkled.  
 Fingers have blunt points.  
 Abdomen protruding.  
 Pads of fat present in supra-  
 clavicular region.  
 Thyroid cannot be felt, as a rule.  
 Less mobile, apathetic.

*Differences between Childhood Myxedema and Endemic Cretinism*

1. Location: Endemic cretinism, according to the majority of the students of this subject, can occur only in regions where endemic goiter prevails. Sporadic cretinism, so-called, can occur anywhere, even in endemic goitrous districts. Even though endemic goiter is prevalent in Canada along the St. Lawrence and in America along the Great Lakes, in the Alleghany Valley of Pennsylvania, in Ohio, parts of New York, Ohio and Minnesota, not a single case which can be accepted as endemic cretinism has been reported in any of these regions nor is the incidence of childhood myxedema any greater in these places.

2. Etiology: The role of the thyroid in endemic cretinism is not uniformly interpreted by all investigators. Kocher and Wagner claim that clinical manifestations of endemic cretinism are due to thyroid disturbances alone. Kutchera, Bircher and Ewald, on the other hand, think that it is due to some other factors in addition to thyroid dyscrasia, feeling that it is a physical as well as an intellectual degeneration not solely dependent upon thyroid pathology, but to some other additional damaging influences in other organs of the body as a consequence of the endemic. One of these causes is that the endemic has been exerting its influence upon the organisms of these individuals throughout successive generations, the degree of the toxicity depending upon the amount of noxious material present in the organism and also in the locality. This latter view is strengthened by the birth of endemic cretins only in endemic locations, for a goitrous mother will bear a well-developed, normal, intelligent child if she removes from the endemic territory.

The role of the thyroid in childhood myxedema or so-called sporadic cretinism has been accepted and proved.

**Influence of goiter in the mother:** In almost every case of endemic cretinism, there is a history of goiter in one of the parents.

In childhood myxedema, in America, there was an incidence of 13 cases of goiter in the mother and of none in the father out of a total of 340 cases, an almost negligible influence.

**Psychic factors:** Fright, worry, mental depression and "antenatal impressions" are reported as prominent etiological factors in the production of endemic cretinism, but are of absolutely no importance in childhood myxedema.

Illness in mother during pregnancy such as rheumatism, tetany, malaria and nutritional factors in both the mother and the child, both antenatal and postnatal, were of no etiological importance in the production of childhood myxedema in our series, but are admitted to be causative factors in the production of endemic cretinism by McCarri-son and others.

3. **Differences in the body skeleton:** In endemic cretinism, the retardation of ossification is much more irregular than in childhood myxedema; certain epiphyses and synostoses undergo normal ossification, while others do not. There is a premature synostosis between the os basilare and the sphenoid with a consequent earlier closing of the fontanels. In the myxedema of children, the enchondrial and periosteal ossification is considerably retarded and takes place later in life. The fontanels remain open for a long time.

4. **Duration of disease:** In endemic cretinism, the disease remains stationary and as a result, the subjects live to an old age. Ewald makes the statement that he has never seen nor heard of a victim of sporadic cretinism living beyond the 30th year. This is based upon observations in Europe. Crotti takes the same view. That what has been called sporadic cretinism in America is probably not the same disease as that so styled in Europe may perhaps account for the finding of 13 subjects in our series who were beyond the 30th year, one still living at the age of 64 at the time of publication. Osler noted 7 past the age of 30 in his series.

5. **The presence of goiter:** The incidence of goiter in endemic cretinism has been rated at from 44 to 60 per cent by different observers. Pineles classifies sporadic cretinism as a sub-variety of congenital myxedema and insists that the presence of a goiter immediately stamps a case of cretinism as of the endemic type. By dispensing with the term "sporadic cretinism" for the cases observed in America, we can avoid the pitfalls of a complex terminology as to what is and what is not endemic cretinism. In our series of childhood myxedema, there were 17 cases of goiter out of a total number of 340, an incidence of but 5 per cent.

The thyroid gland in both endemic cretinism and childhood myxedema, when enlarged, may either be completely fibrosed or more commonly the gland is in a state of partial fibrosis and hyperplasia.

## 250 CHILDHOOD MYXEDEMA IN NORTH AMERICA

It may be the site of cystic enlargement or interstitial hypertrophy with a resultant non-functionating gland.

### TREATMENT

In the treatment of endemic cretinism, it has been demonstrated time and again that thyroid extract is not nearly as efficacious as in the so-called sporadic type. This means that the former disease lies further back than the loss of the thyroid, both the goiter and the cretinism resulting from the same influence or else the condition is a complex one and only partly of thyroid origin.

In the treatment of childhood myxedema there is great variance as to dosage, the form of gland used and the method of administration. The dosage ranged from 3/10 grain a day to 45 grains a day of thyroid extract. Some used the powder, others the extract in tablets. To make matters still more complicated, the dose was designated as so-and-so many tablets without indicating the content of the tablets.

There can be no uniformity in the treatment of this condition until the thyroid extract used is standardized in the process of manufacturing and in the designation of dosage. While all the products must conform to the requirements of Pharmacopeias, there is no law governing the standardization of the processes of drying, defatting, and refrigerating of the original gland substance. The different methods in vogue by the various packing houses and endocrine manufacturers and the consequent products differ in many respects.

At the present time, to insure beneficial results, it is best to decide upon a certain manufacturer's product and continue to prescribe it by name, because of the variations in strength of the supposedly same dose of different firms.

The dosage seems to depend upon individual susceptibility and not upon either weight or age. The amount of thyroid that can be taken without producing toxic symptoms depends upon the amount of antogenous thyroid of the subject as well as his susceptibility to the hormone. There is no means known at present of ascertaining these, hence it is best to start with small doses and work up to the point of tolerance. The tolerance may vary from two grains of thyroid a day to more than 45 grains (Manson's case). Wood, in discussing Lamb's case, referred to a child who by mistake took 20 to 30 tablets of thyroid extract at one time without any harmful effects. He did not state the dose of each tablet. In contradistinction to this, Lamb's patient developed signs of acute thyroiditis when more than ½ grain a day was taken. When first introduced, large doses were in use, but now there seems to be a swinging toward the other extreme, for the present tendency is towards smaller doses at the onset with a gradual increase. The tolerance is thus increased, so that a child who was unable to take ½ grain at the onset can be given two or three grains within a short time. The method of some is to administer the gland on alternate weeks with intervening periods of rest, while others prescribe it



for a month and then rest. Still others advise a continual administration, with a graduatory upward dose.

The reaction produced by a dose beyond the child's tolerance is essentially that of acute thyroiditis and comprises nervous, gastrointestinal and cardio-vascular symptoms such as extreme restlessness, crying spells, loss of sleep, vertigo, headache, diarrhea, vomiting, syncope, tachycardia, flushed face, rapid rise in temperature, falling out of the hair and general exhaustion. Upon the appearance of any untoward symptoms, the thyroid must be immediately discontinued, to be resumed only when these have disappeared. Upon resumption, it is advisable to start with a smaller dose.

The results obtained in the treatment of childhood myxedema has fully justified the hopes held out by Horsley, Murray and Mackenzie years ago. It is the one triumph of organotherapy that is unquestioned. We will not attempt to essay a statistical analysis of the results obtained in this series. Many cases were absolutely cured, others were ameliorated, while still others were not influenced at all. The outcome depends upon several factors: the amount of thyroid deficiency, the time of the onset of the treatment, the age of the patient, and the regularity with which the treatment is carried out, together with the length of time under treatment. The secret of success is early diagnosis, with early and long continued treatment. The physical defects such as those of walking, teething, crawling and bodily development are more amenable to treatment than the mental defects. In children with pronounced mental retardation, the mentality may improve to a large extent, but still never reach the normal. Some always remain a few years behind others of their age, while others develop up to a certain mental age and then remain stationary.

The initial signs of a beneficial result are generally a rise in temperature and an improvement in the appetite. There may be a preliminary loss of weight followed by an increase, with an accompanying increase in height. The child becomes brighter, shows an interest in its surroundings and in itself. The hair and skin become softer in texture and the latter loses its myxedematous appearance. The shape of the face changes. Constipation and even enuresis are cured. Abdominal distention is reduced and sometimes umbilical hernia disappears. The blood may show an increase in the hemoglobin. Du Bois found that the total energy metabolism was raised almost to the normal on the third day of treatment.

#### SUMMARY AND CONCLUSIONS

1. Cretinism as it exists in Europe does not exist in America. Not a single case of true endemic cretinism has ever been reported in America. The sporadic cretinism as encountered in Europe differs from what has been termed the same disease here. There seems to be such an indefinite understanding as to just

what is meant by the term sporadic cretinism, that it seems advisable to dispense with it, at least in America, and to restrict the term cretinism to the endemic type found in Europe and Asia. The so-called sporadic cretinism of America is really an intense and exaggerated form of hypothyroidism and as such should be known by the term of childhood myxedema or myxedema in children.

2. Childhood myxedema is not uncommon in America, although there are some localities where it is not often seen. The incidence is probably greater than that indicated by the 340 cases reported in the literature. There were only 4 of the congenital myxedematous type and 31 cases of the juvenile type. The rest were of the infantile myxedematous type.

3. The greatest number of cases was found in New York and Pennsylvania. This finding is probably due to the large immigrant population in those two states. Geographical location had no apparent bearing upon the prevalence of this disease.

4. Hereditary influences appear to be of little etiological importance, although there were several instances of more than one case of childhood myxedema in the same family.

5. The incidence in females was twice as great as in males.

6. Treatment with thyroid gland products is of great though not unfailing benefit. Some cases are curable. Mental retardation is not so amenable to treatment as physical deficiency. Prognosis depends upon the age at which treatment is instituted and upon the regularity and continuance of treatment.

#### BIBLIOGRAPHY (Exclusive of Case Reports)

- Murray, George R.: *Twentieth Century practise of medicine*. N. Y., 1895, William Wood & Co., 4, 750.  
 Howard, C. P.: *J. Am. M. Ass.*, 1907, 48, 1226, 1325, 1403.  
 Carlson, A. J.: *Am. J. Physiol.*, 1914, 33, 143.  
 Dock, George: *Wm. Osler, Modern medicine*. Phila., 1909, Lea & Febiger, 6, 447.  
 Noyes, W. B.: *N. York M. J.*, 1896, 43, 902.  
 McCarrison, Robert: *The thyroid gland in health and disease*. (N. Y.), 1917. Wm. Wood & Co.  
 Smith, G. E.: *Endocrinol.*, 1919, 3, 262  
 Koplik and Lichtenstein: *Arch. Pediat.* (N. Y.), 1902, 19, 81.  
 Pineles, F.: *Wiener klin. Wchnschr.*, 1902, 15, 1129-1136; *Verhandl. d. Versamml. d. Gesellsch. f. Kinderh. deutsch. Naturf. u. Aerzte*, 1902 (Wiesbaden), 1903, 167-169.  
 Crotti, André: *Thyroid and thymus*. Phila., 1918. Lea & Febiger  
 Tredgold, A. F.: *Mental deficiency (Amentia)*. 3 ed., London, 1920. Baillière, Tindall and Cox.  
 Falta, Wilhelm: *The ductless glandular diseases*. 2 ed., Phila., 1916. P. Blakeston's Son & Co.  
 Kocher: Quoted by "H. O." in *Boston M. & S. J.*, June 24, 1897.

## BIBLIOGRAPHY

**Case Reports of Childhood Myxedema or So-called Sporadic Cretinism in America.\* 1897-1920.***(Arranged in chronological sequence.)*

- Munson, E. L.: N. York M. J., 1895, **62**, 513.  
 Koplik, H.: N. York M. J., 1897, **66**, 309-317 (3 cases).  
 Marvin, J. B.: Internat. Clin. (Phil.), 1897, 7. s., **1**, 173-176.  
 Moore, D. L.: Pediatrics (N. Y. & London), 1897, **3**, 610-614, 2 pl.  
 Adams, J. L.: Pediatrics (N. Y. & London), 1898, **5**, 287-292.  
 Jellinek; J. Am. M. Ass., 1898, **31**, 1304 (2 cases).  
 Shields, E.: N. York M. J., 1898, **68**, 476.  
 Wolfstein, D. I.: Am. J. M. Sc., 1898, **115**, 300.  
 Dodge, F. A.: Northwestern Lancet (St. Paul), 1898, **18**, 397.  
 McPhedran, A.: Canadian J. M. & S., 1898, **4**, 275, (17 cases.)  
 White, F. F.: Boston M. & S. J., 1899, **140**, 257.  
 Campbell, G. G.: Montreal M. J., 1899, **28**, 594.  
 Cooper, St. C.: Memphis M. Month, 1899, **19**, 256.  
 Putnam, W. G.: Montreal M. J., 1899, **28**, 592.  
 Burnett, S. G.: Kansas City M. Rec., 1900, **17**, 256.  
 Morse, J. L.: Ann. Gyn. & Pediatry; Abst., Arch. Pediat., 1900, **17**, 626 (2 cases.)  
 Murdoch, J. M.: J. Psycho-Asthenics (Faribault, Minn.), 1900, **4**, 81 (14 cases.)  
 Freeman, R. G.: Arch. Pediat. (N. York), 1900, **17**, 595. •  
 Herrman, C.: Arch. Pediat. (N. York), 1900, **17**, 596 (3 cases).  
 Packard, F. A. & Hand, A.: Am. J. M. Sc., 1901, **122**, 289.  
 Abt, I.: Clin. Rev. (Chicago), 1901, **14**, 359.  
 Demaree, E. W.: Med. Herald (St. Louis), 1901, **20**, 395.  
 Hamill, S. M.: Arch. Pediat. (N. Y.), 1901, **18**, 62.  
 Gaddie, D. W.: Louisville Month. J. M. & S., 1901, **7**, 375.  
 McCrae, J.: Montreal M. J., 1901, **30**, 604.  
 Barbour, P. F.: Pediatrics (N. Y.), 1901, **11**, 327.  
 Clark, J. F. & McGrew, W.: Medical Fortnightly (St. Louis), 1902, **21**, 342.  
 Davisson, A. H.: Pediatrics (N. Y.), 1902, **19**, 700.  
 Kelly, W. D.: St. Paul M. J., 1902, **4**, 325.  
 Lindsay, C.: Med. Standard (Chicago), 1902, **25**, 231.  
 Price, E. O.: Indiana M. J. (Indianapolis), 1902, **21**, 149.  
 Mills, W. S.: N. York M. J., 1902, **75**, 325.  
 Peter, L. C.: Arch. Pediat. (N. Y.), 1902, **19**, 134.  
 Gordinier, H. C.: N. York State J. M. (N. Y.), 1903, **3**, 391-395 (3 cases).  
 De Witt, J. P.: Cleveland M. J., 1903, **2**, 365-368.  
 Newell, F. F.: Med. Rec. (N. Y.), 1903, **64**, 896.  
 Beard, F. M.: Am. Pract. & News (Louisville), 1903, **36**, 26-28.  
 Engleman, Rosa: J. Am. M. Ass., 1903, **40**, 430-435.  
 Fletcher, F.: Columbus M. J., 1903, **27**, 549-552.  
 Hirsch, J. L.: Maryland M. J. (Baltimore), 1903, **46**, 282.  
 Shelly, E.: J. Am. M. Ass., 1903, **40**, 434.  
 Gordon, A.: Am. Med. (Phil.), 1904, **7**, 229-231.  
 Kieger, F. J.: Am. Pract. & News, 1904, **38**, 417.  
 Acker, G. N.: Arch. Pediat. (N. Y.), 1904, **21**, 347-349.  
 Clark, J. F.: Pediatrics (N. Y.), 1904, **16**, 198 (2 cases).  
 Randall, E. G.: Hahnemann Month. (Phil.), 1905, **40**, 683.  
 Liedloff, A. G.: St. Paul M. J., 1905, **7**, 892.  
 West, J. C.: Pediatrics (N. Y.), 1905, **17**, 434-436.  
 Still, E. M.: Med. News (N. Y.), 1905, **86**, 833-838 (16 cases).  
 Lamb, Isabel H.: Wash M. Ann., 1905-06, **4**, 174-177.  
 Van Sickle, F. L.: Tr. Lackawanna Co. Med. Soc. (Scranton), 1905, **1**, 134.  
 Heiman, H.: Arch. Pediat. (N. Y.), 1905, **22**, 847.  
 Sanderson, H. H.: J. Michigan State M. Soc., 1906, **5**, 187 (3 cases).  
 Everhard, Eleanor S.: J. Am. M. Ass., 1906, **47**, 205.  
 Soper, R. W.: J. Am. M. Ass., 1907, **40**, 1674.  
 Clark, J. F.: J. Am. M. Ass., 1907, **40**, 559.  
 Caille, A.: Post Graduate (N. Y.), 1907, **16**, 755.  
 Macallum, W. G. & Fabyan, M.: Johns Hopkins Hosp. Bull. (Balt.), 1907, **18**, 341-345, 2 pl.

\*Cases reported prior to 1897 were covered by William Osler in the Transactions of the Congress of American Physicians and Surgeons, 1897, **4**, 169-206.

## 254 CHILDHOOD MYXEDEMA IN NORTH AMERICA

- Nawlin, J. B.: Old Dominion M. & S. J. (Richmond), 1908-9, **7**, 408-410, 1 pl.
- Judson, O. F. & Bradley, W. M.: Arch. Pediat. (N. Y.), 1908, **25**, 523.
- Minton, H. B.: Tr. Homeopathic M. Soc. (N. Y.), 1909, **53**, 253-257.
- Bloom, J. D.: New Orleans M. & S. J., 1909-10, **62**, 162.
- Simmons, S. E.: J. Am. M. Ass., 1909, **52**, 1576-1578.
- Charles, Etta: J. Indiana M. Ass. (Ft. Wayne), 1909, **2**, 470-473.
- Shaw, J. E.: Kansas City M. Index-Lancet, 1909, **32**, 352.
- Hoag, W. B.: Arch. Pediat. (N. Y.), 1910, **27**, 369.
- Niles, N. L.: Providence M. J., 1910, **11**, 154-165 (3 cases).
- Thistle, W. B.: Canadian Pract. & Rev., 1910, **35**, 357.
- Brim, B. B.: Toledo M. & S. Reporter, 1910, **30**, 563-565 (2 cases).
- Manson, L. S.: Med. Rec. (N. Y.), 1910, **77**, 7-10.
- Ryman, H. D.: Am. J. Clin. M. (Chicago), 1910, **17**, 280-283.
- Price, G. E.: Am. Medicine (N. Y.), 1911, **6**, 407-411.
- Glasgow, M.: Women's M. J. (Cinn.), 1912, **22**, 199.
- Rankin, G. C.: Kentucky M. J. (Louisville), 1912, **10**, 175.
- Ross, W. H.: Long Island M. J. (Brooklyn), 1912, **6**, 120.
- Kimball, A. C.: J. Cutan. Dis. incl. Syph. (N. Y.), 1913, **31**, 271-273.
- Stone, F. L.: West. M. Rev. (Omaha), 1913, **18**, 201.
- Du Bois, E. F.: J. Am. M. Ass., 1914, **63**, 827.
- Herrman, C.: N. York State J. M. (N. Y.), 1914, **14**, 394 (41 cases).
- Williamson, G. M.: Journal-Lancet (Minneap.), 1914, **34**, 501.
- Beier, A. L.: Wisconsin M. J. (Milwaukee), 1915, **16**, 14-15 (2 cases).
- Talbot, F. B.: Am. J. Dis. Child. (Chicago), 1916, **7**, 145-148.
- Edelman, M. H.: Arch. Pediat. (N. Y.), 1916, **33**, 932.
- Herrman, C.: Arch. Pediat. (N. Y.), 1917, **34**, 830 (3 cases).
- Gordon, M. B.: Arch. Pediat. (N. Y.), 1918, **35**, 577 (21 cases).
- Anders, J.: Contributions to med. and biological research (N. Y.), 1919.
- Paul Hoeber, Vol. 1, 270-305 (43 cases).
- Gordon, M. B.: Unpublished (5 cases).