THE HUMAN EPIPHYSIS.

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INTRODUCTION.

The epiphysis or pineal body is a cone-shaped structure resting on the groove between the superior colliculi of the midbrain. The pineal recess of the third ventricle extends into its base so that on sagittal section the body appears to be attached to the brain by a double stalk. The upper limb of attachment is occupied by the habenular commissure; the lower by the posterior commissure which separates the pineal body from the upper end of the Aqueduct of Sylvius. Superiorly the structure is firmly adherent to the under surface of the velum interpositum between the two veins of Galen.

Recently brought into prominence as a possible specific in the field of endocrinology this organ has attracted attention since very early times. Many theories regarding its function have been advanced in the course of nearly three hundred years, during which time many investigators have contributed a heterogeneous collection of facts and fancies. The earliest speculator was René Descartes (1649) who noted that the pineal body was unpaired and occupied a commanding position with reference to the ventricles of the brain. At a time when animal spirits were held to dwell in the ventricles it was reasonable for him/

him to suppose that the pineal body should be the special seat of the controlling soul. At the present day the suppositions as to the function of this structure are also reasonable but possibly no more accurate.

The subject has been approached from many angles. Earlier scientific investigators adopted histological methods and it is interesting to note that the pineal body was regarded as a gland as early as 1837 (Hollard). An account of the pineal eye in Lacertilia given by Leydig in 1872 next directed attention to its homologues in the lower vertebrates. The findings of comparative anatomy however, far from elucidating the problem of the significance of the organ, rendered it more complex than ever. Not only was it a potential gland, it was also a potential visual organ. Of interest academically, such conclusions detracted from the practical importance of further study till evidence of a clinical nature reawakened universal interest. In 1910 Pellizzi described a definite syndrome characterised by premature sexual development. This he called macrogenitosomia praecox and attributed to disease of the pineal body. Thereafter attempts were made to establish the exact nature of the influence exerted by the pineal body. A fresh stimulus was given to the study of its histology, both human and comparative/

comparative; clinical and pathological data were sifted and correlated; experiments were carried out to study the effects of removal, injection of extracts and oral administration; a chemical analysis was undertaken; even variations in weight received their due consideration.

Much of this recent work has been carried out without reference to other branches of study, and, as might be expected, attempts to establish varying hypotheses have resulted in reports of a widely conflicting nature.

In this paper special attention will be paid to the earlier stages of the development of the human pineal body in the hope of establishing a definite relationship with the conditions found in the lower vertebrates. With this essential foundation an examination will be made of the histological features found in the foetus, the child and the adult. Any indication of possible function will then be tested by reference to clinical and experimental evidence.

In any comparison of the human pineal region with that of the other vertebrates, the problem of nomenclature immediately arises. The pineal organ of human anatomy is not necessarily homologous with the pineal organ of comparative anatomy, which, in many cases, refers to one of/

of two pineal outgrowths. To avoid confusion the term epiphysis will be used where only one outgrowth exists and will be regarded as being comparable with either or both of the outgrowths found in the lower classes. In the section on comparative anatomy the nomenclature of Studnička (1896) will be adopted, as, being the most widely used, it facilitates reference to the literature. The structure which lies posterior, dorsal or to the right will be termed the pineal organ, that lying anterior, ventral or to the left the parapineal organ.

COMPARATIVE ANATOMY.

CYCLOSTOMES. The epiphyseal complex consists of two vesicles each of which is connected to the brain by nerve fibres. Situated more or less in the median plane, the vesicles are in close contact and so disposed that one, usually referred to as the pineal organ, is placed close to the roof of the cranial cavity and lies above and posterior to the other vesicle or the parapineal organ. Both vesicles present appearances suggesting an attempt at visual adaptation, but the pineal organ is the more highly developed both in size and in histological differentiation.

It is generally agreed that the vesicles arise independently, although Ahlborn (1883) described a single outgrowth of which the proximal part became greatly reduced and the distal part divided into two. There is still some dispute as to the primitive position of the vesicles. Ahlborn noted that the parapineal organ lay somewhat to the left and apparently became fused with the left habenular ganglion. Gaskell (1890) described nerve fibres passing from the parapineal organ to the left habenular ganglion and from the pineal organ to the right habenular ganglion. Taking into consideration the histological appearances in the/

the vesicles, the indication of the parapineal organ as a left sided structure, and the nerve supply of the two vesicles, he postulated a primitive pair of eyes with the habenular ganglia serving as optic ganglia. The fact that the nerves of the ordinary paired eyes of the adult Petromyzon do not decussate made his suggestion still more probable. Dendy (1907) agreed with Gaskell that the vesicles were originally paired structures and that they were connected with the respective habenular ganglia. Further, he explained their median position on the assumption that this position was more advantageous for the exercise of the visual function. The pineal organ, by this reasoning, could be regarded as being displaced so as to overlie the parapineal organ and would explain the increased differentiation of the one and the accompanying degeneration of the other.

There are, however, observers, who contradict the main basis of this inviting theory, the identification of the habenular ganglia as optic ganglia. Retzius (1895) demonstrated that the fibres from the pineal organ are connected to the posterior commissure. Again Studnička (1905) maintained that the connection of the parapineal organ with the left habenular ganglion was secondary, it having/

having been connected originally with both ganglia.

Whether the organs were originally paired or median in position, it is at least agreed that both show some evidence of visual structure. Dendy (1907) indeed, found sufficient histological differentiation in the pineal organ to warrant him believing that it is still functional, at least to the extent of registering variations in the intensity of illumination. Tilney (1928) agreed that the attempt at visual adaptation was well advanced, but doubted its functional value.

ELASMOBRANCHS. In this, the first order of the gnathostomatous fishes, the epiphysis is represented by a single vesicle which is generally identified as the pineal organ.

Its origin as a simple evagination is however disputed by Locy (1894). Working with embryos of Squalus acanthias, he found that the cephalic plate possessed two pairs of accessory optic vesicles which, with the primary optic vesicles, admitted the possibility of three pairs of eyes being formed. Of these vesicles the primary pair developed into the lateral eyes, the first accessory pair became incorporated with the walls of the thalamencephalon and the second accessory pair fused to form the epiphysis. He/

He believed then that the epiphysis was double in origin and homologous with the lateral eyes. He also thought it probable that the enlarged distal end of the epiphysis in this fish was homologous with the pineal eye of other forms.

Later workers including Minot (1901) and Tilney (1928) failed however to find similar evidences of a bilateral origin, nor could they discover any tendency towards the formation of an eye. They inclined rather towards the possibility first suggested by Galeotti (1897) of its being glandular in function.

TELEOSTEI. The presence of both a pineal and a parapineal vesicle has been demonstrated. The latter however is rudimentary and does not persist into the adult state.

The vesicles can be regarded as arising independently. In Coregonus albus (Hill 1891) the posterior vesicle or pineal organ appears first and in the middle line. The anterior vesicle or parapineal organ appears later, slightly in front and to the left of the posterior. Both possess cavities opening separately into the cavity of the brain. In Salmo fontinalis (Hill 1894) a common passage connects both vesicles with the brain cavity, but Hill suggests that the earlier stages would possibly show two separate outgrowths which, as they grow dorsally, would carry/

carry part of the brain wall with them and so form a common median passage. The position of the vesicles in this fish is interesting in regard to the theory that they were originally paired organs. While in Coregonus the parapineal organ lies only slightly in front and to the left of the pineal organ, in Salmo the vesicles lie nearly in a transverse plane.

In both cases growth in the parapineal organ soon ceases and although a rudiment persists throughout life it can have no functional importance. The evidence concerning the function of the persisting pineal organ is somewhat contradictory. Hill, in Coregonus albus, describes histological appearances which would suggest a glandular rather than a nervous structure. Then, in Salmo fontinalis he describes nerve fibres as taking origin from the cells in the distal part of the organ and running to the posterior commissure. Studnička (1905) states that the organ cannot be considered as a gland but illustrates it as a convoluted structure connected to the brain roof cavity by a hollow stalk. Galeotti (1897) alone commits himself as to the nature of this structure. Working with Leuciscus he found fuchsinophile granules in the cells of the pineal organ and these he regarded as evidence of a secretory function.

AMPHIBIA. The pineal organ may appear as a simple flattened vesicle or may consist of two parts. The former condition is found in the Urodeles and the Apoda. In the Anura where its appearance has attracted most attention, there is an end-vesicle connected by a slender nervous stalk to a more proximal portion. The parapineal organ is generally regarded as being completely suppressed.

The "end vesicle" was first described by Stieda (1865) as a "frontal subcutaneous gland" but de Graaf (1886) discovered its relationship to the epiphysis. He interpreted it as the distal portion of a single epiphyseal outgrowth which becomes constricted off and comes to lie first between the brain and the cranium and then outside the cranium close beneath the skin. The radial arrangement of the cells of the upper wall of the vesicle and the presence of pigment in some of these cells led Béraneck (1892) to compare it with the pineal vesicle of the Cyclostomes. He also noted in embryos of Bufo the presence of an outgrowth in front of the habenular commissure. This outgrowth soon disappeared but, he thought, could be regarded as the representative of a parapineal anlage. On the other hand Cameron (1903) described two bilateral outgrowths of which the right one or pineal element disappeared by fusing with the left or parapineal/

parapineal element. End vesicle of adult then he regarded as the parapineal organ, the pineal organ being represented only by a part of the proximal portion of the epiphysis.

Again, conflicting opinions have been expressed with regard to the function of the epiphysis. Béraneck and Cameron, while differing on the homology of the end vesicle agree that its structure is visual in nature. Other observers as early as Galeotti (1897) and as recent as Tilney (1928) find more evidence of glandular function.

REPTILES. There are great variations in the constitution of the epiphyseal complex in reptiles. In Lacertilia and Rhynchocephalia both the pineal and the parapineal elements are well developed; in the Chelonia and Ophidia the pineal organ may be well developed and the parapineal organ absent; in the Crocodilia there is no trace of either organ.

Again, there is a difference of opinion as to the degree of independence possessed by each of these structures when both are present. One school, represented by Strahl (1884), de Graaf (1886), Spencer (1886) and Selenka (1890) maintained that the parapineal organ was produced as a secondary differentiation constricted off from the distal part of the pineal organ. The main support of this theory was the discovery by Spencer of a nervous "Pineal Stalk" connecting/

connecting the parapineal organ to the pineal organ and present in the adult state of all reptilian forms studied by him.

Another school represented by McKay (1886), Klinckowström (1894), Schauinsland (1899) and Novikoff (1910), regarded the parapineal organ as an outgrowth from the anterior wall of the pineal anlage.

A third group of investigators including Hoffmann (1886) and Strahl-Martin (1888) postulated the division of an original single outgrowth into an anterior parapineal and a posterior pineal organ.

Finally there were those who decided that the structures arose independently. These included Béraneck (1892), Dendy (1899), Leydig (1890), Francotte (1894, 1896), and Warren (1911). Béraneck succeeded in demonstrating that the so-called "Parietal Stalk" of Spencer was attached not to the pineal organ but to the roof of the diencephalon in the region of the habenular commissure. Dendy (1899), working with Sphenodon, further maintained that not only were the two organs quite independent but that they were originally paired in character. He described the parapineal organ as a left anterior or primary parietal vesicle; and the pineal organ as a medial posterior or secondary parietal vesicle/

vesicle. Both vesicles were potential eyes, but the left alone develops in this way. Though unsuccessful in tracing nerve fibres beyond a point between the posterior ends of the ganglia habenulae he presumed that their ultimate origin would lie in the left habenular ganglion. Francotte (1894) believed in the original independence of the two structures but reconciled this belief with Klinckowström's observations by agreeing that they may fuse at an early age.

There is less diversity of opinion where the function is concerned. Leydig (1872) was the first to point out that the parapineal organ in reptiles was eye-like in structure. This has never been denied and some observers believe that in Sphenodon at least the parapineal organ is completely adapted for visual function.

The pineal organ may consist of one or two parts, one part only existing in the Ophidia. When two portions are present they are connected by a narrow stalk. The distal portion is comparable with the end vesicle found in the Amphibia, but there is no structural evidence of any attempt to form an eye. Attempts have been made to homologise it with the parapineal organ in those forms where the parapineal organ is absent, and absence of the end vesicle is often found when the parapineal organ is present/

present. Unfortunately in Pseudopus (Studnička 1905) there is both a well marked end vesicle and a well developed parietal eye. The proximal portion shows a greater degree of differentiation. It increases in size, its walls become folded, and there is a suggestion, more marked in the Ophidia, of a possible glandular function.

BIRDS. In the adult the epiphyseal complex is represented by the pineal organ only. The anlage of a rudimentary parapineal organ has, however, been demonstrated.

The presence of two outgrowths in the epiphyseal region has been reported by Lieberkühn (1871), Parker (1892), Klinckowström (1892), St. Remy (1897) and Hill (1900). Studnička (1905) who cites these cases, refuses however, to consider that the presence of two epiphyseal anlagen has been established, regarding the occasional presence of an extra outgrowth as being pathological. Cameron (1904a) again, believes strongly in the theory that the epiphysis was originally a paired organ, and describes in the chick bilateral outgrowths. Of these the right one was small and soon merged with the other.

In all cases one outgrowth alone persists, the second when present, either disappearing or fusing with its neighbour. The fate of the persisting outgrowth has been traced/

traced by Mihalkovicz (1874, 1877) and his findings have been accepted by all subsequent investigators. According to him an original simple outgrowth gives rise to a number of vesicles by a process of budding. These later separate off, become surrounded by connective tissue and form with the original outgrowth a club-shaped glandular like organ. Tilney (1928) maintains that the epiphysis is a true gland, this being exemplified not only by the character of the cells comprising the structure but also by the constant alveolar pattern in which they are arranged.

MAMMALS. The pineal organ is present in all Orders except the Edentata. A parapineal anlage may appear but is inconstant and transitory.

Krabbe (1929) working with embryos of Talpa, Lepus, Equus, Canis and Lobodon describes a cell mass lying in close relation to the habenular commissure and rostral to the developing pineal organ. This structure soon disappears but from its position and relations it could reasonably be regarded as a parapineal element. There is no suggestion of any visual or glandular differentiation.

A complete description of the development of the pineal organ was made by Mihalkovicz in 1877 and little has been/

been added to his account since, most of the more recent work having been purely cytological in character. He described the initial changes as being similar to those found in Birds, resulting in a primary evagination with many secondary diverticula. Later, the greater part of the lumen of the original outgrowth becomes obliterated, the remainder persisting as a pineal recess. The obliteration of the secondarily formed vesicles finally gives the appearance of a number of follicles forming a solid glandular-like organ.

Warren (1917) and, more specifically, Pastori (1927) supply information on the topographical relations of the mammalian epiphysis which is of interest in relation to the operative procedures now undertaken to investigate the effects of removal of this structure. They describe two main types. The first type is found in man, the carnivora and the ungulates. Here the pineal organ is relatively small in size, spheroidal or conoid in shape, and lies completely under cover of the corpus callosum. An example of the second type is found in the rodents where the epiphysis is club-shaped, consisting of a long stalk expanding distally into an end vesicle. This vesicle appears from under cover of the corpus callosum and may lie in close relationship to the endocranium/

endocranium. It is unfortunate that the type which most closely resembles that of man should be the one which cannot be removed without damaging other parts of the brain substance.

RÉSUMÉ. 1. The parapineal, an obvious feature in the Cyclostomes, Lacertilia and Rhyncocephalia, is a mere rudiment in the Teleosts and is completely suppressed in the Elasmobranchs, Amphibia, Birds and Mammals. The anlage of a parapineal organ, more or less transitory, has however been noted in all classes; in Elasmobranchs by Locy (1894); in Amphibia by Béraneck (1892) and Cameron (1903); in Birds by Lieberkühn (1871), Parker (1892), Klinckowström (1892), St. Remy (1897), Hill (1900) and Cameron (1904a); and in Mammals by Krabbe (1929). The parapineal organ then is probably a constant feature throughout the vertebrate series but is a structure which tends to degenerate and disappear.

2. The independent origin of the pineal and parapineal organs is disputed by Ahlborn (1883) in the case of the Cyclostomes and by many observers in the case of the Reptilia. General consensus of opinion however is in favour of the complete independence of the two structures throughout all the Vertebrate classes.

3. When/

3. When the parapineal organ persists into the adult state it shows signs of visual differentiation. These are most marked in the Lacertilia and the Rhyncocephalia.

4. Arguments have been put forward in support of a theory that the pineal and parapineal organs represent original paired visual organs. In the Cyclostomes, Gaskell (1890) based his conclusions on the position of the organs, their histological appearances and their nerve connections with the respective habenular ganglia. Ahlborn (1883) had previously noted the lateral displacement of the parapineal organ and Dendy (1907) corroborated Gaskell's observations. Again the bilateral position of the organs has been noted in Elasmobranchs by Locy (1894); in Teleosts by Hill (1891, 1894), who further noted an extreme case in Salmo; in Amphibia by Cameron (1903); in Reptiles by Dendy (1899), and in Birds by Cameron (1904a).

That habenular ganglia function as optic ganglia in Cyclostomes is however contradicted by Retzius (1895) who demonstrated that the pineal organ is connected with the posterior commissure; and by Studnička (1905) who pointed out that the parapineal organ is originally connected with both habenular ganglia, and that it only loses its connection with the right ganglion at a later stage. Again, the pineal organ/

organ which, unlike the parapineal organ persists as a well developed structure in the great majority of vertebrates, presents few evidences of visual differentiation. In Cyclostomes there is an eye-like formation, but in no other class is this present unless we accept the questionable visual characters which may be seen in the end vesicle of the amphibia.

We find then that while the possibility of an original paired origin cannot be entirely refuted, the evidence in favour of such a theory is more suggestive than conclusive.

5. In classes where only one organ persists the surviving structure is generally regarded as a pineal organ. The possible fusion of the parapineal organ with the pineal organ to form a compound structure is however suggested by Locy (1894) for the Elasmobranchs, Cameron (1903) for Amphibia, and Cameron (1904a) for Birds.

6. In all classes except the Cyclostomes, the pineal organ is generally regarded as being glandular in nature. This opinion is founded on the glandular-like appearance which the organ presents, particularly in the Ophidia, Birds and Mammals; its extreme vascularity; the alveolar pattern in which the cells are usually arranged, and the character of/

of the constituent cells. Fuchsinophile granules described by Galeotti (1897) as occurring in the pineal cells of Elasmobranchs, Teleosts and Amphibia are cited as special evidence of a secretory function. On the other hand, Jordan (1911, 1921) in a histological investigation of the pineal body of the sheep, finds no cytological evidence of secretory function, although he agrees that the general structure is suggestive.

DEVELOPMENT.

Very little attention has been paid to the development of the pineal body in the human subject. This is surprising when one considers the enormous amount of work which has been done on this structure from the standpoint of comparative anatomy, histology, physiology, pathology and medicine. Till within comparatively recent years the chief source of information from the embryological point of view has been the account furnished by His in his classical description of the development of the central nervous system. Then in 1916 Krabbe made the first attempt to supply a more complete account. With a series of fifteen embryos, including representatives of every month from second onwards he was able to present the main outline of its foetal history and to throw an entirely new light on the original conception of its origin. Not only was there present the diverticulum already described by His but there was in addition a cell mass lying immediately in front. Other workers on the development of the epiphysis - Hochstetter (1923), Orlandi (1928) and Globus and Silbert (1931) have confined themselves to a study of the cytological changes which occur during the later months of foetal life and in the early years of infancy.

In/

In this section due consideration will be given to the work of the above authorities in an attempt to find some developmental significance for the diverse functions claimed for this structure. In view of the findings of comparative anatomy particular importance is attached to the discovery by Krabbe of a second pineal anlage. Accordingly a further series of embryos illustrating the morphological changes which take place during the earlier months will also be examined.

The nomenclature of Krabbe will be adopted throughout. The walls of the outgrowth which forms the posterior part of the pineal anlage he called the posterior pineal anlage; the cavity of the outgrowth the pineal diverticulum, and the cell mass which forms the anterior part, the anterior pineal anlage.

In tracing the changes undergone by these parts, all of which occupy a median position, it is essential to study their appearance as seen in (medial) sagittal section. The embryos examined by Krabbe were all cut sagittally. All my material had been cut transversely in varying planes and this necessitated reconstruction in every case. With a view to reducing error to the least possible limit, these were all made by linear projection on millimetre graph paper. To/

To ensure a common base line from which all measurements might be made drawings were oriented as accurately as possible in relation to the preceding drawing with the aid of the projection lantern.

FOETAL DEVELOPMENT. Plate I consists of four figures which illustrate the appearances presented in the mid-sagittal plane of the mesencephalon and part of the diencephalon of four embryos of the first half of the second foetal month. Figure I is a section of the 15 mm. embryo of Krabbe, and figures 2, 3 and 4 are linear projections of embryos of 12.5, 15.5 and 16 mm. respectively. The position of the epiphyseal anlage is indicated in each case by an arrow which in figures 2, 3 and 4 also indicates the plane of section.

During this period of development, the contour of the brain roof shows no sign of any boundary between the diencephalon and the mesencephalon. In sagittal sections, the posterior commissure p.c. is readily recognisable, and affords a guide to this boundary zone, and consequently to the site of the epiphyseal formation which appears immediately cranial to this (fig. 1). In transverse sections, the commissural fibres are not easily seen and the region of the epiphysis can only be found approximately by making a reconstruction of the brain roof contour and comparing it with/

with sagittal sections.

Figures 5, 6, 7 and 8 of Plate II show at a higher magnification the epiphyseal region of the brain roof of the same four embryos. In his 15 mm. embryo, Krabbe describes both an anterior pineal anlage a.p.a. and a posterior pineal anlage p.p.a., the latter being constituted by the walls of a shallow pineal diverticulum p.d. (fig. 1 and fig. 5). Somewhat similar appearances are presented by the other embryos of this period.

Plate III shows transverse sections of the epiphyseal anlage of embryos of 12.5, 15.5 and 16 mm. seen at the level indicated by the arrows in Plates I and II. A comparison of Plates II and III shows that in each case the striking feature is the mass of cells which forms the anterior anlage. These cells are readily distinguishable from remaining cells of brain roof, being rounder, more closely packed together, and staining more deeply. Fig.9 illustrates a transverse section through the mass in the 12.5 mm. embryo, the earliest stage at which this formation could be recognised; and shows it to be placed in the marginal zone of the roof plate where it produces an almost imperceptible elevation of the surface. In the older embryos there/

there is a progressive increase in size in all directions (1) leading to the formation of a marked projection from the roof. This projection is in no sense due to an underlying evagination. In all cases a clearer zone of protoplasm separates the mass from the underlying cells of the roof plate which in this region are so arranged as to form a concavity in which the anlage rests.

Krabbe described a clear protoplasmic area in the centre of the anterior anlage in his 15 mm. embryo. A similar appearance was found in the 16 mm. embryo, but in one section only.

The existence of a posterior anlage at this stage of development is less certain. A shallow longitudinal furrow is certainly present in each embryo in the region caudal to the anterior anlage and undoubtedly represents the pineal diverticulum of Krabbe. The extent of the furrow compared with its depth hardly justifies its description as an evagination, nor is there any differentiation of the cells forming/

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(1) Approximate Measurements.

12.5	....	sagittally	50 μ	transversely	60 μ	thickness	25 μ
15.5	....	"	130 μ	"	100 μ	"	70 μ
16	....	"	150 μ	"	110 μ	"	80 μ

forming its walls which by definition would constitute the posterior anlage. At the most it might be said that there is an accentuation in this region of a furrow which runs the whole length of the diencephalic roof and that this marks the site of the future pineal diverticulum.

During the first half of the second foetal month then we can recognise an anterior pineal anlage which gradually increases in size and becomes more prominent. In the seventh week the appearance of the whole region becomes profoundly altered. An examination of embryos of 17.5(1), 21 and 21.5(2) mm. has been made and the results compared and contrasted with those found by Thyng (1914) in a 17.8 mm. embryo, Bailey (1916) in a 19 mm. embryo and Krabbe 1916 in a 20 mm. embryo. Figures 12 and 13 of Plate 1V illustrate the epiphyseal region, as seen in the mid-sagittal plane, of the/

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(1) I am indebted to Professor David Waterston of the Anatomy Department of the University of St. Andrews for permission to examine and describe the epiphyseal region of this embryo.

(2) I am indebted to Professor James Couper Brash of the Anatomy Department of the University of Edinburgh for permission to examine and describe the epiphyseal region of this embryo.

the 19 mm. embryo of Bailey and the 20 mm. embryo of Krabbe. Similarly Figure 14 of Plate V, and Figures 17 and 18 of Plate Vl illustrate respectively linear projections of embryos of 17.5, 21 and 21.5 mm. In all these embryos the pineal diverticulum is a prominent feature.

Thyng merely mentions the existence of a slight pineal evagination and notes that this represents the first appearance of the epiphysis. His note is interesting in that his embryo correponds so closely in size to the 17.5 mm. embryo, the youngest embryo in which I could find a definite pineal evagination. The length of an embryo is an uncertain guide to its age unless the degree of flexion is known. It is then quite possible that the 13.6 mm. embryo of His would correspond in age with those embryos of 17.5 and 17.8 mm.

Bailey (1916) in a paper dealing with the morphology of the roof plate and the choroid plexuses makes incidental references to the epiphysis. His observations are noteworthy in that he clearly recognised the presence of two pineal anlagen seven months prior to the publication of Krabbe's more detailed account. (Bailey, February 1916 - Krabbe September 1916). In his 19 mm. embryo he described an epiphyseal evagination the top of which was cupped to receive an epiphyseal vesicle, a ball of more lightly staining cells with/

with an irregular lumen in its centre. The illustration of his reconstruction makes it clear, however, that the epiphyseal vesicle, or anterior pineal anlage is in relation, not to the top of the evagination but to its rostral face. (fig. 12).

The relationship of the anterior anlage to the rostral face of the diverticulum is apparent in all the embryos of this period. There is, however, one marked dissimilarity between the 20 mm. embryo of Krabbe and the other embryos. (fig. 13). The anterior anlage is picturesquely described by Krabbe as being attached to the anterior wall of the pineal diverticulum like a mushroom on a tree stem. In other words a part of the cell mass has become separated from the brain roof by a cleft, a. In his illustration it is the rostral part of the anlage which remains free, the caudal portion remaining in direct continuity with the posterior anlage. A separation is also apparent in the embryos of 17.5, 21, and 21.5 mms. but in each case it is the caudal part which becomes separated (figs. 14, 17 and 18). In the 17.5 mm. embryo the relation of the free portion of the anterior anlage to the brain roof is seen in Figure 15, which, with Fig. 16 of Plate V shows the appearance presented on transverse section at the levels indicated/

indicated by the arrows in Fig. 14. The presence of a caudal cleft can be logically explained as a possible consequence of the evagination of the brain roof which lies immediately caudal to the anterior anlage. That it is not an artefact will be proved by its constant presence from this period onward.

The embryos of 21 and 21.5 mm. show a further alteration in the pineal region (figs. 17 and 18). Following on the formation of a pineal diverticulum there appears a commencing invagination, b. of the brain roof at the site of the posterior commissure. The effect of this is best seen in the 21.5 mm. embryo (fig. 18). Here there is a definite line of separation, c. between the caudal wall of the diverticulum and the neighbouring part of the brain roof. The formation of this groove, together with the cleft a. already noted between the two anlagen throws the posterior anlage into prominence and reveals it for the first time as a definite entity.

There is another interesting feature in this embryo. The anterior anlage presents a well marked cavity which reminds one of the cavity noted by Bailey in his 19 mm. embryo, and recalls the clear zone of protoplasm noted by Krabbe in his 15 mm. embryo and the similar appearance found in/

in the 16 mm. embryo. The absence of a definite lining membrane, and a failure to find any sign of a cavity in later stages, suggests the probability of an artefact. On the other hand the findings of comparative anatomy render important any indication of a possible transient vesicular stage.

Figure 19 illustrates a cross section of the anterior anlage of the 21 mm. embryo at the level indicated by the arrow in figure 17 and readily recalls the mass of cells which constitutes this anlage in the earlier stages. Transverse sections at the levels indicated by the arrows in figure 18 are also shown in figures 20 and 21. In figure 20 the anterior and posterior pineal anlagen can be recognised, even at a low magnification, as two distinct entities.

The reconstruction of a 25 mm.(1) embryo reveals in quite a diagrammatic form the essential constituents and relations of the epiphyseal complex (fig. 22). A further invagination of the posterior commissure is accompanied by a sagittal shortening, producing a shallow evagination rostral to/

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(1) I am indebted to Professor David Waterston of the Anatomy Department of the University of St. Andrews for permission to examine and describe the epiphyseal region of this embryo.

to a deeper invagination of the brain roof, the whole forming an S shape. On the external surface two clefts a. and c. clearly demarcate the anterior and posterior anlagen; on the ventricular surface can be seen the deep pineal diverticulum extending into the posterior anlage and, more caudally, a shallow recess, d. marking the rostral convexity of the commissural area.

Figure 23 shows in transverse section the relative position of clefts a, b and c, together with the pineal diverticulum p.d. and the recess d. Again in fig. 24 can be seen in transverse section the opening of the pineal diverticulum immediately cranial to the recess d. and the position of the habenular commissure h.c. which is now apparent and intervenes between the anterior and posterior pineal anlagen. Level at which sections are taken is indicated by arrows in Fig. 22.

A comparison of appearances shown in the 25 mm. embryo with those in embryos of 38.5 (1) and 42 mm. (figs. 26 and 27), and in Krabbe's embryo of 10 weeks (fig. 25) makes it plain that little change now occurs in the general aspect of the/

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(1) I am indebted to Professor James Couper Brash of the Anatomy Department of the University of Edinburgh, for permission to examine and describe the epiphyseal region of this embryo.

the region.

An examination of the more intimate structure of the epiphysis is now of advantage. Throughout the period already considered there can be found no obvious change in the structure of the cells comprising the two anlagen. In the third month there is however a difference in the arrangement of the cells of the anterior anlage. This mass, spheroidal in the 25 mm. embryo, assumes in the older embryos a cocked hat shape. This formation coincides with the first definite appearance of the habenular commissure to which it is applied, and is presumably caused by the habenular commissure. The important feature in this rearrangement of cells is however not the alteration in shape of the structure, but the fact that two anlagen are seen to be in direct continuity at the foot of the cleft separating their outer surfaces.

Plates X and XI show in low and higher magnification respectively the cross section appearances at levels indicated by the arrows in Figures 26 and 27. The continuity of the anterior and posterior pineal anlagen is clearly visible in figures 29 and 31, which illustrate conditions existing in an embryo of 42 mm. During the third month then we see the first step towards the ultimate fusion of these two/

two anlagen.

Vascularisation also begins about this time, small vessels extending in amongst the epiphyseal cells from the overlying mesenchyme.

During the fourth and fifth months of foetal life there is a gradual approximation to the macroscopic appearances seen in the adult. A gradual increase in the size of the two anlagen is accompanied by a progressive fusion and leads to the formation of the definitive epiphysis. An evagination of the roof of the third ventricle which appears at the beginning of the fourth month extends over the rostral surface of the epiphyseal mass and can be recognised as the future supra-pineal recess. At the same time the mass assumes a conical shape, and by the end of the fifth month becomes displaced so that the apex of the cone is directed backwards. This displacement coincides with the assumption by the corpus callosum of its adult position, and is probably brought about by the backward extension of the developing hemispheres.

The epiphysis at the beginning of the sixth foetal month is a structure which resembles that of the adult in shape, position and relations. The only indication of its double origin is the presence of a cleft which extends into its/

its rostral surface and is filled with connective tissue. Pineal diverticulum is replaced by a pineal recess and a cavum pineale, the latter having been cut off from the former by a process of cellular constriction. Vascularisation is well advanced.

This period then marks the completion of our study of the general morphology of the epiphysis. There is still, however, no sign of any cellular differentiation, and it will now be necessary to consider the cytological aspect of development.

RÉSUMÉ. 1. The presence of the anterior pineal anlage of Krabbe (1916) or epiphyseal vesicle of Bailey (1916) has been confirmed. It undoubtedly represents the parapineal organ found in the lower vertebrates. Similarly the posterior pineal anlage of Krabbe or epiphyseal evagination of Bailey represents the pineal organ of lower vertebrates.

2. The pineal and parapineal organs originate as independent structures. The latter is the first to develop, being recognisable at the beginning of the fifth week (12.5 mm) as a cellular mass lying in the marginal zone of roof plate of third ventricle. Two weeks later (17.5 mm.) the pineal organ appears as an evagination of the roof plate immediately/

immediately caudal to the parapineal element.

3. Both structures lie in the median plane and show no indication of an ancestry of paired visual organs. We must note here, however, that Cameron (1904 b) suggests that the human pineal body is a bilaterally developed organ. He claims that each half of the organ is supplied by fibres from the habenular ganglion of the opposite side, an interesting conclusion in view of Gaskell's account of the condition existing in Cyclostomes.

4. It would appear from the observations of Krabbe (1916) and the results of the present investigation that fusion of the pineal and parapineal elements takes place in the human subject. The first indication of such a process can be seen in embryos of the third month (38.5 and 42 mm) and is gradually progressive thereafter till fusion is complete. Initial fusion is accompanied but not necessarily effected by a displacement of the parapineal cells, apparently brought about by the development of the habenular commissure in their immediate neighbourhood.

5. Other points of chronological interest include the invagination of the brain roof in the region of the posterior commissure during the second month; the vascularisation of the epiphysis during the third month; the formation of the suprapineal/

suprapineal recess during the fourth month; and the displacement of the epiphysis into its adult position during the fifth month.

POST-NATAL DEVELOPMENT. Our account of the early development of the human epiphysis shows that it is a composite structure made up of two elements, morphologically comparable with the parapineal and pineal organs of lower vertebrates. Fusion is completed by the 6th month of foetal life, and at this time the cells constituting the epiphysis are essentially similar to those found throughout the earlier stages. Typically they have small, round or oval nuclei, possess little cytoplasm, and, as a result of the relative abundance of chromatin, show a marked staining reaction.

In this section, an attempt will be made to trace the fate of these foetal cells, to note the source of any additional cells, which may enter into the formation of the epiphysis, and to consider any indications of possible function. For this purpose, a series of pineal bodies ranging from birth to old age have been examined, and it has been found that the appearances presented, illustrate three main phases of a progressive structural alteration.

The first phase is one of cytological differentiation

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and covers the period, extending from the sixth foetal month to the end of the first year of infancy. The essential characteristics of this period are shown in fig.32, which exemplifies the conditions found in an infant of six months. It can be seen that two types of cells are present and that these are arranged in a pseudo alveolar pattern. Numerous small deeply staining cells readily recall those of the foetal epiphysis but now show a tendency to become aggregated round circular zones of more loosely arranged paler staining cells. The latter are more mature cells and are larger in size but the difference in the staining reaction indicates that an increase in cytoplasm has been accompanied by a loss of chromatin. A network of fine fibres constitutes the only supporting tissue present. Thin walled bloodvessels can be observed in relation to the peripheral parts of the clearer staining areas.

The pattern in which the cells are arranged, better marked in the earlier months of infancy, becomes less apparent and finally disappears as we approach the end of the first year. The pineal of six months seen in fig.32, marks a transition stage, where an alveolar formation is quite apparent but boundary aggregations are not too well defined. By the beginning of the 10th month (fig.33) all trace of the earlier pattern/

pattern is lost. Foetal cells, greatly reduced in number, are found singly or in small groups, scattered irregularly amongst the more mature cells, which now constitute the main mass of the epiphysis. Of these latter cells, the majority are similar to those previously recognised, but others are fusiform or triangular in shape, and are intimately associated with the delicate fibrous stroma present.

During the second year the foetal cells complete their metamorphosis and the second phase of post-natal development may be said to commence. This period includes the subsequent five or six years and marks the gradual formation of the mature epiphysis.

Fig.34 taken from a pineal of the third year illustrates the main features of this period. The outstanding characteristic is the presence of a series of interlacing fibrous trabeculae which enclose irregular spaces filled with cells. These septa are apparent about the middle of the second year but at more obvious at later stages. Being continuous with a connective tissue capsule and closely related to the bloodvessels which penetrate the organ, they may be regarded as a component, introduced by the vessels and derived from the mesenchyme surrounding the epiphysis. Mast cells were not observed, but in some cases, a few large eosinophil/

eosinophil cells were seen in association with this supporting tissue. The more delicate framework, which first appeared in the early months of infancy is still present, but is associated with the cells constituting the pineal parenchyma, and is probably neuroglial in nature. This conclusion is warranted when one considers the resemblance these fibres bear to the neuroglia fibres seen in other parts of the nervous system, their arrangement independent of bloodvessels, and their early appearance. Again, although neuroglia cells can only be demonstrated by the aid of special staining methods, an indicating of their formation has been seen in the presence of angular cells noted in the latter part of the first year of infancy.

The pineal cells show no marked alteration in structure or any evidence of secretory formation in the shape of specific granules. Round or irregular in shape, they are loosely arranged in the spaces formed by the prominent connective tissue framework. The alveolar appearance thus presented is of interest. A similar pattern found in early infancy, we saw to be a temporary feature, dependent on the arrangement of the deeply staining foetal cells. Its recurrence coincides with the formation of the fibrous trabeculae. Finally, it can be seen in fig.35 taken from an adult/

adult of 30 years that its persistence into adult life, is due entirely to the arrangement of the bloodvessels outlined by their supporting tissue. Bloodvessels when numerous, tend to form a network enclosing more or less circular spaces. It is apparent that if these be made prominent, by their association either with deep staining cells, or connective tissue fibres, a pattern will result which strongly resembles an alveolar formation. The importance of these observations lies in the fact that the characteristic glandular like arrangement seen in the epiphysis cannot be regarded as any proof of glandular function.

REGRESSIVE CHANGES.

After the sixth or seventh year we enter on the final phase of the history of the human epiphysis, a period characterised by alterations in appearance which are usually considered as evidences of regression.

Examples of such changes are shown in fig.36 which illustrates the appearances found in a pineal of 35 years; and can be seen to include an increase in the amount of neuroglia present, the formation of cavities and the deposition of the so called brain sand. Existence of a glial hyperplasia is evidenced by the well marked glial wall which/

which surrounds the cavity and by a formation, known as a neuroglial plaque which consists of a dense bundle of neuroglial fibres deficient in bloodvessels and cells.

Fig.37 taken from a pineal of 36 years shows an area in the neighbourhood of the glial wall of a cavity. It can be seen that regressive changes are not an indication of a generalised degeneration, cells of the parenchyma showing no apparent diminution in number or any alteration in shape or size. On the other hand, the well marked alveolar formation seen at one place is obviously dependent on the course taken by the bloodvessels rather than a specific attribute.

It must be emphasised here that these appearances are equally readily recognisable at any stage of adult life. With advancing age there is a progressive increase in the amount of connective tissue present. Regressive changes, however, may be well marked in the young adult and normal parenchymatous cells may be very numerous in the aged.

DISCUSSION. Full accounts of the histology of the epiphysis have been given by numerous workers, but while there is general agreement on the observed facts, differences of opinion still exist as to the interpretation of some of the appearances presented/

presented. In stating the conclusions afforded by the present investigation consideration will be given to such other work as is relevant.

There can be little doubt but that foetal pineal cells differentiate into at least two mature forms. Differentiation first occurs after the sixth foetal month and results in the formation of larger cells with pale staining nuclei. These cells form the main mass of the epiphysis and constitute the pineal parenchyma. During infancy the remaining foetal cells complete their development by becoming transformed into a supporting tissue which is neuroglial in nature.

Krabbe (1916) describes certain foetal cells as having angular nuclei and postulates these as being the precursors of nerve cells. Diverse opinions have been expressed as to the existence of nerve cells in the pineal. Earlier writers regard them as forming the chief component of the organ; later authors including Cajal (1895) and Rio-Hortega (1922) describe them as forming a definite constituent, while the more recent accounts of Herring (1927), Orlandi (1928) and Globus and Silbert (1931) deny their existence altogether. Neither nerve cells nor medullated nerve fibres could be detected in any of the pineal bodies examined in the present study.

There is general agreement that the connective tissue is introduced along with the bloodvessels and forms a mesodermal component of the mature epiphysis. Globus and Silbert (1931), however, maintain that some of the foetal pineal cells can be seen elongating to form fibroblasts. Apart from the consideration that fibroblasts are typical mesenchymal structures, this assumption is unlikely in view of the fact that the conversion of the foetal cells is apparently completed some months prior to the appearance of the fibrous trabeculae.

The important question with regard to the epiphysis concerns the indications of glandular function which are presented. Arguments in favour of such a function are mainly based on the arrangement and character of the component cells.

Cutore (1910) and Seigmeur (1912) noted a well marked alveolar pattern at birth and considered this as a definite indication of glandular function. Tilney (1928) describes in late foetal life an invasion of dark staining cells which extends from the base of the epiphysis into the mass of undifferentiated cells which constitute the foetal pineal body and there become arranged in convoluted cords demarcating apparent acini. Globus and Silbert (1931) describe a series of primitive tubules which become re-arranged to/

to form solid cords enclosing zones of clear staining cells. Krabbe (1916) from an observation of appearances, obviously similar to those described above, postulates the simple explanation that the pattern visible is produced by the metamorphosis of some of the foetal cells, the remainder persisting along the walls of the bloodvessels and outlining the network in which these are arranged.

My own observations show that this conclusion of Krabbe applies not only to the pattern presented in the early months of infancy, but throws light also on the alveolar formation so characteristic of the adult. In each case the foundation for the walls of the apparent acini is the course taken by the vessels. Thrown into prominence in infancy by the aggregations of foetal cells they reveal a pattern. With diminution in number of these cells all trace of pattern is lost; to recur again with the appearance of a well defined vascular supporting tissue.

Evidences of secretory function in the cells which constitute the pineal body have been described by many authors but there is a lack of uniformity about their findings which tends to emphasise the possibility of glandular function rather than the probability.

Galasescu and Urechia (1911) gave an account of acidophil/

acidophil cells termed by them paravascular acidophils because found in the vicinity of bloodvessels, and ascribe to these cells an important part in the formation of an internal secretion. Krabbe (1911) lays emphasis on the presence of basophil granules which he believes are formed in the nuclei of the pineal cells, pass from there into the cytoplasm and are extruded into the intercellular spaces so reaching the blood, lymph or cerebro-spinal fluid. On the other hand Rio-Hortega (1922) denies any secretory role to the pineal cells and attributes any such function to certain interstitial neuroglia cells which present a granular appearance. Finally Herring (1927) regards the parenchymatous cells as the real functioning element in the organ but was unable to find any demonstrable granules in the cytoplasm which would indicate a secretory function.

In this investigation no appearance has been noted which would afford any reasonable conclusion as to the functional significance of any of the cells constituting the epiphysis.

The fact that evidences of regression appear so early in life is of great interest and has been interpreted as an indication that the pineal body exerts its maximum influence during childhood. The exact significance of these changes/

changes, however, is not yet understood. Krabbe (1916) regards the cavities so frequently found as representing portions of the original pineal diverticulum which normally becomes occluded during the 6th month of foetal life; and the surrounding glial stratum as a later development, which, in the event of the cavity diminishing or closing up will persist as a glial plaque. The frequency with which cavities are found, not only in childhood but throughout adult life, suggests however that this occurrence is a normal feature rather than an embryological defect. The irregular distribution of glial plaques, and of cavities where more than one exists, correspond in no way with the position occupied by the original pineal diverticulum. Finally, one would expect a persisting foetal cavity to show a corresponding survival of the original ependymal lining. No suggestion of this appeared in any of the cavities examined by me nor have such cells been reported except in isolated instances, in which cases a strong possibility exists of them being necrotic parenchymatous cells.

Again the presence of brain sand has to be accounted for. This, Herring (1927) regards as a product of the parenchymatous cells, postulating an internal secretion which as the result of an increased impermeability of the bloodvessels/

bloodvessels, diffuses through the organ instead of being immediately absorbed. The hypothesis of such a localised impermeability is however hardly convincing.

It is probable that all evidences of regression should be considered as indications of a degenerative tendency which is inherent in localised areas of the epiphysis. This may take the form of cavitation or of deposition of calcareous material but in each case such areas rapidly become shut off from the surrounding tissue by a protective overgrowth of the neuroglia. The underlying cause of this degenerative tendency is unknown but it is conceivable that the incorporation of a parapineal element in the epiphysis may have some significance in this respect. The findings of comparative anatomy show that this element is a structure which may persist and present signs of visual differentiation but which usually tends to degenerate and disappear.

FUNCTION.

CLINICAL AND PATHOLOGICAL EVIDENCE.

Diseases of the pineal usually take the form of tumour formation. Many of the symptoms which result from this condition are not specific, but are common to any tumour of the midbrain. An increase in the size of the pineal body may lead to pressure on the superior colliculi or both superior and inferior colliculi; secondly, forward pressure on the midbrain may cause an obstruction of the aqueduct of Sylvius. This in turn produces an internal hydrocephalus affecting the third and lateral ventricles. Finally an increased intracranial pressure in the third ventricle will bring about symptoms referable to the hypothalmic and, more particularly, the infundibular region.

It is necessary then to consider the effect of the above factors before attempting to define the possible effects of an increased pineal activity. Visual symptoms such as dilated pupils with an Argyle-Robertson reflex, ocular palsies with an affection of the conjugate vertical movements, nystagmus and diplopia, are readily referable to pressure on the superior colliculi. Similarly, pressure on the inferior colliculi will explain the partial deafness

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and the buzzing in the ears which may be found. Weakness of the limbs with spasticity and extensor plantar responses suggests a transmission of the pressure to the pyramidal tracts; and giddiness, staggering or rolling gait to the pressure on the cerebellar peduncles.

An increase in the intracranial pressure due to hydrocephalus gives rise to the classical symptoms of headache, vomiting and papillary oedema with a consequent failing eyesight. It may also cause some impairment of memory and attention. As a secondary result of this pressure acting on the hypothalamus we may get somnolence, polyuria, polydipsia and symptoms due to hypopituitarism. Latter symptoms include obesity and a depression of the sexual function, and constitute the syndrome called dystrophia-adiposo-genitalis.

In some cases of pineal tumour a symptom complex has been recorded which cannot be explained by reference to any of the above factors, and has been attributed therefore to an internal secretion of the pineal body itself. Pellizzi (1910) called this syndrome macrogenitosomia praecox because the outstanding features were a marked premature sexual development and a marked premature growth of the body. Then in 1921 Zandren described the case of a boy who grew normally till/

till puberty but whose development then ceased and whose secondary sexual characters failed to appear. Death took place from pneumonia at the age of 16½ years and the autopsy showed a complete absence of the pineal body and a hypoplasia of the testes but no abnormality in the thyroid, pituitary or suprarenals. This case when compared and contrasted with the condition of macrogenitosomia praecox seemed to afford a reasonable basis for a theory that the pineal secretion assists the onset of puberty.

However in 1923 Krabbe reviewed the literature of premature puberty associated with pineal tumours and, in a discussion on the significance of this syndrome, pointed out that the tumours were almost invariably teratomatous and that some substance foreign to the pineal body might be responsible. On the other hand Löwenthal (1920), de Monchy (1923) and Globus and Silbert (1931) described tumours which were epithelial in nature and similar in structure to that of the pineal body of the newly born. Latter authors, indeed, postulated a theory that such tumours are traceable to embryonal rests which may recapitulate any of the stages in the development of the epiphysis and so may be considered as autochthonous teratomata or true pinealomas. In tumours of this type hyperpinealism might be expected and yet in five/

five cases at or younger than puberty (case of de Monchy and four cases of Globus and Silbert) only one showed the signs of macrogenitosomia praecox.

We have seen that the symptoms and signs which may be found associated with tumours of the epiphysis can be referred in great part to secondary disturbances of other parts of the brain. While it is an established fact that genital abnormalities may frequently be found, and may in some cases constitute a definite syndrome, there is at present no justification for regarding such abnormalities as definite proof of a specific pineal function.

EXPERIMENTAL EVIDENCE.

INJECTION OF EXTRACTS.

Experimental work on the pineal organ was instituted by Howell (1898) and then only as a control in experiments on the action of pituitary extracts. Results obtained morever were not sufficient for him to attach any significance to the reactions caused by the pineal body. In 1903 Cyon made intravenous injections on rabbits and found an increase in the heart rate together with some irregularity, but no change in blood pressure. The effect on the heart rate was denied by Dixon and Halliburton (1909) but was corroborated later by Jordan and Eyster (1911) who found that in the heart of a/

a cat systole was energised. On the other hand these latter authorities, together with Horrax (1916) all agreed that a fall in blood pressure resulted, even if only transitory, while Cushing (1912), and Dana and Berkeley (1913) supported Cyon's original finding.

Jordan and Eyster further found that the fall in blood pressure was associated with vaso-dilatation in the intestines and a transitory diuresis with glycosuria. These results were verified by Scott and Ott (1912) who also noted a contraction both of the intestinal wall and the uterus, and a vaso-dilatation in the erectile tissue of the generative organs of a male cat. Fenger (1916) however found that any contraction of unstriped muscle was so slight as to be of no physiological importance.

A galactogogue effect was described by Scott and Ott (1912) but Schäffer and Mackenzie (1912) were unable to confirm this conclusion. Similar contradictory results have been reported in connection with the effect of pineal extracts on growth. Dana and Berkeley (1913) found that guinea pigs, rabbits and kittens showed an increase in weight compared with controls. On the other hand Priore (1915) found not only no increase but an actual retardation in growth.

Finally we may note the findings of McCord (1915) who/

who injected pineal extract into the jugular veins of dogs anaesthetised with chlorotone. Some animals were killed with a single injection, in others there was no reaction at all.

PINEAL FEEDING. The first workers to carry out systematic feeding experiments were Dana, Berkeley, Goddard and Cornell (1913). They found that the administration of a solution of nucleo proteins obtained from the pineal bodies of calves had a definite effect on half grown guinea-pigs, young kittens and young rabbits. In each case the pineal fed animals grew more rapidly than the controls. Kittens also appeared to show an increase in motor activity, intelligence and resistance to inter current diseases. Further it was found that mentally defective children were benefited by pineal feeding. Goddard (1917) repeated the experiments on mentally defective children using controls of corresponding physical and psychological types but was unable to demonstrate any improvement. Berkeley (1920) was more fortunate. Not only did administration of pineal substance lead to mental progress in backward children; in the aged it improved the memory and produced a remarkable cheerfulness and sense of well being. His other experiments on guinea-pigs, rabbits and kittens together with the work done by McCord (1915, 1917) corroborated the conclusion of earlier/

earlier workers that the pineal body accelerates growth. Latter author extended his observations to paramoecia and tadpoles, and a paper written in conjunction with Allen (1917) recorded an interesting observation. They found that feeding of tadpoles with pineal substance, whether fresh, minced, dessicated, or in the form of extracts, produced within half an hour a retraction of skin pigment cells; evidenced by tadpoles previously uniformly dark, becoming translucent.

The results of the administration of pineal substance in cases of mental deficiency are inconclusive in view of the difficulty in assessing any degree of progress. It would appear, however, that an acceleration of growth can be so induced in some cases. On the other hand Sisson and Finney (1920) found that pineal fed albino rats tended if anything to be smaller than the controls. This result, of course, might be due, as Schäfer (1926) suggested, to a loss of a growth factor as a result of the method adopted in making the pineal extract. The significance of the effect on amphibian skin pigment cells is not clear.

<u>PINEAL REMOVAL</u>. The operation of pinealectomy is technically difficult. Its performance on primates, carnivores and ungulates involves an almost certain destruction of additional brain substance, (Pastori, 1927); while in other animals there/

there is always the possibility of severe haemorrhage from the veins adjoining the epiphysis.

Attempts made on rabbits by Sarteschi (1910), Exner and Boise (1910) and Foa (1912) gave negative results in the small number of cases which survived the operation. Experiments made on birds were more successful. Foa (1912) removed the pineal body in chickens and found that after a period of several months it caused in the males a greater development of the testes and an increased growth in the crests as shown by comparison with controls. In 1914 he got similar results and these were again confirmed by Clemente (1923) and Izawa (1923). Izawa further noted that the ovaries of females also showed a premature development while both he and Clemente found in addition an increase in the general body growth. On the other hand Christea (1912) found not only a retardation in growth of the secondary sexual characters, including the crest, spurs and feathers, but a definite atrophy of the testes. Finally Badertscher (1924), from observations on pinealectomised chickens compared with controls over a period of a year, and subsequent microscopical examination was unable to find any indication of any pineal function.

Sarteschi (1913), working with young rabbits and dogs/

dogs noted a hypertrophy of the testes. Horrax (1916) working with guinea-pigs and controlling his experiments with trepanned animals, discovered an increase in the weight of both testes and seminal vesicles, particularly the latter. There was, however, no difference in the body weight. Hoffman (1925) and Izawa (1926) obtained similar results in rats as regards the increased development of the sexual organs. The effect on the body weight was found by Izawa to be dependent on the extent of removal. When this was complete, growth was accelerated in both sexes; when incomplete a slight retardation resulted.

Pineal removal has also been carried out by Adler (1914) and Atwell (1921) on tadpoles; Dandy (1915) on young dogs; Fenger (1916) on cattle, sheep and lambs; and Kolmer and Löwy (1922) on rats. In all these cases the results were negative.

RÉSUMÉ. The evidence afforded by experimental investigation tends to obscure rather than to reveal any possible function which the pineal body might possess. The positive results obtained by the injection of extracts, are invalidated both by the negative results which have been recorded in similar experiments, and by the fact that they show little relation to those afforded by feeding or removal experiments. Again, it/

it would appear that general body growth is accelerated both by the removal of the pineal body and by its administration. The indication of sexual precocity seen by some observers in pinealectomised animals is suggestive but not conclusive when we consider the number of negative results reported and the contradictory findings of Christea (1912). The only conclusion of any value which finally emerges is that the pineal body is a structure which is not essential to life.

CONCLUSIONS.

The human epiphysis is an organ developed from two independent anlagen which represent the anlagen of the parapineal and the pineal organs of the lower vertibrates.

The function of the epiphysis must remain a matter of conjecture. There is no indication of any visual or other neural mechanism. Again, such indications of glandular function as have been found, are inconclusive and capable of other interpretation. Finally, clinical and experimental observations are conflicting in their nature and yield no satisfactory evidence of any endocrine function.

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ABBREVIATIONS USED IN FIGURES.

a	Cleft between anterior and posterior pineal anlagen.
a p a	Anterior pineal anlage.
b	Site of commencing invagination of posterior commissural area of brain roof.
c	Cleft demarcating caudal boundary of posterior pineal anlage.
d	Shallow evagination of brain roof produced by folding of posterior commissural area.
d r p	Roof plate of diencephalon.
h c	Habenular commissure.
m r p	Roof plate of mesencephalon.
p c	Posterior commissure.
p d	Pineal diverticulum.
p p a	Posterior pineal anlage.
tg	Tegmentum.

EXPLANATION OF FIGURES.

Fig. 1. 15 mm. embryo of Krabbe. Mid-sagittal section showing the anlage of the epiphysis, indicated by an arrow, posterior commissure, and the roof plate of the mesencephalon . x 20.

Fig. 2. 12.5 mm. embryo. Linear projection in the mid-sagittal plane of the mesencephalon and part of the diencephalon. The arrow indicates the position of the epiphysis in the roof plate of the diencephalon and the continuation of the arrow indicates the plane of the transverse section illustrated in Fig. 9. x 20.

Fig. 3. 15.5 mm. embryo. Linear projection in the mid-sagittal plane of the mesencephalon and part of the diencephalon. The arrow indicates the position of the epiphysis in the roof plate of the diencephalon and the continuation of the arrow indicates the plane of the transverse section illustrated in Fig. 10. x 20.

Fig. 4. 16 m.m. embryo. Linear projection in the mid-sagittal plane of the mesencephalon and part of the diencephalon. Arrow indicates the position of the epiphysis in the roof plate of the diencephalon and the continuation of the arrow indicates the plane of the transverse section illustrated in Fig. 11. x 20.

Fig. 5. 15 mm. embryo of Krabbe. Mid-sagittal section of the epiphyseal region of the brain roof, showing the anterior pineal anlage and the site of the future pineal diverticulum. x 100.

Fig. 6. 12.5 mm. embryo. Linear projection in the mid-sagittal plane of the epiphyseal region of the brain roof, showing the anterior pineal anlage and the site of the future pineal diverticulum. The arrow indicates the plane of the transverse section illustrated in Fig. 9. x 100.

Fig. 7. 15.5 mm. embryo. Linear projection in the mid-sagittal plane of the epiphyseal region of the brain roof, showing the anterior pineal anlage and the site of the future pineal diverticulum. The arrow indicates the plane of the transverse section illustrated in Fig. 10. x 100.

Fig./

Fig. 8. 16 mm. embryo. Linear projection in the mid-sagittal plane of the epiphyseal region of the brain roof, showing the anterior pineal anlage and the site of the future pineal diverticulum. The arrow indicates the plane of the transverse section illustrated in Fig. 11. x 100.

Fig. 9. 12.5 mm. embryo. A photograph of a transverse section of the brain roof at the level indicated by the arrow in Figs. 2 and 6. The mass of cells lying in the marginal zone of the roof plate constitutes the anterior pineal anlage. x 225.

Fig. 10. 15.5 mm. embryo. A photograph of a transverse section of the brain roof at the level indicated by the arrow in Figs. 3 and 7. The mass of cells forming the anterior pineal anlage is only partly imbedded in the roof plate. x 225.

Fig. 11. 16 mm. embryo. A photograph of a transverse section of the brain roof at the level indicated by the arrow in Figs. 4 and 8. The anterior pineal anlage forms a well marked projection from the roof plate. x 225.

Fig. 12. 19 mm. embryo of Bailey. Outline in the mid-sagittal plane of a reconstruction showing the epiphyseal region. The epiphyseal vesicle of Bailey corresponds to the anterior pineal anlage and the epiphyseal evagination of Bailey to the pineal diverticulum. x 22½.

Fig. 13. 20 mm. embryo of Krabbe. Mid-sagittal section of the epiphyseal region of the brain roof showing the anterior pineal anlage, the pineal diverticulum, the posterior commissure and the roof plate of the mesencephalon. x 20.

Fig. 14. 17.5 mm. embryo. Linear projection in the mid-sagittal plane of the epiphyseal region of the brain roof, showing the anterior pineal anlage separated by a cleft from the posterior pineal anlage or wall of the pineal diverticulum. The arrows indicate the planes of the transverse sections illustrated in Figs. 15 and 16. x 100.

Fig./

Fig. 15. 17.5 mm. embryo. Drawing of a transverse section of the epiphyseal region at the level indicated by the upper arrow in Fig. 14. Shows the separation of the caudal part of the anterior pineal anlage from the cranial wall of the pineal diverticulum. x 50.

Fig. 16. 17.5 mm. embryo. Drawing of a transverse section of the epiphyseal region at the level indicated by the lower arrow in Fig. 14. Shows the marked projection of the attached part of the anterior pineal anlage from the brain roof. x 50.

Fig. 17. 21 mm. embryo. Linear projection in the mid-sagittal plane of the epiphyseal region of the brain roof. Shows the anterior pineal anlage separated by a cleft from the posterior pineal anlage, and the commencing invagination of the posterior commissure. The arrow indicates the plane of the transverse section illustrated in Fig. 19. x 100.

Fig. 18. 21.5 mm. embryo. Linear projection in the mid-sagittal plane of the epiphyseal region of the brain roof. The posterior pineal anlage is a prominent feature, distinct clefts separating its cranial wall from the anterior pineal anlage and its caudal wall from the neighbouring part of the brain roof. The arrows indicate the planes of the transverse sections illustrated in Figs. 20 and 21. x 100.

Fig. 19. 21 mm. embryo. A photograph of a transverse section of the brain roof at the level indicated by the arrow in Fig. 17. Shows the anterior pineal anlage as a well marked projection from the roof plate. x 225.

Fig. 20. 21.5 mm. embryo. A photograph of a transverse section of the brain at the level indicated by the upper arrow in Fig. 18. Shows the anterior and posterior pineal anlagen as two distinct entities. x 10.

Fig. 21. 21.5 mm. embryo. A photograph of a transverse section of the brain at the level indicated by the lower arrow in Fig. 18. The anterior pineal anlage forms a well marked projection from the roof plate. x 10.

Fig. 22. 25 mm. embryo. Linear projection in the mid-sagittal plane of the epiphyseal region of the brain roof. Shows/

Shows the position of the habenular and posterior commissures relative to the anterior and posterior pineal anlagen which are still quite distinct and separate from one another. The arrows indicate the plane of the sections illustrated in Figs. 23 and 24. x 50.

Fig. 23. 25 mm. embryo. Drawing of a transverse section of the epiphyseal region at the level indicated by the upper arrow in Fig. 22. Shows posterior pineal anlage separated by a cleft from the anterior pineal anlage cranially and the region of the posterior commissure caudally. x 50.

Fig. 24. 25 mm. embryo. Drawing of a transverse section of the epiphyseal region at the level indicated by the lower arrow in Fig. 22. Shows the commencement of the pineal diverticulum and the habenular commissure, separating the anterior from the posterior pineal anlage. x 50.

Fig. 25. 10 weeks embryo of Krabbe. Mid-sagittal section of the brain roof showing the epiphyseal region, the posterior commissure and the roof plate of the mesencephalon. Anterior and posterior pineal anlagen are continuous deep to the cleft which partly separates them. x 20.

Fig. 26. 38.5 mm. embryo. Linear projection in the mid-sagittal plane of the epiphyseal region of the brain roof. Anterior and posterior pineal anlagen are continuous deep to the cleft which partly separates them. The arrow indicates the plane of the transverse section illustrated in Figs. 28 and 30. x 50.

Fig. 27. 42 mm. embryo. Linear projection in the mid-sagittal plane of the epiphyseal region of the brain roof. There is no indication of any cleft separating anterior and posterior pineal anlagen. Sagittal shortening is accompanied by a well marked folding in the posterior commissural area. The arrow indicates the plane of the transverse section illustrated in Figs. 29 and 31. x 50.

Fig. 28. 38.5 mm. embryo. Photograph of a transverse section of the epiphyseal region at the level indicated by the arrow in Fig. 26. Shows the anterior pineal anlage/

anlage separated from the posterior pineal anlage by the habenular commissure. x 10.

Fig. 29. 42 mm. embryo. Photograph of a transverse section of the epiphyseal region at the level indicated by the arrow in Fig. 27. Shows the continuity of the anterior and posterior pineal anlagen. x 10.

Fig. 30. 38.5 mm. embryo. Drawing of the transverse section illustrated in Fig. 28. x 50.

Fig. 31. 42 mm. embryo. Drawing of the transverse section illustrated in Fig. 29. x 50.

Fig. 32. Epiphysis of an infant of 6 months showing pseudo-alveolar pattern produced by the circular arrangement of dark staining cells. x 165.

Fig. 33. Epiphysis of an infant of 46 weeks showing irregular arrangement of cells. x 165.

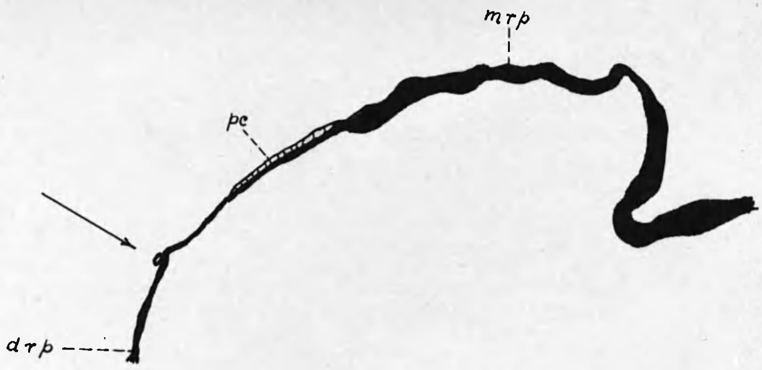
Fig. 34. Epiphysis of an infant of 2½ years showing pseudo-alveolar pattern produced by interlacing fibrous trabeculae. x 165.

Fig. 35. Epiphysis of an adult of 30 years showing pseudo-alveolar pattern produced by the circular arrangement of the bloodvessels. x 165.

Fig. 36. Epiphysis of an adult of 35 years showing evidences of regression in the shape of cavitation, the formation of neuroglial plaques, and the deposition of brain sand. x 10.

Fig. 37. Epiphysis of an adult of 36 years showing glial wall separating a cavity from the pineal parenchyma. Pseudo-alveolar pattern is produced by the arrangement of the fibrous tissue accompanying bloodvessels. x 75.

Plate I



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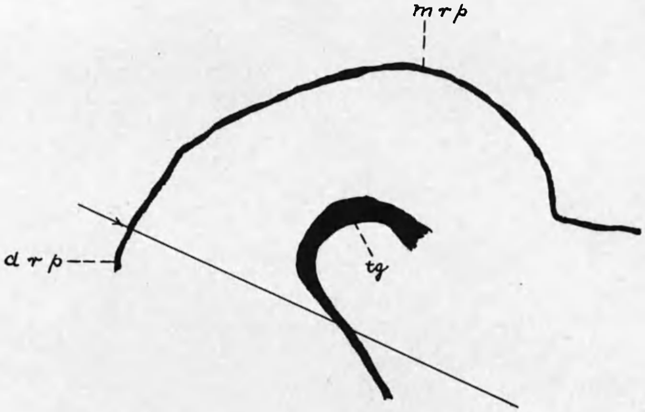

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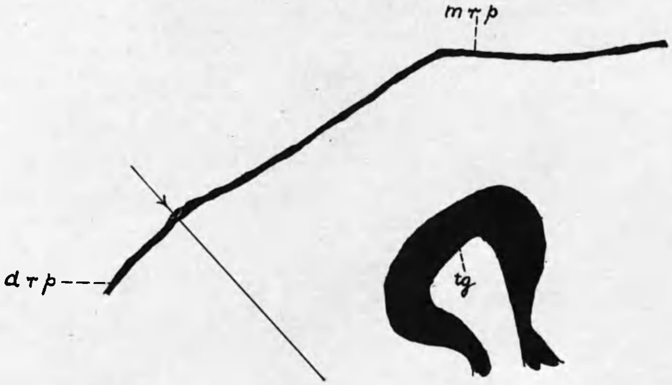

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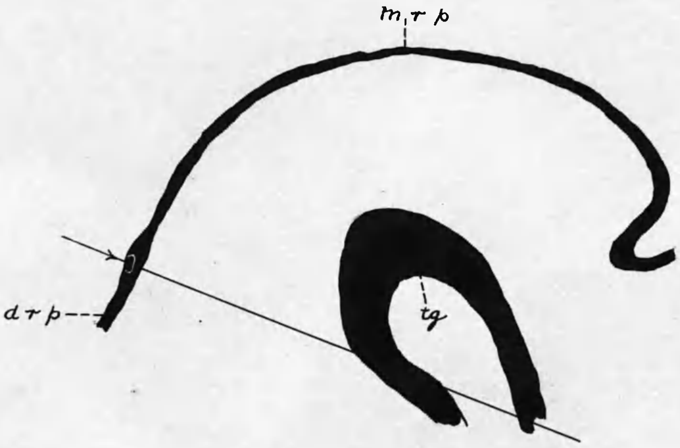

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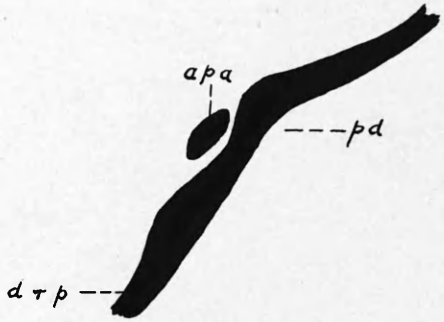

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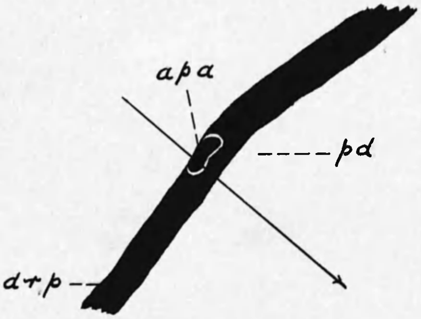

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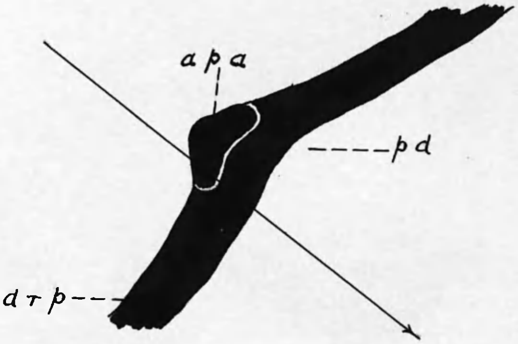

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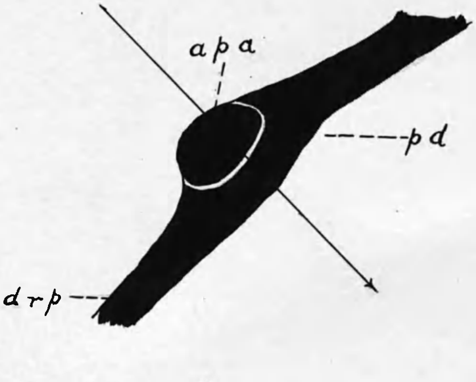
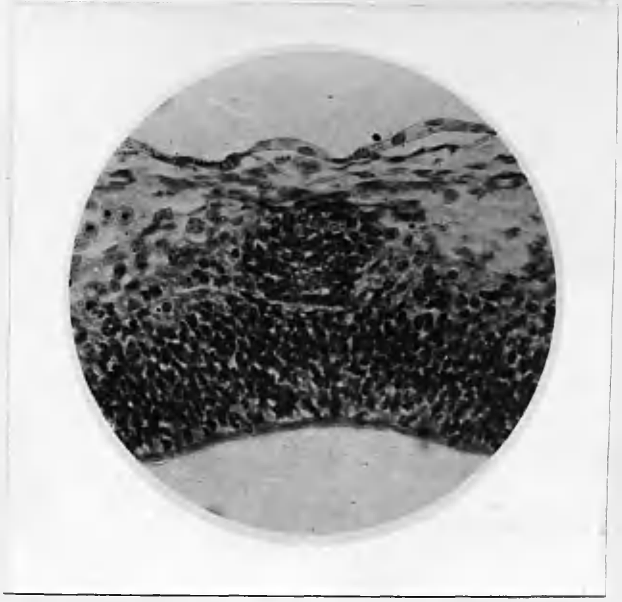


Fig. 8.

Plate 3

Fig. 9.



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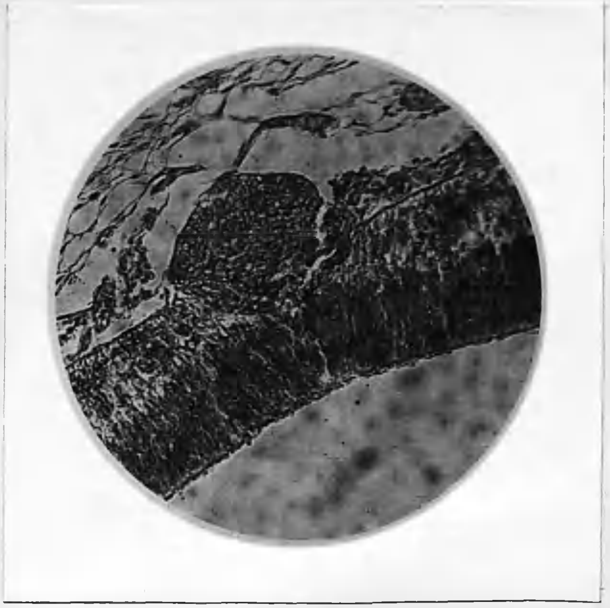


Fig. 11.

Plate 4

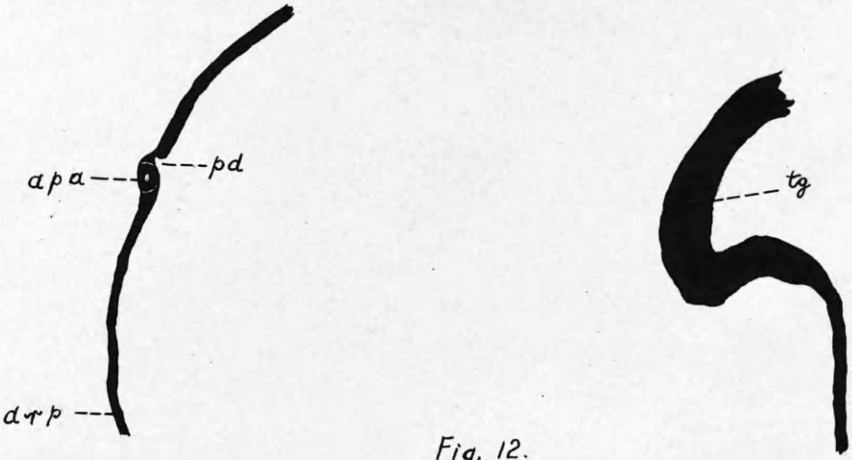


Fig. 12.

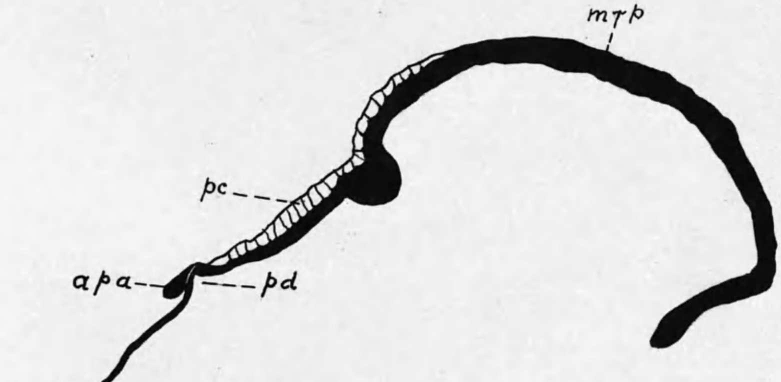
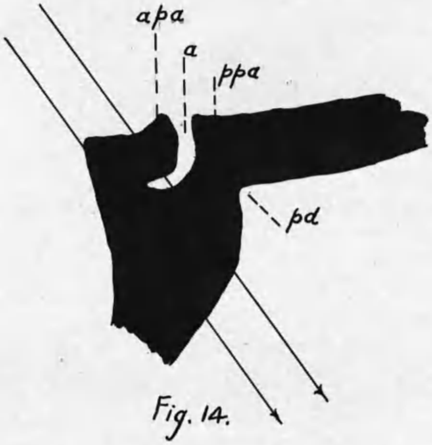


Fig. 13.



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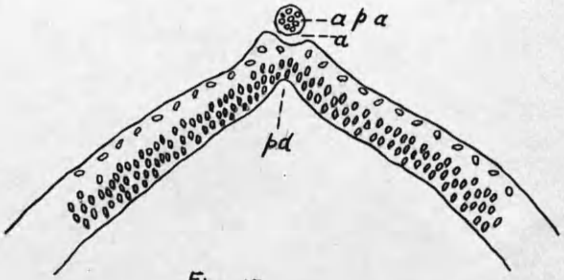

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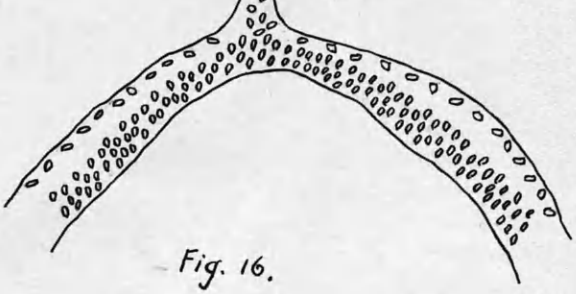

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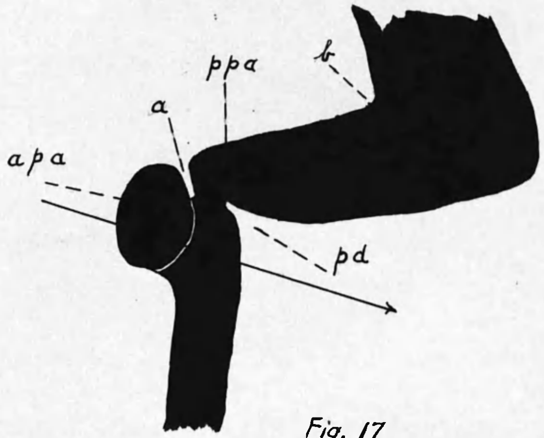


Fig. 17

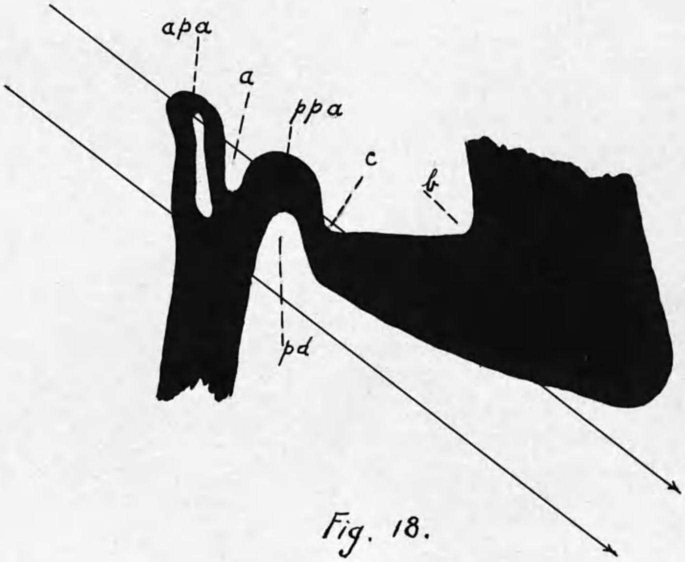
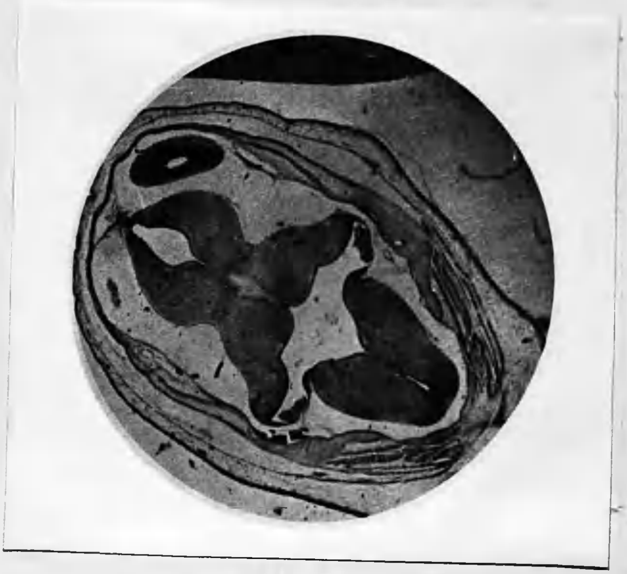


Fig. 18.

Plate 7.

Fig. 19.

Fig. 20.



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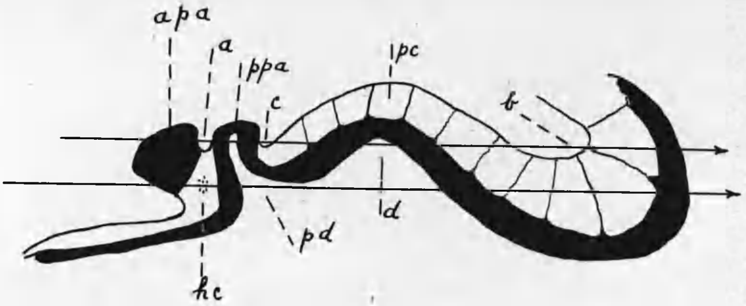

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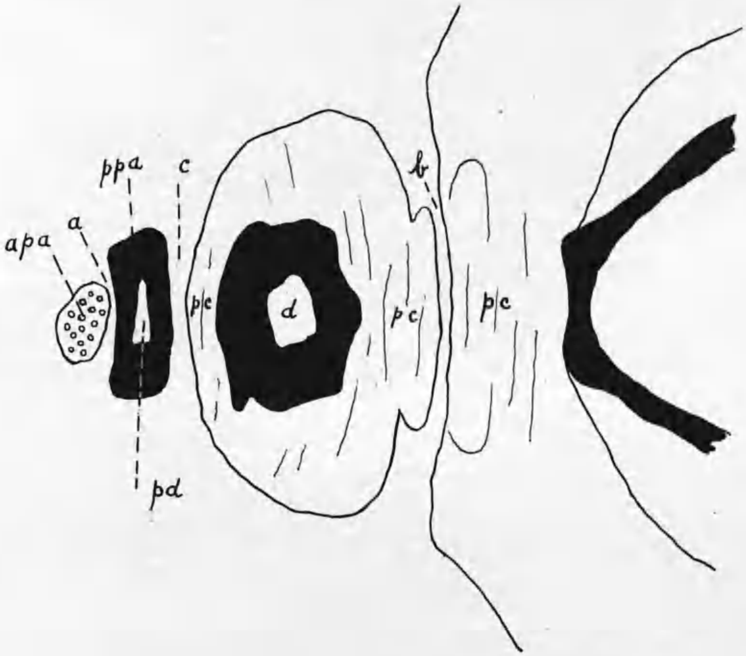

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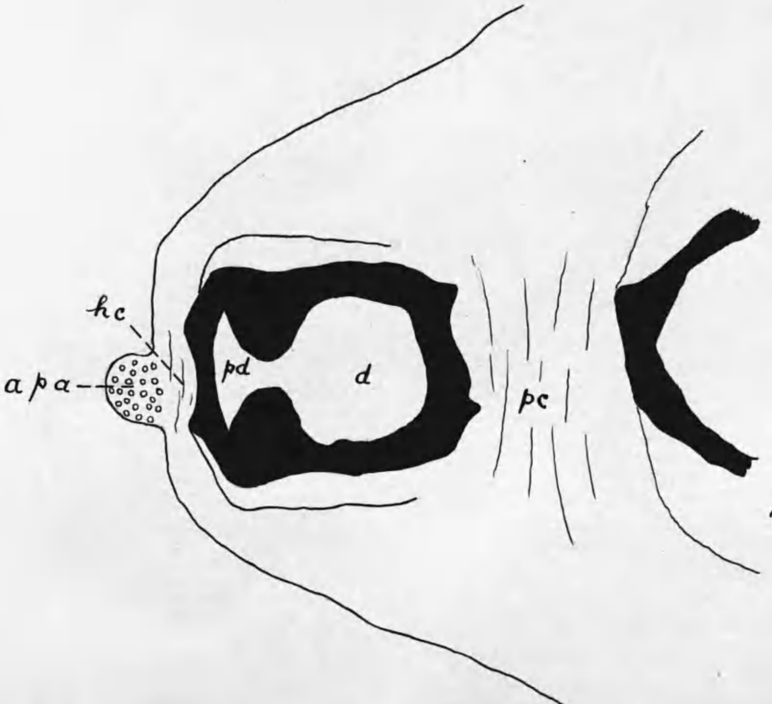
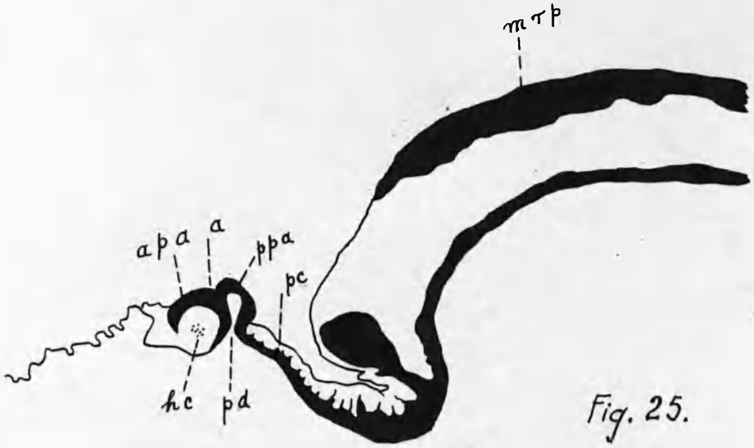


Fig. 24.

Plate 9



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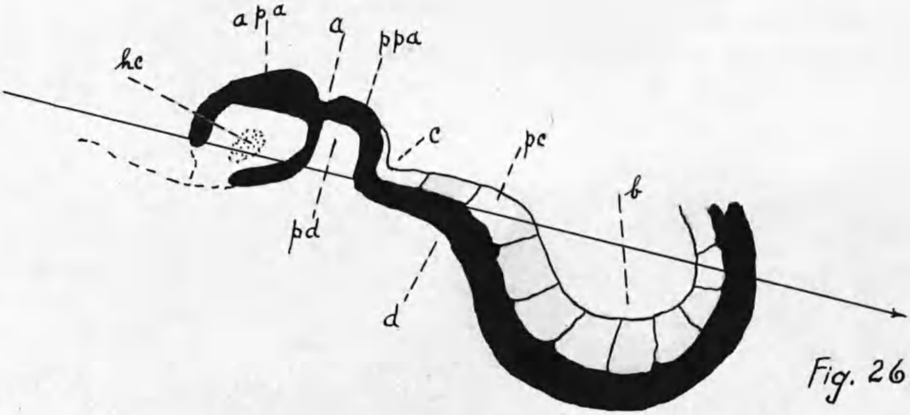

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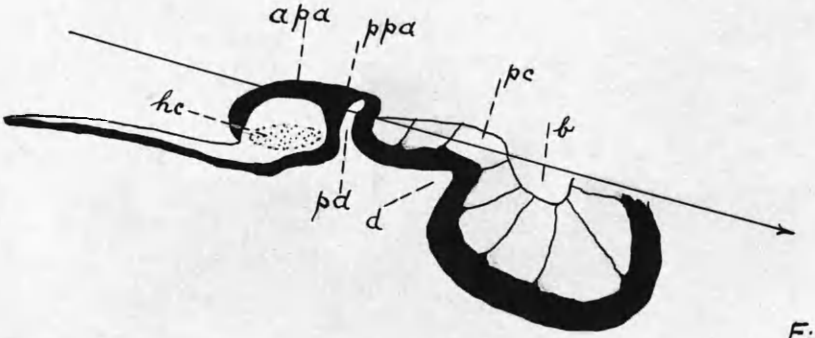


Fig 27

Plate 10

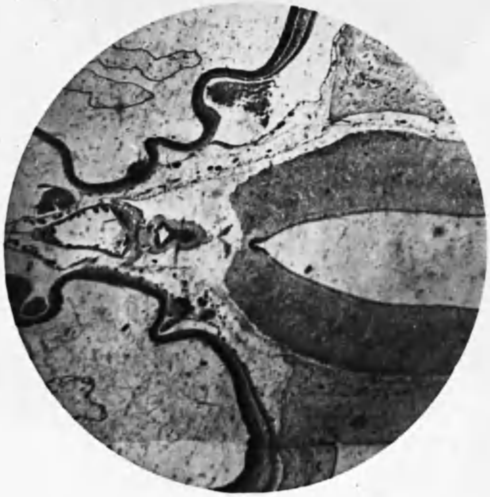
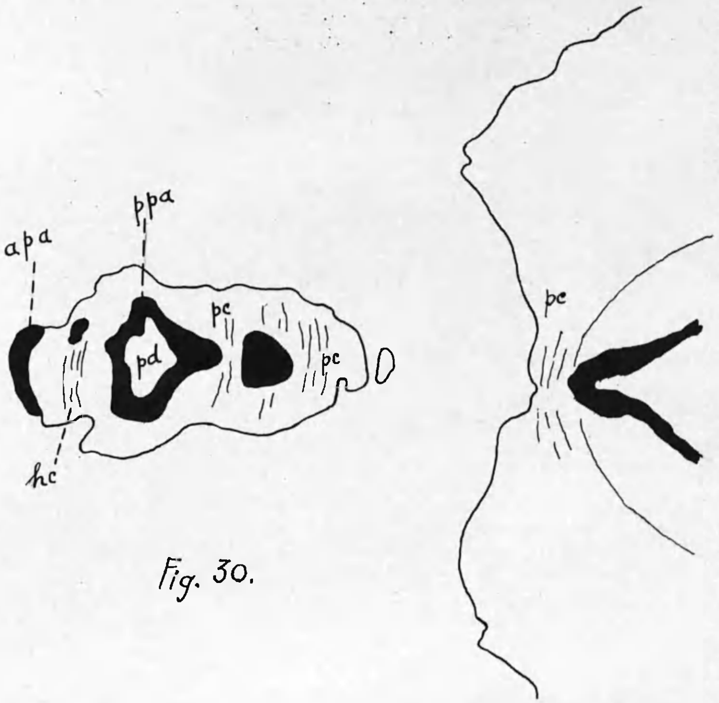


Fig. 28.

Fig. 29.



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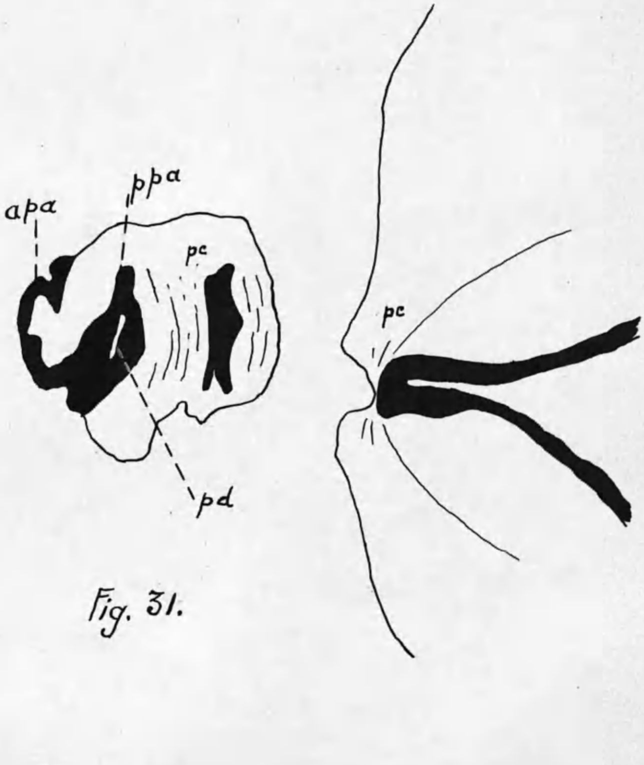
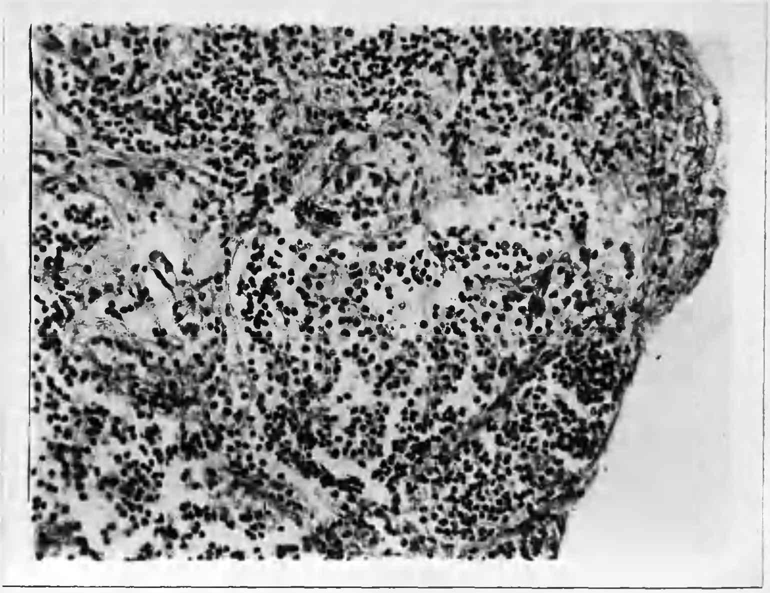


Fig. 31.

Plate 12.



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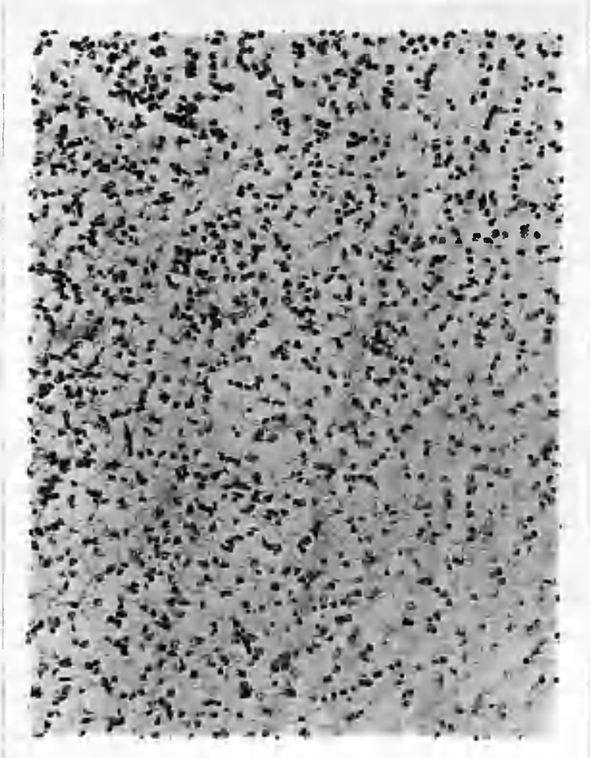

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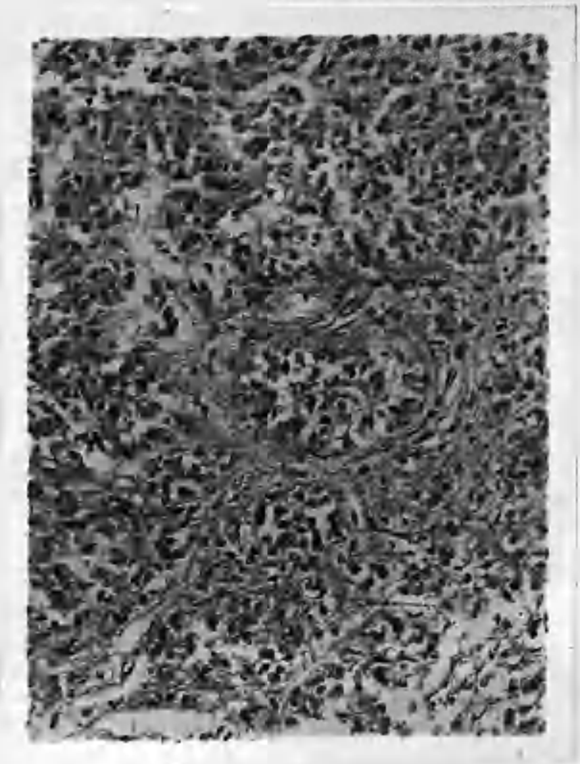

Fig. 34.

Plate 13

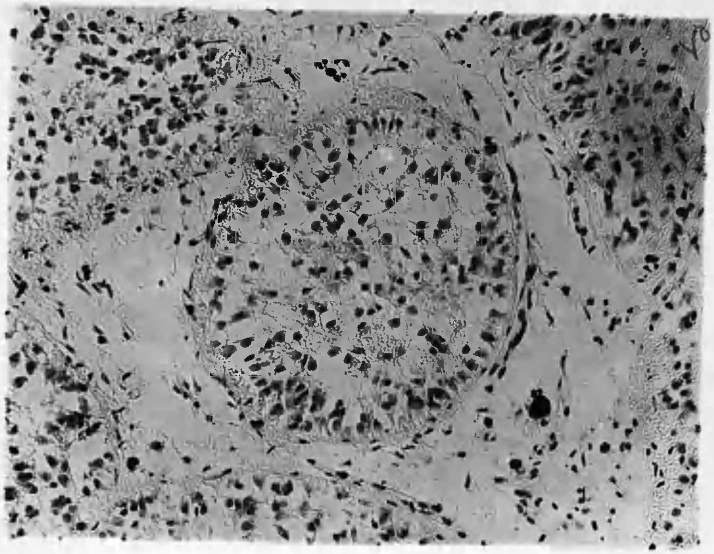

Fig. 35.

Fig. 36.

Fig. 37