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Toxic adenoma of the thyroid : pathology and physiology

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TOXIC ADENOMA OF THE THYROID

PATHOLOGY

PHYSIOLOGY

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INTRODUCTION

The thyroid gland has been observed and studied since the time of Hippocrates, with constant additions to the knowledge of anatomy, physiology and pathology. In the last few years the subject has emerged from the realm of supposition and taken the form of a series of distinct problems studied in a scientific manner.

This paper has been written, not in an attempt to further the knowledge concerning toxic adenoma by additional experimentation, but rather by the coordination of the existing facts.

CONTENTS

History of the Thyroid Gland

Knowledge of the thyroid gland begins with Hippocrates, who while mentioning the tumors of the neck, did not recognize them as thyroid growths, but describes them as a deformity of the body which may undergo changes and produce a thick, heavy material.(1) While Hippocrates made no distinction between the various tumors of the neck, but considered them all the same type of growth, it remained for Celsus, who lived in the same period, to differentiate them.

Celsus recognized the tumors of the thyroid as separate and distinct from the abcesses and gave to them the name of "Bronchocele".(1) Later Aetius, in his description of the Bronchocele, called it a fleshy tumor which arises in the throat from the cortex of the larynx. Leonicenus has a more bizarre explanation of the tumor and want so far as to claim it was caused by phlegm, the phlegm being combined with black bile, which mass caused induration by its dryness.(2)

The first man to have a faint glimmer of the cause of the condition was Arnoldus de Villanova(1230-1313), who while admitting he did not know the cause, stated

1

that diet played a primary role. Baccius(1571), believing tha cause of the disease to be the water supply rather than the diet, gave in support of his theory a description of the people of Salzburg whose source of water supply was a mountain stream and who were all "strumous".

The purpose of the thyroid gland was unknown and unthought of until the time of Eustachius, who claimed that it was for the prupose of lubrication of the larynx and the voice box.(1)

Wharton(1610-1673) was the first to describe the gland correctly and give it the title "thyroid", derived from the Greek word meaning shield.(3) From the time of Wharton to Crewelhin, who lived in 1840, very little progress was made in the anatomical studies of the gland. Crewehlin, after completing a series of dissections, found that there was no duct to the gland, which discovery led to the beginning of the investigation of the true nature of the thyroid.(2)

During the later part of the eighteenth century, attention was again turned to the function of the gland. Forestrius, in 1845, described exopthalmus but thought

2

it was due to straining at childbirth.(1) It remained
for Guiseppe Flagini in 1788 to realize that there was
a connection between exopthalmus, palpitation and
goiter.(1) Basedow, in 1799, gave a clearer account
of the condition and laid the blame to tuberculosis
rather than thyroid disease.(3) Caleb Parry, in 1815,
writing on the same condition, was the first to publish
an accurate account of the symptoms.(4) Twenty years
later Robert Graves, in a monograph on exopthalmus,
attempted to explain the disease and in doing so gave
us one of the most complete and logical accounts of
the condition that has been written.(5)

The next important step in the studies of the
thyroid gland was William Gull's observation on myxe-
dema, which was confirmed by Theodore Kocher in 1883
in his paper on the effect of the removal of the
thyroid gland, and again in 1891 by Murray who was
able to demonstrate the curative effects of glycerine
extract of sheep's thyroid when given to a patient with
myxedema.(6)

Bawman, in 1895, showed that iodine in firm, organic
combination was a constituent of normal thyroid tissue.
It remained for Kendall, in 1916, to isolate a substance

which had the same action as dessicated thyroid. This finding stimulated experimentation on the action of the hormone and resulted in the confirmation of Magnus Levy's work on the regulation of body heat by the thyroid gland.(6)

Since that time much work has been done on the mechanism by which the thyroid gland controls metabolism, but as yet little has been accomplished. However, with our present conception of the interrelations of the thyroid gland with the rest of the endocrine system, it is to be hoped that a conclusion will soon be reached.
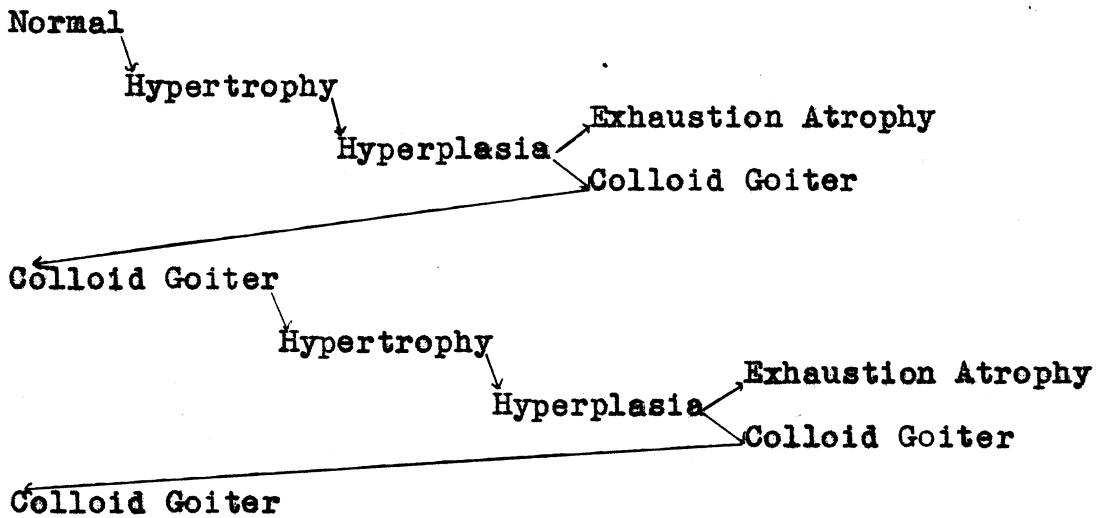
Etiology of Nodular Goiter

Wolfler, in 1880, started a controversy which has been settled only recently when he stated that nodular goiter was derived directly from fetal rests.(7) Virchow was the first man to dispute the theory of Wolfler, and he had, at the time, even less proof than Wolfler. However, his statement that fetal adenoma, or nodular goiter, was nothing more than a different stage of colloidal goiter, met with considerable ridicule and was not considered as being very probable.(8) However, in recent years with the advent of the modern laboratories, considerable work has been done on this problem with a good many theories resulting.

Goetsch, in 1920, published a paper in which he states that not only are the nodular thyroids the results of growth from fetal rests but also the diffuse adenomatosis seen in thyroids is caused by the growth of these fetal rest cells.(9) Parsons also takes the same side of the question and states in addition that the masses of colloid found in the adenomas have as their origin carciogenic tissue. In fact, he goes even as far as to say that the colloid material itself is of the nature of a true tumor.(10)

Rienhoff(11) in 1926, and Rienhoff and Lewis(12) in 1927, called attention to the fact that a great many of the nodules had the appearance of old colloidal goiter. This observation led them to postulate that that nodular goiter was caused by a process of involution following a period of local hyperplasia. In 1931, Womack and Cole further substantiated this idea by their work on dogs. Using an artificial stimulus on the thyroid gland, they found that following removal of the stimulus, involution of the hyperplastic area would occur. Or by the administration of iodine, involution would occur. And in either case, involution was followed by a replacement of the tissue by fibrous tissue, producing a nodule similar to the adenoma.(13) Graham(14) and Thomas(15) in 1928 stated that the adenoma was formed as a result of involution of hyperplastic areas in the thyroid gland, resulting from an old colloid goiter. Hinton(16) explains the formation of the nodules in much the same way as Hertzler(17), on the basis of involutional changes in the thyroid gland. He states that in most instances the nodule is due to an involution of a colloid to a normal phase, leaving areas of colloid encapsulated in the gland here and there.

6

It is more or less an accepted fact now that nodular goiter is really a result of a continuous process of alternating involution and hyperplasia. This is in reality nothing more than Marine's(18) idea of the thyroid cycle, which he published in 1931 and which may be shown as below:

Normal
  Hypertrophy
    Hyperplasia   Exhaustion Atrophy
           Colloid Goiter

Colloid Goiter
  Hypertrophy
    Hyperplasia   Exhaustion Atrophy
           Colloid Goiter

Colloid Goiter

Normal Structure of the Thyroid Gland

A cross-section of the normal gland reveals a smooth, shining surface which when minutely inspected with the naked eye, shows areas of colloid collected in small lobules separated by very scanty, thin, fibrous septa. The follicular markings and the small areas of colloid follicles vary in distinctness according to their number in proportion to the interfollicular stroma.

When the connective tissue investing the normal gland is stripped away, the gland is revealed as a complex mass of tissue which is divided and broken up into many regions of parenchyma. These larger regions are in turn made up of groups of follicles of different number, shape and size, depending on the location, shape and size of the region which the follicles compose. The form of these areas varies visibly and there appears to be a total lack of uniformity not only between those of various divisions of the gland, but also between those of various glands. These areas of the parenchyma may best be described as connecting or antecedent bars, bands, or plates of tissue.(19) The entire lobe of the thyroid is irregularly traversed by bands or systems of connective tissue which carry in them blood vessels, lymphatics and

nerves. It is in this manner that the parenchyma is divided and subdivided into many regions which as previously stated have the greatest diversity in shape and size with but one constant feature, namely, that all of these regions are connected to each other at one or more points on the structure.(20) In the normal gland, in no case is the parenchyma so completely surrounded that it is not connected at one or more points to the next lobule. As the center of the gland is reached, it is noted that the compactness and density of the structure is much greater than that closer to the periphery. This is true of all normal glands and probably represents the result of compression on the peripheral structures of the gland by adjacent structures of the neck such as the trachea, large glood vessels and other structures found in that region.(21)

The connective tissue stroma surrounding the follicles and making up the septa of the gland, are composed of a loose connective tissue which contains in its substance numerous blood vessels, nerves and lymphatic channels. The blood vessels and nerves do not vary in structure or in size from those found in any other normal gland of the body. The lymphatic chain is very complete and nearly surround the entire follicte. These channels

in all reality form rather a "sea" in which numerous columns of thyroid parenchyma are floating. The lymph channels also contain quite a number of small lymph nodules which show no hyperplastic or hypertrophic changes.(22)

The follicles of the normal gland vary a great deal im size and shape. This again depends upon their location in the gland and the size of the area which they make up. The greater majority of follicles being of a comparatively small size. A number of them contain hardly any lumen. The larger follicles which may be up to one m.m. in diameter have a lumen which contains typical colloid. As regards distribution, there appears to be no fixed location in relation to size of the follicales, but rather the large and small follicles appear to be distributed rather equally throughout the gland. The shape of the follicles depends a good deal on the size of the individual follicle. The smaller follicle tends to be more nearly spherical, although there is a variation in the degree of perfectness of the sphere, while the larger follicles appear to have a greater variety of shape, varying from perfect spheres to oblong, various hexagonal and octagonal shaped figures.

10

Some of these bizarre shapes may be explained on the
basis of cupping of the walls from slight external
pressure of the connective tissue stroma, while others
result from resting on a dome of an adjacent follicle.(19)
The outside wall of the epithelium, except for an occasional
facet or cupping is smooth, showing no outpocketing or
buddings. However, the inside of the follicle may show
outpocketing into the lumen and consequently into the
colloid material contained therein.

The cells lining the acini have been the subject
of a great deal of controversy as to the type of normal
cell making up the normal follicle. Marine believes
that the cells are of a low, cuboidal nature, any
columnar cells or other structural types being of path-
ological nature. He differentiates the cells into two
types, the chief and colloidal cells, the chief cells
predominating in the normal gland, the colloid cells
being found in the normal gland but in lesser quantities.
The chief cells are attached to a delicate vascular
connective tissue framework at their bases.(18) The
nuclei are vesicular in shape, stain well in contrast
to the cytoplasm of the cell and often show nucleoli.
The cytoplasm is faintly granular in character and

11

uniform in consistancy and density throughout the cell.
(23) There can be seen, by special staining methods,
mitochondria. They appear as minute rods and are
scattered fairly uniformly throughout the cells.(24)

The colloidal cells, according to Marine's con-
ception, are nothing more than chief cells which have
lived their normal span of life, secreted their colloid,
and are now in the process of degeneration.(21) These
cells differ from the chief cells in having an irregular
density of the cytoplasm and often show vacuoles. The
staining characteristics of the cytoplasm are also
different in that the cytoplasm of the colloid cell
generally stains pale and uneven. The nucleus is pycnotic,
stains deeply and shows very little structural different-
iation. Loeb has shown that mitotic figures found often
in pathological sections are not to be found in normal
cells.(25) Goormaghtigh and Thomas differ in their opinion
of the type of cells that are typical of normal thyroid
tissue. They believe that Marine's conception of columnar
cells in thyroid being pathologic is quite false. They
state that a series of normal thyroids found around
Ghent, Belgium, which is an area in which endemic goiter
is not found, showed four types of cells of which one

12

type was typical columnar epithelial cells.(26) They are supported in this view by Norris, who states that the columnar epithelium found in thyroid tissue is not pathognomonic of hypertrophy of the gland tissue, but rather a normal structure in a normal gland.(27) However, in view of the fact that all hyperplastic thyroids show a predominence of columnar epithelium and that columnar epithelium in the normal gland is comparatively rare, it is my opinion that the strictly normal functioning thyroid, if there is such a thyroid gland, is composed of acini made up of cuboidal epithelium.

The type and amount of colloid in the follicle also varies in the normal thyroid gland. In many sections the central portion of the follicle may contain a portion of colloid which stains deeply, while the periphery may contain a lighter staining colloid, or in other acini the central portion of the acini may be the only part that contains colloid.

Hertzler states that the degree of staining reaction depends upon the age of the colloid being stained. He states that the difference in the degree of staining reaction in the central and peripherial parts of an acini is due to the age of the colloid, that near the center

being stained deeper than that on the periphery because
of the greater age of the central colloid.(28) Murray(29)
and Boyd(30) disagree with most workers in that they
claim that all acini in normal glands are completely
filled with colloid. They state that the lack of colloid
in the acini of normal glands is due to a postmortem
change in which the colloid has undergone degeneration
and been partially absorbed. The epithelial cells,
having torn loose from their basement membrane, migrate
to the center of the acinis and form a solid mass of
cells.

Pathology of Nodular Goiter

The nodule can be palpated and is composed of
sharply localized areas of hypertrophy and hyperplasia,
while the intervening parenchyma of the gland presents
the microscopic picture of the normal thyroid. The
morbid process in most cases remains confined to certain
localized, well defined areas, rather than becomes diffuse
throughout the gland. Boyd(32) states that the site of
the adenoma may be governed by the degree of circulatory
interference that is taking place in a localized area.
He has shown that on microscopic examination the nodule
shows frequently dilation of blood vessels and lymphatics.
(32) Marine and Lenhart attribute the location to the
changes in the circulation of the glands caused by
involution and hyperplastic changes during the cycle
of thyroid disease.(33) In the gross specimen the tumors
or nodules of the thyroid are readily palpable and vary
in size from shot-like nodules to tumorfactions the size
of a man's fist. This lack of uniformity of size has
been explained by various workers in various ways. Keilty
in a paper on the inflamatory nature of toxic and non-
toxic adenomas, states that a very high percent of adenomas,
both toxic and nontoxic, are the results of inflamatory
changes. He attributes the lack of uniformity in size

15

to the different localized areas of the gland.(34)
This may be true in the nontoxic group, but it is highly
improbable that the etiology of the toxic nodules could
be on the basis of an inflamatory nature. Rienhoff and
Lewis have presented the idea that the size of the nodule
is dependant on the number of cycles of involution and
hyperplasia that the nodules have undergone.(12) This
is highly possible but in accepting such a theory, we
must find the primary cause for the location of the nodule.
Marine states that the most probable factor determining
location of the gland is the condition of the circulation
in that area, as any variation in a gland of the blood
supply to different localized areas would cause a differ-
ence in the rate of growth of the tissues in the respect-
ive areas.(21) It seems most logical that variation in
the circulatory system of the gland is the primary cause
of the difference in size.

In the gross specimen on section, the nodules form
sharply circumscribed areas with fibrous incapsulation.
These tumors appear to be composed of parenchymatous
tissue and toward the center contain small cysts and
areas of connective tissue.

Microscopically, the nodules are composed of thyroid

parenchyma in a state of hypertrophy and hyperplasia.
In thebmajority of nodules the acini are of three
structual types:(a)the cells appear as diffuse masses
without the formation of acini,(b)as small acini with
very small lumens containing very little colloid,(c)as
large acini with larger lumens and containing small
amounts of colloid material. The largeracini generally
show the characteristic pappillary infoldings which
give the acini its odd shape.(35) There are a number
of factors which play a part in the type of acini seen
in the nodules. Gale Wilson in a description of the
pathology of nodular goiter, states "small buds can be
seen on many of the acini, but no constriction indicative
of follicular division can be seen". His interpretation
of the buds is by two processes:(a)the infolding of the
distended follicle causes a fusion of the walls of the
follicle so that normally where there was one acinus,
we now have tow or three,(b)he states that the formation
might be due to fusion of a large and small follicle.(36)
Body states that while a great deal of the bizarre shapes
and sizes are due to the foldings of the collapsed foll-
icles, a greater number are the results of budding from
the follicle itself. He has demonstrated this in a

17

number of cases by the use of serial sections in which
he was able to follow through a bud from its point of
union with the original follicle to its dome-shaped
mass of cells.(32) This, incidentally, may account
for the masses of cells without a lumen mentioned by
Goetsch.(37) Collier attributes the difference in
size and shape to the age of the nodule and its
relative position in the cycle of hyperplasia and
involution, stating that the small follicles with
small lumens probably belong to the comparatively new
formed adenomas still in a stage of hyperplasia, while
the older colloidal nodules or nodules in the àtage of
involution show larger acini with larger lumens.(38)

The epithelium lining these acini shows the char-
acteristic histologic changes associated with an increased
functional activity of cells. Marine states that the
process of hyperplasia and hypertrophy is initiated by
an enlargement of the normal cells, which are normally
cuboidol in shape to a columnar type of cell.(39) Later
the process of hypertrophy begins to take place with
the large increase in the numbers of cèlls as can be
seen by the increase in mitotic figures seen on special
examination of the parenchymal tissue. Loeb in 1919

18

showed by his work on the thyroid glands of guinea pigs
that coincident with hypertrophy of the thyroid gland
of the guinea pig a great number of mitosis occurred.
The size of the cells was likewise altered from low
cuboidal to markedly high columnar cells in the hyper-
active glands.(25)

Goetsch in a cytological study of a series of
adenomas of the thyroid, both toxic and nontoxic,
found that there was a distinct difference in the
number of mitochondria present in the cells of toxic
adenoma as contrasted to the number present in normal
gland tissue. While the mitochondria were morphological-
ly the same as those found in normal thyroid cells,
there was a striking abundance of the mitochondria every-
where in the parenchymal cells of the toxic adenoma. He
further states that this is true of all of the cells of
the parenchyma of the nodule whether of the columnar or
cuboidal type. The cells also vary markedly in size and
shape and have a larger nuclei showing nucleoli and
which are richer in chromatin than the normal cell's
nuclei. As a control for this experiment, sections of
normal thyroid gland were fixed and stained by the same
method, and the number of mitochondria seen in the cells

19

was very definitely smaller. This was also found to be true in non-toxic nodular goiters.(24) Key, in 1925, substantiated this work and made some additions to the knowledge of cell structure found in toxic adenomas. He found on careful study of the parenchymal cells of toxic adenomas that they contained minute, clear vesicles in the cytoplasm of a definite shape and located in the apical zone of the cell, the cells showing active hyperplasia having the greatest increase in number. These vesicles he termed the chromophobe antecedent, or the precursers of the colloid normally formed by the normal cells.(23)

In certain areas of the parenchymal tissue there can be seen areas of cellular degenerative. These are most commonly found in the walls of the acini of large size and which are completely filled with colloid. The cells show vacuoles not unlike those of the chromophobe antecedent type, but differing in that they are irregular, generally contain debris, and are not localized to any one area. The cytoplasm is fuchsinophilic in staining qualities, the mitochondria are fragmented, and the nucleus is generally pycnotic in shape.

The amount and properties of the colloid present
in the toxic adenomas has long been the subject of much
speculation. Marine states that hypertrophy is char-
acterized by a definite decrease in the stainable
colloid of the acini.(21) This is further substantiated
by Means, who states that one of the primary character-
istics of a toxic nodular goiter is the lack of stain-
able colloid.(40) Jackson adds support to this view in
his work on the pathology of the toxic nodular goiter in
which he has paid special attention to the size of the
acini and their contents. His findings showed that in
the toxic nodular goiter, 70.1 per cent of the acini were
smaller than those of the normal gland, the measurements
of the normal acini being two to three times as large.(41)

The character of the colloid is also markedly
changed in toxic adenoma. Hertzler(42) and Wilson(43)
describe the characteristic colloid of toxic nodular
thyroid as staining with heamatoxylin rather than with
eosin in the first stage of toxicity. As the process
proceeds, the changes become more noticeable in the
irregularity in the density of the stain, and lighter
staining qualities of the colloid and finally the
presence of vacuoles in the colloid. The significance

of these changes in the properties of the colloid is not definitely known, but Hertzler claims that the first toxicity of the toxic nodular goiter is due to degeneration of the colloid, which in turn sets up the process of cellular degeneration in the acini and parenchymal cells of the nodule. He fails to explain the presence of the large number of mitosis and the change of the cuboidol to the columnar type of cells.(40) This might be explained as a reaction of the tissue to repair the areas damaged by the toxic substance, if there is such a toxin. Further evidence in favor of this view is that the nodules often show areas of glandular tissue composed of columnar cells with increased mitochondria and areas of degenerating acini made up of the typical degenerating cells.

As contrasted with non-toxic nodular goiters, the colloid has poor staining qualities, is vacuolated and is spread unevenly throughout the acini; while in the non-toxic type of nodule the colloid is uniform throughout the acini and stains with the same intensity as the colloid of the normal glandular tissue.

Williamson and Pearse, in 1923, found the lymphatic

spaces of the nodule to have been decreased very markedly partly as a result of the vast increase in number of acini in the toxic gland, but mainly because of the increase in connective tissue stroma and enlargement of small blood vessels adjoining the lymph sinuses as the involution process starts in certain areas of the nodules.(22) Wilson found on examination of a number of specimens that the lymphatic spaces often contained colloid. He attributed this to a rupture of the follicle walls with subsequent release of the colloid rather than an actual physiological process.(36)

A characteristic of the nodule is its definite encapsulation by fibrous connective tissue. Upon careful microscopic examination of the capsule, it appears to be the result of a hypertrophy of the connective tissue trabeculae covering the normal thyroid follicles. Plummer, in a recent paper, thought the increased connective tissue surrounding the nodules may be due in part to an inflamatory process resulting in the characteristic laying down of connective tissue in replacement of the damaged tissues.(44) Broders and Plummer(45) in a later paper on acute capsulitis of partially degenerated thyroid adenoma, show that quite a few of the

23

greatly enlarged adenomas have a thick fibrous capsule surrounding them and on careful correlation of laboratory and clinical finding, they arrived at the conclusion that an acute infection of the preexisting adenomas was the cause of the greatly thickened capsule. These observations, while being true in certain cases, do not apply to the majority, as they show no evidence of acute infection of the nodule or its capsule. Graham(14), Parsons(10), Hertzler(42) and Marine(30) believe that the capsule is the result of the compression on the surrounding tissue with resulting atrophy of the surrounding parenchyma which will be replaced by the connective tissue that normally replaces atrophic glandular structures of the body. In view of the fact that as the nodule enlarges, it causes a good deal of pressure to be placed on the surrounding tissue with resulting loss, or partial loss, of blood supply and finally atrophic changes in the immediate zone of compression with connective tissue replacement of the atrophic tissues, it would seem logical that the capsule was formed by compression in a majority of cases.

Rienhoff and Lewis give further proof for the origin of the capsule.by pressure, by the finding of

small acini within the stroma of the capsule. These areas
of acini, while being made up of almost perfect epithelium
and perfect structure, are nevertheless very much smaller
than those found in normal thyroid tissue. It is the
idea of Rienhoff and Lewis that the compression of the
surrounding tissue caused the lack of development.(12)
Hertzler takes a different view on the matter in his
article on the fetal adenoma in which he says that the
intrastromar acini are a normal occurrence in the stroma
of a normal thyroid gland and should not be considered
pathological changes.(28)

The factor of compression, however, does play an
important part in the production of degenerative changes
in the center of the adenoma, such as cystic areas,
areas of old hemorhage and hyaline degeneration. Marine
and Lenhart attribute degenerative changes of the adenoma
to hyaline degeneration of the blood vessels and of the
lymph channels which they claim is a normal process in
senile atrophy of tissues. In a series of cases studied
microscopically, they found that the majority of degener-
ative changes appreared in nodules of long standing dur-
ation, while those that were of comparatively recent
origin showed few of the degenerative changes.(33)

25

Plummer believes that the areas of hemorhage into cysts
are caused by a secondary infection of the nodules in a
number of cases, but does not commit himself by limiting
the etiologic factors to this one cause.(45) Hertzler
states in his recent treatise on thyroid pathology that
the causes of degeneration are probably caused by a com-
bination of the compression and the senile atrophy
factors.(42) Boyd attributes the degenerative changes
to changes in the circulation of the adenoma, but heglects
to explain the cause for the circulatory changes. He
states, "A striking feature of the tissue is the presence
of large, thin-walled blood vessels, and it is evidently
these which are responsible for the frequent hemorhages."
(32) The genesis of the degenerative process is as yet
quite obscure, but the presence of greatly dilated vessels
some undoubtedly blood vessels and others lymphatics,
suggest that local interference plays a part.

The microscopic picture of the degenerative changes
seen consists of rarefaction of the tissue, the stroma
being replaced by a thin, structureless, clear-staining
material which resembles to a certain extent the colloid
in normal acini. The acini are evidently separated from
each other and show various degrees of disintegration,

26

from acini with no lumen to a few disintegrating cells
scattered throughout the hyaline matrix. As the center
of the nodule is reached, we find areas which are cyst-
like in character and contain varying amounts and types
of material. Some show the characteristics of an old
hemorhage into the cyst. Plummer claims that the
majority of these hemorhages are due to other patho-
logical process aroused by acute infection rather than
any other cause.(45) But looking at the problem from
a different viewpoint, it seems logical that the effects
of pressure play an important part for the following
reasons:(1) The areas of degeneration are nearly always
found within the center of the nodule where the pressure
is the greatest. (2) The thin walls and dilated lumens
of the blood vessels and the relatively few vessels
found in that location point to interference with the
circulation due to pressure with a resulting atrophy
of the tissues.

The occurrence of the cyst-like areas has been
explained by pointing out that in various old adenomas
of the thyroid, there have been found acini of very
large lumens which have been depleted, or contain very
little of their colloid. It is thought that these acini

27

when in the center of the degenerative process, do not
in all cases collapse, but due to the firmness of the
surrounding hyaline matrix, retain to a certain extent
their original shape. As a result, when the pressure
increases due to a supervening infection or whatever
the cause may be, blood vessels rupture into the lumen
of the cyst resulting in the cysts that contain hem-
orhagic areas.

The above mentioned areas of degeneration, if
looked at from the viewpoint of the physiologist, would
be called areas of involution of the gland rather than
degeneration, as they are thought by many to represent
the involutional changes resulting from the gland
adopting itself to the abnormal condition of secretion
and nearing its normal functional level again with a
consequent atrophy of the excessive hyperplastic and
hypertrophic areas within the glandular tissues. This
is further substantiated by the character of the
epithelial cells which in the majority of cases show
signs of degenerative changes as pycnotic nuclei, large
vacuoles and a tendency of the cells to pull loose from
the basement membrane.

Rienhoff and Lewis(12) have found on examining a
number of specimens of known age that the proportion

of hyperplastic and hypertrophic tissue to that showing
involutional changes is roughly proportional to the age
of the nodule and the number of exacerbations and re-
missions it has undergone. They found that as a general
rule, the older the patient the greater would be the
amount of involutional changes found. So that in a
number of young patients the nodules did not show as
great an amount of degenerative changes as did that of
the older ones.

Physiology of the Thyroid Gland

The function of the thyroid gland is to act as a pacemaker of metabolism. This function is performed by means of the secretory products of the gland. Kendall in 1914, isolated from the thyroid a crystalline substance which contained from 60 to 65 per cent of iodine. This substance he called thyroxin.(47) Kendall was unable at the time of his first work to determine the formula of the substance and it remained for Harrington to show that the compound possessed the formula of $C_{15} H_{11} O_4 NI_4$.(48) Kendall in his later work on the action of the substance came to the conclusion that it is the only physiologically active substance made in the thyroid gland. In contrast to Kendall's theory, Sloan believes that the action of the gland depends on the presence of more factors than thyroxine alone.(49)

The mechanism by which the colloid is formed is still under dispute, there being two theories as to its origin, the merocrine and the holocrine. The merocrine type of secretion consists of evacuation of the contents of the cell into the follicle while the cell is not destroyed but regenerates and resumes its function.

30

The holocrine in contrast to the merocrine theory, states that the cell ruptures and its whole structure is used in the production of the colloidal material.

The discharge of the hormone of the thyroid into the blood and lymph streams is caused by a deficiency stimulation rather than an actual nervous stimulation. This has been shown by virtue of the fact that transplants of thyroid tissue devoid of any nervous connection, function efficiently and produce a normal product. We may state then, that the secretion is a result of a deficiency of thyroxine in the blood and tissue in large enough quantities to promote normal metabolism.

The primary function of the thyroid gland that has been found up to the present date, is that of regulation of body metabolism. This was first demonstrated by Magnus Levy in 1895 using the newly developed calorimeter by which method he was able to show the heat production to be lowered as much as 40 per cent.(6) Murray in 1891, added another bit of confirming evidence when he treated a case of Gull's disease with glycerin extract of fresh thyroid and was able to maintain the patient in perfect health for twenty-eight years.(51) Later experimentors and clinicians have found confirming

evidence in their treatments of myxedema and hyper-
thyroidism.

Formerly, it was believed that the thyroid gland had
the power of neutralizing poisons resulting from met-
abolic processes. But the present conception of the site
of action of thyroxine has tended to discredit the de-
toxification theory which has very little scientific
proof for its defense.

Another function assigned to the thyroid is that of
an antibody formation. This problem has been rather
thoroughly studied and while the results are somewhat
contradictory, they do not tend to show any direct
association of the thyroid with antibody formation.(51)

Thyroid Pituitary Relationship

It has long been known to students of goiter that
animals and individuals with large parenchymatous goiters
have greatly enlarged anterior pituitaries. Smith
showed by means of removing the pituitary in tadpoles
without injuring the adjacent brain structures that the
anterior pituitary was a master gland and that it con-
trolled the functional state of many organs, thyroids,

32

adrenals, gonads and others.(52)

The pituitary hypertrophy after thyroidectomy,
is much greater the younger the animal used. Histo-
logically, the elements of the anterior pituitary
becomes hypertrophic but the most striking single
change is the disappearance of the eosinophil granules.
Smith first noted in tadpoles that hyposectomy caused a
marked involution of the thyroid; the injection of fresh
anterior pituitary substance restoring such atrophic
thyroids to normal and even producing hypertrophy in
these glands.(52) It has recently been shown that
fresh emulsions of the anterior pituitary gland when
given to normal young animals causes a marked hyper-
plasia and hypertrophy of the thyroid. There is also
a rapid loss of the iodine store in the gland, an increase
in blood iodine, in the metabolic rate, and in the ex-
cretion of the calcium and creatine and exopthalmus
develops.

It was early observed by many workers that the
daily administration of the thyrotropic factors to rats
and guinea pigs or rabbits brought about, in from thirty
to forty days, a resistance to thyroid stimulating factor
and the thyroid slowly regressed to its quiescent or

colloid state again. Collip and Anderson have shown
that the serum of such recovered animals, while not
preventing thyroid hyperplasia following injection of
the thyrotropic factor, did prevent the characteristic
increase in metabolism, calcium, excretion and the
like.(53)

Thyroid Gonads

The fact that during menstruation and pregnancy
the thyroid frequently enlarges and that the incidence
of goiters in pregnancy, puberty, and the menopause is
increased, has led physiologists to recognize for
centuries that there is a very close relationship
between the thyroid and the gonads. It appears that
effects of the thyroid on the gonads and vice versa
could be explained as effects mediated through the
anterior pituitary. There is abundant evidence to
show that the response of the pituitary to thyroidectomy
is not limited to stimulating an increased production
of the thyrotropic hormone, but that there is an in-
crease in the growth hormone and its gonadatropic factor
as well. A depression of the thyrotropic factor by the
administration of thyroxine probably depresses the
gonadatropic factor. In rabbits that have been thyro-
dectonixed at four or five months of age, there is

noticed at the time of puberty a frequent increase in sexual activity. So also injecting large doses of estrogenic substance appears to decrease the amount of the gonadotropic factor produced by the pituitary as well as depressing the thyroid glands. These effects are understandable if one assumes that the same pituitary cell produces more than one hormonic factor. There is evidence that the eosinophilic cells may be responsible for the production of thyrotropic and growth-promoting factors.(6)

Thyroid Pancreas Relationship

Burns and Marks(54) and Bodansky(55) found that dogs were less sensitive to the hyperglycemic action of epinephrine than normal animals. Bodansky reported that thyroidectomized sheep were more sensitive to insulin than normal animals. Conversely, it has been shown that feeding thyroid or thyroxine to thyroid-ectomized rabbits decreases the hypoglycemic action of insulin. Bodansky believes that the thyroid hormone promotes glycogenolysis and that it is because of this action that the hypoglycemic action of insulin is increased after thyroidecomy and decreased by thyroid feeding. This may be partially explainable on the basis

35

of the thyroid sensitizing the sympathetic nervous
system to action of epiniphrin.

Thyroid Chromaffin Relationship

In 1911, it was shown that if a dose of epiniphrin
was given and the thyroid nerves stimulated simultaneously
the rise in blood pressure is much greater than that
found after the injection of epiniphrin alone. Blau
and McNamara had the same effect after using thyroxine
in conjunction with epiniphrin.(56) These observations
point to the conclusion that the thyroid hormone increases
the irritability of the sympathetic nervous system or
sensitizes in some way the tissues inervated by it so
that they are more sensitive to stimulation by epin-
iphrin.

On the other hand, it has been shown that injection
of one to three mg. of thyroxine in dogs caused a grad-
ual hyperglycemia in the course of three to six hours
and that this did not occur when the adrenal veins were
ligated prior to the injection of thyroid. These would
suggest a direct stimulation of the chromaffin system.

Physiology of Symptoms

Size and shape of tumor----The gland is alsays
enlarged and usually nodose and asymetrical. The nodules
being usually large and irregular shape altho it may
be quite small. The nodule lacks any regular shape;
that is, it may grow to a large size and be regular in
shape. The mass is firm to the palpating finger in
contrast to the gland seen in Basedow's disease which
is usually soft to the touch early in the disease and
finally has fibrous feeling in the later stages. The
nodule lacks any suggestion of pulsation which is very
often felt in Basedow's disease, due to the greatly
increased vasculatority of the gland seen in that con-
dition. The same holds for the phenomena of compress-
ibility which is seen in Basedow's disease and is again
due to the increased vascularity of the gland and results
in the ability of the examiner to compress the diseased
gland to about one third of its size. There is another
characteristic of the nodule in a toxic nodular goiter
and that is its insidious growth. In many cases in
which the nodule is small, the complaint of the patient
is not of a nodule in the gland but rather of palpitation
or of gastro intestinal symptoms. In fact many of these

37

cases have been treated for years as a primary cardio-vascular problem rather than an endocrine disturbance.

Cardiovascular Symptoms

The cardiovascular symptoms of nodular goiter may be outlined as follows:

1. Tachycardia
    a. Palpitation
    b. Dyspnea
2. Auricular fibrillation
3. Congestive heart failure
4. Heart block
5. Hypertension
6. Angina pectoris

The cardiac changes found in hyperthyroidism have been shown to be purely functional and without any permanent pathology in cases that recieve proper treatment. As soon as the undulying hyperthyroid condition is removed, the heart loses its irregularities and comes back to normal in a vast majority of cases. It is only in the cases that are allowed to stand for years that the condition shows lesions of the cardiac musculature.

Tachycardia is usually the first cardiac symptom
to appear and in great many cases is the complaint
that brings the patient to the physician. The tachy-
cardia differs from that in Grave's disease in that it
is usually mild, the pulse rate varying from 90 to 110
in early cases, the only discomforts being attacks of
palpitation, dyspnea and dizziness. In later stages of
the disease the pulse rate may go up to as high as 120
or 135, but is seldom any higher.

As the disease progresses, the attacks become more
frequent and in a majority of cases if the condition is
allowed to go unchecked, arrythmia develops. The common-
est of the arrythmias is auricular fibrillation. Follow-
ing close in the footsteps of auricular fibrillation is
congestive heart failure. Hypertension is also found in
a good many late cases of toxic nodular thyroid. The
question of whether heart block and angina are not the
results of some previous heart pathology rather than
primary with the toxic nodular goiter is still open to
debate. In fact, the question of whether or not all
of the cardiac symptoms of toxic nodular goiter cannot
be explained on the basis of previous cardiac lesions
is still being debated. Foss, in a recent article on

the heart in toxic goiter, states that the majority of
thyrocardiacs are individuals who previous to the onset
of the thyroid disturbance suffered from organic heart
disease.(57) Taking the other side of the question are
Rankin and Grimp, who state that in analyzing 1,045 cases
of auricular fibrillation they found the causative factor
to be hyperthyroidism in 32 per cent of all cases. They
quote also the figures of Willis and Pemberton who make
the statement that 25 per cent of all cases of hyper-
thyroidism fibrillate, with persistance in 10 per cent
of the cases.(58) Hurxthall claims that auricular
fibrillation can be the result of hyperthyroidism in
patients with hyperthyroidism. In his article on hyper-
thyroidism and heart disease, he makes the following
statement, "It is true that auricular fibrillation
occurs more frequently in people with coincident heart
disease and hyperthyroidism. Nevertheless, its cessation
in over 50 per cent of the cases after operation without
any other medication to bring about normal rhythm is
indicative of cause and effect." He goes even further
in his paper when he states that 80 per cent of cases
with hyperthyroidism and congestive heart failure are
caused by the hyperthyroid condition.(59)

In the case of heart block there is a great deal
of question as to whether the hyperthyroid condition
is primary. Stawer in commenting on the frequency of
heart block stated that in his opinion the condition was
very rare.(60) Davis and Smith have recorded six cases
of heart block in hyperthyroidism, but in all cases the
condition followed a severe infection. In a careful
study of the literature they were able to find only
four cases of heart block associated with hyperthyroidism
and all of the four were suffering from severe infection
at the time of appearance of the symptoms.(61)

Angina pectoris, likewise, has been much discussed
as to whether it is the result of hyperthyroidism or a
combination of effects due to previous heart pathology
and hyperthyroidism. Shambaugh was able to produce
angina pectoris in dogs by occuluding the coronary
arteries. He went further into the study and found
that if the coronaries were partially occuluded without
the production of angina attacks, the attacks could
be brought on by adrenalin injections. Levine and
associates have shown that in a series of cases with
angina, an increased sensitivity to adrenalin existed
as they could by small injection of adrenalin, precipitate

attacks of angina. The question is still far from
settled, however.(63)

The exact mechanism by which the cardiac symptoms
are caused is not clearly known, altho there are a
number of theories on the question. Hurxthall in a
discussion of the problem, states that there are a
number of factors which might cause increased heart
action: 1. The demands for increased circulation in the
body as the result of the increased metabolism. 2. The
peripheral dilatation of blood vessels demands a greater
blood supply. 3. The direct effect of the thyroid se-
cretion on the heart muscle. 4. The possibility that
nervous control may be affected.(59) All of these
theories have been at least in part, ruled out by other
experimentors. Yates has shown that the action of thyro-
xin continues after removal of the bundle of His and
after complete denervation of the heart.(64) This has
been substantiated by the work of Markowitz and Yates
who showed that the heart of a chick embryo, grown in
culture, which was completely devoid of any nervous
elements, reacted to the thyroxine by an increase in
rate.(65) These experiments do not exclude the factors
of Hurxthall entirely but show very conclusively that

42

the phenomena is not dependent on any one of them alone.
MacDonald has shown some very interesting results from
his work on the action of thyroxinized hearts. He showed
that if epiniphrin was injected into a heart previously
perfused with thyroxine, the increase in the number of
beats perminute was greater than in hearts not perfused
with thyroxine previous to the injection of epiniphrin.(66)

In conclusion, it must be said that exact mechanism of
increased action with resulting functional disturbances
is far from solved at the present date.

The Basal Metabolic Rate

As a general rule, the basal metabolic rate in
toxic adenoma is considerably less than it is in Grave's
disease. The patient may be very ill with marked symp-
toms of thyrotoxemia and severe cardiovascular disturb-
ances and still show only a slight rise in the local
metabolic rate. A further study of toxic adenoma will
show that a rise in the basal metabolic rate is not always
associated with the same severity of symptoms that a
similar rise in Basedow's disease would imply.

In examining the basal metabolic rates of a series
of cases with toxic adenoma, it is interesting to note
that there is a striking lack of uniformity in the
curves of the basal metabolic rates. The basal metabolic
rate may also vary a good deal in the same case. It may
be low and the patient show beginning symptoms of thyro-
toxemia while in the later cases there may be a marked
increase of the metabolic rate with no increase of the
toxic symptoms.

The course of the disease varies with the individual
cases. In some severe cases the basal metabolic rate may
be as high as plus 50 throughout the course of the disease.
While in others the disease may be present for years with
no notable increase in the basal metabolic rate.

The exact nature of the mechanism or mechanisms causing the increase in the basal metabolic rate are as yet not known. During the last fifteen years numerous invertigators have worked on the problem with as yet no definite solution. One of the earliest theories was to the effect that thyroxine acted on the central nervous system which through increased stimulation caused the rise in basal metabolic rate. This theory has not held up as is shown by the work of Reine and Wolf, who by using guinea pigs which had the nerves to and from the heart severed, found that the thyroxine, when injected intravenously, exerted precisely the same effect as on muscle with an intact nerve supply. This work has received confirmation by a number of other experimentors. Lewis and McEachern showed that when thyroxine was administered to an intact animal by mouth and a piece of tissue removed and placed in physiological conditions that piece of tissue as long as it survived would continue to show the phenomena characteristic of the hyperthyroid animal. This work was done by feeding animals thyroxine by mouth and later removing their hearts and placing them in a normal saline bath. The hearts continued to beat throughout

45

the remainder of their life at a much greater rate than those of the normal animals used as a control.(67) The result of these experiments and those of Reine and Wolfe indicate clearly that the action of thyroxine is not limited to the central nervous system, alone. Davis and DeCorta went deeper into the problem when they were able to show that thyroxine perfused through a heart removed from the body of an animal had the same effect as thyroxine given by mouth. They also found that thyroxine had no effect on macerated tissue.(68)

Numerous investigators have noticed that the carbohydrate metabolism of muscle in hyperthyroidism has been profoundly affected. It has been shown that the glycogen stores have been depleted under conditions which normally led to production of glycogen. Also that lactic acid accumulates in the blood in greater concentration than normally. This had led investigators to postulate that the increased metabolism is due to a consequent greater demand for oxygen to bring about oxidation of the increased amounts of lactic acid. The fact that the muscles of the hyperthyroid animal do utilize more oxygen has been proven by MacDonald.(66) The rest of

46

the theory has been disproven by the work of Andrus and McEachern who showed that by administering thyroxine to tissues and then stopping the carbohydrate metabolism by the use of sodium fluoride, that the increased metabolic rate stilllwas maintained while the carbohydrate metabolism was not completed.(69) McEachern in a later experiment has shown that while augmented oxygen utilization persists in the tissue of the hyperthyroid animal after its isolation from the body, a commersurate increase of carbohydrate metabolism cannot be demonstrated in tissue other than the kidney.(70) So it must be said that the increased basal metabolic rate is not due to an increased carbohydrate metabolism.

Langley stated in 1915, that the increased basal metabolic rate was due to increased muscular tonus, muscular fibrillation and muscular activity.(71) This has not held up as it has been shown that upon anesthetizing an animal in order that he may be free from increased muscular activity and then injecting it with thyroid extract the basal metabolic rate rises to quite a marked degree while the musculature of the animal was quite relaxed through the entire process.

Recently there has been much written about the re-

lationship of the adrenals to the increased basal metabolic rate in hyperthyroidism. Andrus and McEachern in experiments on guinea pigs showed that after removal of the adrenal glands of the animal the high basal rate still could be obtained on the injection of thyroxine.(72)

Andrus and McEachern as a result of a series of experiments completed in 1937 claim that certain respiratory enzymes found in tissues are increased in amount and potency in hyperthyroidism and may be in part responsible for the rise in basal metabolic rate in the condition.(72) No one has as yet repeated or reduplicated the results. It would appear from the work of the numerous investigators that the action of the thyroid gland in causing an increased basal metabolic rate is far from a simple reaction but rather calls into play a number of factors. The only theory which thus far holds good, and it is not entirely complete as yet, is that stating that the thyroxine acts directly on the individual cells, perhaps by means of increased respiratory enzymes, altho this has not been confirmed as yet.

Gastro Intestinal Manifestation

One of the commonest gastro intestinal symptoms of

48

hyperthyroidism is constipation. This frequently takes
the form of a severely obstinate constipation which
ordinary theraputic methods fail to cure. As in the
previous symptoms a great many theories as to its cause
have been presented.

If we take the theory of increased sensitivity of
the musculature of the gastro intestinal tract to
adrenalin as put forth by Mohl(73), the explanation is
fairly simple. Accepting the statement that there is
an increased sensitivity to adrenalin in cases of hyper-
thyroidism we find that the rest of the theory is in
accord with modern concepts of gastro intestinal physio-
logy. The sympathetic nerves to the gastro intestinal
tract causing an inhibiting effect on the musculature
of the gastro intestinal tract, thereby producing a
spasticity of the gut and lack of perstalsis that delays
the emptying time of both the stomach and the intestine.
But at the present time the question as to whether or not
adrenalin acts more effectively in the presence of an
excess of thyroxine has not been settled. Goetsch and
his associates in some recent experiments have shown that
the typical picture of hyperthyroidism can be produced by
the injection of epiniphrin into an animal with a mild

degree of hyperthyroidism. Contrary to the opinion of
Goesch is the recent work of White who has devised a
new method for the quantatative determination of
adrenalin in the blood. His results so far have shown
no increase in adrenalin in the blood of hyperthyroid
patients.(74) W.Timme gives as an explanation of the
gastro intestinal symptoms on the basis of correspond-
ing involvement of the parathyroids in any case of
hyperthyroidism. He states not only in the parathyroids
involved but also the adrenals and anterior pituitary
gland, The exact mechanism depends upon a deficient
parathyroid activity which in time produces an upset
in calcium metabolism and results in spasticity of the
gastro intestinal tract. He further postulates that
in cases of diarrhea in hyperthyroidism the mechanism
is due to a vagotonia which produces effects opposite
from that of the sympathetic system and a consequent
hypermobility.(75) Whether or not this holds is hard
to say as there has been very little work to show one
way or the other. Smithies in a discussion of the mech-
anism of gastro intestinal symptoms in hyperthyroidism
states that there is a definite relationship between
thyroid,adrenals and pancreas. He explains further by

stating that when the supranel gland is speeded up
there follows an acute suprarenalism.(77) According to
Edmonds there is a depression of the pancreas as the
result of the hypo-functioning pancreas. The explana-
tion is not entirely clear by virtue of the fact that
the acute or very sudden rise in adrenal secretion
would tend to promoté a very marked degree of intestinal
spasticity which would be difficult to overcome by the
hypo-pancreatism. However, the fact that diarrhea is
a fairly common gastro intestinal symptom of hyper-
thyroidism has been shown by Scorf who found that in a
series of eighty cases of hyperthyroidism, twenty per
cent had hypermotility of the gastro intestinal system
as shown by the X-ray of the gastro intestinal system
using the Barium meal technique. It may be stated here
that Scorf believes that part of the weight loss occasion-
ally seen in hyperthyroidism may be explained on the basis
of hypermotility of the gastro intestinal tract and a
consequent poor absorption of food substances.(78)

Nervous and Mental Symptoms

The mental symptoms found in toxic nodular goiter
are on the whole somewhat milder than those found in

51

Grave's disease. The mental conditions as seen in toxic
nodular goiter comprise a vast number of conditions.
Katzenblogen and Lutton state that there is no specific
type of psychosis associated with hyperthyroidism. They
have found in cases that they have treated that the
psychosis found most commonly are as listed below:
schizophrenia, anxiety states, presenile psychosis, toxic
delerium, agitated depression, senile depression, recurrent
depression, mania, paranoid reaction, psychonerosis and
epilipsy. From their study of the problem they make two
conclusions: (a) Hyperthyroidism does not coincide specif-
ically with any one type of psychosis. (b) That the content
of psychosis associated with hyperthyroidism does not
differ essentially form similar types without hyper-
thyroidism.(79)

The question as to whether hyperthyroidism is the
primary causative agent in the mental conditions seen
frequently with hyperthyroidism or wether the hyper-
thyroidism is the result of the mental disturbance has
been the subject of a large amount of contraversy.
Kaiser has found that frequently persons with an
autonomic umbalance show an emotional tension and pre-
sent the clinical symptoms of thyrotoxicosis. These

52

individuals show tachycardia, weight loss, palpitation
and even raised basal metabolic rate. However, the
thyroid is normal.(80) Stoddard has shown that the
physical signs of hyperthyroidism with the exception
of exopthalamus are identical with the symptoms mani-
fested by normal persons expressing fear.(81) Pottinger
states that emotional and psychic stimuli influence
cellular activity the same as cellular action and claims
that the hyperthyroidism can be caused by an automonic
upset.(82) Ginsburg's beliefs may be expressed in the
following excerpt from an article on thyrotoxicosis stim-
ulating primary neurosis: "A depressive phychosis may
develop in the course of a thyrotoxicosis, not as a mere
casual phenomena but definitely dependent upon the toxic
products. The condition has cleared up and failed to
recur when the thyrotoxic condition was cured."(83)
Woodbury, however takes a different viewpoint on the
question and claims that it is impossible to assign
to the thyroid any basic causative role in psychosis.
It may, however, aggravate a preexisting phychosis or it
may precipitate a psychosis in a susceptible individual.
(84) Dunlap and Moerch in a study of fifty cases of
mental disease and hyperthyroidism suggest that there is

no connection between the two, other than a coincident one. Their figures based on 1,700 cases out of which fifty were suffering from hyperthyroidism show that there is very little relationship between the two.(85)

Crile has repeatedly emphasized the fact that there is a very improtant relationship between the thyroid adrenal and autonomic nervous system.(86) However, with our present knowledge of the condition, it is impossible to make a definite statement as to whether the hyperthyroidism is the etiological agent or the result of a psychic disturbance.

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