The
Etiology and Treatment
of
Exophthalmic goitre
Part 1.

Etiology
The etiology of this disease is still a debatable question, and although many theories have been advanced by men of every nationality, still we do not seem to have accurately discovered its correct cause. Ever since the malady has been recognized (somewhere in the beginning of last century) there have been found authorities who further theories based upon researches in almost every climate, and it has therefore occurred to me to systematize these various theories to arrange them according to the several systems, with special reference to ten cases of my own which of late I have had the opportunity of observing. Six of my ten cases have been noted in my general practice. The population of Limavady is a little over 9,000; there are eight practitioners of medicine so that the proportion of cases which has fallen to my lot seems to be large, but I do not advance the theory of "climatic influence" as a causative element. The point is however interesting in passing Hereditary Influence then seems to
be no recognized association of this disease with hereditary traits such as the tubercular or syphilitic, but the disease sometimes manifests itself in patients whose family history shows that either father or mother or some near relative have been the subject of a functional or organic nervous disease, and there have been examples quoted of the disease attacking many members of the same family. An interesting example of the latter was shown in the Clinical Society of London lately by Dr. Batty Shaw, where the father and son suffered from the disease. I discovered nothing in the family history of my patients to account for the disease except that the mothers of two were alcoholics. It seems, therefore, that if the nervous theory of the disease be entertained that the predisposition is a want of "nervous tone." The patient may reside an exciting cause to act more prejudicially than it otherwise would.

Sex & Age

Bramwell's Table of
79 cases show a proportion of 73 females to 6 males. The disease appears
to victimize essentially female. In the occurrence of the male must be looked upon as the exception. In the hundreds series of cases 1 were female of one male. It attacks its victims at all ages, but in the female there seems to be a predilection for the menstruating decade. In 7 of my cases the disease first revealed itself between the ages of 15 to 30.

**Alimentary System**

Some of the most distressing symptoms are more attributable to the Alimentary Canal. E.g., vomiting, diarrhea, anorexia, Bulimia, tinctured tongue, jaundice. It is therefore not unreasonable to suppose that some poison may be produced in, and absorbed by, the canal and that the various alimentary symptoms described are not caused by the disease, but rather that the symptoms are those of a disorder of system, which thus favors the production of toxins and these in turn are not properly evacuated. In four of my cases there were marked gastrointestinal symptoms notably constipation with...
recent recurrent attacks of diarrhoea before the observation of the disease, and in one case in particular the treatment of a sharpness during the progress of the disease required a great amount of attention and care. **Circulatory System**

It has been said that there is sometimes an antecedent Choliosis characteristic of the onset of the disease, and this led Baderman to refer the causation to a primanary change in the blood. However, no change in the corpuscles can be found - in any cases demonstrated no corpuscular change. The general fact of opinion, however, does not point to it being primarily a blood disease, but that various changes in the blood stream, notably at puberty, may have an influence in exciting the disease. The thyroid gland itself is commonly affected by the variations in the blood stream, *e.g.* pregnancy, anaemia, puberty, but whether the chemistry of the gland constituents are altered.
or not is open to doubt.
Since the circulatory symptoms
are of so distressing a nature.
It has been stated that an ante-
cedent heart disease may be a
causative agent. Kocher expresses
this by the causative effect of.
Operative procedures in cases of
Grave disease with concurrent
irritation of aortic disease.

It is interesting to note here, the
intervention of "Athyroidism" when
the thyroid is administered.

Internally but here does not-
see to be any conclusive
evidence that the normal secretion
of the thyroid exerts any deleterious
action on the circulatory
system. I have noted no
organic cardiac disease in
any of my patients. Functional
troubts are of course common but
are of no significance in the
consideration of the etiology of the disease
respiratory system.

I have heard of no theory proposed
claiming this disease to have its
origin in this system.
lymphatic system.
A common feature of the disease is enlargement of the lymphatic glands of the neck. (Muller)
This I have noticed in two cases but here does not seem to be an enlargement of the other lymphatic glands in the body. The word has seen painful swellings of the parotid submaxillary glands Renan attributes the disease to a primary faulty circulation of the lymph stream, which secondarily affects the thyroid gland causing a certain amount of cirrhosis. It is difficult to entertain this theory if the enlargement of lymphatic glands were general, and, if there were other evidences of enlargement of the system, it would be worth considering, but probably the localized enlargement of the glands indicates the changes in the lymphatic system to be caused by the disease and not that the primary cause is to be looked for in this system.
Muscular System

The disorders of this system are interesting and complicated. But, it is often to grave doubt that the perverted metabolism in the muscle cells is any causative factor. The theory of the production of a 'toxin' in the muscles due to faulty assimilation may be entertained and Kempke asserts that a "Leptomotor" has been discovered histologically. The evidence is meager.

The results of thyroide feeding in animals produceswithout doubt increased metabolism in the muscles and indeed in all the tissues of the body. The cells are as it were, braced up and exercised by the nitrogenous products. It is feasible, then, to suppose that in atrophalling girls, some product of metabolism, from some cause or other, may be absorbed into the system, thus forming the 'toxin' which generates the disease. But I see no reason to assign to the muscle cells alone this especial function.
Of course tremors early in the disease are a characteristic feature, and also in some cases a marked atrophy of the general muscular system. The condition of the eye muscles, too, shows a variety of abnormal conditions but although these manifestations may be due to some intrinsic change in the muscle cells, the general muscle symptoms seem to me to be due to either a nervous influence, a toxemia or a want of tonicity. In one of my cases which I have had under observation for many years, a scoliosis has developed and is now rapidly getting worse. The hyroid tumor is in this case also unusually large, necessitating faulty respiration and an uplifting of the shoulders. To this, and conceal the only too apparent neck distortion. This may in some degree and the course of the scoliosis.

In all my other cases muscular flabbiness and wasting is a distinct feature.
Nervous System.

There can be found authorities who explain the disease by an affection of almost any part of the Nervous System.

An old theory is that the disease may be due to a local irritation of the sympathetic ganglia in the neck. This is apparently incorrect, because the symptoms are not localized, nor is there any permanent irritation of the pupil dilator. Further there has been found no histological change in the ganglia, and some of the symptoms are not irritative in quality but paralytic. On the other hand, the existence of unilateral cases of the disease is important as suggesting a possible localized sympathetic lesion.

At Johnson's work is at least interesting in that he claims to have cured the disease by cervical sympathectomy, but I do not find that his results are accredited with the support of surgeons in general.
The vasomotor centre in the Cerebro Medulla is secondary if the entire sympathetic system seem to be influenced so that the involvement is not a local cervical one but one situated at the entire sympathetic system. Baseidow in Germany advocates the theory of an alteration in the ganglion cells of the cervical centres but Hoffer again disproves this by the beneficial results of operation. Bramwell in his work mentions changes which have been found in the Medulla e.g. haemorrhages in the 4th ventricle, experimental production of the disease in animals by sections of the Restiform body, but he does not put these considerations forward seriously as explaining the nervous phenomena.

A frequent cause which sickles give as a cause of the disease is fright. It is interesting that in 9 of my cases there is a clear history of mental shock or
Sudden fright. Three examples will suffice: (a) a married servant-girl became pregnant and suffered morbid dread lest her employer should discover her condition. Her pregnancy was discovered during the 9th month and she was subsequently married. After child-birth the disease manifested itself.

(b) A young woman about 30 years old was engaged to be married to a solicitor, who lodged in the same house. The woman's parents died and the solicitor does not fulfill his pledge until forced to. The stress and strain of this man's promise mean poverty to the woman. In both of these cases there was for a long period a degree of mental anxiety - shock. and both singularly enough developed the disease when there was no longer need of anxiety or suspense.

(c) As an example of sudden fright - I may give that of a young girl who was a
visiting a friend's house and
was awakened from sleep
one night by a weird noise
which she was unable to
account for. She was so
alarmed that she ran in
absolute terror to the room of
her hostess, there to remain
the rest of the night. The disease
dates back to this incident in
this particular case.
I think that such examples are
not to be lightly considered, and
are to a certain extent important.
The vasomotor centre can be
affected by various influences,
temporary and it is also evident
that the same centre is involved
in Basedow Disease, so that the
exciting cause in a given case
may be an abnormal stimulus
such as I have given examples
of. On the other hand it is
quite as rational to suppose that
a greater tendency to functional
activity of the receptive nerve
centres may be already present
from an early condition of the
Disease, and that the malady had not manifested itself until some such occurrence as I have narrated had presented itself. The Thyroid gland itself.

In all cases of the disease the thyroid is enlarged and the native constituent of the secretion are present in abnormal amount. Whether there is an increase in which is abnormally present or whether it is pure excessive normal secretum it is difficult to say. The contrast between hyperplasia and Graves' Disease as Brancwell points out seems to indicate that excessive secretion per se is the toxicating factor, and the evidence of operated cases where the area of the secreting surface is diminished and where a cure results seems to favor a hypersecretion theory. The thyroid is notably enlarged in pregnancy and in some of the exanthemata. There does not seem to be evidence of toxemia in these conditions, as the enlargement is
transitory. Hence in some
conditions of the body the thyroid
seems to adapt itself to over-
secretin and Hallini asserts
that the administration of thyroid
preparations by the mouth prevents
the occurrence of enlargement in
the gland state. One of my
cases showed a remarkable
peculiarity of an intermittent
enlargement of the thyroid with
the coincident vascular symptoms
of prostration. I am unable to
account for this condition as
the symptoms are not progressive
and subside after a week
or two. It appears to me to
be a case of "pseudo. yrene,
disease" and due to a hyper
secretin or anemia, distinct
from a true yrene disease which
is defined as due to a
perverted secretion.

What then is the totive of
perverted secretion, matured on
the ground of characteristia of
the disease? It is difficult to
determine. Bulmer has
isolated a protox substance
called "mycopathin" and lanec
zante hypozanthis, coddylgine
bacilli & succeni acids have
also been found. Freulal
claims his "mycopathoixie" as
the toxicating agent but
investigation of this substance
has not so far formed satisfactory
Baumner declare that coddylgine
is the only active constituent of
the hypoid, and that the poisonous
effects of the disease is due to
this.

What then is Coddylgine?
According to Hutchison the colloid
matter consists of two proteins
(a) globulin or hypo globulin
(b) nucleo protenid
If the globulin is subjected to
gastric digestion or a
neutral acid a peptide is
of course the result and coddylg
hypogine. The latter is said to
contain as much as 10% of
codine but owing to the
difficulty in getting the substance
in large amounts, it is not
available to chemists for exhaustive investigation. However it is known that it is a potent toxic substance in small doses. There a marked similarity in its action to the toxics of the infective processes. There is therefore clear evidence of the existence of poisons of the thyroid.

It may further be asked why should codrin be present in the thyroid and square in its relation to Graves Disease or Hashimoto's disease. That the thyroid is virtually a storehouse of codrin to the system but that although codrin is undoubtedly present in the gland it is there not combinable as codolygine and that therefore codolygine is probably active as a whole and in virtue of its peculiar chemical constitution and not by reason of any one element which it contains? Whether this toxic substance or its derivatives.
become functional in Goiter. Disease or whether some other substance deleteriously affects the normal gland making its secretion poisonous, it is difficult to say. Edwards & others do not offer convincing proof of their ability to produce the disease experimentally and chemically the colloid matter of the hypophysis in Goiter. Disease does not clear any deviation from the normal hypophysis secretion, therefore I think we must accept the theory of permitted secretion with some reserve.

Is there any correlation between the hypophysis and ovary? Is there any relation between the secretion of the hypophysis and that of the ovary or uterus?

My attention was called to this possibility by the extraordinary example of the total disappearance of the symptoms in one of my cases after child birth. This led me to the belief that the ovary
might have some influence on the metabolism of the thygroid. It is interesting to note that the above patient has had no further pregnancies although her condition as regards the disease was one of complete recovery. On the other hand, I have two cases where the symptoms came on after marriage and my male patient attributed the disease to an abnormal amount of sexual intercourse so that in any series of cases, I have one case contradicting the other. But although the present state of evidence is to the influence of the sexual organs on the thygroid. Exophthalmic goitre is conflicting, I cannot disassociate the two in my mind and my observations in all cases revert to this hypothesis. The state therefore, of our knowledge as to the causation of Graves' Disease is purely hypothetical and the conflicting
Reversals make it difficult to adhere to one in particular. This confusing state of opinion I have endeavoured to show in the perspicacity of the several theories advanced by authorities at home and abroad, but it appears to me that the determining factor is prevented secretion in the thyroid gland influenced, e.g., in some way unknown, by the testicular or ovarian secretion and that the toxine thus produced deleteriously affects the nervous system so that any exaggerated stimuli received by the brain from any particular system instead of having a temporary effect upon the nerve cells last a lasting permanent effect. So long as the toxine is present, it accounts for the many of various symptoms of the disease.
Part ii

Treatment
Some general points in treatment referable to all cases, are of very

1. **Rest**. During the whole course of the disease mental and

   physical strain should be avoided. I do not go so far as to advocate
   lying in bed but as much rest as possible in the recumbent posture.

   especially after meals is important. One should strenuously avoid

   all forms of excitement and mental strain such as excessive
   reading, attendance at public functions, undue entertaining of
   friends etc. but fresh air, as in all other appendical cases, should

   be encouraged. A system of

   graduated exercise laid down for

   the patient's use. The importance

   of *Rest* I have seen in the case

   of my male patient who would

   not for some reason consent to

   medicinal treatment. He was

   however forced to give up his work

   and I sent him on a voyage to

   the Cape where he resided during

   months. He returned home.
practically, well and all the how.

In his profession, he still avoids the necessity of over exercise
and spoon as his restoration to
health aided by the help of drugs.

2 Diet. In all cases the diet
should be simple and digestible.

The presenting of a wholly milk
and cereals diet, ought not to
be enforced as disastrous results
may ensue.

3 Local Treatment. Although
not always efficacious there should
always be tried incisions of a
mercurial (preferably Lign. Hid. Pic.)
into the omentum over the thyroide.

Galvanism and graduated
pressure, if the patient can bear
it, are also indicated. The latter
mode of treatment I am seriously
considering and am having a
cast of the thyroid made and a
suitable case made
whereby pressure can be ad-
justed.

Therapeutie Agents.

Belladonna is no doubt the
most popular first remedy. Given
in increasing doses. There is no doubt in its efficacy and two of my patients were much benefited by its use. The difficulty in giving large doses, owing to its unpleasant effects, did not permit me to give more than 40 m. per diem. This dose was taken in one case for 6 months but with no appreciable gain. In the other case, arsenic was also given but with questionable benefit.

Digitalis and other cardiac tonics have their adherents but I have had no beneficial results from the administration of Digitalis. Of Certeis (Liverpool) uses with success. Hydrofluoric acid strength 1-600 3/6 to 3/7 hence daily but the character of the acid makes the administration difficult. Similarly codie acid has been given as the Syrup of Hydrocodic Acid (prepared by Gardner of New York) the preparations of ergot and Iron need only be mentioned as therapeutic agents.
Thyroid gland substance.

Mackenzie and Warren have reported several cases treated by tablets of Thyroids, with satisfactory results.

Thyroid gland substance.

It is curious to find that in the literature of this subject, observers contra-indicate the giving of thyroid extract as being positively harmful, while on the other hand, 
\[ \text{E.g. Whitefoot}\] have given examples, with photographs, of cases which have been cured by the extract. The context has had no experience in its use, and the only explanation which appears possible as to its beneficial effect is, that if there is a peculiarity of thyroid gland secretion in the disease, the addition of a normal extract may in some way help to counteract the toxic Spleenic Extract.

In a paper by Wood in an American Journal there is discussed the treatment by Spleenic extract based upon the experience...
of one case of the disease, in which during its course there developed a suppurative splenitis, resulting in a spontaneous cure of the Graves disease. However, Wood seems to have overlooked the fact that the presence of suppurative organisms may have played a part in the cure.

Sodium Phosphato, in heroic doses, as suggested by Kocher I have found to be of questionable value in the treatment of some of my cases. I have had two cases under treatment with this salt. The first case was treated for just 5 months, starting with 60 grains a day and finishing with 240 grains per day. The patient expressed herself better during the treatment, but the general symptoms were in no way alleviated. The pulse rate was still 140, the local tumours quite as pronounced as the tremors of the same character. Still the fact remained that the feeling of nervousness disappeared.
The appetite and apparently the menstrual functions were all improved, for what reason it is impossible to conjecture. The second case also improved as far as the general symptoms were concerned, but although she took as much as 300 grains per diem the result was as far as the prominent symptoms and signs of the disease were concerned was nil. It seems therefore that although a chance case may be much improved by this treatment, for some unaccountable reason (as in the same way as Rest, Spleenic extract, &c &c. are beneficent) it cannot be looked upon as a specific cure. 

Dedgmin and ovarian substance

Following the example of theorists and from my own conclusions in the etiology of the disease I began the treatment by Ovarian substance; but although I persevered for 3 months in 3 cases, in this mode of treatment
my efforts were not encouraging. I next tried on the same patient... Diphysin. There was in the first case a marked amelioration of the symptoms, and the nystagmus decreased by 3 inches. The exophthalmos, so marked in this case, too, was undoubtedly diminished. After 3 months' treatment, the administration was stopped as the patient reported herself better. Her pulse at the beginning of treatment was somewhere about 140 and at the end 100. The tremors lessened, and there was marked improvement in the muscular system. In reality, the whole system seemed to have received, and refreshed up by the treatment. I saw her about a fortnight ago, and she was still in good health, bearing two... The second case has similarly benefited by the treatment, and the most striking characteristic of the administration is a less pronounced...
Atrophalmous. The tumour has diminished 2 cm. from 16 to 14 cm. circumference at the 12th week, and there is also a degree of increased vitality absent before the starting of the Deganin. The third patient has just started treatment.
I do not claim that Deganin is a therapeutic agent of curative power in this disease at present, but still it is interesting to observe the improvement in cases where the treatment has been employed, acting it may be by bracing up the tissues or the pouring into the blood of an antitoxic which in some way effects the metabolism of the thyroid.

**Surgical Treatment**

Although the efforts of physicians have been of great value in the amelioration of the symptoms of the disease, they fall far below the experience of the surgeons who have recorded absolute cures from surgical
interference. I think, however, the time is not yet ripe, to advise patients to resort to surgical procedures at the onset of the disease. Operation seems to be justifiable only after reasonable trial of medical treatment has been tried and failed.

There are dangers in the operation, e.g. the excitement to the patient, anaesthesia &c. It is therefore incumbent on the surgeon to choose a period of quiescence after physiological rest and to supersede general anaesthesia by occlusion of the nerve. Superficial cervical branches.

The several operations that have been advised I shall briefly mention.

1. Laboulaye's exophytopexia - dangerous on account of the susceptibility of the patient to septic infection.

2. Legation of the thyroid done first by Wölfler in ordinary goitre & by Kocher in Graves disease, the theory being that it
causes, atrophy of the gland.

3. Excision of the cervical sympathetic with the 3rd ganglion as practised by Sabouraud, Jouvene & Marianii. The operation is said to lessen the effects of hyperactivity and diminish the goitre but the positive cure is questionable.

4. Partial Thyroidectomy seems to be the favourite and most successful procedure. The following statistics which I have compiled are interesting.

Starr 190 cases mortality 12%.
Lemmerbgh 187 n. 7 0%.
Aixford 58 cases 81% cured.

Ehrhardt 230 cases.
(68% cured.
11% improved.
10% failures.
7% death,

Schulz 20 cases 18 cured.

Welmer 23 n. (18 cured.

Rimbach 18 cases 12 cured.
Kocher. 93 cases.

59 operated on

\[ \begin{array}{c}
37 \text{ cured} \\
22 \text{ less sure}
\end{array} \]

Result:

\[ \begin{array}{c}
45 \text{ or 76\% cured} \\
8 \text{ or 14.0\% definitely improved} \\
2 \text{ or 3.3\% slightly improved} \\
4 \text{ or 6.7\% died}
\end{array} \]

In the light of the above statistics, and despite the theory of physicians, the future treatment of exophthalmic goitre seems to indicate surgical interference in capable hands. One only of my patients desired surgical interference but although in the hands of a good surgeon, under local cocain anaesthesia, a fatal termination was the result.
3. French: M.D. Koch; 1915. 1896
4. Diamond's work in "A treatise of Syphilis. quoted by Kocher Bramwell."
   Also B.M. July 16. 1896. Also
   Hannover. Work in. Physiological
   Chemistry. Halliburton.
7. Quotation from Hutchins. Work
   Practitioner. Apr 1901. The inverted
   commas were inadvertently omitted
   This is the only direct quotation in the
   paper.
8. Experimental work of Edmunds. in
   Journal of Pathology. Oct 71. 1900
13. Practitioner. Nov 1896 & recently
   Koch's. Bramwell. in other journals
   Jan. 1903. (Huntingdon) & Koch 1902.
   Also reference has been made to "Albatts