A CONTRIBUTION TO OUR KNOWLEDGE OF THE HYPOPHYSIS AND EPİPHYSIS CEREBRI.

BY

JOHN MACDONALD BROWN.

M. B. C. M.
Theses Prize Competition

Thesis by J. Macdonald Brown

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"A contribution to our knowledge of the Hypophysis and Epiphysis Cerebri."

Thesis for the degree of Doctor of Medicine by

John Macdonald Brown
M.B. C.M.
(Fellow of the Royal Colleges of Surgeons of England and Edinburgh)

"Oh, world of ours, are you so grey
And weary, world, of spinning,
That you repeat the tales today
You told at the beginning?"

(Austin Dobson)
This Thesis, which represents the work of nearly two years, I respectfully offer to my "Alma Mater".

John Macdonald Brown

5 Lymington Road
West Hampstead
London, N.W.

26th April 1900.
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"Introduction".
Introduction.

The subject of vertebral structures is one always of supreme interest. In their study, wide almost limitless fields of thought and speculation become opened up. The anatomist has often to invoke the assistance of comparative anatomy, embryology, physiology, and sometimes even of palaeontology, in his endeavours to ascertain their true teleology, and even after he has endeavoured to probe their meanings with all the resources that modern science can bring to his aid the results of his labours are not always final and convincing, and there is often a wide margin left for speculative thought.

In older days, when man was regarded as an animal possessed of an anatomy peculiarly his own, and when between him and the lower creation it was held that even in structure, there was a great gulf fixed — these vestiges were for the most part carefully described and figured, and functions assigned to them, at once fantastic and absurd.

In later years, before the dawn of evolution, we found their primitive relations and even structure described with marvellous accuracy, but the anatomists of those days, while refusing to accept the explanations of their existence, as propounded by their predecessors, and often turning ridicule upon them, usually dismissed their descriptions as
To illustrate the early condition of the U-shaped alimentary tube. In its entirety it is seen to be continuous with the vitelline sac.

1. Vitelline sac.

2. Anterior end of primary gut.

3. Chorda dorsalis.

4. Cerebral dilataion.

5. Canal of cord. (nerventerone.)


7. Vitelline duct.

(After Mikhalchevics)
a vestige with the words, "its function is wholly un-
known". It was only when evolution came
upon the scene, that little by little incomprehensible
structures such as vestiges could be viewed in their
proper light, and given a definite position in the
human economy. During the past 50, and
specially during the last 15 years, an enormous ad-
vance has been made in our knowledge of these
oddments of the body, but while most observers are
agreed upon their teleology and structure, there ex-
ists considerable divergence of opinion with regard
to those which uniformly persist — as to why they
persist, as to whether they perform a function or
not, and especially as to what that function may
be.

Pathology has also something to say on the sub-
ject of vestiges, and most of them are encountered
both in the fields of Medicine and Surgery.
When two years ago I began the work, of which this
thesis is the practical outcome, it was my intention
to take up the U-shaped tube of Sutton (to be after-
wards discussed) and investigate the various modif-
ications which it undergoes before passing into its
permanent adult condition, as also especially to
consider any vestigial remains which may persist
throughout life.

I had intended to classify the subject under the
following heads —

II. Hypophysis Cerebri.
III. Epiphysis Cerebri.
IV. Cerebral Body.
V. Urogenital vestigial remains.
VI. Vermiform Appendix.
VII. Michel's diverticulum.

I had made extensive notes of various anomalies of each of these, during my career as an Anatomist in Edinburgh (1884-95) during which period, I paid considerable attention to vestigial structures, and made a point of examining these in all the subjects that came to my Practical Rooms at Surgeons' Hall for dissection.

When I had really begun the work, its immensity appalled me, and considering the difficulties which I as a practitimer of medicine, had to encounter in getting fresh material, I ultimately resolved to limit the scope of this thesis to the consideration of the Hypophysis and Epiphysis Cerebri. This fulfilled neglect, as I possess much material and many drawings, especially of the last three.

While Senior Demonstrator of Anatomy in Manchester in 1880-1 I had opportunity afforded me for working at the Anatomy of the Anthropoides, and I had hoped to make the Vermiform Appendix in man and the Anthropoides one of my leading chapters. Regarding Michel's diverticulum also, I had a good deal to say, but must pass it entirely over. I cannot however resist...
the temptation of taking note of a case which came under my notice some years ago — surely one of the strongest cases on record — where a boy passed perforations an intestinotical piece of ileum, having needles obviante attached to it, and afterward recovered. I have figured the condition at the end of this paper.

Referring to the first subject on my list, viz.: the central canalicular system of the brain and spinal cord, it is apparent, from our knowledge of to-day, that they and especially the fluid which they contain have been awarded an importance, which they do not now seem to merit.

The cerebrospinal fluid was formerly regarded as an essential constituent of the body. Halliburton more recently, concludes his exhaustive paper as follows —

(4) By proposing the question: —

When and under what circumstances is it re-

-creted.

Is its function excretive or nutritive?

Is its composition merely accidental?

Is its function merely the mechanical one of exer-

-cising a necessary pressure upon the organs

which it bathes?

With what answers may be forthcoming to these

questions, this paper is not concerned — personally

I believe that its function if any, must be a very

meagre one at best, and that whether mechanical

or nutritive. St. Clair Thomson's recent monograph
To illustrate the changes which take place in the U-shaped tube as development advances. (modified from Bland Sutton)

1. Spleen bud.
2. Bursal evagination of Hypophysis.
3. Anterior end of primitive gut.
4. Buds which form lungs.
5. Stomach.
7. Bladder, urachus etc.
8. Post-anal gut.
11. Notochord.
upon Cerebro-spinal Rhinorrhoea bears out a similar conclusion.

It occurred to no one that the whole system was a mere vestige until the publication of Bland Sutton's paper in 1888, a paper which was immediately followed by the equally important one of Lastrell. According to Sutton "the cord and brain of the Vertebrates have been evolved from what was originally a portion of the alimentary canal— the central nervous system is a modified piece of bowel."

I have no intention of entering upon the various arguments which he brings forward in support of this theory, but simply mention that he lays stress upon the original continuity of gut and cord, and the likeness in their mode (by lateral plates) and time of development — especially does he draw attention to the fact that each limb of the \( \cup \)-shaped tube has in relation to its walls a chain of nervous ganglia which become respectively sympathetic ganglia and plexuses in relation to the alimentary tract, and the nervous elements of the brain and spinal cord.

In Plate I, this \( \cup \)-tube is depicted. It is seen to be divided into two limbs by the presence of the notochord — a dorsal or neural limb, and a ventral or alimentary one, the latter communicating freely with the vitelline sac.

In Plate II, a later condition is shown. The anterior end of the alimentary limb becomes connected with the stomodeum, as also with the cerebral and...
of the neural limbs, by the pouch of Rathke.
Posteriorly after the involuting of the protodermum, the alimentary limb opens there, while the neururentic canal atrophies, and the so-called pro-anal fistula ultimately only represented by Luschka's gland. The whole of the posterior limb of course becomes brain and spinal cord.

It is a remarkable fact as noted by Recklinghausen and others that congenital abnormalities of one limb is usually found associated with some defect in the other. We all know that abnormalities seldom occur singly. A case in point came under my own notice the other day, a boy with patent foramen ovale, and suffering markedly from cyanosis. On stripping the patient, I found a tiny angular nodule of loose cartilage, (loose and adventitious) over the atlas-axial joints, evidently the rudiment of a supernumerary auricle. Still the association of deformities of both limbs of the U-tube occurring generally together is remarkable, and in itself an argument in favour of Sutton's theory.

Gaskell although approaching the subject on somewhat different lines, agrees in the main with Sutton, and thinks it possible to look upon the spinal cord as not being necessarily a nervous tube.

An archaic alimentary canal thought but in rudiment exists in vertebrates, that it had outlet and inlet; had functions probably akin to its
permanent successor, — but that whether from loss of function or disease, or whether the function became so impaired by the encroaching more highly developed nervous system — in any case it became used as a support for the extending neuralgia. I might here note the experiments of Floyd Anderligen on the Amphitriteus, and describe the archaic month as it does exist in living animals, in order to support Sutton's theory, but prefer to leave them over until discussing the Hypopophysis Cerebri.

As regards the coccygeal body, it is, as we have seen, the vestigial remains of the menuteriae canal and post-anal gut. auchler in his classical paper, describes at great length, the body which has ever borne his name, but discusses it as a vital organ, and not as a vestige. It is a remarkable fact that in the world-famous museum of the Royal College of Surgeons of England, no specimen of auchler's gland is to be found. This minute but interesting organ, only the size of lentil, is embedded in fat just in front of the last modue of the coccyx, between the posterior part of the sphincter ani muscle, and the ano-coccygeal ligament. Its slender stalk pierces this ligament, and consists of a terminal artery from the coccygeal and some nerve fibres, said by Macalister to be both grey and white. I have never been able to trace any fibres from the filament terminals as far as this gland, but have little doubt that such oc-
- casimally may be found, especially in young sub-
jects. For here I ever noted the existence of a fib-
rous band attaching the gland to the rectum.
Indeed, in general, I failed to find any
pland at all, due doubtless to the fact that in these
cases, the organ did not exist as a single body, but
as a series of irregular nodules, separated from each
other by the loose connective tissue of the region, and
most of them removed with it.
Injection proves that its main bulk consists of arteries
much convoluted, and having annular dilatations
upon them, otherwise it is lobular, and contains some
 glandular cells, as also a few nerve cells, nerve fibres,
and a capsule with some muscular tissue in it.
Arnold named it the "Elongatus arterios-sus",
and also its vascular arrangement in his series
of beautiful plates. What function this singular
little body exercises, we can only guess at—pro-
bably something akin to that of the Flavo Intercar-
otia. It has been also compared to the cardiac
heart in Eleo.
It is a ventric, and Geiger eurs regards it as the
ulic of branches of caudal arteries, which became
atrophied at the same time as the caudal marrow
(to which they were primarily distributed) disappear-
ed. Similar nodules are found in tails of mam-
imals as transformations of spinal branches of the
caudal artery, and even in Birds, a taillike condition
of the artery exists. The researches of Arnold, Frank
Meyer, Mitchell, Banks, Sertoli, Jakobsohn, and others have practically covered all the ground regarding this curious little body, but I could not refrain from referring it before passing on to the subject matter of my paper.

It was my original intention, as before stated, to treat of all these vestigial conditions in this thesis, as also to take up in connection with each of them, various developmental and other anomalies. Some of these abnormal conditions are most interesting, let me but cite one.

These are found occasionally in children little polyphoid growths at the umbilicus, called "umbilical polypi"—these were for long enough regarded as new formations of a gelatinous type. Yet their structure is similar to that of the ileum, in other words, they are originally little diverticles of part of the vitelline duct, arising from it just where it leaves the fetal abdomen; and which, however, although the duct itself has disappeared.

In busy London practice has however rendered it impossible for me to devote the time to such a vast subject, and has compelled me to confine my observations to the Hypophysis and Epiphysis Cerebri only.

Before entering upon their consideration let me quote what is said upon the subject of vestiges by Darwin and Wallace.

Wallace remarks, "much of what we suppose to be useless is due to our ignorance; undeveloped teeth, the pinnal gland, the vermiform appendix &c. &c. are
"vestiges of organs probably of great importance to the ancestors of the forms in which they now persist as peculiarities."

Darwin says, "Organs now of trifling importance have probably been of high importance to an early progenitor, and after being slowly perfected at a former period, have been transmitted to existing species in nearly the same state, although now of slight use."

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**Note.**

I am deeply indebted to Dr. Boyd Beadle of Colney Hatch, for his kindness in providing me with most recent material.

I have taken great pains to render the various plates as accurate as possible. With one exception they are taken from preparations and sketches of my own, and have been painted under my constant supervision by a competent artist. Acknowledgment has been made where any diagram is modelled on that of another author.

Lastly, in order to avoid needless confusion in the text
I have appended to each division of my subject, the bibliography proper to it, and have arranged the authors alphabetically.

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Ihr

"Hypophysis Cerebri"
Fig. I.

Sagittal mesial section through head, made by myself, in order to illustrate the respective positions of the Hypophysis and Epiphysis. The Tela Chorii has been removed but the venous sinuses left in position. Both evaginations are seen to be derived from a common cavity. The relations of the epiphysis to the bundle of the Corpus Callosum, and those of the Hypophysis to the sphenoidal sinuses are well defined.

Fig. II.

Sagittal mesial section through the head of a 3 mos. foetus. (Actual size). Note the relatively larger size of the Hypophysis, also the funnel-shaped remains of the "Craniopharyngeal canal." This specimen only came into my possession in the beginning of April 1900.
The Hypophysis Cerebri, also known as the Pituitary Gland, Supraophenoidal Appendage, and Superoophenoidal Appendage, is, as is well known, found at the base of the brain universally throughout the Vertebrata, except in the case of the Amphibia, where known, as we shall see later, it practically exists although in an altered form. It reaches its maximum development in the lower Vertebrata, and with some exceptions gradually decreases as man is approached.

In every case it consists of two lobes, one derived from the mouth, the other from the Cerebrum. Of these, the Anterior or glandular is usually considerably the larger, while the posterior or nervous lobe, although in man, and some of the higher mammals, it has lost many of its neural characteristics, in animals lower in the organic scale it retains its integral nervous structure to such a degree, as to merit the name of the Infundibular lobe of the brain.

Until quite recently, the Hypophysis was regarded physiologically as an enigma. The older Anatomists held that the "Glans pituitam excipiens" as Vesalius christened it, existed for the purpose of providing the nasal secretion, while some of later date either decided that it fulfilled the functions of a blood gland, or held that the nature
of its function, if such existed, was unknown. Still later in the light of embryological research it has been classified as a vestige, whose existence marks merely a former embryonic stage in the development of the individual, and it has been argued, that from the apparently quiescent condition of the anterior lobe, and the manifestly degenerate state of the posterior, that it is a vestige and nothing more, and occupies no place among the organs concerned in the economic functions of the body.

The discovery of Acromegaly by Pierre Marie in 1886, and its constant association with pathological changes in the Hypophysis, gave that organ an importance, which it had never before possessed. Since that time, its development, anatomy, physiology and pathology have been most carefully worked out by the most distinguished observers of the day; and although much controversy still exists between some of these scientists, still this much has been assured — that the Hypophysis has a function, is not a so-called blood gland in the ordinarily accepted sense of the term, and is something more than a mere vestigial structure.

During my career in Edinburgh as lecturer on Anatomy at Surgeons Hall (1884-1895), I always made a point of myself carefully examining the Hypophysis in the subjects which
were allotted for dissection in my Practical classes, and of noting any points which struck me as worthy of record. These notes have however been allowed to be untouched until nearly two years ago, when a very marked example of Acromegaly came under my own care, and the study of this case, which possessed many interesting features, and suggested some problems with regard to pituitary function, revived my interest in the subject of the Hypophysis Cerebri.

In this paper, I purpose to consider —

I. Its development.
II. Its morphology and structure.
III. What is known of its physiology.
IV. Its causal relationships to Acromegaly.

Development.

Beazley long ago said “Embryology is the torch which illuminates the study of organized bodies”, and of no organ in the body could this be said with greater truth, than of the Hypophysis Cerebri. The history of its development is an unusually interesting one, and may be divided into three epochs.

I. 1838 - 1841.
II. 1841 - 1890.
III. 1890 onwards.

First Period. During this time the most varied and conflicting opinions were held regarding its development. But first I may state, that by the older Anatomists, the Hypophysis was considered
to be an integral part of the brain. In 1838, Rathke first described the pharyngeal depression which bears his name, and considered it to be the first trace of the pituitary gland. For over ten years subsequently he disowned this opinion, and only in 1861 he again and finally admitted the existence of the pouch, but accorded to it no importance whatever. Reichert in 1840 denied its presence, and in 1861 he states that the Hypophysis begins at the end of the Notochord, but denies that it can be due to any proliferation of pia mater. In 1878 he becomes sufficiently definite to say that he considers the germ of the Hypophysis is to be found in the material produced for the formation of the Sella turcica.

Höllicher in 1861 maintained the existence of the pouch in man. In 1868 he thought that the gland had its origin in the cellular mass, which primarily united the intestine to the cerebral wall. This last belief fittingly introduces the Second Period which was ushered in by the researches of W. Müller in 1871. In his classical paper he confirmed the existence of Rathke's pouch, and endeavoured to demonstrate that it was developed from the pharyngeal epithelium, and from the connective tissue sheaths of the great cerebral arteries. He also denied what some observers maintained, that its origin had anything to do with the end of the Notochord, which he states has
merely a mechanical function. This of course we know to be true, as although at first sight it might appear that the upper end of the chorda had something to do with hypophysial growth, yet the researches of Bonnet and others shew, that it really bends downwards just under the diverticula and finally blends with the buccal epithelium. Müller describes the invasion of the gland germ by vessels and connective tissue, which induce the formation of solid epithelial tubes, these becoming severed from the common duct at a later period. He also first details the posterior lobe, and shewed how its nervous elements degenerated the higher up ascended the organic ladder, and lastly he maintained from the persistence of the gland throughout vertebrate life, that it must possess a distinct physiological function.

He fell into the error of thinking that the original pouch was derived from the archenteron. Mivart however in 1874 confirmed largely the investigations of Müller and shewed how the hypophysial gland had a distinctly dual origin, the glandular lobe being derived from the buccal mucus membrane, and the infundibular one from the cerebrum. In 1868 Milne-Edwards gave the origin of the pituitary body as the buccal mucus membrane, and in the same year described its origin partly from Rathke's pouch, and partly from the vascular stoma of the upper end of the notochord.
Mikulcoyies was really the first observer to give what we now know to be the true origins of the dual
lobed Hypophysis. He laid great stress upon the
angle formed by the membrane clothing the skull
and the posterior basilar one, and describes how the
vessels passing upwards behind the sphen-eth-
moid part of the cranium forms a canal which
arrives at the infundibulum, becomes transformed
into the glandular lobe, and finally gets shut off
from its original source by the growth of the cart-
laginms skull-bone.
Götte in 1845 in his investigations on the frog,
confirms the conclusions arrived at by Mikulcoyies.
The development of the Hypophysis in the Lamprey
was especially attacked by Dohrn in 1882, and
his results confirmed in 1887 by Scott, in 1888
by Shipley and others, and also by Kuppfer.
Dohrn in his work on Ammocoetes describes the dev-
velopment of the olfactory organ from a median lam-
ina, and believes that by a special process of-
generation that the Hypophysis is thereby derived
from it, and is therefore originally a paired organ.
Kranzhaar and others agree with him in this
belief. In Petromyzon he says this lamina gets
very large and from it develops the roof of the
mouth and also the upper lip, therefore he asserts
that the hypophyseal diverticle is outside the
oral region, and more associated with the olfactory.
He finds that in the Classobranchi, the region be-
The nose and oral plate become turned in due to the size of the fore-brain and the increased head-bend, and thus becomes oral—an appendage of the buccal cavity.

In the Hypophysis of some animals, and even sometimes in the human subject, the presence of an antero-posterior fissure, more or less marked, gives a common biconvex appearance to the glandular lobe, and would thus perhaps seem to favour Dohrn's views. This condition is especially, as noted by Lothringen, seen in the dog.

In this connection one can hardly fail to be struck with the perspicacity of the older Anatomists, who amid shreds of error, seem so often to have had the faculty of seeing and thus stumbling against a germ of truth—without apparently rhyme or reason, they connected the Hypophysis with the nose, to which they declared it supplied the pituitary, juices—well of course we know this idea to be false and ridiculous, still it is curious that in the light of Dohrn's researches, the pituitary gland in development to have a relationship to the olfactory region.

Valentini in his work on the Amphibians, believes that in them the Hypophysis springs from a diverticulum of the internal stratum of the ectoderm whose lower part gives origin to its posterior lobe, while the anterior lobe from the ectoderm from the
Plate IV

-- Fig. I. --

Section through embryonic head to show the hypophysial and epiphysial evaginations (after Mihalckovics).

1. Epiphysial evagination.
2. Buccal evagination of the hypophysis.
3. Cerebral evagination of the hypophysis.
4. Chorda dorsalis, represented as ending in fibres in posterior buccal wall.
5. Anterior end of the primitive gut.

-- Fig. 2. --

Semidiagrammatic sagittal merial section through skull - base and hypophysis.

1. Infundibulum.
2. Processus lingualis.
3. Anterior hypophysial lobe.
4. Fibrous trabecular connecting the capsule of the hypophysis with the dura mater.
5. Infra-hypophysial rims.
7. Diaphragma sellae.
8. Intercommuni rims.
posterior wall of the primitive intestine on a level with the upper extremity of the Notochord.
In this period therefore, the hypophysis is described as having a dual origin — a buccal and a cerebral. The buccal evagination grows upwards and backwards towards the base of the second cerebral vesicle, where it comes into relation with the evagination from that vesicle, and gets firmly attached to it. Minot states that in Mammals, it is the early and close union of the contiguous walls of the two evaginations over the hypophyseal area, which as a purely mechanical condition, causes the formation of the two diverticula. (Plate IV. Fig. 1)
Once formed the buccal diverticule chingatt becomes expanded at its upper end into a largeish flask-shaped vesicle, the lower part remaining as a pedicle. This pedicle becomes atrophic and remains as a mere end for some time, finally disappears. In Selachians however according to Chargy, it persists. It is due to the development of the basi-sphenoid cartilage that all trace of the skull is lost. Although the position of the former passage into the basi-sphenoid persists in some animals such as sharks etc., very rarely indeed is any trace of it found in the human subject. Anitschka, Langert, Ronitzi, Suchomel, Gicchini and Roesi all say that they have noticed it. Anitschka mentions a case of a miscarriage with a pefine lipida, in
which the pituitary was prolonged into the sphenoid, I also found an invagination of the
meninges membrane upon the opposite side.
Langer states that he found traces of this pass-
age, (which he calls the "canalis cranio-pharynge-
en") in 10 per cent. of children at birth.

For my own part I have only once, and that in
a full-term fetus, seen a trace of this canal. * 

Did such a condition as persistence of this canal
exist, it might probably be associated with loss
of cerebro-spinal fluid, with symptoms akin to
the Cerebrospinal Rhinorrhea recently described
by St. Clair Thomson. (See also plate III.) Fig. 2.

The hypophysial are, now lying in the sella turcica
gets flattened, partly by the brain weight, and
partly by the growth of the dura mater to form its
diaphragm, and becomes non rapidly solid.

This solidification is brought about by the rapid
proliferation of hollow buds mainly derived from
the epithelium of its anterior wall. This says
this process begins at the end of the 2nd month,
and takes place in relation to the anterior wall
only, the posterior are remaining inactive. In

Fig. 6. a sketch shows this process.

This anterior budding has been chiefly studied
in rabbits; in birds, both Müller and Nöthnizens
state that the germation occurs from both walls.

These buds elongate and branch into the vascular
tissue outside. They separate from the parent stem
yet entakes to grow, their lumina frequently disappear, and they come to form a highly vascular and complex arrangement of hypophyseal ends.

The remaining original cavity becomes more and more pushed backwards as it moves towards the inmost posterior wall and according to Charpy, disappears early in mammals, although it may persist as a vestige, and retain its epithelial lining.

I do not agree with Höfliger that the main vesicle persists recognisably in man into adult life, but believe that it becomes ultimately represented by some of the little spaces in the boundary zone which contain the colloid material, and to which I shall refer more particularly when describing the structure of the Hypophysis.

The Myelodermal diverticle in many of the lower vertebrates persists as an integral part of the brain, and is largely ganglionic in structure. In fishes according to Schäfer, the cells which compose its walls become converted into nerve cells and fibres, but in mammals it remains small and undeveloped, and dilates into a bulb-like end. The cavity both in bull and yedicle soon disappears, while in inferior forms (especially fishes) throughout life and in the embryo yields vesicles, the lobe remains hollow, and its cavity continues with the ventricles one of the brain, all being lined with cylindrical epithelium. Sometimes, says Schäfer,
remains of the original cavity are seen in the form of a small space lined by columnar epithelium. I have never seen such a cavity, although I have carefully searched for it in nearly a hundred specimens.

In higher vertebrates the nervous elements of this lobe become much obscured by the ingrowth of vessels and connective tissue.

The entire organ is now encapsulated in the same sheath of connective tissue, which is very vascular and blended with the pia mater, which according to many observers of this period is also prolonged between the lobes.

When we enter upon the story of the third period of hypophysial development, it is like entering a world of fairy romance.

It is not that there is any essential or radical change made in the origin and subsequent growth of the hypophysial lobes, for our newer knowledge of today adds but little to what has been already done and known, but it is because in this chapter we get an insight into the "raison d'être" of these processes, by learning their true teleological meanings and significance.

Macabbeus in his brief description of the hypophysio-is, describes the posterior lobe as an oval mass of connective tissue, the thickened end of the infundibulum, and then says "it is probably the rudiment of an archaic sense organ." We have
already seen that according to Gaskell's ingenious theory, the infundibulum is the mouth of an archaic alimentary canal, which thus comes to the surface at the pituitary body.

Wiedersheim says that the hypophysis represents a glandular organ which probably corresponds with the primitive mouth or "palatostoma" of the Proto-
vertebrata, and which is more or less represented by the combined unpaired nasal and pituitary passage of Cyclostomes.

The researches of Kupffer in the early nineties, especially those of Lloyd Morgan in 1894, not only crystallized into definite much of the guess-
work of the few previous years, not only gave us a new insight into the method of its development,
but inverted the hypophysis with a physiological importance, whose significance we do not yet
fully understand, and render perhaps a little more understandable some of the etiological factors
in that most puzzling of diseases, "Acanthoc".

Kupffer found that in the embryos of some lower
vertebrates, notably the Petromyzon and Sturgeon,
that for a brief period there exists a peculiar wagg-
ination directed forwards from the dorsal aspect
of the primitive pharynx, and which he called the
"preoral gut". In the Sturgeon, it is known that
a passage leads into this gut from the exterior,
i.e. the fundament of a separate mouth is estab-
lished over the permanent one. Kupffer affirms
that the whole structure, the preoral cavity and the gut into which it leads, becomes the hypophysis, and he considers that the anterior lobe in craniate vertebrates is a vestige of this old preoral cavity. He maintains that the hypophysis is developed as a thick-walled depression under the median olfactory lamina, whose internal extremity joins the primitive intestine. The pituitary body does not, he shows, arise only from ectoderm, but from the endoderm also. The epithelium of the primitive intestine lying behind the pharyngeal membrane, participates in its formation.

In Amphioxus and Myxinus, there is found a canal which extends from the buccal roof to the brain cavity, a patent canal lined by ciliated epithelium. This buccal-neuric duct, Huxley says, is not to be confounded with Rathke's pouch, but corresponds with "cranio-pharyngeal canal" of Mivart'sies. Andriessen demonstrated the function of this duct by placing living animals in carmine water, and after they had been in the fluid for a couple of hours, he killed them by removal &c., and subsequently examined them. It was there seen that the retained fluid had been carried through the buccal-neuric duct into the ventricular system of the brain, and along the canal of the end that to the neurenteric opening posteriorly. This ventricular system is, he thinks, for the purpose of carrying oxygen to, and removing
waste products from the Nervous System. I am inclined to agree with Collina that it doubtless also serves to convey nourishment.

Similar water-vascular systems are found as we know in Ascidians, Balamoglossi &c., and in the larval forms of Mollusces and Asteroidea.

In Botrylla (Ascidia) there exists during its free life, a tube which joins mouth with that anorectum, and in which the fluid circulates for the nourishment of the nervous ganglia &c. But when the animal enters upon its parasitic stage, the duct becomes obliterated.

In animals as low down in the organic scale, the biological activity of the tissues is doubtless very weak, and granting that toxic substances are found in the tissues, certainly the oxygen of the water would suffice for their destruction.

To return to the Amphibia, there exists at the buccal end of this bucco-nerve duct, a collection of epithelial cells, glandular in nature, known as the "sub-nerve gland," while at the inner end of the duct, there is a cluster of nerve cells encircling it. Undoubtedly the former is the primitive hypophysis, while the latter is the impoundicular dose. As has been pointed out by Meuchten & others, the gland probably proved its secretion into the duct, along which it would be carried in the streams of water, and so on through the central nervous system. The ganglionic mass situated at the entrance of this water vascular sys-
-term consists of nerve cells mostly fusiform in shape. From it proceed fibres which pass down-wards and end near the buccal extremity of the duct. It is thought, that probably it represents some form of a sense organ (e.g. touch, perhaps even taste, of course in an elemental condition) somewhat akin in nature to the palps or organ and ganglionic pileus of the molluscs, which is placed near the entrance of the mouth, and is known to possess a water-tasting function. In the amphioxus it may perhaps serve to test the quality of the fluid passing over it, but to me it seems within the limits of probability, that reflexly the diameter of the canal may become altered or even closed by its agency, under conditions which might necessitate a greater or less supply, or perhaps total rejection of an unmitigable fluid.

The researches of Silvanus Liddon on the ciliated pit of the Ascidians most interestingly and aptly apply themselves at this stage. As a result of her investigations, she states, that the hypophysis at the present time may represent merely a rudimentary of the hypophysal gland and ciliated pit found in the Ascidia. She premises that in these animals, the pit has probably two functions. 1st. It communicates with the brain and probably secretes it, and 2nd. It acts as a duct for the hypophysal gland, which lies immediately ventral to the ganglionic. She found that the gland consisted of a vast number of fine granu-
ular tubes, which unite near the dorsal aspect of the gland, forming two large ducts, which open into the canal of the ciliated pit.

In the vertebrates, in consequence of the development of a blood vascular system, and the ordinary vertebrate excretory apparatus, the hypophysis she thinks has almost atrophied, and quite lost its function. Now when we pass to a blood-vascular system which carries nutrient to the nervous system, the need for an amphibian vascular system disappears, and so the duct disappears. The function of the nervous ganglion is also at the same time practically abolished, and its nerve elements atrophy and fibrose; and as we ascend the vertebrate scale from Petromyzon upwards, this process takes place, one stage increasing in-volution, until man is reached; and in this immoderately late only traces of nervous matter can be found. But as I have to be able to show at a subsequent stage of this thesis, the need for the glandular part of the apparatus remains, whose secretion is probably necessary to act upon or modifying substances serving to nourish the body organs, and specially the nervous system. And as from the bottom to the top of the Vertebrate ladder while duct and ganglion involute and become changed, the Hypophysial gland does not participate in these changes, but remains in Man as in the Amphibius an active organ possessing all
through the Vertebrate class a definite structure and a distinct function.
The anatomy of the lung-mucus duct and its appendages has been worked at by many observers.
Hippfer, Scott, Shipley and many others have devoted much attention to Petrunyak - the classical
works of Petrunyak deserves special mention, in which he
takes up the Myxine - while the long exhaustive paper on the Hypophysis by Haller discusses the
origin of that body in Cyclostomes, Teleostei, Selach-
ii, Amphibia, Sauropsida and Mammals.
The story of the duct &c. may be now briefly stated;
that as we ascend the Vertebrate scale, the
ductus and
ductus obliterator, the structures at its two extrem-
ities come into close proximity, and become more
or less adherent. In man, and some of the
higher mammals the two lobes are so coherent,
that they form a single solid mass, in which
however it is possible (as I shall subsequently
show) to make out parts, which represent the
original tripartite condition of the body - viz.
gland, duct, and nerve organ.
Summarizing our knowledge of the development
of the Hypophysis Cervi, it can be set forth
briefly as follows:

It is developed from three distinct sources.

I. From the buccal ectoderm.

II. From the entoderm to a small extent, that
part of the intestine called by Hippfer the
prosacral part, taking a subsidiary part in
the formation of the buccal evagination.

III. From the thalamencephalon.
The derivatives from the two first sources become
the anterior lobe of the Hypophysis, while from
the third are formed the Infundibulum and the
so-called Infundibular gland (to be afterwards
described).

In some of the lowest vertebrates all three parts
of origin can be individually seen, as in the
case of the Amphioxus.
In the higher vertebrates the intermediate part pract-
ically disappears, while the nervous lobe under-
goes fibroid changes.

"Anatomy and Morphology."
The Hypophysis may be briefly described as an el-
lipoidal mass, occupying the sella turcica, and
attached to the inferior aspect of the Cerebrum by the
pituitary stalk or infundibulum.
On the removal of the brain, it is invariably left
behind, owing to the presence of the rigid diaphragma
Sellae which covers it, and which, although in man
and many mammals is membranous, still in others
(e.g. the sheep), it is represented by a bony plate.
The organ lies in a perfect compartment or box,
whose boundaries are well known, on three sides
its boundaries are bony, it is covered by its diaphragm above, while laterally it is in relation to the inner walls of the cavernous sinuses.

This compartment is entirely filled, or at least practically so, the space being everywhere lined by membranes, except at the small foramen ovale, through which pass the stalks. From this lining there pass everywhere to the capsule, films trabeculae for the most part vascular in character.

When removed by first cutting among the diaphragm and dividing the trabeculae it is noted to be oval in form, greyish-red in color, that its greatest diameter is transverse, and that rimmed by the cavity in which it lies, its upper surface is somewhat flattened.

As regards its size, measurements have been made by many anatomists of which the following table may be regarded as the mean —

<table>
<thead>
<tr>
<th>Diameter</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Antero-posterior</td>
<td>6.0 - 10.5 m.m.</td>
</tr>
<tr>
<td>Transverse</td>
<td>10.0 - 14.5 m.m</td>
</tr>
<tr>
<td>Vertical</td>
<td>5.0 - 9.75 m.m.</td>
</tr>
</tbody>
</table>

It is thus its average weight as 35 - 45 centigram.

My own readings give its average as .6 gramme.

Two very important points have been made out regarding its weight — firstly, that whatever variations may normally occur, depend entirely upon the anterior lobe; and secondly, as distinctly proved by Göttinger and others, that the weight of the Hypophysis in the animal series is not.
relative to the weight of the brain itself, but rather to the general body weight.

Plate III. Fig. 2. It is relatively larger in the fetus and young child. Schönemann gives in 27 cases, the weights as follows —

<table>
<thead>
<tr>
<th>At birth</th>
<th>13 centigrammes</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 10 years</td>
<td>33</td>
</tr>
<tr>
<td>20</td>
<td>574</td>
</tr>
<tr>
<td>30</td>
<td>63</td>
</tr>
<tr>
<td>50</td>
<td>60</td>
</tr>
</tbody>
</table>

Boyce and Beadles believe that to some extent, a relationship exists between the size of the organ and the mode of death — they found it large in persons dying from acute diseases, and smaller in those succumbing to chronic maladies.

The hypophysis has been attacked by Selye, Schüchtemann, and some others to be (in very rare cases) anatomo-pathological, this is I think extremely unlikely, and no doubt its apparent absence was due to some pathological cause.

Capsule. A thick-walled fibrous capsule surrounds the entire gland. It is very vascular, and its external surface uneven and shaggy, due to the presence of the trabeculae mentioned above. This capsule is continuous with the pia mater alone, indeed the pia traced from the dura downwards gradually becomes but upon the capsular surface.

Charpy says that the anterior lobe has an envelope of pia mater, which is prolonged between the lobes. It has been frequently stated that the pia passes...
Figures 1, 2, 3. (after Textit)

1. Posterior view.
2. Sagittal mesial section.
3. Horizontal section.

Fig. IV.

Diagram of sagittal mesial section, shows the two lobes, also

1. Processus lingualis.
2. Hypophysial cleft.

Fig. V. (After Charpy)

Similar to last, but Charpy figures colloid matter in the centre of the anterior lobe, as a normal condition. This is erroneous.

Fig. VI.

Diagram of sagittal mesial section, to show

1. Infundibular cavity.
2. Clefts, the remains of the bucco-nasal duct.
3. The original hypophysial ventricle, whose post. wall is inactive, but from the very active ant. one the hollow buds gradually push the ventricle back, until nothing but a mere slit remains.
between the lobes. Viewed however in the light of recent embryological research, this is unlikely. There is certainly a fibrous septum or layer between the lobes, but of this more anon. Tracing this capsule upwards upon the pituitary stalk, it becomes thinner and thinner, until upon the infundibulum only pia mater exists.

The cohesion of the two lobes is usually so perfect, that but for a somewhat tenacious appearance in the posterior aspect one might well believe the organ to be of homogeneous structure, but a transverse horizontal section reveals its true constitution, for we find the large uniniform anterior lobe embracing at its hilum the smaller rounded posterior one.

In most of the lower animals, this cohesion of the lobes is much less complete, and in the sheep, for example, they can be separated from each other with comparative ease.

I propose to consider the hypophysis as regards its morphology and structure, by taking it up in four sections. I. The stalk. II. Anterior Lobe. III. Posterior Lobe, and IV. Boundary Zone.

I. Pituitary stalk or Infundibulum.

This, continuing along with the Sphen Cingereum passes downwards and forwards (and passing thus the opening in the diaphragm) becomes attached to the Hypophysis about the middle or centre of its upper surface, at a sort of umbilical depression there, so therefore seems to affix itself to the anterior lobe.
Fechin states that both lobes are attached to the infundibulum, and even such a careful observer as Stechschmidt in his incomparable atlas figures the stalk as distinctly fixed to the anterior lobe. Now the stalk is continuous with the infundibular lobe, and is attached to it alone, but the "lingual process" of the anterior lobe passes upwards and is attached along its anterior aspect, and sometimes indeed forms a collar around the stalk-insertion, and so obscures the real stalk-insertion, the actual connection is however at once demonstrated by making a sagittal mesial section. Traced from its continuity with the posterior lobe, the stalk makes a bend forwards along the posterior-superior part of the anterior lobe, until it reaches what is practically the central point of the superior surface of the organ as a whole, when it passes directly upwards, and then backwards, and after a short course ends in the tubers cinereum. It lies free in the diaphragmatic opening, and is enveloped in pia mater, which is somewhat thickened and more firm near its terminations below. Loebelhke describes & figures extreme tortuosity in the vessels of the infundibulum, I have not been able to make out any marked tortuosity in my own specimens, but the vessels are very numerous.

In structure, the stalk is largely fibrous in nature. Sternberg describes fine nodulated nerve fibres descending along its sides into the posterior lobe.
Plate VI.

"Anterior lobe of Hypophysis."
(stained with haematoxylin and eosin).

Fig. I.

(Leiss A. Ocular 2.) shows fibrous stroma—
 glandular acini—some containing colloid—many
 vessels.

Fig. II. (Leiss D. Ocular 2.)

1. Delicate fibrous stroma.
2. Large blood-vessels full of corpuscles.
3. Acins containing colloid, which
    stains bright red.
4. Acins with empty lumina.
5. Solid glandular columns.
In its lower part, some triangular nerve cells can usually be made out. I have never seen a specimen in which any trace of its original lumen existed.

**Anterior or Glandular Lobe**, also called the "Stromaedal lobe", the "Posthypophysis", or "Hypophysis proper". It forms about two thirds of the organ, and is darker in color than the posterior. It is surrounded everywhere by the fibrous capsule already described, except posteriorly, where it ends in an indefinite manner in the boundary zone. It varies considerably in shape, and at first lies inferior to the nervous lobe. The gland tissue as the "processus lingualis" extends upwards along the front of the infundibulum, sometimes almost reaching the optic chiasma. This process is adherent to the stalk, sometimes it is found on its lateral aspects also, & it may even encircle it. This is especially seen in the young and in lower animals. The capsule over the "processus" is very thin indeed.

From the capsule passes inwards throughout its substance numerous fibrous septa, which form a reticular system, and so break up the mass of the lobe into alveolar spaces. These septa carry the blood vessels, lymphatics and sympathetic nerves from the carotid plexus. The vessels subdivide in these septa, and come to form a fine capillary network lying in close relationship with the alveolar cells. As in so many other organs
the connective tissue of this lobe increases with age. On examining a sagittal section under a very low power, usually the "genii" is seen, a button-like projection of the posterior lobe into the posterior glandular area about its middle. It is not that the nervous lobe really projects, but the appearance is due to the forward backwards of the anterior lobe and at the sides. \[\text{Text cut}\] describes this lobe as being smooth and compact in its anterior part, while posteriorly more soft and porous, and near the separating partitions showing small cavities or annules, filled with colloid matter. The lobe, he says is essentially formed of a system of epithelial cylinders, full or hollow, lying in a sea of vessels of the nature of capillaries. Charing says the tubes are 16–20 m. long, are simple or branched, and consist of a layer of cubical epithelium lying upon a membrana propria. Their lumina get filled up, the finds a free lumen of very rare occurrence. He describes colloid matter as existing in tubules, spaces and cells. As will be seen from some of the figures, the lobe is made up of closely packed gland spaces. They are filled with polyhedral granular nucleated cells, arranged in tubes, solid columns, or more irregular masses. The cells are columnar in type, and have been described by some observers as bearing cilia, especially in the larger tubes & posteriorly. I have never detected any cilia, although it is rea-
onable to assume from the nature of the development of the lobe, that they might occasionally be found. Destzit says that in structure this lobe resembles the esirnomatic thyroid and thymus. I consider that its structure is paranatrophic in character — as to its resemblance in function with the thymus gland, to this I shall subsequently refer. The cells are glandular in character. Dochinger has shown that they comprise two kinds, one of which possessing a special affinity for colouring matters, and one not. This he considers to be very important, for it is natural to suppose, that as some present a somewhat similar reaction as does the colloid matter itself, that they are concerned in the secretion of this substance. It is important to note that all observers are not quite agreed upon this point, for it goes to prove that the Pituitary body is something more than a mere vestige or rudimentary organ, it proves it in fact an active one. Flesch and Dobzhansky also by stains, made out two distinct forms of cell, one eosinophilous, the other unaffected by the eosin stain.

Valenti describes the cells as exactly resembling those of the intestinal wall. It has been affirmed by Cadiot and others that this lobe in its cellular structure closely resembles the zona glomerulosa of the adrenal body, although its blood vessels are less abundant.

Edinger quoting Flesch, etc., says that their inc-
-vestigations make possible the recognition of two kinds of cells, small clear ones, and larger granular cloudy ones, and he maintains that some similar elements are found in several very active glands, it is thus probable that the hypophysis also performs some physiological function. In many cases one is obliged to differ from Macalister, who describes the lobe as a brownish, concentric mass of degenerate epithelium-lined tubules.

Personally I can quite corroborate what is said by Eshinger. In this, the cells are distinctly seen to vary in size, some large and more granular, others considerably smaller. Further, it will be observed that the section shows that the great majority of the tubules show an empty lumen, and that the solid ends are very few in number. This condition I have found in practically all my sections, and I therefore venture to differ entirely from Charpy. The same section also shows a marked difference in the staining affinities of the cells.

Colloid Material. Whether this be looked upon as a secretion or the result of a degenerative process, that it is found under normal conditions in the pituitary body, all observers in modern times are agreed. As to what part of the anterior lobe usually shows it, there is considerable divergence of opinion. That most careful and exact anatomist M'Keech, describes the anterior lobe as formed of two substances, one external reddish, and an
internal white, which vary much in their degree of colour and proportionate quantity. We rarely, he says, find one which is homogenous. Schilling Merkel was undoubtedly misled by pathological conditions. Chapter 5 in Poirier's Anatomy gives a beautiful figure of a sagittal mural section through the organ which I have sketched (Plate V. Fig. 5).

In it, although only magnified 4 diameters, there is represented in the centre of the anterior lobe a large mass of colloid material. The drawings and papers published by most other observers, impress one with the idea that it is usually found in the lumen of tubules scattered irregularly throughout the gland, as also in cells and some vessels.

Now I am not prepared to deny that colloid may not be found in tubules anywhere throughout the anterior lobe, even in extratubular spaces, but what I do maintain is that normally it is chiefly found in the boundary zone, where exist spaces for its reception. Of whose nature I will dwell more fully subsequently.

In Myxedema, as shown by Boyce and Beadle, this great scarcity of colloid throughout the main bulk of the anterior lobe, does not exist, but everywhere in its substance are seen tubules containing a greater or less amount of colloid. Colloid I have found to exist in five distinct situations in the Hypophysis Cerubi

1. In the lumina of tubules.
Plate VII.

Junction of the two hypophyscal lobes. (Upper part.)

(stained with haematoxylin and eosin)

Fig. I. (Leiss. A - Oct. 2.)
1. Anterior lobe.
2. Posterior lobe.
3. Fibrous septum.

Fig. II. (Leiss D. - Oct. 1.)
Taken from the upper part of the last section. Colloid seen not only in acini but also in bloodvessel. Also note the fibres ascending downwards from capsule into septum bipinniform in arrangement, and passing into both lobes.

1. Bipinniform fibres.
2. Posterior lobe.
3. Anterior lobe.
4. Pigment collection.
5. Acini containing colloid.
7. Vessel containing colloid.
II. In cells.

III. In blood vessels.

IV. In extra tubular spaces.

V. In the spaces of the Boundary Zone.

In plate VI. (figs. 1 and 2) which represents a section stained with haematoxylin and eosin, the bright red colloid is seen in the tubules. The part figured is in the posterior half of the lobe. In this section also there can be made out traces of a colloid-staining material in some of the larger (eosinophile) cells.

In plate VII. fig. 2. (taken from the upper part of the boundary zone) there are seen in its lower portion the sections of a tubule and blood vessel respectively, both of which contain colloid, that in the vessel being of considerable size. In several of my specimens I made out small collections of colloid lying in the connective tissue outside the tubules. This I found very rarely, and have not drawn a picture to show it. In plate X, which represents some of the spaces in the boundary zone, the colloid is seen to occupy four of these.

The colloid material is invariably found to stain easily.

Central Cavity. Meisel in 1839 says, after describing the substance of the anterior lobe as consisting of two parts as before noted, "we observe on the right side and on the left, on the limit between the two substances, a depression, in which these small ducts, which arise from the
external surface terminate. The posterior part of this depression forms a small canal, which "converging with that of the opposite side, goes towards the centre of the posterior edge of the lobe, and the place where the hypophysis is continuous with the pituitary body - the two canals unite in this place."

Now we know that the primitive cavity sometimes persists in the adult, but it exists only in cleft-like form and in the posterior part of the lobe.

Also that in the fetus, where the hypophysis is relatively larger than in the adult, that a slit-like cavity has been described as being occasionally present. Again as is well known, this vestigial cavity is found in many lower animals, that in Selachians its pedicle persists, and that in Myxine throughout life it has an opening into the digestive tract, just as in mammalian embryos. A central cavity has been described in the human hypophysis, filled with granular debris; no doubt this condition was a pathological one.

I have endeavoured to show in diagram (Fig. 6, plate V.), how by the extreme activity of the anterior wall of the original hypophysial sac, the tubules growing outwards and forward into the connective tissue, gradually push the ventricular cavity backwards, until it ultimately comes to exist only as a vertical slit, lined by epithelium of a columnar type, in which as be-
fore noted, I have never found ciliated cells. Now, I believe, that the occurrence of the original cavity in man whether adult or child is not occasional, but is invariable. True, it must indeed be rare to find a vestigial cavity of any size, but I maintain its constant presence!!

Its vestiges are found in the shape of one of the spaces in the boundary zone. The original cavity or its eddies like remains is thus broken up and subdivided firstly into two, (mainly through the agency of the germ of the posterior lobe) and subsequently smaller spaces are formed by divisions from these.

**Posterior or Infundibular Lobe**, also called the "Nervous Lobe", the "Central Lobe" or "Neurohypophysis". This is much the smaller of the two lobes, is rounded in form and of a greyish-yellow color. It occupies a small marked depression on the anterior aspect of the quadrilateral plate of the Sella. It varies very little in size, it is 2-3 mm. in transverse diameter by 6-7 mm. in vertical measurement. It is more soft, friable and transparent than the anterior lobe. As already stated, the line of demarcation between the lobes is only slightly apparent externally, but is well marked in horizontal or sagittal sections of the organ. Originally a hollow evagination from the cerebral, in the higher Vertebrata it remains small and its cavity becomes obliterated.
Diagramatic Sketches of the Hypophysis in the different groups of the Vertebrata.

Fig. I.
Amphibians — section through buccomaxillary duct
  1. Submaximal gland.
  2. Ganglionic mass.

Fig. II. Fishes.
  3. Infundibular cleft very large, also ventricles in which are vascular ridges (infund. gland).
  4. Plicular lobe.

Fig. III. Amphibians.

Fig. IV. Reptilians.

Fig. V. Birds.

Fig. VI. Mammals.

It will be noted, that as the infundibular cavity gets smaller, so does the glandular lobe increase, as though to compensate for the loss of the infundibular gland, of which by the by traces are seen in Amphibians, Reptiles and sometimes even in Birds.

In Birds the condition is very like that of the Mammals, cavity almost gone, and the glandular lobe large. In Mammals, the posterior lobe is small and solid, the glandular large.
In the lower Vertebrates throughout life and in the embryo of higher forms, the ventricle persists is connected thru' the atrium with the central ventricle, and is usually lined by ciliated epithelium. In many of the lower forms, especially in fishes, the lobe is large, distinctly nervous in structure, and constitutes an integral part of the brain, being known as its "infundibular lobe." In most fishes it retains a large cavity, whose walls are thrown into numerous foldings of a glandular character, very vascular, constituting the so-called "vasculosum vasculosum" or "infundibular gland." Of this vascular structure only a trace remains in Amphibians, while in Reptiles, Birds, Mammals it is usually absent, although according to Wiedersheim traces of it may even be found in man. In the sketchy column in plate VIII., which are modelled on Wiedersheim's works, the differences in this lobe, as regards relative size, position can be readily made out. Surrounding everywhere by pia mater, originally, it becomes later blended with the general capsule of the Hypophysis, and ultimately the lobe is enclosed by this everywhere, except along the plane or surface of its relation with the glandular lobe. What septa pass from the capsule into the substance of the lobe is difficult to make out, undoubtedly small processes carrying vessels do exist, but they do not subdivide its mass as
in the case of the Anterior lobe. The lobe in

indeed is as largely fibrous in constitution, that

it is often difficult to say where capsule ends &

substance begins. The lobe is fairly vascular.

The ventricular cavity is described by Charpy in

the child as a mere chink, difficult to make out,

and rarely found as a vestige in the adult.

Sternberg says cysts are occasionally present, some

with ciliated epithelium in parts, and partly con-

taining colloid. He believes them to represent

remains of infundibular cavity, remnants of the

infundibular gland & dispersed hypophyseal cav-

ity.

I have never seen the ventricle, or even

a trace of it in the human subject. Luschka

states that it exists in the child as degenerated

ciliated epithelium.

Mackel more recently

writes of the infundibulum — "some think it

hollow, some solid; others sometimes solid, some-

times hollow. It may serve to transmit into the

cerebral vessels a fluid which is excited by the

"pituitary gland". Schäfer says that some-

times the remains of the original hollow are seen

in the form of a cavity, lined by columnar ciliated

epithelium. Boyes states that an irregular space

is found in monkeys, but has no definite epithel-

ial lining.

In hydrocephalus an extension of the cavity of the

third ventricle for some distance down the infund-

ibulum has been noted by Danger and others.
Section of this infundibular lobe under a power of a few diameters only, shows an apparent fibrous surface with many sinuous lines giving it a somewhat lobular appearance. The lobe is mainly composed of what has been aptly described by Schwab, and others as a paracromatoid-like tissue, of which the spindle-fibres pass in various many directions.

Valenti describes cells and highly colored nuclei. Luscher figures a molecular ground-substance containing small unbranched cells, large melanized cells, and cells with one or more processes.

Turner states that this lobe is an appendage of the brain, and possesses a framework of connective tissue intermingled with various nerve fibres and small cells. Some polygonal, others fusiform. Also it contains a capillary plexus. This anatomist states that the cavity of the ventricle is prolonged through the infundibulum into the lobe in the fetus. Schäfer considers that the lobe consists chiefly of vascular connective tissue arranged in radiating bundles, between which are numerous branched and spindled cells, as well as a few larger corpuscles containing pigment granules. In the adult, he finds scarcely any perceptible nervous elements.

Van Gehuchten describes it as composed of cells and fibres, the cells of triangular form, with short processes. Masalitsin affirms it to be an oval mass of connective tissue, the thickened end
of the infundibulum.

Charpy believes that in higher vertebrates it is a degenerate organ, nerves in the embryo, connective in fetal life. In the adult he maintains that it is not nerves in structure, but formed up as neuro-mesodermal looking tissue — a network of fibres with connective tissue cells amid a meshwork of vessels — the larger cells containing yellow granular pigment. One may hesitate, he says, as to the function of the anterior lobe of the hypophysis; but as to the posterior, it is undoubtedly degenerate.

But in the nervous state, he continues, what does it represent, an ancient sense organ like the pineal gland, which it so much resembles, or is it the model of origin of the nerves of the pituitary gland, this self-same ancient route? Pflüger describes the lobe as comprising round fro-

iform or branched cells amid a connective tissue atoma — the branched cells probably nerve cells. According to Hertwig, the infundibular lobe is in lower vertebrates, transformed into a small brain lobe, in which ganglionic cells and nerve fibres can be traced, while in the higher forms he found no trace of nerve elements, but spiralled cells closely laid by one another.

Sternberg believes that this lobe persists in mammals as a sort of anterior fibrous terminus, its clavandine generally speaking, like embryonal nervous tissue. It consists of an abundant frame —
work of fine neurogliar fibres with cells spiralled or branched, and an abundance of yellow pigment. He finds that in places the neuroglia forms septa in which are formed cells of varying shape, polygonal, rounded, or spiralled — the cells usually containing pigment.

It is of interest to remember, that in some of the lower vertebrates, notably fishes, the posterior wall of the infundibulum is evaginated into a long narrow epithelial tube, whose walls are thrown into numerous folds, by the presence of many blood vessels — the name “Saccus Vasculosus” being given to the condition, which resembles in character the “neurohypophysis mammillaris”. In Selachians it contains large ridges and nodules of epithelium, and forms in them an evidently functional structure. Stahler in his exhaustive paper on the hypophysis points out that in some of the lower vertebrates e.g. Teleostei, the saccus vasculosus or infundibular gland is a true glandular organ, which develops as an outgrowth from the infundibulum with whose cavity it maintains an open connection, and therefore communicates directly with the central ventricle. In the higher vertebrates (e.g. Mammalia) he finds no trace of this gland, but in its place, a solid outgrowth, the “processus infundibuli”, attached to the stalk and apparently rudimentary in structure. He thinks it possible that the solid process may still
retain some of the glandular structure of the primitive submucous gland.

Berkeley found in the dog, that there was a closed ventricle between the two lobes, and on treating the posterior lobe by Golgis method, found, and describes nervous elements there of the most intricate and bewildering character. He reports as follows — in this lobe are found, immunes nerve cells of several types, a critical layer of ependyma cells, a nervous network, peculiar bodies resembling nerve organs, and lastly gland epithelium cells arranged in part to form tubes or closed vesicles, some containing colloid. In his plate he shews in addition to various types of highly organized nerve cells and very definite tracts of nerve fibres — peculiar comb-like bodies and nerve tufts upon many of the nerve terminations.

If, he says, "the rounded comb-like bodies are follicles, then their nerve endings are certainly very dissimilar to the endings upon the alveoli of the salivary and thyroid glands, or even the adrenal capsules: very much more do they resemble the endings of the mitral cells of the olfactory bulbs, the so-called "Olfactory Glomeruli", and it is more plausible to refer them to some organ of special sense, existing fully developed in the lower forms of animal life than to endings upon secreting epithelium."

He concludes, that the silver method shows that
"Posterior Hypophyseal Lobe."

(Stained with Haematoxylin and Eosin.)

**Fig. I.**

1. Fibres and Cells.
3. Peculiar oval bodies.

**Fig. II.**

1. Vessels in outline.
2. Cells with processes. (Nervous.)
3. Fibres (paranematoid, probably nervous.)
4. Stroma.
5. Peculiar oval or rounded bodies - very finely granular, some with sharp contours.
the Pituitary gland has retained in one of the highest orders of vertebrates, its double role of secretion and nervous function intact, the former perhaps modified — the latter, the original special sense organ, probably simply lying quiescent, not atrophied and only changed in as far as to admit of slightly different arrangement of its constitutional elements. I have quoted verbatim the conclusions arrived at by Berkeley, inasmuch as I have never worked at the hypophysis in the dog and cannot therefore pretend either to verify or dispute them — they certainly are most remarkable, and although many other workers have used similar methods, no one seems to have arrived at like results. Menculan describes the structure of the posterior lobe as consisting of bundles of fibres crossing in every direction, together with scattered pigmented cells, which were formerly regarded as imperfectly developed nerve cells.

Boyle and Beadles describe the general structure of the lobe as consisting of sarcomatous-looking tissue, containing here and there cells resembling gliæ cells. They also consider that pigment cells are a striking feature of this posterior lobe.

I will now tabulate my own observations regarding the constitution of this lobe.

In plate IX are shown sections stained with haem and haematoxylin under low and high powers. Under the low power (fig. 1) the following can be made
out

1. Many fibres.
2. Cells varying in size and shape.
3. Stroma with vessels.
4. Curious oval or rounded bodies.
5. Collections of brown pigment.

Under the high power —

1. Many fibres, sarcornatin-like, and probably nerves in character.
2. Vene cells of varying shape, some with distinct tails.
3. Less definite smaller rounded cells, of a neurophilic type.
5. Veneels with very fine walls, some in outline, some in transverse section.
6. Peculiar rounded or oval bodies, light brown in colour, very finely granular, and some of them possessing a sharp contour.
7. Brown pigment, some in collected masses, some more diffuse.

In this lobe therefore there is a fundamental neurophilic structure, as evidenced by the fine fibrillar meshes and the smaller rounded cells. In this are supported undoubted nerve elements, although of a primitive or degenerated type. Viz. the many fibres and the larger cells. The lobe is well supplied with blood. The presence of so much pigment, not only in collected masses, but also in more diffuse form, seems to me to point to oligen-
erations. And lastly the peculiar oval, non-muscle, 
ated large bodies, what are they, and what do 
they represent? They are not cellloid in charact-
es nor do they present the features of ordinary 
cells — personally I am inclined to think that 
they may possibly represent vestiges of ancestral 
nerve organs, as seen in Amphivas and Petru-
myzon, and also according to Berkeley (in degen-
erate form) even in an animal as high up in 
the mammalian scale as the dog.

In none of my sections have I ever seen glandular 
cells, or anything like an approach to vestiges 
of an hypophyseal gland — altho’ as before noted 
Wiedersheim says that traces of this structure 
are occasionally found in man.
The lobe is in my opinion certainly degenerate, 
still it does possess some nervous elements, and 
it is highly vascular, above all it is constantly 
present, and in almost unvarying size.

May it not possess some remnant of the ancient 
junction preserved by its prototype?

However I hope to refer to this again, when con-
sidering the functions of the Hypophysis.

**Boundary Line.**

Weichselbaum has seen small cavities lined with 
elastized epithelium where the two lobes join.

Berkeley found that in the dog, a closed ventricle 
marks their junction. Edinger states that between
the two lobes of the hypophysis, there is found a
number of epithelial tubules, the lumina of which
he says "as far as I can ascertain are not con-
ected with either the one or the other part of the
hypophysis." By other observers it is stated,
that the two lobes are separated by a narrow lymph
atic space.

When the region between the two lobes is examined,
one is struck by its indefiniteness - there exists
no sharp fibrous or pleural separation between
them, as has been so often described. Under a
high power as seen in Plate X, it can be
noted that the fibres are arranged in a uniform
fashion, curve downwards and into both lobes.
In fig. X. come from oval spaces, or at least they
seem to be distinctly in this so-called fibrous lay-
er, and contain colloid. There are also seen in
the anterior edge of the posterior lobe, two large ves-
cicles in transverse section, and also a distinctly
ovoid space lined by characteristic epithelium.
This space is empty in the specimen. In the
lower half of the figure, the central acini are seen
to be much more loosely related to each other than
in the remainder of the glandular lobe. Some of
them indeed lying distinctly in this fibrous region
and one large oval acinus there is seen distended
by colloid. Lastly in this layer one or more
thin layers of cells are seen partially emmeshed in
it. Development and especially its...
Section through junction of hypophyseal lobes, showing the "boundary zone."

\{Stained with haematoxylin.\}
\{Leiss D. – Ocular I.\}

The boundary zone is seen to comprise the following:

1. Fibres.
2. Alveolar spaces containing colloid.
3. Alveoli derived from anterior lobe.
never teaching shores us that the bucco-venous duct (with its gland at one end, and nervous ganglia at the other) has in the process of evolution become shortened and atrophied, until at last the gland and ganglia come together, and adhere along their juxtaposed surfaces. I do not believe that pia mater has anything to do with the formation of this boundary zone — no doubt it may have completely encircled the infundibular evagination in its first stages of growth downwards from the brain — even this is debatable — but we know that when the brain and central budding come together, they become firmly adherent in the first instance, and any pia mater as such, must from disappear in the process of cohesion.

Now, I do not believe that, although this zone is peripherally attached to the fibrous capsule of the entire organ, it is necessarily a derivative from it. So far as I can learn, there is little or no evidence to support the theory that the gland’s capsule is formed at a later date, than that at which the cohesion of the lobes is completed.

I consider that this boundary zone contains the vestiges of the bucco-venous duct, the trace or traces of the original canals of the glandular lobe, as also some glandular elements involved in its metamorphosis. From the many specimens I have examined, I should propose to describe this zone as follows: It lies between the two lobes...
and of varying thickness in different individuals. It consists of loose bundles of fibrous tissue whose fibres are somewhat parasitized in appearance and arranged in a bipenniform manner. This boundary zone is extremely vascular, and shews about its middle, the bend or genu due to the bending forwards of the posterior lobe in that region as already described, also the acini embedded in its substance, some of them large, and containing colloid. Often one finds one or more acini just on or in the margin of the posterior lobe. In other words, this boundary zone, from its originally loose texture, and the vestigial clefts contained in it, is eminently fitted to provide spaces for the storage of colloid material. On a previous page I maintained that in carefully double-stained sections, while one finds here and there occasionally colloid in an acinus, that such are few and far between - the denser condition of the anterior lobe affording doublets an unsuitable area for the expansion of colloid-containing acini.

Boycie and Beadles, found the junction between the lobes most marked at the genu, and on my asking my opinions to Dr. Beadles (who had himself examined over a hundred pituitaries) he quite agreed with me, that under normal conditions, the colloidal spaces of the hypophysis cerebri are to be found in its boundary zone.
Pons and Valsa, large extra-acellar cystic cells containing colloid, found in this boundary zone, but I have never seen them in any of my specimens. Another feature of this zone, is that the cells quite aldehyde take on a much deeper stain. Royce and Beadles have also noticed this fact & describe also in some of their specimens, branching adenomatous masses of cells (cells which were cyanophilic and contained large nuclei) also undifferentiated multinuclear masses of protoplasm.

I have never found these latter, but in most sections have found a very deeply staining area, somewhat triangular in form, and consisting of more densely packed cells than seen elsewhere throughout the lobe. The position of this area is shown in the accompanying figure.

**Vessels of the Hypophysis.**

The Hypophysis is a very vascular organ. I have found arteries supplied to the organ, derived from six sources:

1. Internal Carotid (cavernous part)
2. Infundibular. (largely No. 5)
3. Meningoperiotic.
4. Diaphragmatic.
5. Posterior Communicating of the Middle Cerebral.
6. Other minute & occasional sources.

These from the Internal Carotid exist in a number of small branches given off by the artery in
Plate XI

"Anterior lobe of Hypophysis."
stained with "Picro-nigrosine" to show vessels.

Fig. I. (Zeiss D. Oc. 1)
Shows very thick vascular capsule (1).
(2) Vascular.

Fig. II.
Shows how richly vascular the lobe is.
(At sections, the cells are somewhat too vividly colored.)
its cavernous part. Those of the second group mainly pass to the posterior lobe, running for the most part on the surface of the infundibular stalks, and although these are occasionally somewhat tortuous, yet as before mentioned, I have never observed anything like the tortuosity described and figured by Luschka. The arteries of the third group are derived chiefly from the dorsal branches of the small meningeal branch of the internal maxillary artery.

Very minute twigs pass into the hypophysis from arteries in the diaphragma sellae. At least two of its arteries are derived from the posterior communicating branch of the middle cerebral. And largely twigs are furnished to the organ, at least occasionally from the anterior cerebral, and probably also from meningeal branches of the ascending pharyngeal and other arteries.

The arteries from the posterior communicating mentioned above pass to the hypophysis along its stalks, in their course lying in pia mater, and freely anastomosing with the infundibular arteries.

The anterior lobe of the hypophysis is thus supplied with blood mainly from the internal carotid and meningeal periosteal arteries, while the posterior lobe of the organ derives its arteries from the infundibular arteries some of which come from the posterior communicating artery.

Veins — The blood appears to be returned from
The Hypophysis, mainly as follows —

1. Into the Carotid Sinus directly.
2. Into the Anterior and Posterior Intercarotid Sinuses.
3. Into an occasional unnamed sinus (often double) which passes below the two Carotid Sinuses under the Hypophysis.
4. Into Cerebral Veins along the infundibulum.

The Hypophysis Cerebi is therefore a very vascular organ. The arteries by subdividing in its capsule, enter its substance, and form for the main part a fine capillary plexus in its stroma, the scanty nature of which must allow the thin-walled vessels to lie in close relation with the axons of the glandular lobes. The blood thus therefore be easily acted upon by the cells themselves. Plate XI.

As will be subsequently noted, the Hypophysis is often compared in structure and probable function with the Thymic gland, and like it, has its chief arteries passing to it in tortuous fashion. The question naturally arises, have the Hypophyseal arteries a vascular potentiality similar to that of the Thymic vessels. Making due allowances for differences between the two organs in size and mobility of position, I believe it will be found that they have. It is known that the Hypophysis becomes engorged during pregnancy just as the Thymic gland does. Probably future investigation will reveal that it also enlarges.
and becomes more vascular during menstruation and other functional states.

And lastly we know that in Acranegaly, Impoedema and probably other morbid conditions, the vascularity of the Hypophysis is very much increased.

**Lymphatics.**

These vessels undoubtedly exist and mainly join those related to the 3rd Ventricule, which open into a fairly large trunk, which passes from before backwards, accompanying the Venae Galenae in the Velum Interpositum. Doubtless also some minute lymphatics run into the lymph vessels accompanying the Submental Lymphatic and other arteries. Schäfer states that the lymphatics originate in cleft spaces between the tubules, and pass to a network in the capsule.

**Nerves.**

Ramon-y-Cajal found on staining the Hypophysis of the white mice with Silver Chromate, an abundant ramifications of nerve fibres forming throughout the entire gland a minute plexus, but he was unable to establish their true nature. These fibres he believes to be the axis-cylinder processes of a group of nerve cells situated behind the optic commissure. Many of these fibres, he says, end in the thickness of the pituitary stalks, some enter into the anterior lobe and some penetrate even between the epithelial cells. In the posterior lobe, in addition to these fibres, he found
nerve cells triangular in form, and possessing short processes.

In the human hypophysis, no stain as yet has succeeded in demonstrating a connection between any part of the brain and the organ, through the insidiousness.

But if and Berkeley stained with Golgi's method, Berkeley affirms that the posterior lobe is mainly composed of neuroglia, containing cells of the most varied kind, but few nerve cells.

It is a matter of great regret to me, that I cannot give any definite results of my own, regarding the staining of the human hypophysis by means of Golgi's methods. I have carefully gone through his process several times, used material as fresh as could possibly be obtained, and on every occasion I was unsuccessful, the vessels only being stained, a result which, I understand from others, is not an unusual one. I am convinced that the process is of little use in the case of the hypophysis, unless that organ be absolutely fresh, that is, obtained immediately after death. In any case, my own results only chronicle failure.
Physiology of the Hypophysis.

As already noticed, the Pituitary body was believed to possess as its one function the production of the nasal secretions. This belief was cherished by the older anatomists for very many years. With our modern knowledge we are apt to laugh at the bare idea of such a function having been ascribed to the Pituitary. And yet when you look at a vertical midsagittal section of the head, such as shown in plate III, you cannot but sympathize with this early error, for the organ is seen to lie in a bony recess separated from the large olfactory cells which are immediately beneath it by a very thin plate of bone, and thus and the olfactory cells were doubtless regarded as reservoirs for the pituita from which the juice could be dotted out for the use of the nasal cavities as occasion required.

This theory of its function having fallen into deserved disrepute, the hypophysis was variously labelled a nervous ganglion, a lymphatic gland, and (especially by Lister), a blood gland. During this period Liger in 1844 wrote that "its precise nature is not well known, and of its functions physiologists are ignorant." Still later it was regarded as a mere vestige, and most observers assigned to it either no function at all, or else presumed that in some general way of a way, it might act as a blood gland.

Until the advent of Cremona, and its acceptance
by the medical world as a distinct disease, little was done to investigate the probable functions of the Hypophysis Cerebri.

Since that time however much has been done, and although personally I have not worked at its practical physiology, yet having recently come across a case of Acronegaly in my own practice, (a case presenting various unusual symptoms), I made it a matter of duty to learn all that had been done in the investigation of the functions of this most enigmatical body, and propose very briefly to recount the main points elucidated regarding these, by the experimental research of others. It is a matter of great regret to myself, that the exigencies of medical practice have not allowed me either time or opportunity to engage in laboratory work upon what to me appears a most fascinating subject, but that pleasure has been denied me, and I can only therefore repeat of the experiments of others, and venture to deduce conclusions from them.

Let me first however recount some of the general opinions expressed regarding the functions of the Hypophysis. Van Gehuchten after describing briefly the anatomical nature of the organ, says—"as regards its physiological value, the clinical, and anatomical-pathological observations of late years, as also recent experimental researches tend to prove that the Hypophysis is an important organ, exercising a manifest influence on the development
of the body — on the development of certain parts of the body."

Laennec considers that the hypophysis is not merely a fetal relic, but that "from its very persistence from the lowest vertebrates up to man, it appears endowed with special functions of its own, and is liable to morbid conditions in the same manner as other internally secreting glands.

Echinger says that the hypophysis of the epithelial part hitherto established in Hypochondria, points directly to the hypophysis performing some definite physiological function.

Wiedersheim believes that in the Vertebrata, the gland mainly secretes the ventricular fluid, but denies that it has the same function in the higher Vertebrata.

Some authors still persist in regarding the Hypophysis as an atrophied organ and nothing more.

The glandular lobe according to Haller possesses in some animals an incomplete systém of ducts that open between the meningeal membranes, and that another believes that there is any connection in whole or in part between these membranes into the cerebro-spinal fluid. Charpy considers that the arrangement of the retina with its vessels brought into immediate contact with the gland epithelium, presupposes a process of absorption, and indicates an active hypothysical function.

I think it best for the sake of cleanness to classify the methods of investigation under five headings —
I. Removal of the gland, and its effects.

II. Results of Stimulation and Irritation.

III. Pituitary Feeding and Injections.

IV. Its analogues with the Hypophysial gland.

V. The Chemistry of the organ.

Removal of the Hypophysis has been practiced by Horsley, Marinesco, Sey, Vassali, Sacchi and others. Their results are remarkably contradictory.

Horsley found that its removal scarcely affected the animal at all, but that certainly it did not live long after the operation. Vassali and Sacchi found that the animals usually quickly died, although a case is recorded where a dog lived for a year after excision of the organ. These last observers record that the following symptoms were noted after operation:

- Permanent fall of body temperature.
- Anæmia and listlessness.
- Fibrillary twitchings + muscular tremors.
- Muscular spasms + tremors (latter)
- Periodic attacks of dyspnoea.

and generally rapid progress towards a fatal issue. They also found, as did Broussais, that many of these symptoms improved when animals were fed on pituitary extract.

Marinesco found that cats lived for only about a couple of weeks after removal of the Hypophysis. Salt's results agreed with those of Vassali & Sacchi, and he considers that the psychic depression and muscular weakness which follow excision of the organ
are due to loss of nutritive efficiency in the nervous system.

Results of Stimulation and Irritation.

Cyrus irritated the hypothalamus by means of light compression and also by a weak electric current, and got immediate consequences, in the form of a quick variation in blood pressure with a notable slowing of the heart beat, whose force is at the same time notably increased. Cyrus endeavors to explain these phenomena as being the result of an excitation of those mechanisms which relieve the brain from injurious influx of blood. The rapidity with which the results followed the stimulation led him to believe that the stimulus is transmitted by the "vagus infundibuli" to vagal centres. In postnatal kittens this observer was able to trace fibres from the infundibulum into the pons, and therefore considers that in these phenomena the Pituitary gland "per se" plays little or no part.

We have already noted that in man, despite all the progress of modern anatomy, that no direct connection has been made out between what cells exist in the posterior lobe of the hypothalamus and the brain, so that in man at any rate, Cyrus's last deduction can not hold good.

Pituitary feeding and injection.

Mairet and Rose found that ingestion and injection of ox-pituitary gland extracts in normal men and animals produced only slight effects, some malaise
and elevation of temperature, slight faeces intestinal turgor, and slight emaciation. They found that intravenous injection was followed by toxic phenomena. Both feeding and injection in the case of epileptics seemed to produce mental excitement, and rather aggravated the convulsive condition of the patients.

Symmonds states that with Pituitary extract, he found a slight fall in blood pressure, together with quickening of the heart's beat, and contraction of vessels, results which are the reverse of those produced by Adrenal extract. In finding them just the reverse, concluded that the effects of Pituitary extract are different and less marked than those produced by Adrenal.

The experiments of Oliver and Schüfer are too well known to require detailed description, suffice it to say, that they found with the use of Pituitary extract two marked effects, viz., a marked rise of the blood pressure, due to contraction of arteries, and distinct augmentation of the force of the heart beat. They state that these results resemble those produced by adrenal administration, but differing from it in causing no slowing of the cardiac beat. Stein found by using extracts of pineal gland—hyper-teremin and slowing of the heart beat.

Howell, whose results and deductions therefore are somewhat remarkable, used in his experiments Sheep's hypophysis. In the sheep, the posterior as well as the anterior lobe is apparently glandular
in character, and he employed extracts of the two lobes separately. He found that extracts of the anterior lobe produced no characteristic effects upon either circulation or respiration — the results in fact were inconstant or negative. But with extracts of the posterior lobe were obtained — very marked prolonged slowing of the heart beat, and an increased blood pressure. In his experiments he employed dried pituitary extracts, and also glycerine extracts, and injected these into the femoral or jugular vein of anesthetized dogs. From his experiments he argues, that the active hypophysal substance like that of adrenal, is destroyed or in some way neutralized in the body so that its action is comparatively temporary. He finds this active material quite different from anything occurring in other parts of the brain, and believes its effects may be direct, or through the nervous system. Howell considers that physiologically as well as structurally, the two lobes are independent structures, and concludes as follows: "the method of injecting extracts appears to teach us nothing with regard to the functional activity of the hypophysis — it neither confirms nor disproves its supposed relationship to the thyroid body. On the contrary, the marked influence of extracts of the posterior lobe suggests that this organ may form a secretion of great importance to the functional activity of the cir-
"vascular organs. Certainly the effects caused by its extracts, tend to disprove the prevalent view that this body is merely a functionless end- -ment of an organ of primitive importance. Its analogies with the Thyroid Gland.

These have been generally based upon —

1. Histological resemblances.

2. Thyreo-priva is usually followed by increase in size of the Hypophysis, and some of the symptoms are like those which follow removal of the Hypophysis itself.

This has been noticed by Scieda, Hopmeister, Rosewitsch, Gley, Picart & Viola &c.

3. In cases of Myxedema or Sporadic Cretinism where the thyroid gland was atrophied or absent, the Hypophysis was found enlarged. Niepee records five post mortems on cretins, & in these he found the Hypophysis much enlarged in every case.

4. In several morbid conditions, the two organs have by many observers, been found both enlarged together.

Schenkman, Leonard, Compte, Monsee and others have all worked at the supposed relationship existing between the two glands. Schenck found that in 17 dogs whose thyroids had been removed, that in only two cases did the Pituit-ary body seem to functionate, and then only slightly. Schenckmann, after examining the
two glands in 112 individuals who had succumbed to various diseases, believes that the two glands are closely associated in function. Comptis concludes, after having examined over 100 cases, that these organs (thyroid, hypophysis) act vicariously towards each other. He states that both enlarge temporarily during pregnancy, and shows that also in Goitre the hypophysis increased in weight, although not proportionately with the thyroid, and explains that cellular enlargement of the thyroid does not necessarily mean an increased introduction of its secretion into the circulation.

Oliver and Schäfer having found in their experiments that thyroid extract dilates arteries, and causes a fall of blood pressure, without however diminishing the heart's beat, thinks that their results seem to indicate that the thyroid and Pituitary are not vicarious in function, as the administration of their extracts produce entirely opposite physiological effects. Howell thinks on the other hand, that these observers use their results to form a hasty conclusion to combat the view of a physiological relationship between the two organs, especially as in their experiments, they made no differentiation between the two hypophyseal lobes. Shattuck observes that they are probably vicarious only in what they have in common, i.e., colloid producing capacity, "the amount of colloid in the
“Pituitary is however so small, at any given time, that in an extract, its action would be masked by the other substances.” He considers that the Pituitary, like the Thyroid and Adrenals, is a composite structure, and has probably more than one function. In the Hypophysis, he says, the chief mass is cellular, much like parathyroid in structure, with cell-columns ramifying through a close capillary network, and this mass quite covers the colloid-holding component of the organ.

According to Chevrel, the Hypophysis has many analogies with the Thyroid gland. It secretes a juice useful for the nutrition, or destructive to organic toxic substances. It is frequently the seat of colloid cysts, and very rarely shows calcareous infiltration. It markedly hypertrophies in Acromegaly.

In connection with calcareous infiltration, many mention that Pichard in 1801 says that “sometimes but rarely we find within or on the surface of the Pituitary gland, a solid or sandy substance (calcareae calcinatae).” Personally I have never found calcareous matter in connection with the Hypophysis, and am inclined to think that Pichard has confused the Hypophysis with the Epiphysis.

The Chemistry of the Hypophysis.

The Hypophysis is found to contain iodine in the form of iodothymin, just as is noticed in the Thyroid gland.
The administration of dried pituitary or of pituitary extract in man increases in a marked degree the excretion of Phosphoric Acid in the stools — this process probably depending upon processes in the secretory tissues. Schöpf considers that this might explain the inverse phenomena of hypertrophy of bone tissue in Acromegaly, through hypofunction of the Hypophysis.

He has also noticed excess of Phosphoric acid in the stools of the Acromegalic.

Such then, as far as I can ascertain, are the facts elicited by experiment regarding the functions of the Hypophysis. There can be little doubt that the organ has a most complex structure, and that both as regards development and probable function, it occupies a peculiar position among organs.

Collini, tracing its function from archaic forms, says that after the luminous duct has become obliterated, the function of the gland is not abolished — its juice is still carried by the nervous system, and arrives there by lymphatics and bloodvessels. He believes that the Hypophysis "determines the decomposition of a substance for tissue, which is very rich in Phosphorus and Ash. It is difficult to say which tissue is, probably it is the connectives."

Brown-Segur calls its secretion an internal one. Sternberg says that the idea which was held half a century ago, is now again accepted, that so-called "bloodvessel glands" withdraw some kind of material from the blood, and return it to the cir-
-ulation in an altered form.

Aicenti and Viol is considers that the colloid sub-
stance is forced into a series of spaces, analogous
to lymph spaces, and enters the circulation in a
manner unknown.

Vassalen and Lacchi believe that the chief func-
tion of the Hypophysis is to elaborate an internal re-
creation, a product necessary to the animal economy.

D'Alberda thinks that the Hypophysis may lie in the
path of important relations between the viscera and
body tissues on the one hand, and the co-ordinating
centres presiding over their trophicus upon the other.

Schäfer thinks that an internal recreation is furnished
to the blood by the Hypophysis, and that this
recreation besides increasing the contraction of the
heart and arteries, may perhaps influence the
nutrition of some of the tissues, especially of bone
and those of the Nervous System.

Jeffroy lays great stress upon a second important
function, which he maintains is possessed by the
Hypophysis, viz... the control of the development &
relationship between the osseous and muscular
systems.

Meecham considers that the pituitary recreation either
by itself or in conjunction with that of other duct-
less glands, is of profound importance to the ani-
mal economy, and is chiefly concerned in the
nutrition of the nervous and muscular systems.

He also thinks it remarkable, how the symptoms
produced by the removal of the Hypophysis Co-

vixis with time deduced by Andriesen upon purely

morphological considerations.

So far as a study of the development, anatomy, and

experimental physiology of the Hypophysis can teach

us, we now know that the organ, although in one

case a vestigial one, is nevertheless an active veste-

gone in which a morphological transformation has ta-

ken place, but whose essential functions remain as

necessary to man, as to the archaic forms.

Whatever functions may be possessed by the anterior

lobe, and there are some grounds for believing that

others may exist — it has one very evident one viz.

the production of a secretion. The eminent structure,

the rich vascularity and the relations of the animal

cells to these vessels show this lobe to be an actively

functioning organ. In my own mind there is no

doubt but that the cells eliminate the colloid from

the blood receive it into their lumina, which duct-

like pass it on in some probably indirect manner

into the spaces in the boundary zone — fit receptac-

les for it. From there it is again passed into

the circulation largely by the lymphatics of this

region and also by the blood vessels (see plate XI)

That this secretion has a profound action upon

the general nourishment and growth of the body

tissues is certain.

So to the role played by the posterior lobe of the

Hypophysis, we are in complete ignorance. We
have seen that in lower vertebrates this lobe is not only nervous in nature but is also in part glandular in structure, but that in man no trace of the infundibular gland can be made out, despite Hirsch's statement, that sometimes traces of it exist. I have already pointed out that any vestiges of this gland are probably lost in the story by zone. Arguing from Huxley's experiments, it would seem that whatever secretion it may produce or function it may have, are widely diverse in character from those of the anterior lobe.

In the fishes, the posterior lobe probably not only indirectly receives most of the secretion of the anterior lobe, but also adds to this one of its own, before passing it on into the ventricular system of the brain. As to what the action of this anterior lobe may be, as to whether the active properties of the anterior lobe secretion are increased, altered or modified, one can only hazard the weakest guess. It is, however, as in the lowest vertebrates of all—the amphiuma, the frog, (the representative of this infundibular lobe) apparently had some of the characteristics of a sense organ, and seemed to exercise a controlling influence on the ingress of water (and with it the secretion of the sublumenal gland) into the ventricular system, it seems to me possible that in higher vertebrates, although its anatomical features have become much altered, it may still in some unknown fashion influence the ingress.
of the secretion of the anterior lobe into the blood, and through it, into the nervous system.

The fact that the posterior lobe is always present, and that even in man (albeit small) it practically always retains a similar size, and is very vascular, proves, I think, that it has some work to do, despite the fact, that the microscope pronounces it to possess only a degenerate fibrous structure.

And we ought not, I think, to forget, that it is not so many years ago, that our mind scientific, confused itself about the meaning of the hypophysis at all, and had anyone authoritatively declared (what we now know to be true) that the anterior lobe was an active glandular organ, with more that its secretion was one, fundamental, to the nutrition and growth of the body, his opinions would doubtless have been at once relegated to the limits of physiological romance.

Of course the posterior lobe is a degenerate organ, but is a persistent one, and from what we know of its archaic history, it may have retrograded & atrophied, up to a certain point, and yet still possess some controlling or other function, whose nature may perhaps be disclosed in the near future.

It seems to me impossible to consider the healthy functions of the hypophysis cerebi, without first considering some of the pathological problems presented by this fin de siécle disease, Kermigyld.
and this I propose to do in the succeeding Chapters.

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Acromegaly.
"Acromegaly."

I have no intention of entering fully upon the symptomatology or pathology of this disease, regarding which hundreds of papers have been published since the early eighties, when Pierre Marie christened the lesion and first fully described it.

When I first went into its bibliography, stimulated by having had a case brought under my own care, I was simply appalled to learn how much had been written on the subject. It became an impossibility to read all the papers that in this and other countries had been published, but I did go through most of the important ones, and have annexed to this chapter the bibliography of those, together with a complete list of the publications on the subject during the past two years.

I propose first very briefly, to tabulate the leading features of my own case, and thereafter to discuss the various opinions which have been advanced regarding the role played by the hypophysis in the causation of the disease, finally to summarize what I believe to be the leading functions of the organ under normal circumstances.

F. C., a houseman, of 54 years of age came under my observation early in December 1898. He complained of weakness, headache, palpitation, dyspnoea and pains in his limbs. As a boy he described his skin as covered with little blemishes spots, which condition earned for him
among his playmates, the sobriquet of "the Spotted Leopard." He maintained that until he was 17 years of age, these spots were quite smooth and flat on a level with the skin. After this time he noticed that the spots began to get raised, and at the same time to lose their color. They then gradually became small lumps, and have continued to increase in size and number ever since, although less so of late years. The tumours cause him no discomfort whatever. The case was undoubtedly one of molluscum vil-
comum, but what to me was of far greater inter-
rest was the fact, that the patient was certain-
ly a victim of Connegale.

It was quite apparent on a most unprejudiced examination that the mandible was prognathism,
the lower incisors biting in front of the upper ones,
his hands were apadelike, and his forearms considerably longer than normal. His feet and
ankles were enlarged, and he experienced much
pain in walking — this pain he attributed to
his exposed and arduous life as a hawker.
A careful subsequent examination revealed the
following points,

1. Overgrowth of the Extremities.
2. Hypertrophic Coindition of the Skin.
3. Enlargement of Viscera.

1. Overgrowth of the Extremities.
   Superior Extremities. The hands were broad
thick and apodelites, the fingers spatulate. The metacarpal and phalangeal bones were thicker than normal and there was also considerable enlargement of the soft parts, especially near the palmar veins hypertrophied.

The radius and ulna were at least 1½ inches longer than normal, and were chiefly thickened in their lower half. The Carpal also was somewhat massive, and the radio-ulnar joints were slightly enlarged.

**Superior Extremities.**

The feet were much swollen, the swelling was not however that of edema or myxedema, but a uniform enlargement of soft and hard parts alike. The feet were long and the bones much thickened, almost irregularly so. The ankles were considerably enlarged. The Tibia and Fibula were if anything somewhat longer and thicker than normal.

**Facial Extremity.** The face was markedly prognathous, the jaw angle projecting very much more forwards and lower than normal. The orbital ridges were extremely pronounced, there seemed to be some increase in size of the malar arches. The lower half of the nose was large and renoulet, and the ears were large. The tongue was big and renoulet, the pharyngeal wall much thickened, and contained an excessive number of adenoid patches. The tonsils
were hypertrophied and there was an adenoid mass in the roof of the nasopharynx.

Penile Externality: The penis was of great length and size. It measured in the dependent position about six inches, and was proportionately thick. The patient had noticed the increase in the size of the patient of late years, also that with this increase, the sexual power became diminished. The testes were if anything smaller than usual, the scrotal wall lax and thinned.

II. Hypertrophic condition of the Skin.

The patient suffered much from hyperhidrosis. The skin everywhere was coarse and thick, especially in the buttocks, backs of neck, palms and soles. The filaments previously referred to, were more numerous in the legs than the arms, and existed abundantly in both palms and soles. They were very numerous in the face, and varied in size from a millet seed to a small bean. Minute and hardly seen raised over the cheeks and near the Alae nasi, they were more pronounced over the chin and in the submaxillary region, while below and behind the ears they were in large numbers, and some of them were the size of coffee beans. The pinnae and nose were free of them. The tumors crowded the scalp, especially in the occipital region. Very numerous in upper neck, especially at the sides and behind. On the trunk, they occurred,
Plate XIV.

"Molluscum Fibrosum."

Section stained with haematoxylin and eosin.

Fig. I. (Leica A - Oc. 2.)

1. Epidermis.
2. Corium.
3. Hair follicle.
4. Sweat glands.
5. New growth, - begins under this cutis, and has some slight infiltration round it.

Fig. II. (Leica D - Oc. 2.)

Section of the fibrous new-growth shows -

1. Spindle cells.
2. Deeply staining infiltrating round cells.
3. Vessels show good walls, and are normal - not as in sarcoma.
all over the chest, and upper half of the abdomen (especially on the flanks, and near the nipples) & some of them were as large as a walnut. Over the scapula they were very large, some engul ferate. The back was thickly crowded with them.

I excised one of these growths from the flexor aspect of the arm for purposes of microscopic examination. It was found to be composed of actively growing fibrous tissue, and it has the structure of a fibroma of the corium. It invades and destroys all the appendages of the skin. It has numerous vessels, which are however not thin walled as in Sarcornata.

Plate XIV shows the structure under high and low powers. Fig. 1. (L.P.) shows that the growth begins under the epidermis, and has some slight infiltration around it. Fig. 2. (H.P.) shows that the cells are mainly spindles, but there are also some deeply stained infiltrating round cells. The vessels have normal walls.

The skin of the scalp, face, and axillae was thin and coarse, over the rest of the body-surface there was scarcely any, and the genital hairs was practically absent.

**Splenomegaly.** (III.)

The heart, liver, and spleen were much enlarged, but there seemed to be no alteration in size of the thyroid gland; nor could I make out any marked post-natal dullness, which is so often described in such cases as indicative of enlarge -
ment and remicicence of the Virgins Island. As far as could be ascertained, the kidneys were larger than normal. The patient passed much urine. The specimens examined showed Sp. Gr. 1027 and contained some sugar, and a very ap-
preciable quantity of albumen.
The spine was somewhat kyphotic in the upper dorsal region. The patient complained of great weakness, had a voracious appetite, and suffered much from thirst. His mental condition was rather clouded, and he had a dull stupid look. He also complained of dullness of vision, but I could not make out any special retinal changes.
The photographs on the opposite page were taken under disadvantageous circumstances by an a-
mateur and is very poor indeed, for not only is it blurred and indistinct, but the fingers and lower part of the penis are excluded from the plate. From the fact however that the patient was a very small little man, the extreme length of the forearm bones is very well seen in the right arm. I gave instructions that a profile view was to be taken of his face, as also plates of his hands and feet, but by some mistake, these were never car-
ried out. I had also made arrangements to have him photographed, but my patient shortly afterwards disappeared, and I have seen nothing more heard from him since.
This I extremely regret, for I had intended to
follows out a series of therapeutic experiments, not only with animal extracts, but with other remedial agents.

In discussing Scurvycahy, it is with the sole object of endeavouring to ascertain its relations to the Hypophysis Cerebri, and as to the nature of the role played by that body in the causation of the disease. As far back as 1707, Littre frames, that if the orifice becomes obstructed or inflamed (atrophyed), a crema and lingering disease would result.

The different theories as to its causation may be classified into five groups.

I. The Atrophic theory which tries to show that Scurvycahy is a reverse to an ancestral type.

Campbell traces the resemblance between the acromegalic man and the anthropoid ape, arguing upon the theory, that in morbid processes, ancestral peculiarities are being continually laid bare. My friend Professor Woods Hutchinson, while comparing the skulls of Anthropoid Apes finds that the Gorilla, who in jaws, frontal sinus, hands, feet and spine is almost ludicrously acromegalic, shows in 5 out of the 6 skulls examined, the marked large bowl-shaped sella turcica. But there is no evidence to show that in the Gorilla, the Hypophysis is usually morbidly affected; or that any acromegalic symptoms develop in that animal. Dr. Hutchinson also informs me that he has seen a case of the disease
in a horse, and that an instance of Thyreomegaly in a dog has recently been described in one of the veterinary journals.

II. A second intenable theory ascribes the causation of the disease to persistence of the Thyroidus gland, which although often enlarged, is also (as I believe in my own case) frequently absent, and when present, fatty. Furnivall records its persistence in only nineteen out of 49 cases of Thyreomegaly. In one of his cases, where the patient was accidentally killed, he could find no trace of the thyreoid gland at all.

Marie notes that Thyroid persistence is often found in cases of Thyreomegaly, and almost invariably in Cretininism. He has also found it in Grave's disease, & believes it may reappear in Myxedemous cases, developing after puberty or adult life. Robertson cannot understand this reappearance of the Thyroids, and believes its enlargement not of a compensatory nature, but rather that "its enlargement is part of the morbid lesions bound up with the profound changes occurring in Thyreomegaly, Cretininism &c."

We know that by many scientists, the Thyroid is believed to be the great lymphatic gland of fetal and early child-life — that is to say, during the chief period of developmental growth. In Thyreomegaly, where vast nutritional and hypertrophic changes are occurring in many tissues at an abnormally late period, may it not in such cases (where some rem-
nant of the gland exists) itself takes on a functional sympathetic activity and increased growth. 9. Or again, assume that in Acromegaly, where it has been found enlarged, some small state of the system still existed at the onset of the disease, why should it not share in the reorganization of the changes which are now known to affect other glands and organs. 9.

Either of these explanations seems to me more probable than the obscure and involved one quoted from Pollock.

The third or Neurotic theory is supported by Steno- Reddinghamsen, Bolechmickoff and others, who main- 
ain that Acromegaly is a neuropathic lesion. They base their hypothesis mainly upon the fact that changes have been found in sympathetic and other ganglia, as also in peripheral nerves.

Furnival found the sympathetic ganglia enlarged in only 9 of the 13 cases in which he had specially examined the sympathetic, in the other 6 they were normal. In the remainder of his 49 collected cases he did not look for them. Dalton found the central canal of the cord obliterated in his case. Reynolds found in the central nervous system excess of neuro- 
glia with a tendency to canine degeneration.

Byron Brownwell formulates another modification of this theory, viz. that the hypophyseal enlargement, which is primarily the result of a nervous change, produces in turn by disturbance of its internal regu- 
lation, nutritional changes in the body tissues and organs. The theory that the hypophyseal en-
-largement is only a part of the hypertrophic condition which involves many of the tissues and organs of the body, as the result of a primary hypophysitis does not nowadays receive much support.

Schöffer considers that the neurotic changes noted in the various parts of the nervous system are as small varied and inconstant, that "they themselves cannot be looked upon as the causes of the neurotic symptoms, and until we know more of the neurotic centres, the primary cause for the symptoms of acromegaly will remain obscure, and must be placed in a line with other trophic affections, e.g. Actinopathia Syringomyelia &c."

A fourth hypothesis insists upon thyroid changes as being a cardinal factor in the production of acromegaly. In 49 cases, the thyroid was normal in only 5, and was generally found to be somewhat enlarged.

Shattuck says, that although in acromegaly, enlargement of the thyroid is often present, it is usually of a paraphysial nature, and has a deficiency of glandular tissue. Nor has it been found in the enlarged thyroid, these parietal foldings, which occur in the true compensatory or vicarious hypertrophy, such as follows partial excision of the thyroid, and which are so prominent a feature in the goitre of Graviss. disease. Meacham after quoting various acromegalies associated with morbid conditions of the thyroid, says, "these facts, together with the effect of thyroid feeding
in Hermegaly. lend extra color to the view, that it is not so much the internal secretion of the Pituitary that is at fault, but that its secretion is somewhat interdependent upon that of the Thyroid. In health they work harmoniously together, but if one is in any way deranged, the other endeavors to compensate for the deficiency with unsatisfactory or even disastrous results.

I ought to have mentioned one curious cause assigned by Freud and Vireitable for the disease—"an inversion in the evolution of the genital life"—whatever that may mean!.

And lastly, the more commonly accepted idea of its causation, is that its primary cause is to be found in an Altered Condition of the Hypophysis whose internal secretion becomes increased, altered or perverted.

Furnivall collected 49 cases of Hermegaly where post-mortem examinations had been made, and found in all of them, that the Hypophysis was affected. He gives an extended list of these cases with the various pathological lesions found in that organ, and concludes by saying that the pituitary body is always altered in Hermegaly. "The changes in its structure differ widely, but they are always the same, changes that commonly occur in cases of lesions of the pituitary body not clinically associated with Hermegaly. Dalton says that the primary cause of the disease is some changes taking
place in the Hypophysis, and thinks it would advance our knowledge, if we could be certain that
the primary effect was a true hypertrophy of the
parts affected, followed at some future time by their
degeneration, with or without the development of
fibrosis.

Dressel believes that the Hypophysis exercises
a tropic effect or influence upon the nervous sys-
tem, and considers that the hypophysal hyperte-
rophy might explain some of the symptoms of Fe-
romegaly. He thinks that the gland stands in
a similar relationship to that disease, as does the
Thyroid to Myxedema and Graves disease.

Meehan says that as the gland has for its main
function, the production of an internal secretion,
which has for its object the preservation of the bal-
ance between the nervous and muscular systems,
that therefore it is not unreasonable to suppose,
that the symptoms of Sromegaly are due to some
alteration in the internal secretion of the gland.

Rogowitsch believes that the pituitary destroys tox-
ic substances.

Marie and Marimexo say that Sromegaly is a
systematic secondary dystrophy following on the per-
version of function of the Hypophysis, which would
accumulate toxic substances in the extremities, so
as to produce an irritation which is the point of de-
porture of Acromegalic alterations.

Massolongo starts with the conception that the
pland is hypertrophic in acromegalic subjects, and from the fact that sometimes persistence of the Thyrmus has been verified — it being admitted that these glands exist for the development of the organism — deduces that the continuation of the function of these glands after fetal life is at an end, produces the picture of Acromegaly, even before the physiological period of development has well ceased.

Tamburini believes that hypophyseal changes may result in two forms of disease, firstly, a functional hypertrophy of the gland, with hypersecretion of substances, tending to increased body growth; and secondly, Sarcomas and Cystic degenerations of the gland, with cessation of its glandular function, and followed by cachexia and death.

Frenet says that the gland has nothing to do with the ordinary laws of development.

His detailed careful list of 37 autopsies, showed the Hypophysis diseased in them all. Sarbo, Friedrich, Arnold, Bonardi and others have described cases where the Hypophysis is stated to have been normal, but there is, I think, some doubt as to the correctness of the diagnosis in their cases.

Generally speaking, the Italians school explain the causation of the disease by hypertrophic changes, in the Hypophysis; while by French thinkers they are believed to be due to alterations in its function.
The consensus of medical opinion therefore, affirms that disease of the hypophysis in some form, is the primary cause of Pituitary, but it is the knowledge of the exact nature of this change in the functions of that organ, which has not yet been arrived at.

Marie, Soucy - Coute and many others believe, that in the vast majority of cases, the condition of the hypophysis in Pituitary is one of simple hypertrophy, associated perhaps with some degenerative process.

Dreschfeld, while concurring mainly in hypophyseal causation says that the points opposed to it are —

1. Tumors of the organ occur without Pituitary.
2. The morbid changes in it are found so varied.
3. Its morbid state may be a symptom and part of the disease.

He found in 36 autopsies, that the hypophysis in whole or in part was affected, either hypertrophy with or without Colloid, an edematous condition, or some definite new growth such as sarcoma or glioma existed.

Summell says with regard to what relationship may exist between Pituitary, Hypnoid, and Thymus diseases, and changes in the nerves and nerve centres, the future has still to decide. Shattuck believes the condition of the hypophysis in Pituitary to be one of hypertrophy, since he found that the peripheral glandular cells were larger than the
the central one, or those of the normal gland, and he insists that this larger size may be taken as an evidence of more active growth. For in his case, he could find a trace of colloid material anywhere throughout the substance of the organ. He maintains that the problem presented in acromegaly is — whether there is a perversion or absence of pituitary function, and he considers that as many lesions of the hypophysis are associated with acromegaly, that the problem of its causation is due to its altered physiology, and has passed into the domain of chemical physiology. He thinks that, in those cases of tumors, tubercles and epithelium of the organ, where there are no acromegalic symptoms, the absence of these can be accounted for by assuming that none of these lesions are necessarily as destructive of the gland tissue, as to entail a complete absence or perversion of its function. Rolleston also affirms that primary tumors of the pituitary need not give rise to acromegaly.

Dalton found that the appearance of the morbid organ suggested a cavernous, but probably consisted of a great multiplication of the normal pituitary cells, followed by their rapid degeneration. Hunter found extreme vascularity, with recent hemorrhages, and thickening of the capsule — the gland substance itself increased, but normal in structure with Colloid. Neal found the enlarged
structure to consist of polyhedral cells, large in size, and without visible intervening substance—scarcely a trace of stroma, the cells simply lying in a meshwork of vessels.

Byron Browne well thinks it quite possible that the Pituitary like the Thyroid may exercise a marked influence on the nutrition of the nervous system, and perhaps on the other tissues of the body. He considers that the enlargement of the Thyroid and Thyromys as commonly associated with hyperemia, may be compensatory, that the enlargement of the bones and soft parts is probably of the nature of hypertrophy, while the changes in mammae, testes and ovaries are clearly atrophic in character.

Roderick discerning the nature of the pituitary change, argues that were it due to the suppression of the secretion, the gland would be atrophied or destroyed, and not, as is usually the case enlarged, also that pituitary feeding would lessen the symptoms—that were it due to excessive secretion, pituitary feeding would aggravate abnormal symptoms, which it is found not to do. He seems to agree with Maris and Marimero as to the prevented action of the Hypophysis, I think that some toxin may be produced in the abnormal secretion itself; or that the prevented action of the gland, by interfering with the normal action of other internal secretions, may stimulate its tissues.
to overgrowth.

Burr and Ritchie, in a most interesting paper, after describing a case of empyema of the thyroid gland, where no Acromegalgy existed, declare that disease of the hypophysis is the only cause of this disease, but that for its production must be complete, i.e., must affect the entire glandular structure. They consider that in most of the reported cases of pituitary disease or tumors has it been shown that the glandular part of the organ was completely destroyed — in some cases no microscopic examination was made, and in the others only for the purpose of determining the nature of the growth. They believe that the destruction of the gland, as practiced by Marinsco, Valsalva &c. in the dog, not having been followed by Acromegalgy, is no argument that similar results would occur in man, seeing that excision of the Thyroid in the dog does not always produce Myxodema. In all other glands, they maintain, there is a surplus of tissue, or at least if a part be lost by accident or disease, the remainder may do the same amount of work as was done by the entire organ, and assuming from the fact, that in operations on the Thyroid, as long as some of that gland is left myxodema is avoided, and that in experiments on animals the smallest piece of pancreas left is sufficient to prevent glycosuria — as if some part of the hypophysis remains normal, it may either do the work of the entire gland or at least be sufficient to inhibit excessive growth in
the bony extremities. Collina does not think that acromegaly is due to excess of function, because it then must always exist in relation to hypertrophy, and not, as is sometimes found with some neoplastic condition—nor does he believe that it can be due to perversions, because it is were possible to conceive that a neoplasm can prevent the function of the affected organ, it is impossible to understand, how tumors in such varied form, could all yield an identical perversion.

Before summing up the various opinions regarding the functions of the hypophysis cerebri, to say nothing of its alleged condition in acromegaly, I purpose running over the leading tissues involved in this extraordinary disease. Our earlier ideas of the disease gave form to the belief that its symptoms were connected mainly with being hypertrophic, and that in definite locations, the skull, forearm, legs, all other hypertrophic changes were spoken of as being of less importance, or at any rate, as if they were of spasmodic occurrence. Now I propose to show that there is probably no organ or tissue in the entire body that is not involved in the hypertrophic changes—that in short, the name "acromegaly" is a misnomer, that the disease is not merely affecting hard tissues and muscles, but also organs, and the finest forms of tissue that we possess. I have previously pointed out that the disease is apparently not confined to man, nor is it
limited to any particular human race.

**Bones.** Not only are the bones of the skull and ex-
- tremities enlarged, but also in varying degree all
- the bones of the body, ribs, sternum, vertebrae and pel-
- vis have all been noted enlarged. In my own case
- the sternum was markedly so. It must not be for-
- gotten that the altered condition of the hands and fig-
- ies due to hypertrophy of soft parts as well as bones, as
- has been demonstrated by Gilbert and others with the
- Röntgen rays.

**Joints.** Don'ters nearly all joints are involved,
- but the wrist, ankle, elbow and knee most markedly.
- Growth of cartilage, increase of fluid, and other con-
- ditions resembling an arthropathy have also been des-
- cribed by some authors. In my case the costal car-
- tilages were enlarged, especially at their external ends.

**Muscles.** Undoubtedly hypertrophy, as best seen
- in arms of the limbs, latter they probably undergo
- fibrosis, as evinced by increasing weakness.

**Blood-vessels.** It was specially noted by Dr.
- Innes that the extrema were considerably hypertroph-
- yed, at a later stage fibrosis and atheromas
- changes must occur. My patient had pronounced
- atheromas vessels.

**Lymphatics.** The submaxillary, mediastinal,
- mesenteric glands and generally speaking, all glands
- have been found enlarged. The lymphatic structure
- in the throat are usually affected, in my case not-
- only were the tonsils large, but the lymphatic tissues
at the back of the tongue were somewhat enlarged, that he complained of stiffnes of his tongue, and occasionally some difficulty in swallowing. There were also numerous adenoid patches in the pharynx and especially, was there a large adenoid mass in the roof of his nasopharynx. This last was very much like what one finds in the "adenoids" of children but appeared harder and more firm. Remembering that Hirschel's tonsil practically marks the site of the original opening of the crano-pharyngeal canal, the presence of this mass seems to me of extreme interest and curiosity.

Nerves. The perineurium is often found thickened.

Viscera. In Osborne's case where the viscera were carefully weighed, the following were the results:

- Heart = 41 ounces. Left lung = 41 ounces.
- Thyroid Gland = 101 grams. Liver = 7 lb. 2 ounces.
- Spleen = 36 ounces. Right Kidney = 11 ounces, and the left = 10 ½ ounces.

I have previously alluded to various visceral enlargements in my own patient. Similar results have been published by many observers.

The alimentary canal has been found inflamed, and Dalton found the submucosa thickened, and both mesenteric and solitary glands enlarged.

The testes, ovaries, breasts have been occasionally found increased in size, although some authors say they are usually somewhat atrophied. In my own case, the testes were if anything somewhat smaller than usual.
Central Nervous System. Various changes in brain and cord have been described. The hypophysis itself has been found the seat of almost every known form of growth in Permeage, in which it is sometimes found simply enlarged, inflamed or degenerated. The organ sometimes not only fills the much enlarged fossa, but overlaps into the three great cranial fossae. It may be as large as to hollow out the sphenoidal lobes of the brain. It is a remarkable fact that even when of enormous size, it seldom gives rise to marked brain symptoms, probably on account of its tucked-in position. The hypophysis cerebri has also been found enlarged. Syringomyelia has been noted by Petren and others. Otherwise marked brain changes have not been often recorded. I have no doubt however, that were the different parts of the brain and cord carefully microscopied in a typical case of the disease, that hypertrophic changes of cells, fibers &c. probably followed by later fibrosis, would be made out.

Skin. This is usually much thickened, often pigmented, sometimes myxomatous, and occasionally covered with crops of reticulated wart-like growths, or molluscum fibrosum. Marie believed that the last named was practically a constant condition. This is not however the case, as many patients are seen with no evidence of this skin condition. Gordon Brown claimed a case similar in this respect to my own before the Lancetian Society in 1892.
appendages of the skin become involved in hemoegaly, the term cancer Ec. as previously noted, and in a case where Marinesco minutely examined the ballot, he found hypertrophic changes even in the cubrems and subcutaneous glands.

Dolton thinks that the explanation is mainly due to the increase in number of the functioning cells, and that after a time, the nutrition of these cells cannot be kept up, so that they degenerate, and cirrhotic changes follow. During the hypertrophic stage there will probably be an increase of function, while the later degenerate condition may produce varied symptoms. He thinks that these may be explained by the variability of the thyroid symptoms, as also glycosuria, albuminuria, pyelitis, Ec due to fibrosis of liver, kidneys, and stomach respectively.

Hemogaly thus is a condition, in which as the result of morbid or modified action of the Hypophysis, a genuine hypertrophy, marked in its effects, and universal in its distribution, although in varying degree, takes place in the individual. It is a grave, general and progressive disease, usually very chronic, a disease with an insidious beginning about adolescence usually, often in adult life, but never congenital. Nearly 300 cases of hemogaly have been recorded, and in the few where it runs a rapidly fatal course, it is generally found that the Hypophysis is the seat of cancer.

No microscopic theory has yet been advanced to at-
Attempts to explain its causation, but who knows but that may come to the front in the near future.

The connection between Acromegaly and Gigantism is a very interesting one. Brissaud maintains that they are but greater and lesser manifestations of the same morbid process. He says that primary hyper trophy of the skeleton and secondary enlargement of the soft tissues are produced during a definite period of time, and that then, the osteogenetic process is arrested. If the process of overgrowth occurs during childhood and youth, the result is Gigantism. If during adult life, acromegaly.

The few examinations of giant's skulls made, seem to corroborate this, e.g. the skull of the Irish giant, Cornelius Mc Grant, had a Sella Turcica large enough to contain a melon.

Soffry says, that by inflammatory or congestive changes, the Hypophysis gets unusually active, that marked hypertrophic development of the oesims and muscular systems follows, and as the youth becomes a giant, and the adult an Acromegalic.

Conclusion.

Having thus investigated what is known regarding the relations of the Hypophysis Cerebri to Acromegaly, I propose very briefly again to summarize the conclusions I came to with regard to the hypophyseal function, and to consider them in the light of acromegalic changes. We already saw, that in archaic forms, in which a water-vascular system existed in relation to...
to the central neural canal, that the lacunosemic duct preserved a hypophysial apparatus, although primitive in form. In the preceding chapter I have sketched the process of evolution of this hypophysis from this archaic type, through the various classes of the Vertebrata, and have endeavored to show that its presence was as necessary in man as in the amphibia.

It may, I think, be accepted as a fact, that the hypophysis Cerebi is essential to vertebrate life, for we have seen that without its normal activity rapidly fails, and its disease produces, although more slowly, a similar result. There are strong reasons for supposing that some such similar mechanism controls the trophism of invertebrate animals, and of this the eiliated part of the Ascidians affords the best example.

I have also attempted to show that while the glandular lobe of the organ had for its main, if not its only function, the production of a secretion — a secretion fraught with immense potentialities as regards the trophic processes of the body — that the posterior lobe, which in lower types seemed to combine the functions of a nervous and secretory organ with those of a glandular one, had as far as the microscope could reveal, lost in man all glandular elements, and only retained a degenerate nervous structure. That although such was the case it seemed to me not improbable that this posterior lobe might have retained some vestige of the function preserved by its archaic proto-
type, and might either serve to modify in some way the secretion of the glandular lobe, or perhaps regulate its production or absorption.

And now, we are in Remnagaly, confronted with a condition, in which, as the result of disordered function of the Hypophysis, the processes of general body growth are allowed to run riot.

I have already passed in review, the varied opinions held regarding the causation of the disease, and very confusing and conflicting some of them appear.

Notice has been already taken of the striking resemblance in structure and apparent function between the Simproid gland and the Hypophysis, both produce an important internal secretion, and the logical conclusion in the case of both is, that the arrest of this secretion is followed by extensive changes in body tissue.

In the case of the Simproid, myxedema and mental changes ensue; while in that of the Hypophysis, the hypertrophic changes of Remnagaly follow, in addition to mental depression, which however appears to occur at a later date than in the case of Simproid disease.

That some sympathetic or compensatory relation exists between these two organs cannot possibly be doubted, and that despite the apparently contrary results afforded by experimental physiology, for we have seen that in Myxedema, that the glandular lobe of the Hypophysis shows the majority of the tubules all through its substance filled with colloid, as though stimulated to increased activity, and endeavoring to provide an ex-
cess supply, to atone for the deficiency in the Thyroid metabolism. I do not for a moment mean to suggest that the two colloids have exactly similar functions.

There is evidently in all organs and tissues, an inherent tendency towards growth, and this is evidenced to some extent by the wonderful power possessed by the bodily organisms in the processes of repair—in every tissue old cells and fibres are constantly getting worn out and replaced by younger and newer ones, and this process is seen nowhere better than in the blood itself. Some checks must however be provided to ensure that this great potentiality be kept within bounds, and to my mind this exists in the form of the pituitary portion, which in small quantities is being constantly introduced into the blood, and may act either directly upon the tissues themselves or indirectly through the medium of the nervous system, most probably the latter.

When the hypophysis becomes inflamed or hypertrophied, all traces of colloid, as we have seen, disappear; in other words, the restraining influence is lessened or removed, and the natural tendency towards increased growth proceeds unchecked, with the result that all organs and tissues in varying degree, participate in the hypertrophy. It seems quite logical that this increase of growth should especially manifest itself in the extremities, and in the earlier days from knowledge of Hrommegaly, the changes in tissue and in the
Akull, constituted such a marked symptomatology, that observers rushed to the conclusion, that the lesion affected these parts mainly if not solely, and they accordingly christened the disease "Acromegaly".

We have likewise seen that probably no organ is left untouched, and no tissue is so delicate to escape the altered trophic influences, and in the post undeniably aplacemonomegalv and other changes escaped notice amid the gross alterations in bones &c.

Again let me say; that I am convinced, that every tissue and organ in the entire body becomes in some measure affected in Acromegaly. Of course varying degrees of disease in the Hypophysis will produce symptoms varying intensity.

The question must arise what if in cases of tumors of the Hypophysis, where no acromegalic symptoms followed? Perhaps as Pfeiffer suggests, that in these cases there always remains some small area of the glandular tissue normal in structure and healthy in function, which is capable of furnishing sufficient colloid to the blood to keep the body in health. This seems to me an exceedingly likely idea — for have we not already seen that in animals a small portion of healthy tissue left, arrests myxœdema; also a little bit of pancreas left, and glyceremia does not take place.

It may be argued that at best, the size of the Hypophysis is so small and the amount of its secretion so insignificant, that the immense changes which take
place in neurology are out of all proportion with its small and inconsiderable functions, but Physiology can furnish us with many other instances, where substances produced in exceedingly small quantities (e.g., digestive ferments &c.) are yet capable of exerting great far-reaching influences. In early childhood and youth, the hypophyseal secretion may be less in amount or weaker in action, and so allow these vast changes to take place which in that period of existence are associated with normal healthy physiological growth. We have already noted the ideas held regarding the relation of Gigantism to neurology, so I need not again refer to them. But me however finish my paper on the Hypophysis Cerebri by stating that I believe the normal secretion of that organ essential to health and even to life itself. In adult life its presence and action are such that while repair and growth are capable of taking place within certain limits, that after 25 years of age (the anatomical majority) no important changes take place either in relative or in the increase in size of parts or organs, so long as the hypophyseal secretion remains normal in amount and healthy in quality.

And thus it is, that in the light of newer scientific knowledge, that the Hypophysis Cerebri once looked upon as a vestige, and with either no function or some very small one, comes to the fore front as a vital organ with functions of prime importance.
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The

"Epiphysis Cerebri."

"The Epiphysis Cerebri."

It has been shown in the preceding account of the Hypophysis Cerebri, that that organ is vestigial in character, but has a very decided function. The Pituicyl gland is also a vestige of the neurosecretory, but it appears to be only that, and to possess either no function at all, or some very rudimentary one, whose nature has not yet been fathomed.

From the fore and midbrain (especially in lower vertebrates) are given off on the upper aspect several evaginations of which the three most important are the "epiphysis", the "parapophysis", and the "petrosal organ". Of the probable nature and destiny of these I shall treat later on. I mean however first to take up the epiphysis as it is ordinarily seen and described in the human brain.

The pineal gland or conarium, so called from its shape, and also epiphysis from its position and development, is a small reddish body found lying in a depression between the toes of the quadrigemina, in the so-called "fossa conarum". Its general anatomy is as well known, that I shall merely for the sake of completeness, run over its leading features, before taking up the results of my own work upon the subject.

Its size is quoted somewhat differently by different authors — Selevich gives it as 7-8 mm. long, 4-6 mm. broad; Poirier 10-12 mm. long, 5-8 mm. broad; and 5 mm. thick; Lord, 5-9 mm. long, 3-8 mm. broad, and 2-4 mm. thick —.
It will thus be seen that there is considerable disparity between these measurements. My own agree more closely with those being 6-8 m.m. long, 3-7 m.m. broad and 3-4 thick. In other words, the size of the epiphysis varies considerably within certain limits, and one cannot have examined a large number of human brains without having noticed considerable variations not only in its size but also as regards its shape. It lies in the brain with its long axis practically horizontal, and is usually described, having as a summit or apex, a body, a base, and three pairs of peduncles by which it is attached to other parts of the brain.

The body lies just in the recolled "great fissure," and points backwards and somewhat downwards. Often pointed, at other times rounded or irregular. It lies quite free above the dura, and a fibrous band has sometimes been noticed attaching it to the dura mater, of the significance of which more anon.

The body as before noted lies in the fossa ambient, and lies above it the bursa of the corpus callosum and the ventricles Galenae, while laterally it is in relation to the choroid plexuses of the 3rd ventricle, to which it is intimately attached.

The body is directed forwards, and is close into two horizontal terminals by the "recessus pinealis," the external remains of the original evagination from the thinned roof of the 3rd ventricle.

Peduncles. The superior peduncles or "rheni" appear
according to Schüller, to rise anteriorly by the side of the fornix from the depth of the olfactory field, and each has received an afferent tract from the fornix, ends in the ganglia thalamica. It passes along the surface of the optic thalamus, becoming continuous with the upper lamina of the pineal base, constituting the so-called "pedunculus conarii." These peduncules are glistening white in appearance. The ganglia are located just in front of the epithysis but somewhat laterally.

The inferior peduncles are very slender, and come from the inferior lamina at the pineal base. They pass downwards and outwards and end in the substance of the optic thalamus. The middle peduncles pass transversely outwards from the sides of the base of the organ, lying along the upper border of the posterior white commissure, and end obscurely in the optic thalamus.

According to most observers, all these peduncles contain nerve fibres.

It is very interesting the distribution of these peduncles with that of the optic tracts. The optic tract is, we know, connected with the posterior part of the optic thalamus through the pulvinar, and external geniculate body, and it is in this region that nerve impressions from the optic nerve are brought into relation with consciousness, by being transferred along the optic radiation of Gratiolet to the occipital lobe of the cerebrum. The tract is also con-
Diagram to show the relations of the pia mater to the epiphysis.

Sagittal mesial section.

(modified after Charpy)

Note the intimate attachment of the pia mater to the apex of the organ, loose elsewhere.

1. Corpus Callosum.
2. Cerebellum.
3. Volumen Interfossorum.
4. Recessus (Pinealis).
5. Conarium.
6. Remains (externally) of the original ventricles. (Recessus Pinealis.)
Necti with the anterior quadrigemina, which act as centres for movements of the eyeballs, believed by many to be

Now, as will be seen later, the Epiphysis is probably the proximal remains of an archaic visual organ, which existed unpaired and cyclopic in the parietal region of the forehead. These paired peduncles therefore probably represent the brain con
nections of this prismatic nerve. How closely they resemble that of the optic tract! — ending as they seem mainly to do in the posterior part of the Op-
tic Thalamus, and doubtless also originally con-
nected with the anterior quadrigemina.

The anterior peduncles appear to have had, or to still have, some additional coordinating function, as they practically act as white commissures be-
tween the olfactory and visual areas.

Hill and others believe that the ganglia habenulares were probably the optic ganglia of the prismatic nerve.

The relations of the epiphysis with the pia matter are of a very intimate nature. I cannot agree with Ferrua, that "it lies enclosed within the veium inter-
positions but have found its relations to the pia to resemble what is shown in Plate XV (page 141), a
modified sketch gone by Charpin.

Some years ago, I paid very special attention to the direction of the epiphysis, and found that as a rule the pia had little or no attachment to its upper surface, but was especially adherent to its apex and sides. As seen in Fig. XV, the recesses
Plate XVI.

Fig. I.

The Epiphysis in Birds.

Note the club-shaped condition of the organ, its relatively large size, that it reaches to the periphery, and is nearly vertical in direction.

1. Epiphysis.
2. Pallium.
3. Cerellemum.
4. Hypophysis.

Fig. II.

The Epiphysis in Mammals.

The organ is relatively much smaller than in birds, and its direction nearly horizontally back.

Words.

1. Epiphysis.
2. Pallium.
3. Cerellemum.
4. Hypophysis.

N.B.
In neither birds nor Mammals is any trace found of the "parietal organ."
supranucleus of Reilgus is a small cul-de-sac opening widely into the ventricular cavity in front. It is mainly formed by the veins of Galen running the velum transversum from the upper aspect of the organ. The space is limited behind and laterally by the "pia mater", as also at the sides towards the pineal body by little white bands from the peduncles, called "cerebral recesses". It is lined by an ependyma, continuous with that of the 3rd ventricle.

The epiphysis, to which curious organ Leydig gave the name of the "sixth sense", exists throughout all the vertebrates, except in the case of the amphibians. Wengel (quoted by Meredith) reports its absence in 6 out of his hundred cases. This statement is no doubt quite erroneous.

In man the epiphysis develops about the sixth week, after the general development of the brain is quite advanced. What we do know of pineal development is mainly due to the researches of Molkholm in birds and Kranzhaar in white mice.

Developmentally, the pineal structure consists in reality of two evaginations, the posterior of which is the epiphysis or corporo-æ, and an anterior one which either springs from the thalamencephalon immediately in front of the epiphysis, or appears as a bud from the epiphysis itself. This latter is the so-called "parietal organ", and normally has atrophied and disappeared in most vertebrates.
Plate XVII.

In these diagrams, the Epiphysis is colored in red, the Parietal organ in blue. For description of modifications of these in following groups see text.

The Epiphysis in Fishes.

1. Cerebrum.
2. Cerebellum.
3. Hypophysis.

The Epiphysis in Amphibians.

1. Cerebrum.
2. Cerebellum.
3. Hypophysis.

The Epiphysis in Reptiles.

1. Cerebrum.
2. Cerebellum.
3. Hypophysis.
As we know, the pineal gland in man and the mammalia is a small rounded body which is directed backwards always, and usually its apex points slightly downwards also. In them it represents the epiphysis alone. (Plate XVI. fig. 2.)

In birds it again represents the epiphysis only, it is relatively of large size and almost vertical in position. Its massive free end or summit extends as far as the dura mater. As we shall see later, in both mammals and birds the original evagination buds and ramifies in tubes. In them it is practically a solid organ consisting essentially of solid epithelial tubules, and is probably glandular in nature and function. (Plate XVI. fig. 1.)

It is when we come to the Reptilia, that light is shed upon the true nature of the pineal apparatus. The researches of Baldwin Spencer, Dandy and others apparently show us without chance of contradiction, that in it we are dealing with a sense organ, related to vision.

Both epiphysis and parietal organ are concerned in its formation. The latter becomes a vesicle in the lizards and in Varreria lies in the parietal foramen. The vesicle is thickened dorally to form a lens, while the remainder is developed into pigmented retinal structure, which is connected with a rudimentary nerve.

This pineal eye also contains some vitreous masses, is surrounded by capsular connective tissue, and is in some measure furnished with a cornea, infrared as the skin and tissues around it are transparent and
The head of "Varanus Salvadori".

\{ Drawn by kind permission of the \}
\{ Council of the College \}

**Fig. I.**
Sagittal mesial section. The pineal apparatus is colored in red. Note the pig-
mented spot in the peripheral vesicle, just
under the epidermis.

**Fig. II.**
Head of Salvadori seen from above.
Note - the light-colored scale (x) which
covers the pineal eje.
free from pigment. Such a perfect eye is by no means found in all lizards, and sometimes only in the embryonic state, can its traces be made out. At first sight, the function of the two evaginations (viz. the epiphysis and parietal organ) are easily made out, apparently the parietal organ becomes the eye, while the epiphysis forms its neural stalk. This is however not always so, and although in Varanus, the two are closely connected, yet in its embryonic state, the nerve seems distinctly to arise from the brain in front of the epiphysis and quite independent of it. The parietal organ undoubtedly becomes the eye, was originally attached to the brain, its stalk however from some cause seems to disappear and to become replaced by a permanent epiphysial one. In Plate XVIII, is given a representation of the condition as seen in "Varanus Salvator".

In Plate XVII Fig 3.—, the double nature of the parietal structure is seen diagrammatically. The fact that originally the parietal eye had a stalk of its own, and that its connection with the epiphysis is a secondary one, raises a very interesting subject for speculation. Professors, speaking of the epiphysis, says, it is an ancestral ocellar organ, which becomes the parietal gland, and which does not seem to agree with the parietal eye of reptiles. It must not be confused with the paraparaphysis which does not appear to be related to organs of sense. Of this however, we shall treat more fully later on.
In the Amphibia the pineal organ has disappeared, and the epiphysis is frequently found as a long stalk passing forwards and somewhat upwards towards the region of the parietal foramen, but it does not extend beyond the dura mater, and is often found ending in a bulb-like process. (Plate XVII, Fig. 2.) Wiedersheim notes the interesting fact, that the extra-cranial part of the apparatus is represented by the term rept "in Rana temporaria."

In the Fishes its character varies somewhat among the Dipnoi, there is found a long stalk ending in a vesicle which lies in a space in the centraignions behind roof, while in the Teleostei it does not pass to the roof of the skull, and the pineal organ is only seen in early embryonic life. Among the ganoids there is an atrophied condition of pineal pedicle and bulb, lying in a depression in the cranial vault, and in Chasmistes, &c., a similar condition exists. Myxine is described as having a single vesicle, devoid of pigment. Whitewell in his interesting paper on the epiphysis in the Lamprey, describes two vesicles, the lower smaller and representing the rudimental pineal stalk &c., while the upper larger one contains pigment, and is apparently retinal in type. He found that the integument over there was quite transparent.

I am not concerned with the differences of opinion which exist as to whether this pineal eye (when it is present) is invertebrate or vertebrate in character, from its method of nerve connection, and from the
fact, that the retinal rods appear to face into the
central hollow of the ocular vesicle, it has certainly
invertebrate affinities. Poirier says, it has no
homologue in the vertebrates, but from a physiolog-
ical standpoint, it somewhat resembles the median
eye of crustaceans. Whatwell argues that the primate
eye might rather be looked upon as a "phylogenetic
representative of a developmental stage in the verte-
brate eye."

What is of moment to us at present, is that we now
have some idea as to what the ommatidium is a vestige
of, although the relics of the ocular apparatus have
perished in birds and mammals. The primate eye
says Ishihara, is certainly older than the lateral ones,
and exists only functionally in the common ancestors
of the vertebrates.

It is of interest to note (vide Plate XVI) that in Verte-
brates and Reptilia that the direction of the epi-
physis is upwards as far as the periphery of the brain,
when it passes forwards; in Birds, as far as I can
judge from the few specimens I have examined, its
direction is nearly vertical; while in the Mammalia,
due to the excessive development and growth of the cer-
vical hemispheres, it gets pushed backwards, even
as already seen amongst primates. Turner also
mentions the tectumae as a factor in producing this
change in its direction, personally I am more inclined
to lay stress upon the appearance in Mammals of the
Corpus callosum, whose bundles, in the higher forms
at least, must do something towards its production. Turner describes the pineal gland as being enormous in the Walrus, and to a less extent also very large in the Seal. Its large size in the Squalians is also noted by Bernoulli. Turner found in the Walrus that it passed backwards and somewhat upwards, resting upon the Corpus Quadrigenius and middle line of the cerebellum, under cover of the tentorium. Its enormous size made it visible from above posteriorly, when its projected between the hemispheres.

As has been already pointed out, the pineal gland in man, is not as is popularly supposed, very mobile, on account of the firm attachment of the pia mater to its borders and apex.

When enlarged, the organ tends to become flattened and heart-shaped, and must in hypertrophic conditions considerably stretch the vault, and may even perhaps affect ventricular blood supply.

Having now briefly sketched the development, evolution and macroscopic anatomy of the Epiphysis, I now propose to describe its minute structure, and will do so under the following heads

\[ \begin{align*} 
\text{I. Its Capsule.} \\
\text{II. Its Ventricle.} \\
\text{III. Pinal Substance.} \\
\text{IV. A cerebral or brain gland.} \\
\text{V. Its nerve elements.} 
\end{align*} \]

after which I mean to discuss the probability of its possessing a function in man and mammals.
Coronal section through the Epiphysis Cerebri.

1. Central cavity — no epithelial lining.
2. Internal Zone — neuroglial network and very few cells.
3. External Zone — divided by capillary trabeculae into large areas, crowded with cells.
4. Capsule — fibrous and very vascular. Trabeculae pass from into substance.
5. Peduncles — very vascular, some of the vessels of large size.
6. Aervulus Cerebri — in masses of varying size, usually in locular spaces.
7. Recessus Pinealis.
princais". Lord believes that when a cavity is present, that it is due to a degenerative process, produced by the calcification of the septa, and the subsequent union of loculi. With this view I venture to distinctly disagree. No doubt cystic conditions due to degeneration are occasionally found, but the development of the gland and its analogues render the presence of a vestigial cavity quite an ordinary event.

The vesicle sometimes becomes cystic, and cases have been described and figured where tolerable cavities were found—in 5 cases going on in which the gland was 2-3 times larger than normal, but in none of these was the vesicle much dilated.

Rippled Substance.

Before taking this up, I wish to draw attention to Plate XIX, which is a semi-diagrammatic view of the entire organ. In the centre is seen the vesicle, somewhat irregular in form, the tissue forming its immediate envelope retaining somewhat deeper than the surrounding substance. Immediately external to this lies the inner zone of the parenchyma, and within this the broader external zone broken up into large areas by the capillary trabeculae, and comprising a zone rich in cellular elements, also containing large crystalline masses stained dark purple. Outside this is seen the capsule sending in its trabeculae. The pedicles are seen to consist of fibres which run up into the substance of the organ, passing in their course mainly between the cellular areas, and becoming lost
"The External Epiphysial Zone."

(Stained with haematoxylin and eosin.)

(Leiss. D. - Occas. 1.)

Fig. I.

1. Some of the coarser trabeculae. The parenchyma
is irregularly divided into lobules, but there are
very poorly marked – neither lobules nor cells are
as distinctly glandular in character as in the Hyp-
ophysis.

2. Blood vessels.

Fig. II.

A large mass of Acervulins, showing irregular Sur-
face, and exquisite many concentric lamination.
These crystals stain deeply, and are each behind
the others, in the trabeculae, or internal zone, and
never in the ventricles. The space which surrounds
the crystal is due to shrinkage of the embedding
material. (Celloidin.)
in the fibres of the inner zone. Sparse minute cells, rounded in form, are also found in the peduncles. And lastly, the whole organ is seen to be very vascular, the vessels being especially large and abundant in the peduncles, capsule, and trabeculae.

The division of the parenchyma into the zones is very distinctly seen, and the definition between them is a fairly sharp one.

Outer Zone: This is considerably the thickest of the two. It is mapped out into large areas by the coarser trabeculae derived from the capsule. Each area is seen to possess a very fine stroma, neurogliar in type, derived from capsule, pia-mater, and peduncles, or at least continuous with the fibres of these structures.

Each area is made up of ill-defined lobules or follicles containing rounded or oval cells. No lumina can be made out, nor is the tubular arrangement distinct as e.g. in the glandular lobes of the Hypophysis. Many of the apparent follicles are much distorted and contain peculiar crystalline masses of so-called "brain sand." Here and there one can see cells with fine processes, as also many very small rounded cells. Normally no pigment is found in the entire epiphysis, but some states that in old age yellow pigment is found in the cells, and Poiring speaks of the vascular trabeculae, as containing yellow pigment.

The lobules have no lumina, but themselves contain a minute adenoid meshwork of fibres, many of them attached to cells. In the meshes the cells are crowd-
Plate xxi.

Sections of the Internal Zone.
(Stained with haematoxylin and eosin.)

Fig. I.
(10 cm. D. - Ocular. 1)

Shows fine neuroglial networks with almost no cells.

Fig. II.

So placed as to show the entire thickness of the internal zone. (10 cm. D. - Ocular. 1)

1. Cavity or ventricle - has no epithelial lining, but is bounded by a net-work of fine deeply-stained fibres.

2. Internal Zone.

3. External Zone. Shows numerous cells and trabeculae.
ed, and are of various shapes, mostly rounded or oval, many of them granular. Some debris of cells is also present, and Lord describes a pellicular gum substance which he says retains very slightly, but which I have been unable to make out. (Plate XX, Fig. 1.)

inner zone. This surrounds the ventricle, and varies in thickness. It is composed practically of atoma only, the cells being very few in number. The structure of both zones, especially the inner one, is very neuroglial-like, and has been likened by Ogles to that of one of the layers in the cerebellar cortex. (Plate XXI, Figs. 1 and 2.)


Hard gritty masses are characteristic of the epithelium, not only in its substance and on its surfaces, but also they are found in neighboring parts, e.g. choroid plexuses and on the pia-mater elsewhere in the brain.

Chapin describes them as found in the follicles, the ventricle, trabeculae, vessels, peduncles, and choroid plexuses. I have found them chiefly in the follicles of the outer zone and near the apex, more rarely in the trabeculae. They vary much in size and form, some of them more angular, others very like amyloid bodies. They stain readily, and as seen in Plate XX, Fig. 2, from very beautiful objects with laminas concentric arrangement. They are generally surrounded by a vacant space, varying in size, which I am convinced is from the shrinkage of the tissue due to embedding in celloidin. Chemically, the crystals are
said to consist of Carbonate and Phosphate of Calcium with traces of Magnesium Phosphate, these bound together by an albuminoid material.

Turner speaks of amphiacemos and gritty calcareous particles, Macalister mentions them as Corpora Amy.

acea and botrysicol concretions of Calcium carbonate. Schäfer on the other hand draws no distinction, and does Institut. Lord makes a distinction between brain sand which he considers due to calcification of septa and amorphous bodies. The latter he says are usually found near the apex and are due to amorphous degeneration of cells which then unite and form a nodular pale yellow, readily staining body, which fills the loculus.

Personally, I have been unable, with the apparatus at my command, to discern any such bodies, all I have made out are the masses already described, and which I believe possess one and all similar constitution and characteristics, although in some the laminar arrangement is more perfect than in others. Again, the oval form so often assumed is due to the mass taking the weight of the loculus in which it has been formed, while the larger masses are then more irregular shape to the fact, that septa have disappeared and several smaller masses have coalesced into one large crystalline formation.

In infancy, the parenchyma, and to a less extent the stroma are infiltrated with calcareous concretions, which are practically constant throughout life. Meckel states that they appear about the sixth year.
and that before their appearance "we find in its place a more vicious mars, which is not more in-
frequently found at an advanced age, and which, then sometimes even co-exists with the concretions."
Some of the eminent anatomists remarks regarding the vesicules are so quaint that it venture to quote even
further. After stating that in young men, the con-
cretions are only found around the organ and in the
caucus, while in old men they occur mainly in exclus-
ively in its substance, and affirming that the brain
and is least in youth and advanced age, he says
"The calcule of the pineal gland are not a patholog-
iccal appearance, and the cause or the effect of the dis-
ceases of the mind as Magagni and others assert,
because they are found in very small quantity in
four individuals who were fools. Still the co-
incidence of their rarity with mental derangement
is curious, inasmuch as the fineness of these concret-
eons in young and old men, seems to lead to some-
thing analogous."

Blood vessels. As before noted the arteries are very
numerous and are derived from those of the choroid
plexus of the third ventricle. The veins open into the
venous plexus. Vasa vasorum are no doubt also pre-
sent, but upon these I am not qualified to speak.

Nerves. Nerve fibres cannot be made out until you
come to the peduncles. Certainly some of the retinal
fibres seem to pass into these, but they alone no
neral characteristics. Ramus - y - caudal found
sympathetic fibres entering with the vessels. Holzkirschners nerve fibres are present in the organ and describes multipolar cells throughout the stroma. Nerve cells do in a sense exist (in Plate 21 Fig. 1) one can make out several pyramidal cells with fragmentary processes. Cajal agrees here also, he has noted cells like cerebellar ones, but could not find axis cylinders. Darkschewitsch believes that the nervous nature of the epithelium cannot be contested, being so apparent from the richness of the fibrillary connections with the internal brain capsule, optic tract, amni, fascia of Meynert, optic fillet and posterior cerebral commissure. Hagemann's work with ehrlich staining describes true nerve fibres with true nerve cells. Hentschel thinks that the only nervous elements are those connected with the vessels. Cionini by Golgi's and Weigert's methods found only neuropila and not nerve cells, and nerve fibres only in the base of the gland.

Verstue says, that contrary to ancient authors, nerve cells or fibres belonging to the gland itself do not exist, "the few nerve fibres which have been pointed out, are really supports for the vessels."

And so I might go on quoting author after author, one believing that nervous elements do exist, the next denying their presence altogether.

So is as often the case, the truth I believe is really to be found between the extremes — some few nervous cells with atrophied processes can be recognised, but these are few and few between. So regards nerve
fibres, they appear in the organ itself to be so degenerate, as usually to defy recognition.

The volume and size of the Epiphysis is relative to the size of the brain, presenting in this respect a marked contrast to the Hypophysis.

Macalister and others maintain that the organ is proportionately much larger in the foetus than the adult, and my own observations agree with this statement. Tschekal also finds it larger in the foetus and child. According to W. Bellum it is also of greater size in females.

I might mention that during the past few months I have repeatedly tried staining the Epiphysis by Golgi's methods in the hope of ascertaining more definitely the condition of its nerve elements, but without success.

My results were practically negative, only the blood vessels taking on the stain, which is well known to be a common occurrence with the somewhat capricious Golgi stains.

Functions.

The Epiphysis, as some of the older Anatomists called it, the "Pineal Body" has always excited much interest from the earliest times. To quote from Charpy

"from all time, the pineal by its character of an unpaired and median organ, its relation at the entrance of the cerebellar cavities, its peduncles in the form of veins, - has excited the curiosity of observers. Who without knowing its structure, have attributed to
Galen taught it the door for the passage of the spirit and also entertained the much more practical belief that it was controlled in a sort of atroparque fashion, the veins which bear his name. This last seems to me to have a ring of possibility in it, inasmuch as when the organ becomes enlarged, it must, from the nature of its connection with the pia mater, drag upon the venuis interposituim, and so, as we have already noted, may exercise under such conditions, a definite though small influence upon blood supply in the third ventricle of the brain.

Descartes considered the pineal to be the chief seat of the soul. Magendie thought that by acting as a plug or valve, that it regulated the flow of the cerebrospinal fluid through the Sylvian Aqueduct, but this theory presupposes the gland to be very movable whereas we have seen that it is not so.

In 1882 Rushbord gave as his opinion that the Epiphysis was the remnant of a visual organ for the sense of heat, for animals in geological epochs, and speaks quite particularly of its practical value in protecting great monsters such as the Ichthyosaurs and Pleiosaurus from the effects of the solar rays as they lay basking on the banks of prehistoric rivers and by the shores of Pliocene seas!!

The researches of Graaf, and especially of Spencer in 1886 and the many subsequent investigations since that time leave little doubt as to what the
epiphysis (as we now know it) is the rudiment of
now we have to consider, what is it in the human
being, is it a mere vestige and nothing more — has
it a function or none? We now know that it attained its full development in
prehistoric Saurians, that this is maintained to a
lesser degree in a few living Saurians, but that in
birds and mammals, the organ has developed into
a somewhat glandular structure. We have seen that
in birds it is relatively large, and is found as regards
structure to possess many tubules with alburniform
contents. McCollum says that in birds it is supposed
to be associated with their “homing” instincts.
Notice has also been made of the relatively immense
grise to which the organ attains in Selachians.
Whatever function it may possess in Mammals,
and the last mentioned fact indicates that in such
cases at least, it probably does possess one — it is
clearly not a nervous one. By various authors it
has been compared to a mere ganglion, a blood
gland and a lymphatic gland.
Nicolson says, that “histology shows that the praeal
gland has a structural degeneration, incompatible
with a real active function, whatever that function
may be.” The presence of the brain gland
is generally held to be the leading argument, in fav-
our of the epiphysis being an utterly degenerate or-
gen, and had this sand occurred in the epiphysis
alone, then it might absolutely have been classed as
a degeneration, and the pineal functions written down as obsolete, or next door to it. But we have seen that deposits identical in structure and chemical composition are found elsewhere in the brain,—in the choroid plexuses and in the pia mater elsewhere, and that with a frequency so great as to be accounted normal deposits in a normal encephalon.

Of course comparative anatomy has taught us the true theology of the Epiphysis Cerebi, although I do not consider that Yezierski and many others are right when they affirm that in man and the higher vertebrates, the epiphysis, namely, called the pineal gland, is morphologically the pineal eye of the Riggs, much abridged! Still if the epiphysis have no function at all, why does it continue to exist in the higher Vertebrata with such unvarying volume and relations, why do its three pairs of peduncles retain such marked position and endings—why its difference in size in age, and even according to some in age?

In a word, is it not just possible that the Epiphysis may possess some function, although hitherto we have not been able to fathom it?

We know that the Hypothalamus, Pituitary and even the Thymus have some distinct relations towards the production of such substances as colloid, mucus etc., may not the Epiphysis have a like relation to some allied substance?
common consent almost, the organ is believed to process no active function at all, it is very amusing to find an "animal extract" of it figuring in the current price list of well-known London Druggists. To learn from advertisements that it is opaque in cases of functional brain conditions, cerebral softening, dementia and chronic mania.

Ogle reports a strange coincidence where in a case where hypertrophic changes occurred in the penis, scrotum and testis, the autopsy showed as the only recognizable lesion, a new growth involving the pineal gland. Pathological changes in it have also been associated with conditions of chronicity or brawny-like states, although as Ogle remarks, this is perhaps not directly due to disease of the pineal itself but rather to the position of the growth, and its interference with surrounding structures. Stupor is moreover a very common symptom of advanced cerebral disease.

A very fanciful theory assumes that the Epithysis has something to do with the production or modification of dreams. I am not aware that this theory has been seriously brought forward, as a page in psychological romance, it would be a fascinating one. The dreamer fast asleep, and his lateral eyes veiled, and optic nerves inactive — this ancient remnant of a protoreptile eye congealed and rendering irregular stimuli to the right area!!

A learning was devoted to the pineal gland late...
to the pineal gland by the pathological Society of London, but the practical outcome of the discussion amounts to little or nothing. Lord believes that the Epiphysis is pathologically potential for two reasons, firstly from its containing embryonic cells, it favours the formation of new growths, and yet statistics prove that tumours are of rare occurrence. Secondly, from cystic origin and degeneration normally present, degenerations would tend to become very active.

In cystic conditions of the organ, the cysts were found frequently lined by columnar cells, "arranged always like a palisade". Ogilvie maintains that there is a striking resemblance in these cells to cells found in some forms of pineal body as depicted by Baldwin Spencer.

Cystic disease, hyperplasia and Carcinoma were found to be the least uncommon diseased conditions of the Epiphysis. Tumours were exceedingly rare.

Normally, as we have already noted, pigment does not exist in the Epiphysis, so Campbell finding in an enlarged pineal, layers of densely pigmented bodies, surrounding the dilated venousile, jumps to the conclusion that these are analogous with the retinal ones of the pineal eye. That this idea is erroneous, the development of that eye clearly demonstrates — as in Semionos processing the retina into, we have already noted that it is derived from the "parietal organ", and not from the Epiphysis at all.
Conclusion.

Before summing up my opinions regarding the Epiphysis Cerebi, I wish again to draw attention to Plates XVI and XVII, in which I have sketched diagrammatically the conditions of these two evaginations, the parietal organ and the epiphysis as they are found in the five great groups of the Vertebrata. In all of the diagrams the parietal organ is colored in blue and the epiphysis in red. In the Fishes (Fig. 1) the condition varies somewhat. Any trace of the parietal organ is in some, only seen in embryonic life, while in such as the Lampreys as before noted, two distinct vesicles exist. I have therefore merely dotted in the parietal organ.

In the Amphibians (Fig. 2) all trace of the parietal organ is lost, and its base trimmed out in the ventricular roof etc. In most lizards (Fig. 3) the parietal organ becomes the pineal eye, and has in embryonic life a separate life of its own, the functions of this stage is later assumed by the modified epiphysis.

In Birds (Fig. 1) again, the parietal organ has entirely disappeared, and only the epiphysis exists. This is very large, somewhat elongate in appearance, and is as previously noted, probably glandular in nature. In Mammals (Fig. 2) the pineal apparatus is represented by the epiphysis alone. Although in man and most mammals it is relatively small in size, still in some (e.g. Sowarium), it is very large indeed, and even in man presents a glandular structure, although somewhat degenerate in character.
The deduction from a study of these observed facts seems to me an obvious one — that the pineal eye with its stalk was formed in the protovertebrates from the parietal organ, and from it alone.

No doubt, in some living lizards, the pineal stalk is formed by the epiphysis, but development shows us, that this is a secondary and adaptive change. If this be granted, the question at once arises, what then is the epiphysis, and what did it represent in ancestral forms? The long list of papers appended in the bibliography shows the interest which Spencer's researches have excited regarding the pineal gland, and some of them contain interesting speculations on the subject. My own opinion (which differs from any one I have ever come across), is, that the epiphysis represents not an organ at all, but an archaic glandular organ, situated somewhere near the periphery of the brain — while the stalk is the vestige of its duct by which the secretion of the gland was conveyed to the cerebral vessels. I therefore regard its occurrence in the role of an occular nerve (as seen in Plate XVII) as a mere adventitious circumstance.

Arguing on the lines of hypothymical analogy, the duct becomes obliterated and lost, the whole structure is thus abandoned and becomes useless, and whatever secretion it may produce, becomes an "internal one." In birds its glandular nature is beyond question, and what other explanation can be offered regarding the excessive size of the epiphysis in the Walrus Seal?
In man no doubt, its relative size is insignificant, yet the outer zone of its cellular substance is certainly glandular in type, although degenerate in character.

May not even the frequent presence of a central cavity in the Epiphysis represent something more than a mere developmental vestige — may it not represent the receptacle for the glandular secretion, just as do the spaces in the boundary zone of the Hypophysis in the case of that organ?

May not the Epiphysis, even in man, have a relation to some organic secretion, just as the Hypophysis has to colloid, although presumably to a much smaller degree? Is there any trace of such found in the organic basis of the accumulator?

Was not the secretion (in birds, the seed and malus at any rate) some definite role to play in central endosmosis or changes?

These and such like questions, naturally present themselves. I do not for a moment wish to insist that in man the pineal gland has any function at all, — if it have, analogy scarcely makes it of a glandular nature.

I do not agree with Weggert, who, from the nature of its nervous attachments, considers the Epiphysis to represent a nervous ganglion. As the parietal organ arises, not only in close juxtaposition to the Epiphysis but even sometimes from a common evagination, and also that (as seen in some lizards) its atrophic function is sometimes delegated to the Epi-
- physis — it is surely natural to assume, that, the nerves plexuses which coming from various parts of the brain, to pass to the pineal eye, and in order to do so enter the base common to both Carnicul Organ and Epiphysis, that after the disappearance of the former, these nerves tracts get arrested at the pineal base, and end indeterminately in it.

Whatever the secrecy of the Pineal gland has been or even may be, its function in the generality of vertebrates must be of a very subsidiary character compared with that of the Hypophysial secreting.

To sum up my conclusions in a sentence, the Epiphysis is the vestigial remains of an archaic glandular organ, which although in some living animals is large and functional, is in man as utterly degenerate in structure, that its function may be written down as non-existent. The degeneration is declared by the altered glandular structure, the epithelium-less only occasional central cavity, and the presence of calcareous masses.

Under any circumstances, it is not the representative of the pineal eye!
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This is an accurate drawing of a specimen brought to me by one of my students at Surgeons Hall, Edinburgh, some years ago. A doctor in the country had sent it to him, and wished me to verify his opinion as to what he thought it was, viz.,

the vermiform appendix, with piece of the large bowel. He stated that a boy in his practice had suffered from symptoms of acute intussusception, and some days afterwards passed this in his stool. The patient recovered. I found it to be a piece of small intestine with a "Meckel's diverticulum", which had a small cyst-like ending.