The Hypophysis Cerebri and its relation to Marasmus in Children.

A Thesis for the degree of M.D.

by

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The Thyroid gland and its relation to Marasmus in Children - a histological, pathological, and clinical investigation.

by John W. Simpson, M.B., C.M.

One cannot be connected for any length of time with work in a children's Hospital without being struck by the very large number of marasmic infants who are brought there for treatment - either to the out-patient department or to the wards themselves. When one follows out the subsequent history of such cases, one finds that while a few improve and even recover, a very large number succumb and help to swell the already high percentage of deaths among young infants in the poorer districts of large towns.

Having become specially interested in the study of the thyroid gland and its function, I have examined during the last two or three years the thyroids of children who have died in hospital - the cases representing all the usual diseases found in such an institution. Among them were many marasmic infants and the invariable similarity of the condition of the thyroid gland in such cases was so striking as to lead me to devote considerable attention and research to the relation between it and the disease of marasmus. The results of my investigations and the conclusions arrived at are shown in the following pages.
Part I. Historical.

Richardson in his historical sketch "The Thyroid and the Parathyroid glands," points out that the use of animal organs in medicine dates from very early times.

Plinius states that the Greeks and Romans used the testicles of asses and even the semen for impotence: and to this day in Albania these organs are used for the same purpose. In our own Materia Medica we find that pepsin, pancreatin, codliver oil, all of which are animal extracts connected with the digestive functions, are official, and the use of other organs or their extracts is but a short step in organotherapy.

In recent times Brown - Séquard reawakened interest in this subject by his experiments in removing glands from animals and observing the results. He argued that every gland in the body, whether it possessed an excretory duct or not, produced a secretion which was necessary for the well-being of the organism, and that it should be possible, when an organ ceased to functionate, to substitute the secretion of healthy glands either by transplantation, by hypodermic injection of the extract, or feeding by the mouth. This has been amply confirmed in the case of the Thyroid/
Thyroid gland. Not so many years ago the most advanced text books gave the "Thyroid" but a passing reference; it was supposed to have some relation to the voice, or to regulate in some compensatory manner the intracranial blood supply, but nothing was known of its true function and importance. It was in 1873 that Sir Wm. Gull read his paper "On a cretinoid state supervening in adult life in Women," but it was only in 1877, after Ord had recorded the clinical symptoms in 5 cases of cretinism, the post mortem appearances in one of them being described by Greenfield, that attention was first drawn to the Thyroid, the gland in this case showing an advanced state of fibrosis.

It is now known, as Schäfer has pointed out in his "Text book of Physiology," that certain organs have a special influence upon some of the metabolic processes of the body. This is perhaps most strikingly shown in the case of the Ovaries and Testicles, removal of which in early life profoundly modifies development; the pancreas, again, has an obscure but important part to play in connection with carbo-hydrate metabolism and it is possible that its influence is in part due to some substance which it yields to the blood and which influences the carbo-hydrate/
hydrate (and nitrogenous metabolism) of other tissues. "There are certain organs also of a glandular structure, destitute of ducts, which are in some cases at least absolutely essential to the due nutrition of the body. These substances are no doubt formed by a process of secretion, but since they do not find their way to any free surface by means of a duct, but presumably reach the blood by means of the lymphatics or blood vessels of the organ, they have been termed 'internal secretions.'"

DEVELOPMENT OF THYROID.

That the thyroid is a secretory gland, no one who studies its structure and its mode of development can well doubt. Murray describes fully its development. "In the embryo it develops in 3 different parts; a median diverticulum of the hypoblast which lines the pharynx of the embryo is formed between the ventral ends of the second visceral arches, while a lateral diverticulum is developed on each side from the posterior wall of the fourth visceral cleft. In man the median portion persists for a time as a hollow vesicle from which a small canal, the thyroglossal duct, leads to an opening on the dorsal surface of the tongue. At a little later/"

later stage the vesicle becomes solid, and the duct disappears, while its external opening on the surface of the tongue persists as the foramen caecum in the adult. The two lateral divisions fuse with the central portion, forming a mass shaped like a horse shoe, encircling the embryonic larynx. All three portions become separated from the hypoblast, from which they originated and develop into a mass of branching cell-cylinders. These cell-cylinders are later divided up, by the ingrowth of the connective tissue, containing blood vessels, into separate vesicles. These gradually increase in size and become hollowed out by the accumulation of the colloid substance which is secreted by the epithelial cells into the lumen of the alveolus. It is important to notice that the thyroid gland is developed primarily as an outgrowth of the pharyngeal hypoblast, and in some lower animals this connection with the pharynx is still maintained. Andriezen directed attention to the fact that the thyroid gland is represented in ascidians by a mass of glandular tissue, and in amphioxus by a hypobronchial organ which pours its secretion directly into the pharynx. In higher forms (such as fishes) the gland is embedded in the surrounding tissues, but the duct which/
which communicates with the pharynx still remains.

Thus the developmental history clearly shows that the gland as we now find it in man is descended from a secretory gland which originally was provided with a duct, through which the secretion passed into the pharynx, just as the secretion of the salivary glands still flows into the mouth. In this we find an explanation of the fact that the activity of the thyroid secretion is not destroyed by passage through the stomach, but still can produce all its usual physiological effects when swallowed and absorbed from an alimentary canal, as it doubtless was by our remote ancestors. So that (as has been proved by experience) feeding by the gland acts as efficiently as injecting its extract. This mode of evolution seems to indicate that a ductless gland with an internal secretion is a higher state of development than a duct gland with an external secretion.
HISTOLOGY OF NORMAL THYROID.

We find that in an adult the normal gland is invested by a firm fibrous capsule, which sends in septa, partially dividing it into lobules of various sizes. Still finer divisions of this connective tissue framework surround the individual follicles, and give support to the small divisions of the blood vessels, lymphatics and nerves. The follicles or vesicles vary considerably in size and shape and are lined by a layer of cubical epithelium and filled up with a secretion called colloid. This colloid substance stains usually uniformly, but scattered through it may sometimes be seen white blood corpuscles, epithelial cells, and the remains of red blood corpuscles, a marked degree of this, however, being pathological. Now the child's thyroid differs slightly from that seen in the adult. Sarbach mentions that the connective tissue is more strongly developed, and the shape of the vesicles is more irregular. Schäfer has also pointed out that the glandular structure is more obvious in young than in old animals, and as age advances the organ undergoes a gradual process of degeneration, so that in advanced life its normal glandular structure can sometimes only with difficulty be recognised.

We/
We have now seen that in a normal thyroid, the vesicles are filled with colloid; let us now look briefly at the method of formation and the absorption of this material, and then ascertain further what is the composition of the thyroid secretion.

The colloid substance is the secretion of the epithelial cells which line the alveoli. Hürthle has shown by observations made on normal glands, and on portions of glands in which increased secretory activity had been stimulated, that the secretion may be formed by the epithelial cells in two ways.

The colloid may be either formed in droplets in the cells, and then gradually extruded into the lumen of the alveolus, or whole cells may break down and be discharged into the colloid substance, a part of which they thus help to form. In the first method the same cells continue to secrete, while in the second its place is taken by one of the reserve cells. It is doubtful if both these methods obtain during normal secretion, the first being probably the usual manner in which secretion takes place. The large amount of secretion which is found in many alveoli indicates that under ordinary circumstances it is not discharged as soon as it is formed, but that the central portion of the alveolus serves/
serves as a reservoir where the secretion is stored for a time before it finally escapes from the gland.

It has before been mentioned that, as the thyroid is a ductless gland, the secretion can escape only by the lymphatics or veins. The evidence which we possess indicates the lymphatics as the usual path, for it was shown by King and Horsley that when pressure was applied to the gland, the colloid could be squeezed from the acini into the interacincus lymphatic spaces. Biöndi and Hürthle have found that this escape of the secretion from the alveolus may occur in two ways. The wall of the alveolus, not necessarily as the result of distension, becomes thinned out at one point and finally ruptures, allowing the colloid to escape directly into the lymphatic space outside, while the empty follicle collapses and forms the starting point for a new one.

Hürthle has found that the secretion can also pass out from the alveolus without rupture of the wall. He injected Berlin blue into the lymphatic spaces of the gland, using an intermittent pressure, and found that it passed on into the interior of the alveoli through minute intercellular channels in which it could be seen. He also found that when the secretory activity was stimulated the colloid itself could be seen lying in these intercellular channels, continuous with the colloid in the alveolus at one end.
end and with that filling the lymph spaces at the other, proving that it was passing from the former position to the latter. By one or other of these methods, then, the secretion flows into and mingles with the lymph which bathes the interalveolar spaces of the gland, and with it is eventually discharged into the blood stream into the innominate vein and so discharged to all parts of the body.

No doubt, as in other glands, the activity of the secretion varies according to circumstances but of these we possess but little information.

COMPOSITION OF THYROID SECRETION. At one time the thyroid gland was considered to be an excretory rather than a secretory gland, and the excretion a mucinoid substance the retention of which led to an accumulation of mucin in the body and the production of the subcutaneous swelling in myxoedema. Further investigation has shown that the colloid substance is a true excretion which does not contain mucin. Our knowledge of the actual composition of this secretion is by no means complete, but several important constituents have now been separated out from it. It was early proved that the gland contained considerable quantities of extractions viz./
viz. Xanthin, Hypoxanthin, Kreatin etc., indicating high metabolic activity, but none of those could be looked on as the active principle. The most careful research work was continued by numbers of physiological chemists, both in Germany and England, but it was not until 1896 that Professor Baumann of Freiburg isolated a body containing Iodin in organic combination in the thyroid of man and of many animals, this substance possessing the physiological characteristics of the gland. Baumann describes the substance which he isolated, and named "Thyroidin" as a brownish amorphous compound which decomposed on heating, giving off the odor of pyridin, insoluble in water but sparingly soluble in alcohol and dissolving readily in dilute alkalis. It is precipitated by acids, and gives no proteid reactions, and constantly contained phosphorus." He further showed that this body was as active as the thyroid extract itself, and from this he concluded that "Thyroidin" was the active principle of the gland. These views were substantiated by Oswald. This substance called "colloid" which we find filling the vesicles is, according to Oswald, a mixture of Thyro Globulin and Nucleo Proteid. The thyro-globulin forms much the larger part of the colloid material/
material, and it combines with the Iodine to form an Iodine albuminous substance. From this substance can be separated the complex substance which Baumann calls "Thyroidin." The nuclei carried the phosphorus. Baldoni analysed the thyroids from a number of animals, and he found that in some goitrous glands there was a thyroglobulin which did not contain Iodin. The thyroglobulin containing no Iodin was proved to be physiologically inert, which shows that the physiological activity of the thyroglobulin depends on it containing iodin in the molecule.

I would specially draw attention to this relationship of iodin to the colloid, as I shall point out afterwards, in discussing the gland in Marasmic children, that this colloid material containing iodin seems to be very important.

Oswald made an analysis of the thyroglobulin of human glands, and one of the points which suggests itself from the analysis, is, that there is in some glands, if not in all, a quantity of thyroglobulin containing no iodin, which argues in favour of the theory that the thyroglobulin is secreted iodin free, and that the iodin enters into combination with the previously formed thyroglobulin.

The
The question therefore arises, does the thyroid contain iodin thyroglobulin only when colloid is present, or at least visible under the microscope, and if not visible under the microscope is iodin absent from the gland? If iodin is absent from a gland in which no colloid can be found, it follows that the thyroglobulin must be first excreted from the cells before it combines with the iodin and becomes active. The result of a number of analyses has apparently proved that the amount of iodin bears a direct relation to the amount of colloid substance. Age, however, has undoubtedly an influence on the iodine contents of the gland. In children the gland proportionally contains the least quantity of iodine.
FUNCTION OF THE THYROID SECRETION.

There are at least three theories regarding the function of the thyroid gland.

I. That there is a form of digestion in the gland whereby the toxic substances of metabolism are converted into useful and necessary substances for the organism by the action of an enzyme, and that in the absence of these necessary substances the symptoms are produced.

II. That it secretes an antitoxin for the poisonous products of metabolism.

III. That it is a secretory organ which is necessary for the metabolism, or for the nourishment of the system.

Notkin is the great advocate of the 1st theory. He thinks that there are two substances being continually produced in the body as a result of metabolism, one a toxin which produces tetanic symptoms if allowed to accumulate, the other a peculiar proteid substance which, if similarly allowed to accumulate, produces the cachetic condition known as myxoeedema.

According to this theory, it is the function of the thyroid to antagonize these substances.

The 2nd theory - the antitoxin one - has been expressed in two ways.

1st./

* The thyroid and parathyroid glands (Richardson)
1st. That the antitoxin in the gland seizes on the toxin in the blood, acting upon it in the gland itself, and that it is only the neutralized toxin which passes into the blood stream. This theory is supported by Ewald, Blum and others.

2nd. Albu, on the other hand, believes in the doctrine of auto-intoxication. It presumes that constantly during life the normal metabolism is producing lower chemical forms derived from the proteid, which, accumulating through failure of excretion or neutralization, poison the system, producing various symptoms. The antitoxin theory of the function of the gland presumes that the active principle of the gland neutralizes or decomposes one or more of those toxins into innocuous substances.

Thirdly, there is the internal secretion theory. "That this internal secretion theory, which was propounded originally by Schiff, is in the main the true one, is shown by the fact that beneficial and not toxic effects follow the exhibition of the thyroid juice, both in cases of thyroidectomized animals and in myxoedema and other affections in man. Moreover/

* The Thyroid and Parathyroid glands. Richardson P.69
Moreover, extracts of thyroid gland produce distinct physiological effects in the normal subject. It seems to have a distinct action upon the vascular system; and it has further been noticed that feeding with thyroid tends to cause increased metabolism in the body.

Lorrain Smith found that in animals which have been deprived of the thyroid body, the reaction to changes of temperature is abnormally rapid. When normal animals are exposed to a cold atmosphere, the production of CO₂ becomes increased, consistently with the increased oxidation which is necessary to cause an increased production of heat. This increase of CO₂ does not take place immediately, but only comes on after a certain period of time; the temperature of the body being in the meantime maintained normal by those physical changes which occur in the circulation, and which allow the quantity of blood brought to the skin, and the amount of heat thereby lost from the general surface of the body, to be varied. Now, it is precisely these vasomotor changes which appear to be lacking after removal of the thyroid; for the production of CO₂ becomes almost immediately increased by exposing thyroid - ectomized animals to a low temperature."

Schäfer, who has done so much work in connection with the thyroid, has come to this conclusion:

"That the thyroid gland yields an internal secretion which subserves a useful purpose within the body and the effects which follow thyroidectomy are probably due to a loss of that secretion. Whether the gland also possesses the function of destroying toxic products of metabolism which would otherwise tend to accumulate in the blood, a function which has been attributed to it by some authors, is a point the evidence regarding which is at present insufficient."
PART II. PATHOLOGICAL APPEARANCES OBSERVED

IN THYROIDS.

In this connection I have examined thyroids from about 70 cases of different diseases - Acute and Chronic.

These I will detail under 3 groups.
(1) Acute Diseases e.g. Broncho Pneumonia, etc.
(2) Tuberculous Diseases \{ A. Acute
      B. Chronic.\}
(3) Marasmus.

Before however doing so, I would like to refer to the gland as seen in premature and new-born children dying at birth.

Roger and Garnier have examined the thyroids of several newborn children dying from asphyxia, and they have noticed that in all there was marked congestion, and epithelium to a certain extent filling up the vesicles. I have only had one case, a large child 10½ lbs in weight, which presented by the breech, and before the head could be born, the child was asphyxiated. The weight of the gland was certainly above the average, 85 grains. The microscopical appearance (section 80) showed complete absence of colloid, calcublation well marked off by fibrous septa; a/
Section of glands from dead born (full term) child - Healthy.
a large number of the vesicles appeared collapsed, but the cellular lining of the vesicles appeared healthy, though in most it seemed detached from the wall. No fibrous tissue increase. There is well marked vascularity, haemorrhage appearing at some parts inside the vesicles.

Roger and Garnier have also examined three thyroids from 6 to 8 months old foetuses, and they found the gland normal in two. In the other there was little colloid and very marked desquamation of epithelium.

Askanazy and Elkes also examined several glands from more premature foetuses (4½ to 6½ months). They found the vesicles contained colloid material, blood vessels were badly developed, and the epithelium for the most part was arranged in heaps or solid cylinders.

I have examined two premature cases, one a child of 7½ months, of 3 lbs. 4 oz. in weight, and whose thyroid weighed 11 grains. No history was got of the supposed cause of prematurity. Here a large number of the vesicles filled with colloid, some vesicles being of a fairly large size but in this they vary very much. Shape also varies considerably. A number of vesicles seem to be broken/
broken up into smaller ones. There are a very large number of very small vesicles. Some vacuolation. No increase in fibrous tissue; a good deal of cellular increase between vesicles, also some of the smaller vesicles filled with cells. A number of vesicles empty, and in some which contain colloid there are frequently seen a network arrangement.

The other case was a foetus of 8 months, which was born alive, but owing to faulty tying of the cord the child bled to death before the error was discovered. The weight of the foetus was 5 lbs 4 oz, and the thyroid weight 24 grains. The cause of prematurity is not known. (Illegitimate child). In this section the vesicular arrangement is almost completely obliterated by cell infiltration. Great increase in the vascularity. The vesicles that are patent have no colloid.

There is great increase in the intravesicular fibrous tissue, the vesicles being mostly filled with cells.

I. ACUTE DISEASES.

In studying those sections one must bear in mind that the follicles in infants increase in size and number according to the age of the child, and/
and 2nd, as Sarbach has pointed out, the shape of the follicle is frequently elongated, a remnant of the tubular form. In acute diseases one is immediately struck by the extraordinary changes that have been produced in the gland, by the action probably of toxins circulating in the blood. All degrees of changes have been observed in the sections, from an almost total destruction of the follicles, as to make the gland almost unrecognizable as such, down to a condition where little departure can be seen from the normal. In no case does one see what might be called an absolutely normal gland, the nearest approach being some sections which appear healthy except in a few areas.

Section 21 for example, from a case of Broncho Pneumonia, may be taken as a fairly normal gland occurring in an acute disease. Here vesicles vary, as expected in an infant; in size and shape, some are oval, some elongated, some triangular; Colloid filled nearly all the vesicles, the lining epithelium was well marked, a single layer and cubical. There was no increase of fibrous tissue.

At small areas however in this section one sees some lobules with no colloid content, and in those vesicles there was marked cell proliferation. Even in/
Even in some with colloid this cell proliferation was also seen.

Sections 51 (Broncho Pneumonia), 17 (Septicaemia), 5 (Broncho Pneumonia), 42 (Pneumonia), 19 (Empyema and Pericarditis), 9 (Acute Endocarditis), and 6 (Acute Toxaemia), show much the same appearances, but in some there is more fibrous tissue to be seen than in section 21 (described).

In the other sections 38 (Pneumonia and Empyema), 40 (Gangrene of Lung), 18 (Broncho Pneumonia), 15 (Broncho Pneumonia), 23 (Broncho Pneumonia), 8 (Broncho Pneumonia), 53 (Cerebro Spinal Meningitis after operation for Spina Bifida), 18 (Haematoma of Brain), 36 (old Tubercular elbow - Pneumonia), 7 (Pericarditis and Endocarditis), 20 (Septic Peritonitis), the appearances show much more advanced thyroid degeneration. There are several well marked changes running through most of them.

1) There is marked disappearance of colloid. In several there is none, and in all there is a great deficiency, and what colloid there is, is nearly always seen occupying the vesicles at the margin of the gland.

2) The vesicles without colloid are filled up by infiltrated cells, in a few cases however the vesicles/
vesicles remain patent without any cell infiltration.

(3) Great increase in the fibrous tissue. In practically all these cases this is seen, and in a number the fibrous tissue is intravesicular.

(4) In the great majority there is very evident vascularity, in several sections Red Blood Corpuscles are seen completely surrounding the vesicles.

In going over the histories of these cases mentioned, one is struck by the fact that in those sections showing well marked colloid, the children had previously been healthy, and had developed an acute disease to which they rapidly succumbed.

In those showing want of colloid, increase of fibrous tissue etc. the children had for the most part been in a previously debilitated condition, except in three cases (Haematoma of Brain, Cerebro Spinal Meningitis and Septic Peritonitis) and there the children were only a week or two old. Roger and Garnier's conclusions are somewhat different. They examined the thyroids of 22 adults and 19 children dying from acute diseases, and state that changes in the adult were more frequent than in the child;
child; that the gland became enlarged, slightly hyperaemic, and the connective tissue was slightly changed, the lymph vessels contained large quantities of colloid, but the blood vessels did not seem to be much affected. The follicles appeared smaller than normal, and were filled with colloid mixed with degenerated desquamated epithelium. The cells attached to walls of follicles were often raised up and projected into the colloid material. The epithelium of the follicles often seen in several layers. They also mention that they did not think that the severity of the changes in the gland had any connection with the stage of the disease at which death occurred, and did not seem to be affected by intercurrent disease.
### Acute Diseases

<table>
<thead>
<tr>
<th>No. of section</th>
<th>Age</th>
<th>Weight of Thyroid in grains</th>
<th>Cause of Death</th>
<th>Colloid</th>
<th>Fibrous Tissue</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>13 mths.</td>
<td>21 grs.</td>
<td>Broncho Pneumonia</td>
<td>Well marked</td>
<td>not increased</td>
<td>At parts see Vesicles with no colloid, with marked cell proliferation.</td>
</tr>
<tr>
<td>01</td>
<td>20 mths.</td>
<td>25 grs.</td>
<td>Broncho Pneumonia</td>
<td>Well marked</td>
<td>slight increase</td>
<td>Some vesicles have no colloid and in these marked cell proliferation.</td>
</tr>
<tr>
<td>01</td>
<td>20 mths.</td>
<td>25 grs.</td>
<td>Broncho Pneumonia</td>
<td>Well marked</td>
<td>slight increase</td>
<td>Marked vacuolation. No proliferation of cells.</td>
</tr>
<tr>
<td>01</td>
<td>18 mths.</td>
<td>45 grs.</td>
<td>Broncho Pneumonia</td>
<td>Well marked</td>
<td>no increase</td>
<td>Some vesicles lost colloid and in these have cell proliferation.</td>
</tr>
<tr>
<td>01</td>
<td>10 mths.</td>
<td>50 grs.</td>
<td>Broncho Pneumonia</td>
<td>Very little</td>
<td>marked increase</td>
<td>Vesicles small - marked cell proliferation into vesicle.</td>
</tr>
<tr>
<td>01</td>
<td>3 yrs.</td>
<td>50 grs.</td>
<td>Lobar Pneumonia</td>
<td>Very little</td>
<td>marked increase</td>
<td>Vesicles small - Slight cell proliferation into vesicles.</td>
</tr>
<tr>
<td>01</td>
<td>2½ yrs.</td>
<td>25 grs.</td>
<td>Lobar Pneumonia</td>
<td>none</td>
<td>marked increase</td>
<td>Vesicles small and many empty. Very vascular. No proliferation of cells.</td>
</tr>
<tr>
<td>01</td>
<td>19 mths.</td>
<td>36 grs.</td>
<td>Empyema and Broncho Pneumonia</td>
<td>Well marked</td>
<td>no increase</td>
<td>Vesicles contracted, filled up with cellular elements.</td>
</tr>
<tr>
<td>01</td>
<td>12 mths.</td>
<td>38 grs.</td>
<td>Empyema &amp; Pericarditis</td>
<td>Well marked</td>
<td>slight increase</td>
<td>Vesicles contracted and empty - not much cell proliferation.</td>
</tr>
<tr>
<td>01</td>
<td>7 mths.</td>
<td>37 grs.</td>
<td>Empyema &amp; Gangrene of Lung.</td>
<td>Very little</td>
<td>marked increase</td>
<td>In parts see destruction of vesicles by fibrous growth.</td>
</tr>
<tr>
<td>01</td>
<td>6 yrs.</td>
<td>135 grs.</td>
<td>Empyema, Abscess of Lung.</td>
<td>none</td>
<td>marked increase</td>
<td>Vesicles small, many in many places filled with cells.</td>
</tr>
<tr>
<td>01</td>
<td>10 yrs.</td>
<td>125 grs.</td>
<td>Acute Endocarditis</td>
<td>Well marked</td>
<td>no increase</td>
<td>Marked cell proliferation into vesicles.</td>
</tr>
<tr>
<td>01</td>
<td>9 yrs.</td>
<td>95 grs.</td>
<td>Rheumatic Peri. and Endocarditis</td>
<td>Deficient</td>
<td>increased</td>
<td>Find at areas vesicles contracted with loss of colloid - lobular arrangement.</td>
</tr>
<tr>
<td>01</td>
<td>7 mths.</td>
<td>25 grs.</td>
<td>Gastro Intest Toxaemia</td>
<td>Well marked</td>
<td>increased in areas</td>
<td>See in places degeneration of vesicles with cell proliferation.</td>
</tr>
<tr>
<td>01</td>
<td>4 wks.</td>
<td>21 grs.</td>
<td>Purulent Meningitis</td>
<td>none</td>
<td>not increased</td>
<td>In areas marked destruction of vesicles.</td>
</tr>
<tr>
<td>01</td>
<td>18 days.</td>
<td>18 grs.</td>
<td>Oedema of Brain.</td>
<td>Very little</td>
<td>marked increase</td>
<td>Vesicles small, a number completely obliterated and crammed with cells.</td>
</tr>
<tr>
<td>01</td>
<td>20 days.</td>
<td>16 grs.</td>
<td>Septicaemia</td>
<td>Deficient</td>
<td>marked increase</td>
<td>Majority of vesicles filled with cellular contents.</td>
</tr>
</tbody>
</table>

Marked vascularity.
II. TUBERCULOUS CONDITIONS.

The pathological changes in the thyroid, accompanying tubercular conditions elsewhere, have been studied and reported on by many observers.

Roger and Garnier, Quervain, Sarbach and others.

Roger and Garnier, who examined the thyroids of 7 adults and 2 children, reported the pathological changes to be as follows:

(1) an active growth of epithelium.
(2) new formation of follicles.
(3) frequently an increase of colloid material.
(4) a connective tissue increase.

In the parenchyma they found a great increase of cells between the follicles, and in the connective tissue they often observed follicles that were disappearing.

These changes they believe due to toxins.

Quervain states very definitely that when an increase in the fibrous tissue of the thyroid is observed in young children, it is nearly always due to tubercle. From the examination of a large number of sections, obtained from a number of diseased conditions, I do not think this statement can be made as definitely as Quervain supposes; that an increase of fibrous tissue is/
is a constant accompaniment of tuberculous conditions is undoubted, but at the same time this fibrosis I have found as strongly marked in many other conditions. In acute conditions, such as certain cases of Broncho Pneumonia etc., it is present, and in all marasmic thyroids, but more especially in the marasmus that follows congenital syphilis.

Tubercle certainly, more than the great number of other chronic diseases, has some special influence in causing fibrosis in the thyroid, because, as Quervain points out, there is no marked fibrous increase in such chronic conditions as Cancer, Chronic Bright Diabetes, etc.

In number 3 of my sections, some of the points mentioned by Roger and Garnier are well brought out:

(1) Marked increase in the fibrous tissue, especially seen in the centre of the gland.
(2) In the middle of this fibrous tissue one can see traces of lobules in the shape of epithelial cells. As in acute conditions, the most healthy looking vesicles are seen at the margin.

It is evident from an examination of the other sections that where fibrosis is well marked there is deficiency of colloid and proliferation of cells. In a great number of the sections there is marked vascularity.
<table>
<thead>
<tr>
<th>No of section</th>
<th>Age</th>
<th>Weight in grains</th>
<th>Cause of Death</th>
<th>Colloid</th>
<th>Fibrous Disease</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>43</td>
<td>28 yrs</td>
<td>20 grs</td>
<td>Tuberculous Meningitis</td>
<td>Well marked</td>
<td>Increased in areas</td>
<td>Marked vascularity - where no colloid - cell proliferation.</td>
</tr>
<tr>
<td>12</td>
<td>40 grs</td>
<td>4 yrs</td>
<td>Tuberculous Meningitis</td>
<td>Well marked</td>
<td>Increased in areas</td>
<td>Destruction of vesicles by fibrous increase</td>
</tr>
<tr>
<td>45</td>
<td>52 grs</td>
<td>4 yrs</td>
<td>Tuberculous Meningitis (old tubercle)</td>
<td>Well marked</td>
<td>Increased</td>
<td>Where colloid wanting vesicles filled with cells. Vascularity.</td>
</tr>
<tr>
<td>44</td>
<td>54 grs</td>
<td>4 yrs</td>
<td>Tuberculous Meningitis (old tubercle)</td>
<td>Deficient</td>
<td>Increased</td>
<td>Vascularity increased - many vesicles filled with cells.</td>
</tr>
<tr>
<td>46</td>
<td>48 grs</td>
<td>3 yrs</td>
<td>Tuberculous Meningitis (old tubercle)</td>
<td>Very little</td>
<td>Marked increase</td>
<td>Vessels empty and contracted - vascular.</td>
</tr>
<tr>
<td>37</td>
<td>108 grs</td>
<td>3 yrs</td>
<td>Tuberculous Meningitis (tub. abdomen)</td>
<td>Very little</td>
<td>Marked increase</td>
<td>Great destruction of vesicles by cells &amp; fibrous tissue.</td>
</tr>
<tr>
<td>36</td>
<td>78 grs</td>
<td>3½ yrs</td>
<td>Old tubercle elbow operation</td>
<td>Very little</td>
<td>Marked increase</td>
<td>Disappearance of vesicles - marked vascularity.</td>
</tr>
<tr>
<td>41</td>
<td>36 grs</td>
<td>6 yrs</td>
<td>Tub. Ankle Pneumonia</td>
<td>Well marked</td>
<td>Increased in areas.</td>
<td>Vascularity present - number of vesicles contracted cell proliferation</td>
</tr>
<tr>
<td>48</td>
<td>72 grs</td>
<td>6 yrs</td>
<td>Tub. Spine</td>
<td>Very little</td>
<td>Marked increase</td>
<td>Vesicles filled with cells - vascular.</td>
</tr>
<tr>
<td>14</td>
<td>32 grs</td>
<td>3½ yrs</td>
<td>Tub. Peritonitis</td>
<td>Well marked</td>
<td>Slight increase</td>
<td>Where colloid absent, cell proliferation.</td>
</tr>
<tr>
<td>47</td>
<td>34 grs</td>
<td>10 mths</td>
<td>Tub. Peritonitis</td>
<td>Well marked</td>
<td>Increased</td>
<td>Where colloid absent, cell proliferation.</td>
</tr>
<tr>
<td>22</td>
<td>20 grs</td>
<td>9 mths</td>
<td>Tuberculosis Br. Pneu.</td>
<td>Well marked</td>
<td>Increased in areas.</td>
<td>Where colloid absent, cell proliferation.</td>
</tr>
<tr>
<td>24</td>
<td>32 grs</td>
<td>6 mths</td>
<td>Phthisis</td>
<td>Very little</td>
<td>Increased</td>
<td>Vesicular formation difficult to make out - marked cell proliferation and vascularity.</td>
</tr>
<tr>
<td>3</td>
<td>68 grs</td>
<td>20 mths</td>
<td>Phthisis</td>
<td>Deficient</td>
<td>Increased in areas.</td>
<td>Vesicles destroyed by fibrous ingrowth.</td>
</tr>
</tbody>
</table>
case has some colloid but well marked fibrous tissue increase.

Section 53 is the only one that shows a fair amount of colloid, and in this case the child was older than the ordinary run of atrophic infants. The history was that it had been a healthy child, but it took an attack of vomiting and diarrhoea and after that (for 2 or 3 months) it wasted. Nothing definite was found at the post-mortem, beyond what one gets in purely marasmic cases.

The 3 "Pyloric Stenosis" cases are interesting for this reason - cases 25 and 32 were more or less wasted children when operated upon, they lived for some time after operation, but eventually died of marasmus. Their thyroids showed the ordinary third changes described; the child was in good condition, being operated on almost as soon as the diagnosis was made, before wasting had taken place. The child however succumbed to the operation a day or two afterwards. No great departure from what one expects to get in a normal thyroid was observed.
DESCRIPTION OF SECTIONS FROM MARASMIC CASES.

34. Marasmus:

R.M. 3 months. Bottle fed. Put out to nurse, nothing known about child- on admission vomiting, has very subnormal temperature.
Family history good. Father and mother healthy.

Full time child. Healthy when born.

Only a few small vesicles with colloid contents at one end of section. Whole of the rest of the gland shows no spaces. Lobules fairly distinct, but vesicles completely obliterated as result of increased fibrous tissue formation, cell proliferation and haemorrhage.

Shows that fibrous increase is present between the vesicles, and vesicles entirely filled up with epithelial proliferation. Numerous Red Blood corpuscles mingled with cells. Even those vesicles with colloid show cell proliferation.

56 Marasmus.

L.B. aged 3 months. Complaint- wasting (for 7 weeks.)
Bottle fed.

Family history good.

On admission to hospital - emaciated - skin dull grey, harsh and dry. Simply wasted away - had diarrhoea.

P.M. Marasmus and Diarrhoea.
The general appearance of the section shows a marked lack of colloid, but here and there a lobule may be seen with several vesicles with some colloid in them, but even in these the majority of the vesicles have become contracted, and there is increase of fibrous tissue, and development of new vessels. In the other parts the vesicles are all contracted with fibrous tissue infiltration. There is also vascularity.

Those vesicles with colloid contents appear healthy; in some of the healthy vesicles there is evident detachment of epithelium lining, with haemorrhage round the margin of the vesicles.

35. Marasmus.


Vesicles all empty, lobules well marked - vesicles within lobules collapsed and empty - few in number owing to the fibrous tissue increase. Shows haemorrhage as before. In most parts vesicles/
vesicles difficult to make out, their place being taken by groups of cells, great fibrous tissue increase.

61. Marasmus.

A.D. 4 months. Child's weight 7 lbs. 10 oz.

Complaint: weakness - emaciation.

Father and mother healthy. Baby farming case, not much history. Troubled with vomiting and diarrhoea.

On admission. Very emaciated - features old looking - skin very wrinkled, child cold and blue looking.

P.M. condition appears to be pure Marasmus - some terminal Broncho Pneumonia.

Section 61.

Vesicles vary in shape and size. A great number of the vesicles are very small. Complete absence of colloid. The vesicles are in a large number of cases patent, without cellular infiltration. Great increase of vascularity.

H.P. Fibrous tissue increase - marked vascularity all through gland, in many places surrounding vesicles. Cellular infiltration between vesicles - a large number of vesicles seem just to have lost colloid, and in these the vesicles are lined by a single layer of cubical epithelium.
well marked Subnormal Temperature chart.
Section 62. Marasmus.

C.S. 3 months weight 5 lbs. 5 oz.
Complaint: wasting - Vomiting and constipation.
Family history good. Premature child - 8 months foetus, so that in reality only 2 months old.
Bottle fed. Child brought in thin and emaciated.

Section 62. The vesicles are very irregular in size and shape: At margin the vesicles are large and mostly filled up with colloid. In the centre of the gland the vesicles seem broken up into smaller ones - some contain colloid, some empty and some full of cells.
Slight intravesicular increase of fibrous tissue. At margin of gland several healthy vesicles are seen but at margins also see marked cellular appearance between vesicles, and also see cells going into colloid.
In the centre of gland see numbers of empty vessels and in others with colloid see marked infiltration of cells, frequently displacing altogether the colloid.

Section 29.

I.W. 3 months. Marasmus:

Child's weight 5 lbs. 8 oz.
Complaint/
Complaint: wasting. Illegitimate child. Father and mother healthy. Fairly well nourished child at birth. Never on breast. Brought up on bottle, feeds very irregularly, at first on condensed milk; child seemed to thrive on this for a little, but soon began to waste and has been going steadily backward.

Section 29. Well marked lobular arrangement. Vesicles vary in size and shape. A number of vesicles seem to be broken up into smaller ones. The colloid in a number of vesicles displaced by cell infiltration, but a number appear healthy and full of colloid. Increase of fibrous tissue, vacuolation seen.

H.P. Very marked increase of fibrous tissue, well marked cellular increase into same vesicles.


H.B. 6 weeks. 3 weeks premature - Mother not able to nurse child, appeared fairly healthy when born, put on milk and water, never seemed to thrive. Came into hospital in an emaciated condition.

Developed Broncho Pneumonia and died in two days. Entire absence of vesicular formation and colloid content/
content. Lobular distribution still well marked off by great increase of fibrous tissue. Contents of lobules seem to be contracted vesicles with no colloid, but infiltrated with cells. Fibrous tissue increase is seem to be extremely marked between the various vesicles. It has obliterated them. Vascular.

Vesicular arrangement is lost and its place taken by masses of cells.

53. Marasmus.

D.R. 7 months. Admitted with history of vomiting and diarrhoea for some months. Bottle fed child. Child was very emaciated on admission.

Colloid is fairly abundant, at same time general impression is of destruction of vesicles with cellular infiltration, particularly in centre. On the whole there is marked increase of fibrous tissue.

Shows the marked increase of fibrous tissue with consequent destruction of vesicular formation. Seems to be haemorrhage, but difficult to distinguish owing to staining.
Subnormal Temperature Chart
55. Congenital Heart. Marasmus.

Family history good.
Child has well marked exophthalmos. No bulging of fontanelle.
Some small vesicles filled with colloid at one pole of the gland. Marked increase of fibrous tissue throughout whole gland, separating off the different vesicles themselves. Compared with slide 34, does not show the same amount of collapse of the vesicles, and not the same amount of cell infiltration. Haemorrhage again well marked as in 34.
Shows very marked increase of fibrous tissue with haemorrhage, the haemorrhage having evidently destroyed a large number of vesicles. The majority with colloid contents are small and most show commencing cell infiltration into vesicle.

Section 66. Congenital Heart. Marasmus (Specific)

W.L. 2 months. Weight 7 lbs. 8 oz.
Complaint: diarrhoea. Suspicious specific history in mother, not a healthy house. Appeared healthy at birth, 20 days on breast, then put on bottle, did/
did not suit. Put on condensed milk, got on fairly well, then took an attack of diarrhoea, and has been wasting since.

Section 66. Vesicles very irregular in shape and vary in size. All empty of colloid, marked infiltration of cells between vesicles. Lobular arrangement well marked.

H.P. Marked intravesicular increase of fibrous tissue - great cell increase round vesicles. A number of vesicles full of cells.

57. Congenital Syphilis - with Marasmus.


Complete absence of colloid in vesicles, very marked fibrous increase throughout gland. Vesicles all empty of colloid and filled up with cells.

Section crowded with red blood corpuscles. Vesicular formation almost impossible to make out. Vascularity and fibrous increase very well marked.
Section 67. Congenital Syphilis and marasmus.

L.D. 6 weeks. Weight 5 lbs. 8 oz.

Illegitimate child. Baby farming case, so cannot get/
get much history about child. Seemed healthy when born, but at 3 weeks developed evidences of Congenital Syphilis. Child since then has been wasting.

Section 67.

Vesicles very small, largest seen at margins, very irregular in size, all vesicles devoid of colloid, great increase in vascularity; a large number of the vesicles, especially in the centre of the gland, crammed with cells. Marked intravesicular increase of fibrous tissue, great number of vesicles filled with cells, and also great proliferation of cells between vesicles. Enormous increase in vascularity. The haemorrhage in some cases almost completely surrounding vesicles.


History A.S. Family history good. Home surroundings good. Full time large child. Had typical history of Pyloric stenosis with well marked peristaltic moves. Well marked projectile vomiting. When child came into Hospital it was thin and with shrunken, deep wrinkles over forehead, skin dry, Legs/
Legs and arms are kept drawn up in a state of spasm. Hands clenched. Thumb across palm.

Section 25.

Colloid contents only evident at two parts of the gland at the extreme margin. Rest of gland shows complete obliteration of the vesicular formation, with marked fibrous development and haemorrhage. In the parts with the fibrous tissue the vesicular formation has its place taken by masses of epithelial cells, fibrous tissue, and red blood corpuscles. The vesicles at the margins seem fairly healthy, though even here increase of fibrous tissue.

32.

R.C. Congenital Pyloric Stenosis. Weight 51bs. 9 oz. Father and mother healthy. Child had typical history of Pyloric Stenosis. Began vomiting when 2 weeks old, the vomiting being projectile in character, marked constipation, well marked peristaltic waves across stomach. Child brought in in an emaciated condition, and eventually died of marasmus.
32 Section. Vesicles, irregular in shape, vary in size, but difficult to make out as they have almost completely disappeared. No colloid to be seen. Vesicles filled up with cells, great increase of fibrous tissue.

H.P. Vesicles seen full of cells, complete absence of colloid material.

30.


Weight 7 lbs. Father and Mother healthy, except that during last month of pregnancy mother had albuminuria. Other children healthy. Child was slightly under 7 lbs at birth. On breast for 14 days but stopped then as milk seemed to disagree. Child vomited. Put on bottle. Child still continued vomiting and it was brought to Sick Children's Hospital. It proved to be a typical congenital Pyloric Stenosis. It was not a wasted baby and was operated on at once. It only lived for 5 days after the operation.

30 Section.

Vesicles very irregular in size and shape. Most of the vesicles are full of colloid. A number of the vesicles seen to be broken up into numbers of smaller ones. Great cellular increase between vesicles/
vesicles and increase of fibrous tissue, well marked vacuolation.
A number of vesicles, however, seen empty.
H.P. See the breaking up of vesicles by cellular and fibrous increase. See quite a number of healthy vesicles with single layer of cubical epithelium. There are however a number of vesicles full of cells. Colloid in some vesicles taken on stain more deeply than in others.
<table>
<thead>
<tr>
<th>No of section</th>
<th>Age</th>
<th>Weight of child</th>
<th>Weight of Thyroid in grains</th>
<th>Cause of Death</th>
<th>Colloid.</th>
<th>Fibrous Tissue.</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>3 months</td>
<td>7 lbs. 6 oz.</td>
<td>20 grains</td>
<td>Marasmus.</td>
<td>Very little</td>
<td>marked increase.</td>
</tr>
<tr>
<td>56</td>
<td>3 months</td>
<td>7 &quot; 8 &quot;</td>
<td>16 &quot;</td>
<td>Marasmus &amp; Diarrhoea.</td>
<td>Very little</td>
<td>marked increase.</td>
</tr>
<tr>
<td>25</td>
<td>5 weeks</td>
<td>4 &quot; 10 &quot;</td>
<td>11 &quot;</td>
<td>Marasmus.</td>
<td>None</td>
<td>marked increase.</td>
</tr>
<tr>
<td>61</td>
<td>4 months</td>
<td>7 &quot; 10 &quot;</td>
<td>27 &quot;</td>
<td>Marasmus.</td>
<td>None</td>
<td>marked increase.</td>
</tr>
<tr>
<td>62</td>
<td>3 months</td>
<td>5 &quot; 5 &quot;</td>
<td>13 &quot;</td>
<td>Marasmus.</td>
<td>Deficient</td>
<td>slight increase.</td>
</tr>
<tr>
<td>29</td>
<td>3 months</td>
<td>5 &quot; 6 &quot;</td>
<td>13 &quot;</td>
<td>Marasmus.</td>
<td>Deficient</td>
<td>marked increase.</td>
</tr>
<tr>
<td>13</td>
<td>6 weeks</td>
<td>5 &quot; 8 &quot;</td>
<td>10 &quot;</td>
<td>Marasmus.</td>
<td>None</td>
<td>marked increase.</td>
</tr>
<tr>
<td>53</td>
<td>7 months</td>
<td>7 &quot; 3 &quot;</td>
<td>12 &quot;</td>
<td>Marasmus.</td>
<td>Well marked</td>
<td>increased.</td>
</tr>
<tr>
<td>55</td>
<td>6 months</td>
<td>6 &quot; 2 &quot;</td>
<td>14 &quot;</td>
<td>Congenital Heart Marasmus.</td>
<td>Very little</td>
<td>marked increase.</td>
</tr>
<tr>
<td>66</td>
<td>2 months</td>
<td>7 &quot; 8 &quot;</td>
<td>18 &quot;</td>
<td>Congenital Heart Marasmus.</td>
<td>None</td>
<td>marked increase.</td>
</tr>
<tr>
<td>57</td>
<td>4 months</td>
<td>7 &quot; 12 &quot;</td>
<td>12 &quot;</td>
<td>Congenital Syphilis. Marasmus.</td>
<td>None</td>
<td>marked increase.</td>
</tr>
<tr>
<td>54</td>
<td>9 weeks</td>
<td>5 &quot;</td>
<td>13 &quot;</td>
<td>Congenital Syphilis. Marasmus.</td>
<td>None</td>
<td>marked increase.</td>
</tr>
<tr>
<td>67</td>
<td>6 weeks</td>
<td>5 &quot; 8 &quot;</td>
<td>10 &quot;</td>
<td>Congenital Syphilis. Marasmus.</td>
<td>None</td>
<td>marked increase.</td>
</tr>
<tr>
<td>25</td>
<td>7 weeks</td>
<td>6 &quot; 4 &quot;</td>
<td>15 &quot;</td>
<td>Congenital Pyloric Stenosis.</td>
<td>Very little</td>
<td>marked increase.</td>
</tr>
<tr>
<td>32</td>
<td>7 weeks</td>
<td>5 &quot; 9 &quot;</td>
<td>12 &quot;</td>
<td>Congenital Pyloric Stenosis.</td>
<td>None</td>
<td>marked increase.</td>
</tr>
<tr>
<td>30</td>
<td>5 weeks</td>
<td>7 &quot;</td>
<td>24 &quot;</td>
<td>Congenital Pyloric Stenosis.</td>
<td>Well marked</td>
<td>increased.</td>
</tr>
</tbody>
</table>
Having now glanced at the development and physiology of the thyroid, its chemistry, (especially as regards the colloid material,) and the different theories advanced in connection with the function of the gland, let us see from an examination of sections taken from marasmic cases, combined with results obtained from experimental research, if they can in any way account for some or all of the clinical symptoms of this disease.

In other words has this "Internal secretion" anything to do with the condition of marasmus, so frequently seen among the children especially of the poorer section of the community?

Marasmus is the name applied to a condition of extreme wasting, (frequently associated with gastrointestinal disturbance) seen in infants under 18 months old. The course of the disease is usually chronic, and in the majority of cases ends fatally.

The term "marasmus" is usually reserved for those cases which are dependant on the failure of the digestive organs to make good the wants of the body incident to life, while at the same time there is an absence of any organic disease, except perhaps a catarrhal/
catarrhal or atrophic condition of the alimentary tract.

I would include also under marasmic conditions these cases of Congenital Syphilis which die in a very wasted condition, because, from examination of the thyroid, it seems to me possible that it may play a not unimportant part in bringing such cases to a fatal termination.

In order to indicate the probable connection existing between the thyroid gland and a marasmic condition, let us now consider the etiology of marasmus.

**ETIOLOGY OF MARASMUS.**

The chief factors in the production of infantile atrophy may be briefly stated thus :—

1. Constitutional weakness or want of vitality.

   This may be due to:—
   
   (a) Prematurity of birth.
   
   (b) Disease in parents, and consequent inherited tendency to dyspepsia on the part of the infant.

   (c) After-effects of some serious illness, such as Pneumonia, which may leave the infant prostrate and therefore unable to recover its /
its full powers of digestion; this state of prostration may gradually pass into a condition of atrophy.

II. Improper food.

Infants fed at the breast of a healthy mother never suffer from atrophy, at least if the surroundings be at all favourable. It is the artificially fed infant that becomes atrophic.

III. Unhealthy surroundings.

That these certainly have a marked influence on infantile digestion is a fact of such daily experience as to need merely to be mentioned at this stage.

I. CONSTITUTIONAL WEAKNESS.

(a) Prematurity of birth.

(a) Premature children, as every one knows, are very difficult to rear.

We have shown by our sections that the thyroid may appear more or less normal in a premature child; very often, however, there is a scarcity in the amount of colloid present, and as the colloid contains the active principle, it follows that the child must suffer from this deficiency. It has been shown moreover by various observers that age has an important/
important influence on the Iodine contents of the gland. In infants the gland contains proportionately the least quantity of Iodine. Bourcet has always found a small amount of Iodine in the thyroids of healthy newborn children, but this is not confirmed by other observers.

Richardson analysed the thyroids of several children who died immediately after birth and also of a few prematurely-born children; he has never been able to find a trace of Iodine, or of blood-pressure-reducing substance.

We may therefore conclude that the thyroid of a newly born child contains little or no iodin. As I have already pointed out, in treating of the chemistry of the gland, that "the thyroglobulin containing no Iodin is proved to be physiologically inert," it follows that new born and young infants have an insufficient quantity of true thyroid secretion in their own glands. Consequently the more premature the child, the greater likelihood is there that no active principle is present in the thyroid gland, and therefore a greater degree of risk would be added if the child had to be brought up on the bottle.
(b) Disease in parents.

It is generally recognised that children of unhealthy parents are more predisposed to various illnesses than children of healthy parents. We are now in possession of certain facts in relation to the thyroid, which may throw some light on at least one condition commonly seen in infants whose parents are unhealthy, viz., the tendency to fall into an atrophic state. During pregnancy there is a marked modification of the thyroid gland in the mother. Freund observed augmentation of volume of gland in 45 out of 50 women. Lange noticed that the enlargement commenced about the 4th month in primiparae and the 5th month in multiparae. The gland commences to diminish 7 or 8 days after confinement and soon returns to a normal condition. It has also frequently been noticed that a suppression of menstruation often produces a swelling of the gland, which swelling disappears on the re-establishment of the flow. There seems to be a balancing as it were, between the flow of blood and the size of the gland. This is extremely interesting from the fact, pointed out by Gautier, that the menstrual blood contains Iodin and arsenic, both of which substances are a part of the normal secretion of the thyroid. It has been noticed that sclerosis of the thyroid in adults is/
is almost invariably found in tuberculous disease and in chronic alcoholics, and Charrin and Nathan Gerrier showed that it also existed in the newly born offspring of tuberculous mothers.

Halstead, in the course of his observations on dogs, adds another proof of this interesting point, viz. that the condition of the thyroid in the mother has a direct bearing on the thyroid of her offspring. A bitch who had had most of her thyroid removed was impregnated by a normally healthy dog; she gave birth to 8 puppies, whose thyroids were at least 12 times larger than normal. This seems almost as if nature were trying to make up for the deficiency of the thyroid secretion in the mother. These observations made by Halstead have been confirmed by Horsley. As showing also the effect of diseased parentage on the child, John Thomson mentions in his article on cretinism, in the medical encyclopedia, that "In the few cases in which cretin-women have become pregnant, and delivery has taken place, the infant, although not myxcedematous, has been atrophied or hydrocephalic at birth, and has died soon afterwards."

If, now, as I believe, the thyroid secretion in the child plays an important part in the assimilation of its food, it seems probable that an unhealthy parentage/
parentage may lead to such an alteration in the newborn infant's thyroid as to eventually account for the atrophic condition so commonly seen in marasmic children.

(c) After-effects of illness e.g. pneumonia etc.

We have shown in our sections the results of the actions of toxic agents on the thyroid gland. In going over the acute diseases and noticing the great changes that may take place in the thyroid, one can quite understand how the gland may be so damaged as to be unable properly to fulfil its functions.

It has been pointed out by several observers that cretinism may supervene after some acute disease. This we can well understand, but deficiency in the thyroid secretion does not of course necessarily lead to cretinism. It is a recognised clinical fact that numbers of children, after an attack of, say, Broncho Pneumonia or Acute Diarrhoea, suffer subsequently from an apparently disordered digestion, and gradually become atrophic. I am inclined to think that this atrophic condition is largely due to the degeneration of the thyroid (observable in such cases) with the absence of at least the greater part of its internal secretion. The thyroids in these cases show a great similarity to the thyroids of children dying of pure marasmus.
II. Improper Food.

One of the commonest causes of atrophy is the giving of improper food. It is a noteworthy fact that children fed at the breast of a healthy mother, if the surroundings be at all favourable, never suffer from marasmus. Often even under bad hygienic conditions a child entirely on the breast will thrive splendidly. It is the artificially-fed infant that is prone to suffer from atrophy; the more unsuitable the feeding the more apt is the child to become affected; when once this condition of atrophy has begun, and digestion has been seriously weakened, the infant continues to waste in spite of more wholesome food being supplied. This is especially true of infants under 4 or 5 months of age.

It is true that frequently in out-patient work at the Sick Children's Hospital one finds an atrophic baby who is being brought up on the breast; on going into the history of the case, however, one invariably finds that the child is also being supplied with other very unsuitable kinds of nourishment.

A child brought up on the bottle is frequently very difficult to rear. One of the chief reasons for this is no doubt that cows' milk forms a much denser/
denser clot in the stomach than human milk. The proteids of milk are of two kinds - caesin and albumen - and a reliable estimate has given six parts of caesin to one of albumen in cows' milk, and the proportion of the two in human milk as equal. When one remembers that albumen is a much more easily digested form of proteid than caesin, it is evident that there is here an important practical difference between the two milks. The mineral salts, also, in the two kinds of milk, show important differences in the form in which phosphorus occurs. In human milk phosphorus is present solely, or almost solely, in an organically combined condition, while in cows' milk less than half of the phosphorus is in this form of combination. It will therefore be evident that in most cases, and certainly in that of all feeble infants, pure cows' milk will be found to be difficult of digestion and requiring some modification to render it suited to the digestive powers of the infant. Even with all the known methods of modification, - dilution- peptonizing etc.- one finds frequently that the child does not thrive, because as Hutchison puts it, "a truly humanized" "cows' milk" is a chemical impossibility."

In addition we know that human milk includes a /
a considerable proportion of unknown "extractive" bodies which contain nitrogen, while cows' milk contains considerably less of these.

It has been shown that thyroglobulin is excreted along with the milk by the mammary gland in the human subject, the child receiving in this manner the amount necessary for its metabolism. This seems to be extremely important when we compare the condition of the thyroid secretion at birth and for some months afterwards of a child and that of a calf. The child has no iodine (or at most very little) and therefore little or no thyroidin in the thyroid, while in the calf the thyroid gland contains iodine even in Utero, as well as the substance which increases the pulse rate and reduces blood pressure. It seems probable therefore that, as the calf is already supplied with thyroidin, the cows' milk will not contain the same amount of thyroidin as human milk does. This may throw some light on the frequent occurrence of atrophy in artificially-fed children. Still another fact seems to me to point to the great influence exercised on the growth of the child by the thyroid secretion contained (even in small amount)
in human milk. Why is it that mixed feeding (if the mother be healthy) is preferable to complete artificial feeding? If the mother be unable for any reason to do more than give the child the breast at night, while during the day it is artificially fed, the infant is nevertheless found to thrive very much better than when fed solely on the bottle. Of course the obtaining of the "natural feeds" in the 24 hours must in itself be beneficial, but the mere quantity imbibed does not seem to me proportionate to the great good received. May the benefit not be largely due to the child obtaining from the mothers' milk a certain amount of thyroid secretion which very materially assists the digestion of the artificial foods?

III. Unhealthy Surroundings.

Infantile digestion is undoubtedly influenced by its surroundings. Infants born in poor circumstances breathe the foul air of crowded and badly ventilated dwellings; they are exposed to cold; they frequently lie day and night in contact with damp and filthy napkins; they are strangers to fresh air and sunlight, and also often to all the numerous little attentions and cares which are such important factors in preserving the health of the infant.

Warmth/
Warmth, cleanliness, fresh air and sunlight beyond doubt greatly influence the digestive processes. This, I think, is well seen in everyday experience. Why is it that we seldom find marasmus in the children of well-to-do people who can afford all the necessary comforts for their infants? These children may not thrive well, they may even be exceedingly difficult to rear, but we extremely seldom see any well marked case of marasmus among them.

In this connection it is interesting to note the effect of good hygienic conditions on Thyroid-ectomized animals. Swale Vincent and Jolly in their paper on the "Thyroid and Parathyroid" say that they found it possible to keep thyroidectomized animals alive for a prolonged time by careful regulation of their surroundings - by warmth, cleanliness and fresh air - on the other hand, if the animals were kept in very badly ventilated and cold cages, they very quickly developed symptoms and died.

Horsley also noted the effects of cold on animals suffering from want of thyroid secretion.

In May 1885 thyroidectomy was performed by Horsley on a sheep. Climatic conditions being favourable, no marked change was observed in the condition of the animal until May 1887, when it was shorn/
shorn. Immediately afterwards, extremely cold weather supervened, and symptoms of acute cachexia, loss of appetite, spasms, tetanic contractures and subnormal temperature rapidly developed and were soon followed by death.

Physicologists have gone thoroughly into the subject of metabolism during inanition, and one main fact emerging in all experiments is this as stated by Schäfer: "in spite of the withholding of food all the excretions continue, not certainly to their normal amount, but at least to a considerable extent. For a considerable time, as a result of the oxidation of fat and body proteids, the temperature of a fasting animal is maintained to about its normal amount. Toward the end of starvation, however, the temperature begins to sink, and finally rapidly falls, the meaning of this being that the animal has now practically exhausted all the nutriment which it can take from the tissues, and that the amount of oxidation has become reduced, so that the temperature is no longer capable of being maintained at normal. The change is also, in part, due doubtless to the fact that the heat-regulating functions of the nervous system are beginning to break down in consequence of the deficiency of nutriment. It has been suggested that an animal dying of starvation practically dies of cold; and it is undoubtedly true that the life of a starved animal/
starved animal can be prolonged considerably by the employment of artificial warmth, since this diminishes the amount of oxidation necessary for maintaining the animal heat, and thus economizes the energy-producing substances within the body: but it is, of course, not possible for the artificial warming of an animal to prolong life to any great extent under circumstances of complete deprivation of food." Now a marasmic child is in much the same condition as a starving animal; true, the child receives food, but as this food is not assimilated, it is useless for purposes of nutrition. We are not surprised, therefore to find the same symptoms and results in both cases.

In concluding this part, I would draw attention to the symptoms which in animals (monkeys) result from the operation of Thyroidectomy.

These symptoms produced by a loss of thyroid secretion furnish a very interesting comparison with the symptoms associated with Marasmus in children.
To show atrophied condition of skin.

Malnourished child.
<table>
<thead>
<tr>
<th>MARASMUS IN CHILDREN</th>
<th>THYROIDECTOMY IN ANIMALS</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) Attitude of child. Legs are flexed at knees, which are drawn up over abdomen toward chin. Arms are flexed - hands clenched, the thumbs being pressed into the palmar surfaces, very like the condition one gets in tetany. Legs and arms are in a condition of spasm, often making it almost impossible to straighten them out.</td>
<td>(A) Attitude of monkey. Murray describes this position thus: &quot;The head is bent, the trunk is curved forward, the knees are drawn up so that the chin rests upon them, the joints of all the limbs being in a position of flexion. Contractures frequently occur owing to a tonic spasm of the flexor muscles. In fact, this attitude is, I believe, partly a result of these contractures, as the limbs are often found to be rigid when it is adopted.&quot;</td>
</tr>
<tr>
<td>(B) Skin usually dry and wrinkled, liable to develop sores.</td>
<td>(B) Skin dry - sores frequently develop.</td>
</tr>
<tr>
<td>(C) Sometimes Trismus and Tetany.</td>
<td>(C) Muscular tremors and Tetany almost a constant symptom.</td>
</tr>
<tr>
<td>(D) Marked subnormal Temperature - tends to become more normal under thyroid treatment.</td>
<td>(D) Marked subnormal temperature - tends to become normal under thyroid treatment.</td>
</tr>
<tr>
<td>MARASMUS IN CHILDREN</td>
<td>THYROIDECTOMY IN ANIMALS</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>(E) Blood - shown diminution in Haemoglobin, decrease in Red cells, increase in white cells.</td>
<td>(E) Blood - shows diminution in Haemoglobin, decrease in Red cells, increase in white cells.</td>
</tr>
<tr>
<td>(F) Retraction of head seen frequently in last stage of disease.</td>
<td>(F) Retraction of head frequently seen in last stage.</td>
</tr>
</tbody>
</table>
TREATMENT OF MARASMIC CASES

WITH THYROID AND ITS RESULTS.

Having now gone into the reasons which led me to believe that the thyroid secretion played a very important part in this condition of marasmus, let me now state the results of treatment by thyroid; for after all, this is the essential test of the real value of these observations. As I have already stated, all our best authorities agree as to the almost total hopelessness of marasmus when once a true state of atrophy has taken place.

Statistics amply bear this out, for they show an appalling infant mortality from this disease in all our large towns. I have examined the last 15 cases admitted into the Sick Children's Hospital and treated in the usual way. The results are as follows:—7 have died — 7 have gone out not improved (none having gained and most of them having lost weight) while one has improved. Now these are the returns in spite of the most careful dieting and nursing, and they would certainly seem to show that at present our method of treatment is of little avail. So far, I have not had a sufficiently large number of cases to warrant the drawing of any absolutely definite conclusions; but the giving of thyroid accompanied by careful/
careful dieting, has up to the present, yielded most surprising and gratifying results. In recording the results of treatment, one has of course to take into account the fact that in outpatient work, one frequently sees wasted children, fed in the most haphazard way, who, when the diet has been carefully regulated and the instructions as to cleanliness, warmth, etc., carefully carried out, at once begin to improve and gradually but steadily recover. These cases are really not true marasmic ones, but might be classified under the term "Improper feeding."

Some of my cases may probably be of this kind and might without thyroid treatment have eventually recovered, but as a matter of fact all had been under observation for some time, and I think I can safely say that at least 5 out of 7 cases were true marasmic ones. The first two cases which I now detail were under Dr. John Thomson's case in his ward in the Sick Children's Hospital; and later he kindly allowed me to treat them.

CASE I.

Thomas Orr, aged 3 months (an only child) was admitted to Sick Children's Hospital on Feb. 10th 1906. While the home surroundings were fairly healthy/
Subnormal temperature closed steadily losing weight

Low temperature, weight remained stationary
healthy, the child had rarely been taken out to the fresh air as the mother had to look after a shop. The child appeared healthy at birth and was fed at the breast for a month; then, as it did not seem to be thriving well, it was put on the bottle. Various kinds of food were tried - peptonized milk, Mellin's food, Nestle's food, barley water and milk etc. but none seemed to suit, the child becoming more wasted and emaciated every day. When admitted to hospital, the child was extremely feeble, looked very pale and had a pinched and "ancient" expression. The skin of the legs and arms wrinkled a good deal and felt very cold to the touch. The infant was very irritable and cried a great deal; the appetite was fair, but the taking of food was almost always followed by vomiting. (not projectile in character). The upper part of the abdomen was noticed to be more prominent than the lower part; there was also marked gastric peristalsis, with waves about the size of a walnut, coming out under left costal margin and travelling over to right side, increasing in size on the way. These peristaltic contractions occurred at the rate of 3 or 4 to the minute. In the ward, the child was carefully dieted and treated in the usual way and almost from time of admission the vomiting practically/
practically ceased: nevertheless, the infant continued steadily to lose weight.

On March 6th, I began treating the case with thyroid and the table appended giving the weight at different dates will best illustrate the effect of this method of treatment.

<table>
<thead>
<tr>
<th>Admitted.</th>
<th>Feb. 10th 1906.</th>
<th>Weight 6 lbs. 12 oz.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feb. 14th</td>
<td>6 lbs. 6 oz.</td>
<td></td>
</tr>
<tr>
<td>Feb. 16th</td>
<td>6 lbs. 8 oz.</td>
<td></td>
</tr>
<tr>
<td>Feb. 19th</td>
<td>6 lbs. 11 oz.</td>
<td></td>
</tr>
<tr>
<td>Feb. 26th</td>
<td>6 lbs. 8 oz.</td>
<td></td>
</tr>
<tr>
<td>Mar. 2nd</td>
<td>6 lbs. 4 oz.</td>
<td></td>
</tr>
<tr>
<td>Mar. 6th</td>
<td>6 lbs.</td>
<td></td>
</tr>
<tr>
<td>Mar. 8th</td>
<td>6 lbs. 2 oz.</td>
<td></td>
</tr>
<tr>
<td>Mar. 12th</td>
<td>6 lbs. 8 oz.</td>
<td></td>
</tr>
<tr>
<td>Mar. 16th</td>
<td>7 lbs.</td>
<td></td>
</tr>
<tr>
<td>Mar. 19th</td>
<td>7 lbs. 1 oz.</td>
<td></td>
</tr>
<tr>
<td>Mar. 23rd</td>
<td>7 lbs. 1 oz.</td>
<td></td>
</tr>
<tr>
<td>Mar. 26th</td>
<td>7 lbs. 3 oz.</td>
<td></td>
</tr>
<tr>
<td>Mar. 30th</td>
<td>7 lbs. 9 oz.</td>
<td></td>
</tr>
<tr>
<td>April. 2nd</td>
<td>7 lbs. 11 oz.</td>
<td></td>
</tr>
<tr>
<td>April. 6th (last date of observation for Thesis)</td>
<td>7 lbs. 14 oz.</td>
<td></td>
</tr>
</tbody>
</table>

a gain of 1 lb. 14 oz. in one month.
The chart shows the temperature to have gradually risen. Between March 19th and 23rd the temperature remained subnormal and during that period the child put on no weight.

CASE II. (Christina Brown) age 5 months.

This case furnishes even better proof than Case I of the results of treatment by thyroid. The child, who was also in Dr. Thomson's ward, was first admitted in December 1905. The weight was then 7 lbs. 2 oz. Two weeks later she was sent out unimproved, the weight then being 6 lbs. 12 oz. On Feb. 1st, 1906 she was readmitted to hospital with a bad prolapse of the bowel. Careful dieting was again tried, but the child continued to lose weight. The prolapse improving, she was sent out on Feb. 13th and came to me in the out-patient department, on Feb. 17th. Her weight then was 6 lbs 8 oz. The dietary continuing as in ward, the loss in weight steadily went on, till on March 7th the child was reduced to 6 lbs 4 oz.

Thyroid treatment was then begun and the following table shows the results:--
expected was being seen.
Readmitted to ward. Thyroid treatment continued.

<table>
<thead>
<tr>
<th>Date</th>
<th>Weight</th>
<th>oz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mar. 7th</td>
<td>6 lbs.</td>
<td>4 oz.</td>
</tr>
<tr>
<td>Mar. 15th</td>
<td>6 lbs.12 oz.</td>
<td></td>
</tr>
<tr>
<td>Mar. 21st</td>
<td>7 lbs. 2 oz.</td>
<td></td>
</tr>
<tr>
<td>Mar. 22nd</td>
<td>7 lbs. 4 oz.</td>
<td></td>
</tr>
<tr>
<td>Mar. 26th</td>
<td>7 lbs.12 oz.</td>
<td></td>
</tr>
<tr>
<td>Mar. 30th</td>
<td>7 lbs. 9 oz.</td>
<td></td>
</tr>
<tr>
<td>April 7th</td>
<td>7 lbs.15 oz.</td>
<td></td>
</tr>
<tr>
<td>April 14th</td>
<td>8 lbs. 5 oz.</td>
<td></td>
</tr>
</tbody>
</table>

Child taken out by Mother.

(five observation for Thesis).

Notice in chart the marked subnormal temperature with gradual rise on the giving of thyroid. At one period in hospital (March 26th to 30th) the child lost 3 oz - this loss being accounted for by an attack of diarrhoea which soon stopped on the reduction in quantity of the thyroid administered.
The results of my other cases I shall give in the form of tables and in less detail. They were all wasting babies, brought up on the bottle. Their diet was of course regulated under hospital direction.

CASE III. (Charlotte Moore. 3 months). Out-patient Department. Feby. 21st. Weight 6 lbs. 5 oz.

No thyroid was given, the diet simply being regulated. The child came back one week later (Feby. 29th) having lost 1 oz. The same diet was continued and thyroid added.

February 21. 6 lbs. 5 oz.
February 28. 6 lbs. 4 oz.  
March 7. 7 lbs. 4 oz.  
March 21. 8 lbs. 4 oz.  
April 5. 8 lbs. 14 oz.

CASES IV. and V.

The next two cases were twins. They had been treated in out-patient department for some time; the children, however, were steadily losing weight. They were admitted (March 19th) to a ward under the care of Dr. Burn Murdoch who kindly allowed me to treat them.

Case IV./

March 19th    Weight 5 lbs. 12 oz.
March 22nd    5 lbs. 6 oz.
March 24th    5 lbs. 10 oz.
March 26th    5 lbs. 11 oz.
March 28th    5 lbs. 12 oz.
March 31st    5 lbs. 14 oz.
April 2nd     5 lbs. 13 oz.
April 4th     6 lbs.

On the 8th April the child became ill and vomited frequently. The temperature rapidly rose and the patient showed symptoms of commencing pneumonia. The child rapidly became worse and died on April 10th.

The post mortem examination showed acute Broncho.-Pneumonia.

CASE V. Agnes Cullaghan. (4 months. twin.)

March 19th    6 lbs. 12 oz. admitted to ward.
March 24th    6 lbs. 6 oz. Thyroid began.
March 26th    6 lbs. 9 oz.
March 28th    6 lbs. 11 oz.
March 31st    6 lbs. 14 oz.
April 2nd     6 lbs. 13 oz.
April 4th     6 lbs. 15 oz.
April 7th     7 lbs. 2 oz.

CASE VI.
CASE VI. George Mathieson (4 months) attended out-patient department suffering from marasmus. He was dieted and put on Thyroid and since then has steadily gained weight.

March 21st 8 lbs. 6 oz. Thyroid given.
" 24th 8 lbs. 10 oz.
" 28th 9 lbs.
April 2nd 9 lbs. 7 oz.
" 7th 9 lbs. 10 oz.
" 14th 9 lbs. 15 oz.

This case shows a gain of 1 lb. 9 oz. in 24 days.

CASE VII. Mary Muir (3 months old) attended out-patient department suffering from marasmus.

She was put on thyroid and now (April 4th) looks very much better. The actual weight cannot be ascertained on account of surgical condition necessitating the child being wrapped in bandages.

To these hospital cases I will only add the history of two occurring in my private practice. Neither child, in spite of good surroundings and careful feeding, thrived satisfactorily until thyroid treatment was begun when a very marked improvement was manifested/
manifested.

This seems to show that thyroid treatment may be beneficially administered long before a marasmic condition has been reached.
CONCLUSIONS.

(1) Undoubted changes are frequently found in the thyroid gland in infants, in acute diseases, (E.G) Broncho Pneumonia, and in chronic conditions, (E.G) Tuberculosis.

(2) Undoubted changes also occur in the thyroid glands of infants dying of Marasmus.

(3) In Marasmic cases these changes consist chiefly in a disappearance of the colloid, and an increased fibrosis.

(4) The greater number of true marasmic children in spite of careful dieting and good hygienic surroundings, fail to improve and ultimately die. In them one of the most marked post mortem changes is seen in the thyroid gland (as already stated).

(5) In these cases of Marasmus which have been given small doses of thyroid extract in addition to the ordinary dietary, marked improvement sets in almost immediately, an improvement which is steadily maintained.
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