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Thesis by W. Quarry Wood, M.D.

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FUNCTIONAL ACTIVITY IN THE ENDOCRINES

The Physiological and Pathological Significance
of the
Histological Findings.

By
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Thesis presented for the degree of Ch.M., Edinburgh
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CONTENTS .

Significance/

The/

INTRODUCTORY.

Within recent years the endocrines have advanced rapidly in surgical interest. Great strides have been made, not only in the direction of a better understanding of the biochemistry of the principal glands, but also in the treatment of their diseases by surgical measures. The principal hormone of the thyroid appears to have been isolated and to have been produced synthetically by Kendall, and the work of Plummer, Goetsch, and Wilson, has done much to elucidate the pathological affections of this gland. Brailsford Robertson believes that he has succeeded in isolating the active principal of the anterior lobe of the pituitary. In the direction of surgical therapy, the scientific method and careful technique of Crile, Mayo, Judd, and others in their work on the thyroid gland has been followed by the most happy results, more especially in the treatment of the various forms of toxic goitre. Operations on the pituitary, especially in the hands of Frazier & Adson, have been followed by much greater success than formerly.

Treatment by methods of grafting or transplantation is becoming better understood, and there is little reason to doubt that this line of treatment, in cases of endocrine deficiency, will become established presently/

presently on a sound basis. Recent experience has shown that in the suprarenal deficiency of Addison's disease - so long intractable to any form of treatment- there is every hope of obtaining curative results by grafting, if the graft is embedded in a suitable position.

Knowledge still lags, however, in the case of many of the endocrines, both in regard to their physiology and their pathology. The function of the pineal gland is largely a matter of conjecture, the fate of the secretion of the posterior lobe of the pituitary is still under discussion, and much remains to be learned of the function of the parathyroids and of the suprarenal cortex.

The object of the present investigation is to examine the principal endocrines in a state of functional activity, comparing the appearances with those of the organs in a quiscent state, and to consider the bearing of the signs of secretory activity of the healthy gland on the physiology and also on the pathological affections in each case.

It is well known that in certain states of the organism, especially those of excessive sympathetic excitation, such as occurs in rage or fright, as shown by Cannon, and at certain periods of life - dentition, puberty, menstruation, and pregnancy - there is an excessive demand on the activities of the endocrine organs. These activities reach their zenith in pregnancy, which condition throws a greater strain on the organism than any other physiological process. It is becoming increasingly evident that in pregnancy there exists/

exists a condition of pluri-glandular activity in which all, or the majority, of the endocrines are functioning more actively than normal. A comparison of the histolcgical appearances in non-pregnant and pregnant animals is therefore likely to show certain differences between the resting and the active phases of endocrine tissues.

In order to examine the finer details of cell structure it is necessary to obtain an immediate coagulation of the living protoplasm. It is only by immediate fixation of the tissues from newly-killed animals that a satisfactory result can be obtained. A specimen from a healthy human subject at the desired periods is rarely, if ever, available, and the tissues examined after death from infective or toxic causes are practically valueless from the point of view of the study of the normal organ or tissue. Even in cases of death of healthy subjects from injury there is inevitably delay in obtaining and fixing the tissue, and in the interval secretion products disappear and extensive degenerative changes may take place in the cell protoplasm.

In the present research the animals employed have been healthy guinea-pigs and rabbits. The guinea-pig has been a specially suitable subject for examination, the principal endocrine glands being all of/

of large size and easily discovered and stained. Elliott & Tuckett have shown that this animal possesses a larger suprarenal in proportion to its size than any other of the usual laboratory animals. The same probably holds good with regard to the thyroid and the thymus. Tissues from the human subject have also been examined in certain cases, but owing to the delay between the time of death and the fixation of the specimen, the results, as a general rule, have been less satisfactory than in animals. In the case of a few operation specimens, however, it was possible to fix the tissue while it was still warm, and these specimens gave good histological results.

THE PITUITARY.

Secretory activity in the pituitary is accompanied by well-marked histolcgical changes. Much interest has been excited by the hypertrophy which the gland undergoes during pregnancy, and special attention has been directed to the changes which take place in the pars anterior in this state. An examination of the posterior lobe in pregnant animals reveals evidences of secretory activity which are equally striking.

MATERIAL And METHODS EMPLOYED.

For the purposes of the present investigation the/

the pituitaries of 24 animals were examined, 16 guinea-pigs and 8 rabbits. Of the guinea-pigs 8 were pregnant and 8 non-pregnant. In the guinea-pig the exact duration of the pregnancy was unknown, but it was possible and helpful to divide the animals roughly into 3 groups according to the size of the gestation sac. These have been termed early, mid-, and late pregnancy. In the case of the rabbits the date of ~~the~~ impregnation was exactly known. The gestation period in this animal is 28 days, and the following series has been examined:-

(1) Two non-pregnant animals were examined as controls. One ofthese was killed in the winter months, at which season the endocrines are probably in their most quiescent condition in this animal, and are least likely to be affected by activity of the reproductive system.

(2) One animal 7 days pregnant.

(3) " " 11 " "

(4) " " 17 " "

(5) " " 23 " "

(6) " " 26 " "

(7) " " one week after delivery.

This series serves to illustrate the condition of the gland at short intervals throughout the whole of pregnancy and immediately afterwards.

In/

In order to avoid damage to the pituitary it is necessary to fix it *in situ*. Unless this precaution is taken, the intraglandular cleft is apt to be broken into and other damage is liable to occur. Accordingly, the plan adopted, both in the guinea-pig and the rabbit, was to remove a segment of the base of the skull for a considerable distance around the sella turcica. The gland was left undisturbed in the sella during fixation and dehydration. Before embedding in paraffin an incision was made in the sagittal direction through the dura mater on each side of the sella and the dura was stripped from the sella turcica, taking the pituitary with it. To facilitate orientation the strip of dura was made longer in the antero-posterior direction. The fixative used was either Zenker's or Flemming's solution. In most cases the organs were cut so as to obtain serial sections in the sagittal plane across the central part of the gland. Cushing has emphasized the fact that only by median sagittal sections including the stalk can a proper estimate of conditions be obtained.

As a routine procedure, the sections were stained with Heidenhain's iron-haematoxylin, alone and in combination with eosin, acid fuchsin, and congo-red. Of the aniline dyes the combinations of thionin blue and/

and eosin and methylene blue and eosin were employed. An acid solution of toluidin blue was found to give excellent differential staining. Saffranin was also used as a routine reagent and was especially useful in the investigation of the pars nervosa.

MORPHOLOGY.

In order that the succeeding remarks may be readily comprehensible, it is necessary to recapitulate, as briefly as possible, the essential facts with regard to the structure and development of the pituitary. It more or less completely fills the cavity of the sella turcica of the sphenoid, and is connected with the tuber cinereum at the base of the brain by means of the infundibulum, a short stalk which encloses a prolongation of the cavity of the third ventricle - the infundibular recess. The dura mater gives a complete covering to the pituitary. As it approaches the sella turcica it splits into two layers, the lower of which lines the cavity, while the upper becomes attached to the four clinoid processes and forms a roof to the space - the diaphragma sellae. This is perforated in the centre by an aperture through which the infundibulum passes.

The pituitary shows a very intimate relationship to/

to large venous channels (see Fig. 2) as well as to the vessels of the circle of Willis. It is surrounded by the circular sinus, which is composed of the cavernous sinuses on each side and the anterior and posterior intercavernous. The third cerebral nerves pass from behind forwards on either side in close proximity to the pituitary. The optic chiasma is situated above and in front.

The gland is made up of two lobes and the subdivision is evident to the naked eye. In the human subject the anterior portion is a hard kidney-shaped lobe, concave posteriorly, pink or yellowish-pink in colour, forming a marked contrast with the posterior lobe, which is very soft and paste-like and pearly-white in colour. The two lobes are joined together and enclosed in a common fibrous capsule. When they are pulled apart, separation takes place along the intra-glandular cleft, a narrow space which, as first pointed out by Kolliker, represents the residual lumen of Rathke's pouch, the pharyngeal diverticulum from which the epithelial portion of the gland developes.

The guinea-pig and the rabbit provide examples of the two types of mammalian pituitary most commonly met with. In the guinea-pig the <u>diaphragma sellae</u> is translucent and the two lobes are both visible from above. The posterior lobe is rounded and whitish and lies above and behind the much larger anterior lobe. The anterior lobe bulges forwards and outwards so that in this animal the pituitary is more or less discoid

FIG. 1. PITUITARY OF GUINEA-PIG.

THE POSTERIOR LOBE LIES ABOVE AND BEHIND THE ANTERIOR.

THE CLEFT IS WELL DEFINED.

THE STALK SHOWS THE PROLONGATION OF THE THIRD VENTRICLE.

THE INVESTING DURA MATER IS INTACT.

IRON HAEMATOXYLIN + CONGO RED. X23.

in shape. Fig. 1 shows a median sagittal section of the pituitary of a non-pregnant guinea-pig. The posterior lobe lies above and behind the anterior. The intra-glandular cleft is well defined. The pars intermedia, forming the posterior wall of the cleft, is continued so as to form a complete investment for the pars nervosa. This investment is specially thickened in the neighbourhood of the neck, the region where the stalk joins the pars nervosa, and is prolonged upwards on the stalk towards the base of the brain. The stalk is hollow and the prolongation of the third ventricle extends well down towards the pars nervosa. This type of pituitary is also met with in the dog. The figure shows the manner in which the dura mater is related to the pituitary. The rabbit's pituitary is shown in Fig. 2. The pituitary of this animal corresponds to the type met with in man. The posterior lobe lies directly behind the anterior, instead of above and behind. The cleft is partly obliterated, being broken up into several isolated segments. The pars intermedia affords only a partial investment to the pars nervosa, leaving a considerable portion of the posterior aspect uncovered. It shows a localised accumulation in the region of the neck, but does not invest the stalk. It is seen again in the region where the stalk is attached to the tuber cinereum. The sella turcica in the rabbit is narrow and deep, so that/

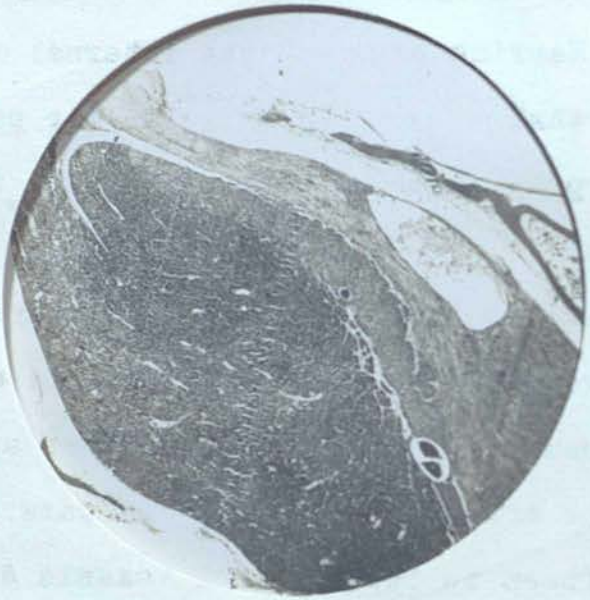


Fig. 2 Pituitary of rabbit.

The posterior lobe lies directly behind the anterior. The cleft is partly obliterated. The stalk is solid. This represents the condition met with in the human subject. Iron haematoxylin & congo red. X23.

that the pituitary is more or less ovoid in shape, with the long axis in the antero-posterior direction.

BLOOD-SUPPLY

The details of the blood-supply have been thoroughly investigated by Herring and by Dandy & Goetsch. Herring examined the internal circulation and showed that the main vessels of the pars anterior and of the pars nervosa respectively are independent of one another. If the pars anterior is successfully injected with carmine-gelatine, it appears to be a close net-work of vessels. The vessels are so abundant that a photograph of this part appears almost black. The arteries supplying the pars anterior consist of fifteen to twenty small vessels derived from the internal carotid which reach their destination by passing down the stalk. The smaller vessels in this part of the pituitary are sinusoidal in character. Some of the veins from the pars anterior run up the stalk and discharge into the large cavernous sinuses on either side of the pituitary; while other veins appear to pass into the posterior lobe in which they run beneath the pars intermedia.

The posterior lobe is supplied by a median artery which enters the postero-superior surface. This vessel arises from the union of two symmetrical branches/

branches from the internal carotid and has been termed the azygos artery. The veins of the posterior lobe are situated beneath the cells of the pars intermedia, and they unite to form venous channels, most of which pass out through the postero-superior surface in conjunction with the azygos artery, and empty into the cavernous sinuses or the posterior intercavernous. The arrangement of the vessels of the pituitary is peculiar in that the arteries supplying the pars anterior have an origin different from that of the artery supplying the posterior lobe; whereas the veins of the two lobes are not entirely independent of each other. This vascular distribution is important in regard to the physiological interdependence of the two lobes.

DEVELOPMENT.

In a human foetus of 2.5 m.m. in length the pituitary is represented by what is known as the hypophysial angle. This angle is produced by the junction of the upper limit of the pharyngeal membrane with the roof of the primitive stomodeum. When this membrane breaks down, the hypophysial angle, which is ectodermal in origin - as was first shown by Balfour - becomes deepened to form Rathke's pouch. According to Herring, when the hypophysial angle becomes deepened into a definite/

definite pouch by the bending forwards of the stump of the pharyngeal membrane - which causes the upper surface of the angle to curve backwards and downwards - a portion of the adherent cerebral vesicle is dragged down and forms a hollow process behind the pouch. This cerebral recess represents the first appearance of the infundibular or neural process. At this stage there is no connective tissue between the cerebral vesicle and the buccal epithelium; consequently a very close union is formed between the two parts, and the juxtaposition of the structures concerened is maintained during the subsequent stages in the development of the pituitary.

The further stages are well-defined. The pouch of Rathke next becomes triradiate and then shows numerous diverticula branching out anteriorly and laterally, so that the pituitary becomes a much enlarged racemose body. The infundibular process becomes more and more intimately blended with the hypophysis, and gradually in the human subject and in most mammals the central cavity disappears except, perhaps, for a small pouch of the cerebral vesicle at the neck. In the cat and the opossum the central cavity persists. Most of the rabbits examined showed a persistence of an isolated part of the cavity in the substance of the pars nervosa. The residual lumen of the hypophysis - the /

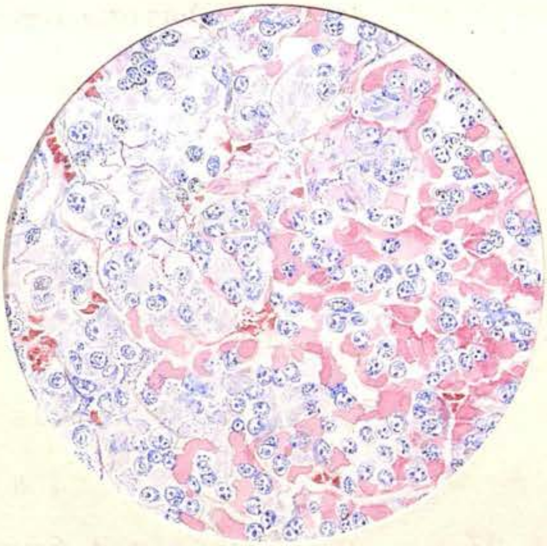


FIG. 3. THE TWO TYPES OF CELL IN THE ANTERIOR LOBE OF THE PITUITARY OF THE GUINEA-PIG.
THOSE ON THE RIGHT ARE EOSINOPHIL; THOSE ON THE LEFT ARE MAINLY CHROMOPHOBE.

ACID TOLUIDIN BLUE. X 330.

the remains of Rathke's pouch - from which diverticula can be traced, is closely applied on its posterior aspect to the neural surface. This thin posterior wall of the cavity of Rathke's pouch eventually forms the pars internedia or juxtaneural epithelium.

Ultimately, in mammals, the branching processes of the pars anterior fuse, or become compressed together, to produce a more or less compact structure. In elasmobranchs this tubular or branching arrangement is the final state of development.

From the manner of development of the anterior lobe, cell inclusions are sometimes found to exist along the line of the so-called "canalis craniopharyngeus". In a systematic study of a series of 51 human subjects of all ages Haberfeld found with regularity a small glandular strand, varying from 1 to 7 m.m. in length, situated in the mucous membrane just behind the ala of the vomer. This he designated the "Hypophysis pharyngea". This collection of cells has been known to constitute the source of a neoplasm in the adult. Dandy and Goetsch have also been able to demonstrate a remnant of the other end of the canal. They found between the layers of dura in the central part of the floor of the sella turcica another epithelial rest, which they have termed the Parahypophysis. This is fitted into a small depression in the bone and consists of a cluster of chromophobe cells.

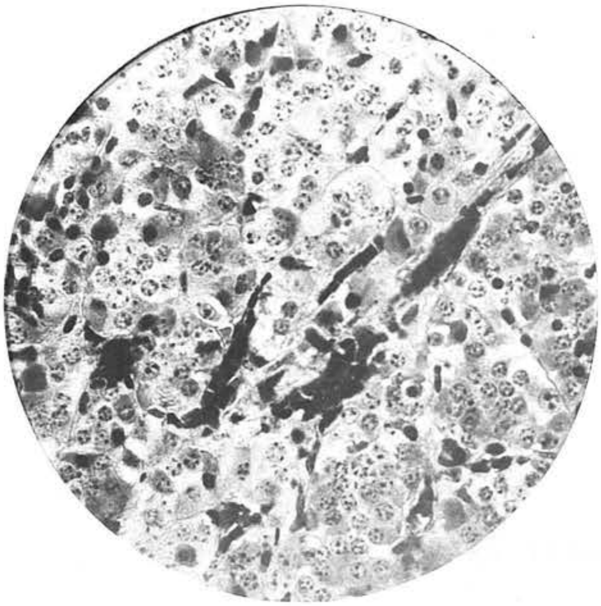


Fig. 4. THE TWO TYPES OF CELL STAINED WITH THE COMBINATION OF IRON-HAEMATOXYLIN AND EOSIN. THE DARKLY STAINED CELLS ARE THE CHROMOPHILS; THOSE IN THE UPPER PART OF THE PHOTOGRAPH ARE MAINLY CHROMOPHOBE.

X 390.

HISTOLOGICAL ANATOMY.

The Pars Anterior of the pituitary is made up of a branching compact net-work of epithelial columns and threads supported by a frame-work of fine connective tissue. The columns are separated from each other by large sinusoidal blood-spaces which are a striking feature of this part of the gland. These sinuses are lined with a single layer of epithelium and the secreting cells, in many cases, are placed directly on the vessel wall. This arrangement is of great importance in the consideration of the method of the escape of secretion. Flesch & Dostoiewsky, working independently, were the first to describe two types of cells with different staining affinities, and Lothringer followed with a definite description of the staining characters of the two varieties - the chromophil and the chromophobe. Schönemann divided the chromophils into two sub-varieties - (1) the eosinophilic or acidophilic, and (2) the basophilic or cyanophilic cells. The question as to whether these cells are distinct varieties or the same cell in different states of functional activity will be discussed later.

In the human pituitary all three types of cell are present. In the guinea-pig and in the rabbit, as Blair Bell has pointed out, there are no true basophil cells, the cells being eosinophil and either chromophobe or/

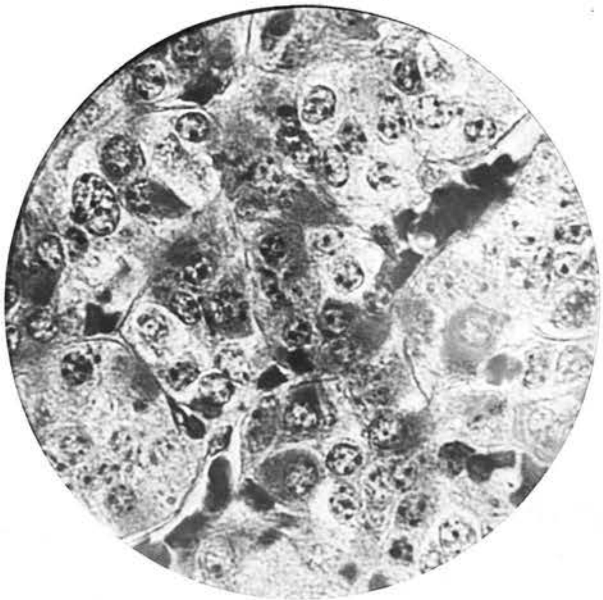


FIG. 4ª: THE CELLS OF THE PARS ANTERIOR STAINED WITH IRON HAEMATOXYLIN ALONE. THE DARKLY-STAINED CELLS ARE CHROMOPHILS, DENSELY PACKED WITH GRANULES. THE CHROMOPHOBES ALSO CONTAIN GRANULES, BUT THEY ARE MUCH FEWER IN NUMBER.

X 710.

or showing a very faint basophil staining of the protoplasm. Kojima has described basophil cells in the pituitary of the rat. The eosinophil cells stain a bright pink with eosin and an acid solution of toluidin blue (See Fig. 3). They are spheroidal or polyhedral in shape, with a nearly homogeneous protoplasm which is full of fine granules. Studnicka states that the granules are more abundant on the side of the cells adjoining the blood-sinuses, but I have not been able to verify this observation. In the animals examined the granules appear to be equally distributed throughout the cell. The nuclei stain well with haematoxylin and are rounded and well-defined. They are usually described as being commonly central in position, but in the guinea-pig they are nearly always eccentric, so that the position of the nucleus cannot be regarded as characteristic. The eosinophil cells stain very well with iron haematoxylin and the granules show up distinctly with this stain. (See Fig. 4.) This fact seems generally to have escaped observation, but a careful comparison of sections stained with eosin and with iron-haematoxylin shows that the cells with the bright-pink protoplasm in the one case correspond to the darkly-staining cells in the other.

The chromophobe cells are also rounded or polyhedral in shape, though sometimes ill-defined. The cytoplasm/

FIG. 5. PHOTOGRAPH OF A SECTION STAINED WITH ACID TOLUIDIN BLUE. THE DARKER CELLS ON THE RIGHT WERE STAINED A BRIGHT PINK; THOSE ON THE LEFT ARE MAINLY CHROMOPHOBE.

X 390.

cytoplasm is faintly granular, while the nucleus is large and centrally placed, either round or irregular in shape, with a chromatin net-work which stains distinctly with basic dyes, though less readily than that of the eosinophil cells. The basophil cells of the human pituitary are large cells with nuclei eccentrically placed and with homogeneous and granular protoplasm which stains dark blue with haematoxylin. The cytoplasm may contain rounded vacuoles.

Rogowitsch described the existence of nucleated masses of embyronic tissue in the anterior lobe. H. Stieda made a similar observation and described as "Kernhaufen" masses of embryonic tissue full of closely packed nuclei, having little protoplasm and no cell borders. I have observed this appearance in the rabbit, chiefly in the neighbourhood of the lateral margin of the intra-glandular cleft.

The distribution of the various types of cell in the anterior lobe varies considerably in different species. The statements of different observers as to the arrangement in the lower animals are in many cases conflicting; thus, Blair Bell believes that no two pituitaries in any animal or human being are alike in this respect. Tilney, on the other hand, believes that the chromophils and the chromophobes tend to be limited to definite regions of the gland. The discrepancies/

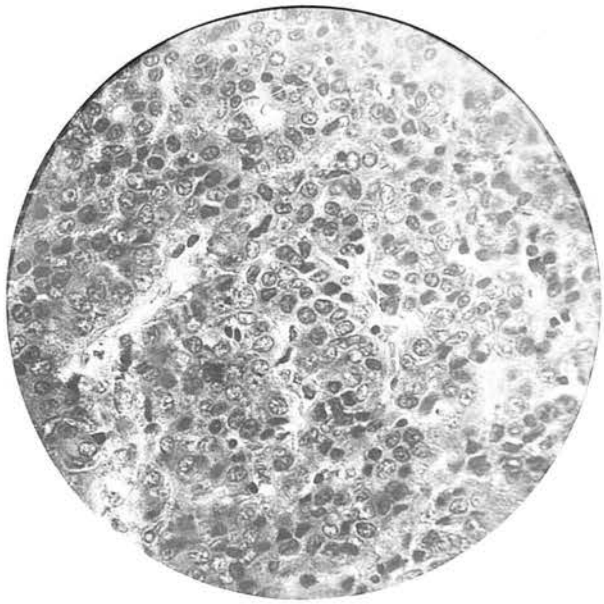


FIG. 6. SYNCYTIAL-LIKE ARRANGEMENT OF THE CELLS IN THE PARS ANTERIOR BESIDE THE CLEFT IN THE RABBIT. THE NUCLEI ARE SMALL AND DARKLY-STAINING. THE CELL BOUNDARIES ARE FREQUENTLY INDISTINCT.

IRON HAEMATOXYLIN + EOSIN X 380.

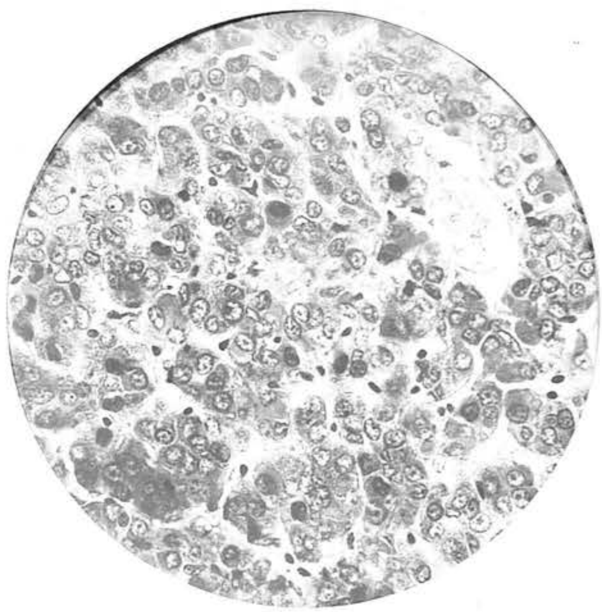


FIG. 7. THE USUAL APPEARANCE OF THE PARS ANTERIOR OF THE RABBIT - FROM THE SAME SPECIMEN. THE NUCLEI ARE LARGER AND STAIN LESS DARKLY.

IRON HAEMATOXYLIN + EOSIN. X 380.

discrepancies are probably due to the want of a uniform method of sectioning the pituitary and to failure to take into account the state of physiological activity of the gland.

The arrangement of the types of cell in the two animals examined was in certain regions remarkably constant. In both the rabbit and the guinea-pig the eosinophils predominate, but chromophobes are always abundantly present. The two varieties of cell are intermingled over the greater part of the anterior lobe, but in certain regions the one type is found to the almost complete exclusion of the other. In the rabbit a median sagittal section always shows a septum of connective tissue passing downwards from the capsule on the superior aspect of the gland about halfway between the pars intermedia and the anterior border. The area lying in front of this consists almost entirely of chromophobe cells , both in the non-pregnant and in the pregnant animal (Figs. ~~7 &~~ 8). In the guinea-pig the cells in front of the lower end of the cleft are almost entirely chromophil. In the human subject, according to Cushing, the eosinophils are usually most abundant towards the centre of the anterior lobe, while the basophils are most numerous towards the periphery. Chromophobes are relatively scarce and are found in the neighbourhood of the cleft and scattered elsewhere throughout/

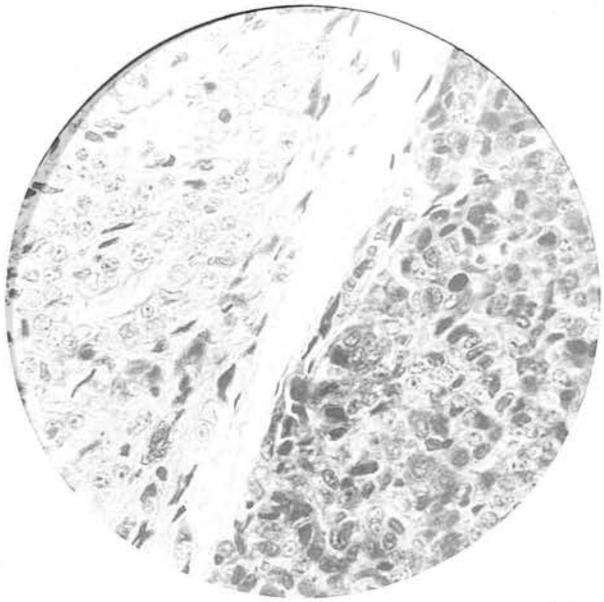


FIG. 8. THE ANTERIOR LOBE OF THE PITUITARY OF THE RABBIT IN THE REGION OF THE CONNECTIVE TISSUE SEPTUM MENTIONED IN THE TEXT.
THE CELLS IN FRONT OF THIS (TO THE LEFT) ARE CHROMO-PHOBE; THOSE BEHIND IT ARE CHROMOPHIL.

IRON HAEMATOXYLN + EOSIN. X390.

throughout the pars anterior.

Under certain conditions the eosinophil cells are seen to be arranged in a vesicular manner with masses of acid-staining secretion in the centre. Blair Bell states that this arrangement is not met with in the rodents, but I have observed it in both the rabbit and the guinea-pig, though it is not common in either. The significance of this appearance will be discussed later. In the human pituitary vesicles containing basophil colloid substance are sometimes seen; the cells surrounding the substance are chromophobe or faintly eosinophil. Thaon & A.S. & H.Grunbaum have described the presence of secretion in the blood-vessels and sinuses of this part of the gland.

Thaon, Erdhein & Stumme, and others have directed attention to the lipoid particles that may be demonstrated in the epithelial elements of the pituitary. These bodies stain with Sudan III, Scharlack R, and osmic acid and are soluble in ether and alcohol. The amount of lipoid material varies enormously in different pituitaries and probably in different circumstances. The stained lipoid bodies vary in size from dust-like particles to globular masses considerably larger than the nuclei of the cells. We are not yet in possession of enough information to draw satisfactory conclusions as to their exact nature and import.

There are no nerve cells or medullated nerve fibres/

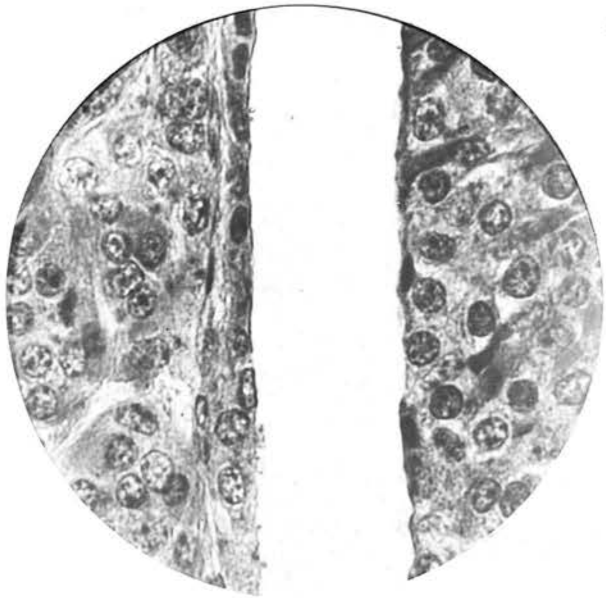


FIG. 9. THE INTRAGLANDULAR CLEFT.
THE PARS ANTERIOR IS ON THE LEFT; THE PARS INTERMEDIA ON THE RIGHT. THE CELLS BOUNDING THE CLEFT IN FRONT ARE FLATTENED, WITH DARKLY STAINING NUCLEI.

IRON HAEMATOXYLIN + CONGO RED X 710.

fibres in this part of the pituitary. Berkley has described sympathetic nerve fibres derived from the carotid plexus. These sympathetic fibres, which are very fine and varicose, come off the main stem approximately at a right angle, cross the sinuses to run an irregular course among the epithelial cells, and finally break up into branching terminations with numerous ball-shaped endings which lie in the intercellular tissue.

The existence of lymphatic vessels in the pars anterior has not been definitely settled. Thaon has failed to find any. Caselli, however, asserts that lymphatics are abundant, while Herring states that there is considerable doubt as to whether they exist or not. Edinger believes that lymph spaces separate the epithelial cells from the blood-sinuses. Most observers, however, agree that lymphatics, if present, must be extremely few in number.

THE INTRAGLANDULAR CLEFT.

The cleft - the residual lumen of Rathke's pouch - intervenes between the pars anterior and the pars intermedia. In the guinea-pig (Fig. I) it is a well-defined fissure extending across the greater part of the gland, both in the vertical and the transverse direction. It is limited below by a thin strip of pars anterior which becomes continuous with the pars intermedia/

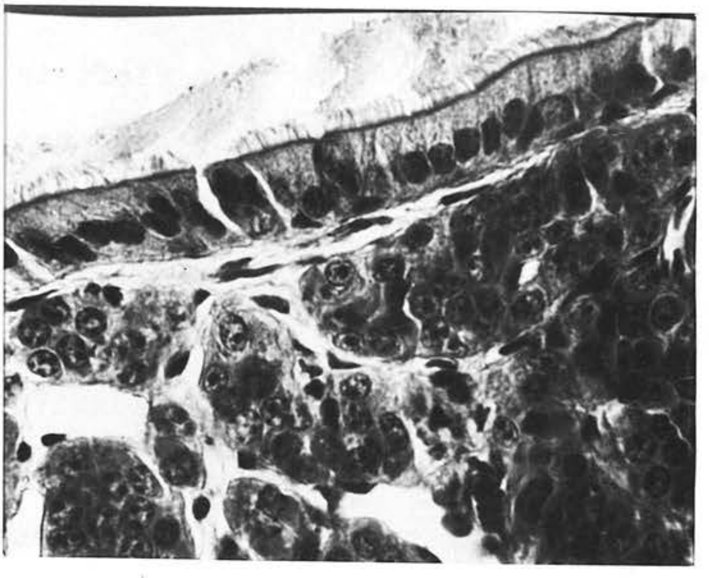


FIG. 10. CILIATED COLUMNAR EPITHELIUM BOUNDING THE CLEFT IN THE GUINEA-PIG. THIS SPECIMEN WAS FROM A PREGNANT ANIMAL AND THERE IS VISIBLE SECRETION IN THE CLEFT.

IRON HAEMATOXYLIN + EOSIN X 710.

intermedia. Unless great care is exercised in handling the specimens this strip is apt to break down. In the resting state the cavity is lined with flattened cells in about the upper two-thirds of the anterior aspect (Fig. 9). The lower third of the anterior boundary is covered with columnar epithelium which is commonly ciliated (Fig. 10). This condition of the epithelium of the lower part of the cleft is constant as regards the guinea-pig, though I have not found any reference to it in the literature. The posterior boundary of the cleft consists of the cells of the pars intermedia. In the resting phase the cleft usually appears empty, but when the gland is functioning actively it may contain visible secretion . In the rabbit the cleft presents the appearance usually met with in the human subject. It is partly obliterated and broken up into isolated segments, forming separate cavities which may contain colloid secretion. These cavities are lined with columnar ciliated epithelium (Fig. 11). The frequency with which ciliated epithelium is met with as the lining of the cleft appears generally to have escaped notice.

Kojima describes the cleft in the rat as resembling the condition met with in the rabbit; it is partly obliterated and may form a chain of isolated cavities. Herring states that the anterior lobe in the cat is usually separated from the cleft by a single layer of flattened/

Fig. 11. Ciliated columnar epithelium bounding the cleft in the rabbit. The cells are on the surface of the pars intermedia. The cleft contains darkly-staining colloidal material.

Iron haematoxylin & eosin X 710.

flattened cells, which are larger than endothelial cells and are continuous at the anterior and posterior ends of the cleft with the cells of the epithelial reflection. He makes no mention of ciliated columnar epithelium in relation to the cleft in this animal. John Fraser has recently shown that in the human subject in early life the cleft may be quite well developed, and may show important variations as to its contents, which depend on the state of physiological activity of the gland.

Pars Intermedia: This portion lies mainly behind the intra-glandular cleft. At the lateral margin of the cleft it becomes continuous with the epithelium of the pars anterior without any sharp line of demarcation, though the cells of the two parts are readily distinguished from each other where they intermingle (Fig. 12). It is for the most part applied to the surface of the pars nervosa which abuts on the cleft and to the neck of the gland which connects the pars nervosa with the infundibulum, but the extent and distribution vary in different animals and in different states of physiological activity. In the guinea-pig the pars intermedia is well developed and forms a thick layer behind the cleft. It is continued as a thin layer almost or quite completely around the pars nervosa and shows a marked accumulation at the neck of the/

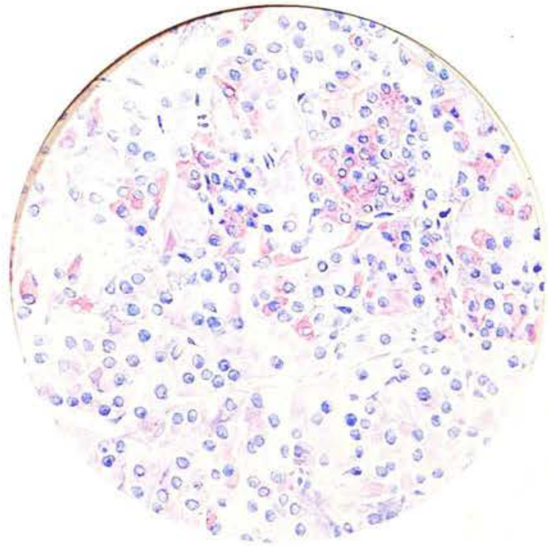


Fig. 12. The intermingling of pars anterior and pars intermedia at the lateral margin of the cleft. The pink acid-staining cells of the pars anterior are easily identified.

Acid toluidin blue X 330.

the gland (Fig. 13). In addition, it is prolonged upwards on the stalk towards the base of the brain. In the rabbit also, the pars intermedia is well-marked behind the cleft. It does not extend so completely around the pars nervosa as in the guinea-pig, usually leaving the posterior aspect uncovered. The accumulation in the region of the neck is less evident but is distinctly present. In this animal the stalk is uncovered, but the epithelial investment appears again at the base of the brain in relation to the tuber cinereum.

In the adult human subject the pars intermedia is poorly developed. It forms a thin layer, covering the pars nervosa where it adjoins the cleft. At the upper end of the cleft and around the neck the cells are more numerous but never occur in large numbers. John Fraser has recently shown that in early life the pars intermedia may form quite a thick layer behind the cleft.

The cells of the pars intermedia are usually neutrophil or faintly basophil in their staining reactions and form a marked contrast to the bright pink eosinophils of the pars anterior. In the rabbit and the guinea-pig the cells are polygonal in shape and contain numerous fine granules which are faintly basophil. The epithelial elements lining the cleft are /

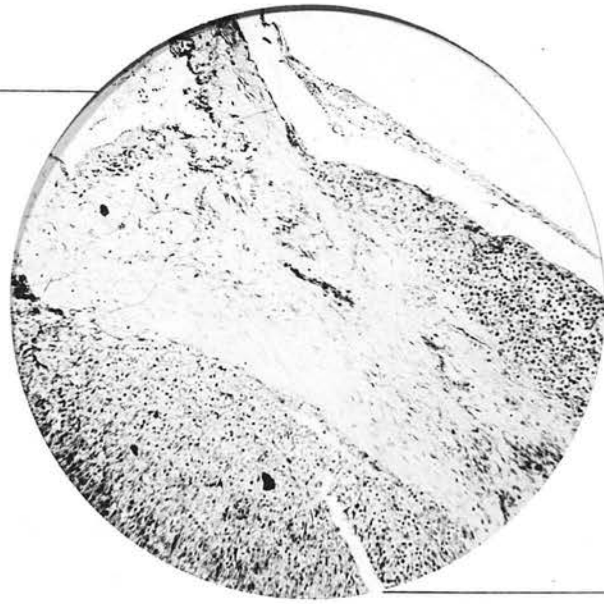


FIG. 13 THE NECK OF THE PITUITARY IN THE GUINEA-PIG SHOWING THE THICKENING OF THE PARS INTERMEDIA IN THIS REGION.

THE INFUNDIBULAR RECESS OF THE THIRD VENTRICLE AND THE INTRAGLANDULAR CLEFT ARE SEEN.

IRON HAEMATOXYLIN + CONGO RED.

are often flattened on the free surface and are triangular in shape, with an angle projecting into the cells behind; and the cells which are in contact with the pars nervosa may also resemble in shape the foot cells of the testicle. The pars intermedia sometimes shows wedge-shaped processes, groups of cells, or isolated cells passing into the pars nervosa (Fig. 14). The significance of these appearances will be referred to later . In many animals, supporting spindle-shaped cells, arranged vertically to the surface, are seen among the epithelial elements. They are described by Lothringer, Gemelli, Trautmann, Herring, and Atwell, and are best demonstrated by the Cajal or Golgi methods. Stendell has suggested that these cells are elements which have wandered into the pars intermedia from the pars nervosa. Atwell has observed in the rabbit embryo distinct regions of contact, at which the pars nervosa appeared to be sending projections into the pars intermedia. These contacts vary in number from two to five and are apparently transitory, being observed most constantly in the 16-day embryos, and never later than the 20th day of development. It is suggested that this may be the means by which the transfer of cells is accomplished, However, another possibility must be kept in mind, and that is that these appearances may be due to the sporadic recurrence of a condition common in the lower fishes/

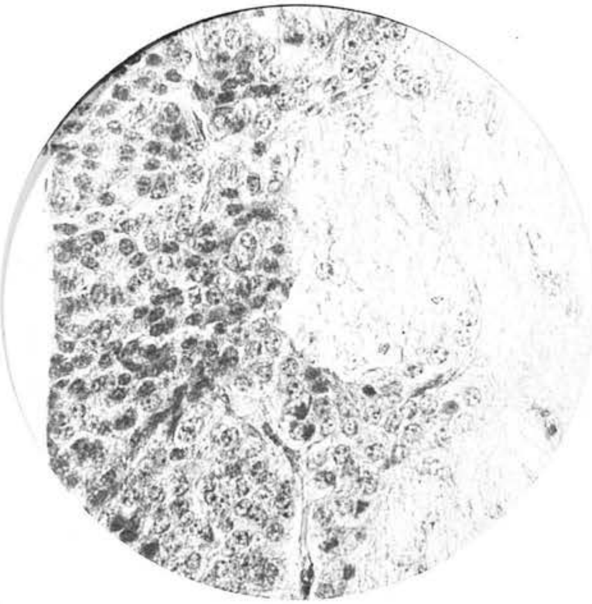


Fig. 14. THE PARS INTERMEDIA OF THE GUINEA-PIG SHOWING WEDGE-SHAPED PROCESS PASSING INTO THE SUBSTANCE OF THE PARS NERVOSA.

IRON HAEMATOXYLIN + ACID FUCHSIN X390.

fishes, where the interdigitation of the pars nervosa with the pars intermedia is very extensive.

A prominent feature in some animals is the presence in the pars intermedia of vesicles containing secretion. In the cat and the dog they are particularly abundant in the region of the neck and contain much granular secretion. In the human pituitary colloidal secretion is sometimes found in the pars intermedia around the neck of the gland, and in certain circumstances the vesicles may also be found at a lower level. In the rabbit these vesicles are well-marked and contain colloid substance (Fig. 15). They differ in their arrangement from that of the cat and the dog in being most abundant behind the cleft - below the level of the neck - and are usually larger than the vesicles found in these animals. It is an important fact in the consideration of the secretory process of the posterior lobe that vesicles do not occur in the pars intermedia of the guinea-pig.

Lewis & Maurer have recently subjected the pars intermedia to a careful cytological study, making use of careful fixation methods followed by the granular stains. They find that two kinds of cell occur in the pars intermedia: (1) cells related to the colloid-containing vesicles and evidently the secretory source of the colloid; (2) the secretory cells which are the characteristic/

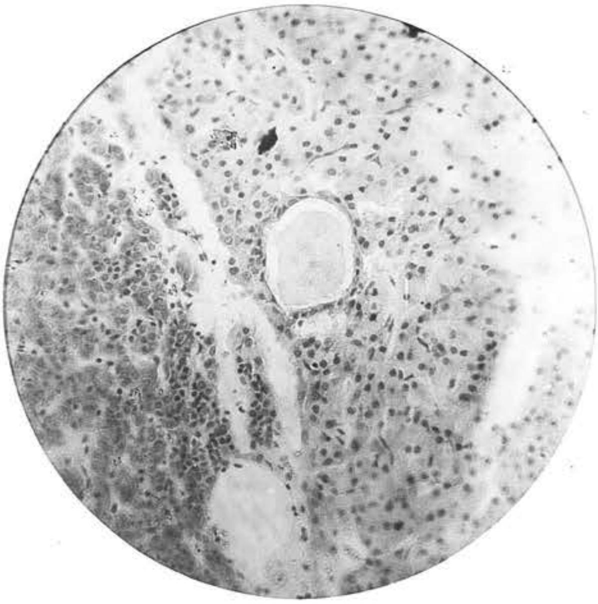


Fig. 15. A vesicle in the pars intermedia of the rabbit lying close up to the pars anterior away from the pars nervosa.

Acid toluidin blue X 84.

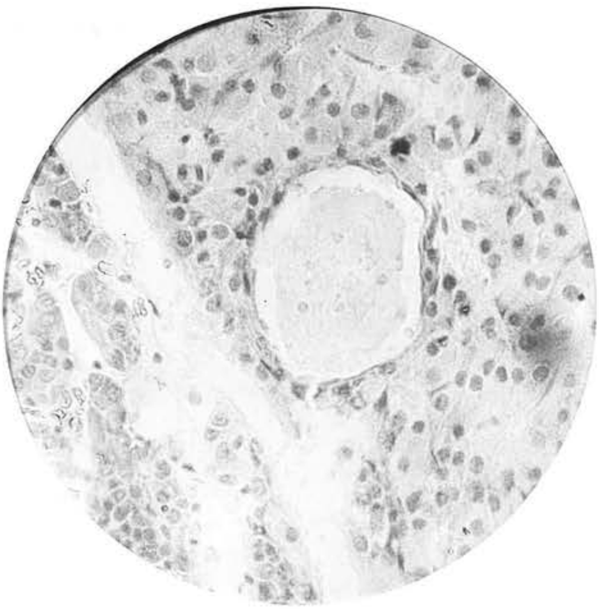


Fig. 16. A higher power of the same. X 390.

characteristic elements of the pars intermedia, and which are finely granular and basophil or neutrophil. The appearance of the cells lining the vesicles in the rabbit does not support the view of Lewis & Maurer that they are the secretory source of the colloid. In Fig. 17 the lining cells are flattened with darkly staining nuclei and present a distinct resemblance to those of a thyroid vesicle in the resting state of the gland. They never show the appearances of active secretion such as are seen in the cells of an active thyroid. It seems probable that they are merely containing cells and that the contents of the vesicle are derived from the surrounding granular cells.

A notable feature which distinguishes the pars intermedia from the rest of the epithelial part of the pituitary is the absence of blood-vessels. Large blood vessels are numerous at the junction of pars intermedia and pars nervosa, but capillaries are completely absent from the pars intermedia or are very few in number. A striking contrast, as pointed out by Herring, is thus afforded between the highly vascular epithelium of the anterior lobe and the non-vascular epithelium which covers the pars nervosa. This peculiarity indicates a difference, if not of function, at any rate of the mode of absorption of the products of the epithelial cells.

Thaon states that there are no lymphatics in the pars/

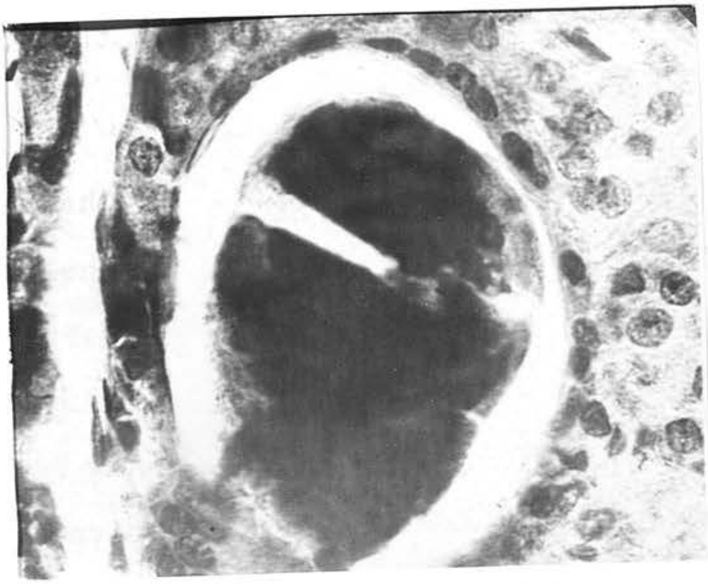


FIG. 17. A VESICLE FROM THE PARS INTERMEDIA OF THE RABBIT. IT CONTAINS COLLOIDAL MATERIAL. THE LINING CELLS ARE FLATTENED WITH DARKLY STAINING NUCLEI.

IRON HAEMATOXYLIN + EOSIN. X 710.

pars intermedia. In some animals, such as the lemur, supporting connective tissue is abundant, but in the rabbit and the guinea-pig and in many other animals it is entirely absent. In the rabbit, however, there is a well-marked layer of connective tissue immediately behind the pars intermedia in which numerous large vessels are found. In the guinea-pig this layer is scanty or absent.

The "Pars Tuberalis". This term has been applied by Atwell and others to the epithelial layer which clothes the infundibulum and the tuber cinereum and is prolonged forwards towards the optic chiasma (Fig. 18). Tilney describes it as being made up of cell masses with occasional small relatively thick-walled acini. He states that this portion is distinctly more vascular than the pars intermedia and that the cells are basophilic with scanty cytoplasm. Baumgartner in reptiles, Parker in marsupials, and Atwell in the rabbit and the ox, have noted the acinar character of the pars tuberalis as one of its most striking characteristics. These acini are spoken of by Tilney as being walled by two layers of cells, while Parker & Atwell have noted a single layer. Atwell also emphasises the fact that the pars tuberalis never shows a tendency to invade the neural tissue in the manner/

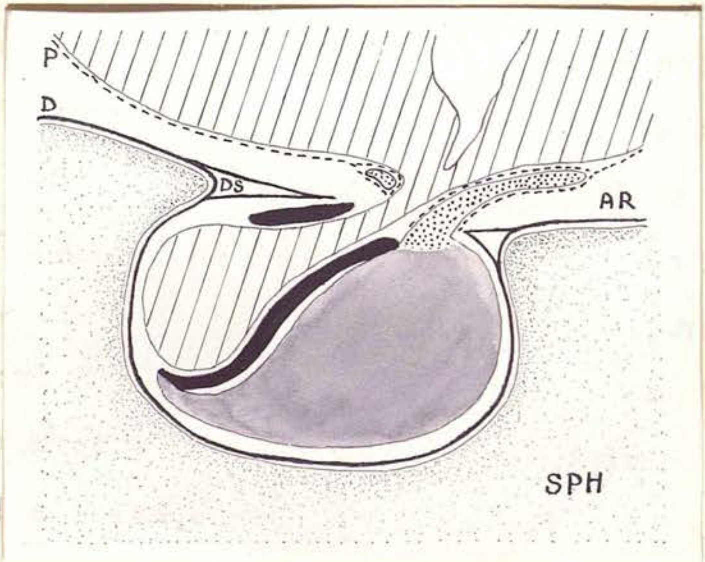


FIG. 18. DIAGRAM OF THE PARTS OF THE PITUITARY AFTER ATWELL. THE "PARS TUBERALIS" IS PROLONGED UP THE STALK TO THE BASE OF THE BRAIN.

GREY WASH = ANTERIOR LOBE PROPER.

COARSE STIPPLE = PARS TUBERALIS.

SOLID BLACK = PARS INTERMEDIA.

LINED = NEURAL LOBE AND DIENCEPHALIC FLOOR.

P = PIA MATER.

AR = ARACHNOID SPACES.

D = DURA MATER.

DS = DIAPHRAGMA SELLAE, WITH INTERCAVERNOUS SINUS.

SPH = SPHENOID BONE.

manner so characteristic of the pars intermedia, and that the ectodermal supporting cells sometimes found in the pars intermedia have never been described for the pars tuberalis.

The last-named observer describes a special mode of development for the pars tuberalis. He states that it has a paired origin from two buds, which appear early at the ventral end of Rathke's pouch, near the attachment of the epithelial stalk. These, the lateral lobes, or tuberal processes (Tilney) are at first some distance from the attachment of the neural lobe. As development proceeds, however, they acquire a position near the brain wall, and, after fusing in front and behind the infundibulum, spread out to form a thin layer under the floor of the diencephalon and hypothalamus. The residual lumen never intervenes between the pars tuberalis and the anterior lobe proper.

Only a few attempts have been made to assign a distinctive function to this part of the gland. Atwell & Marinus believe that the pars tuberalis is incapable of producing the effects on uterus, intestines, and blood-vessels characteristic of the posterior lobe complex. Marinus has likewise stated that when fed to rats the pars tuberalis does not produce the growth effects of the anterior lobe proper

Herring does not make any distinction between this/

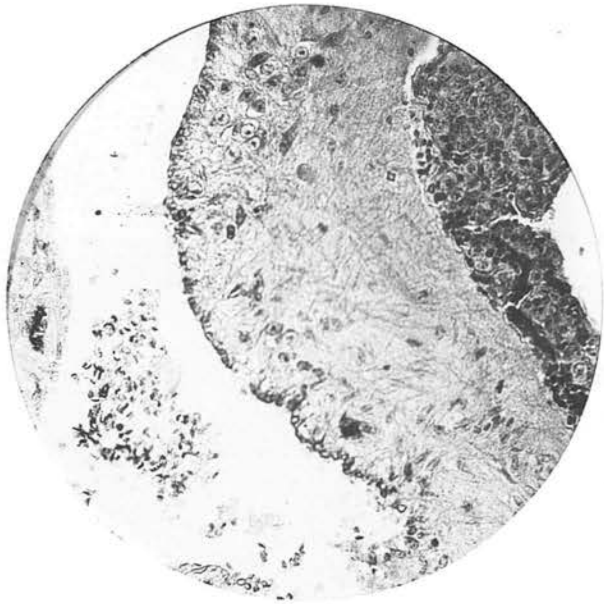


FIG. 19. THE "PARS TUBERALIS" IS SEEN IN RELATION TO THE STALK. THE CELLS RESEMBLE THOSE OF THE PARS INTERMEDIA.

IRON HAEMATOXYLIN + EOSIN X 210.

this part of the gland and the pars intermedia. He regards the vesicles found in this region as the same as those so abundant in the cat, around the neck. In the rabbit this part of the gland is very scanty in amount; there is no epithelial covering of the infundibulum, but there is a small accumulation of cells at the attachment of the stalk to the tuber cinereum, which resemble very closely the cells of the pars intermedia. In the guinea-pig the investment of the stalk is well-marked, especially on the posterior aspect (Fig. 19). The chief difference in this animal between the pars tuberalis and the pars intermedia lies in its vascularity. Numerous blood-vessels pass freely between the cells (Fig. 20), whereas in the pars intermedia behind the cleft vessels are scanty or absent. I do not agree with Tilney as to the basophil staining of the cells; in the guinea-pig at least, the cells are neutrophil and exactly resemble those of the pars intermedia proper. Vesicles do not occur in the pars tuberalis in this animal. In the actively-functioning gland I have found abundant hyaline bodies among the cells of the investment of the stalk. These are exactly similar to those which are found among the cells of the pars intermedia in the active state, as will be described later, and appear to demonstrate conclusively/

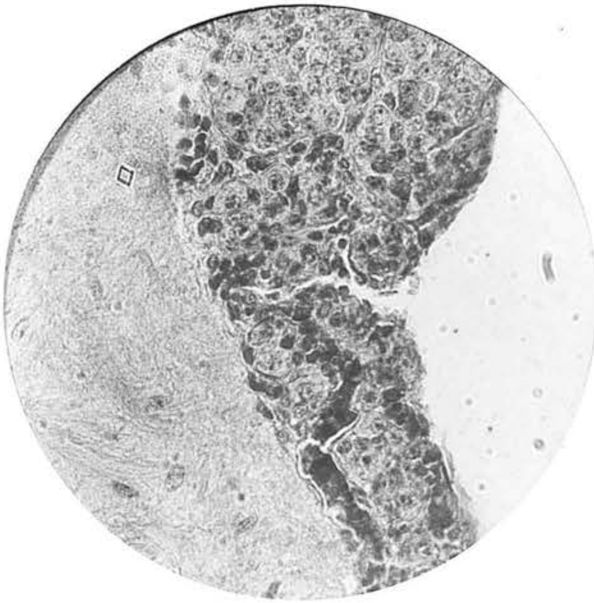


FIG. 20. THE "PARS TUBERALIS" IN THE GUINEA-PIG SHOWING THE NUMEROUS BLOOD VESSELS.

IRON HAEMATOXYLIN & EOSIN X 380.

conclusively that the function of the two parts is the same. There seems to be no sufficient justification for making a physiological distinction between the pars intermedia proper and this prolongation upwards towards the base of the brain.

The Pars Nervosa: This part is chiefly composed of neuroglia fibres and cells. Many of the fibres arise from these cells, others from the ependyma cells of the infundibular recess. The configuration and distribution of the neuroglia-cells and their fibres have been depicted by many writers. Many types of neuroglial cells are to be found, and these varieties relate chiefly to the profusion or otherwise of the processes arising from them. In the rabbit the fibres present a whorled arrangement, the general trend of which is towards the stalk. In the guinea-pig they form a looser net-work, the fibres of which also converge on the stalk.

Herring was the first to describe the presence, in the pars nervosa, of small hyaline bodies, highly refractive when unstained (Fig. 22). They are scattered throughout the nervous substance and stain only faintly with eosin. By over-staining with safranin, or by staining deeply with acid fuchsin or congo-red, I have found that these bodies show up well. Their significance/

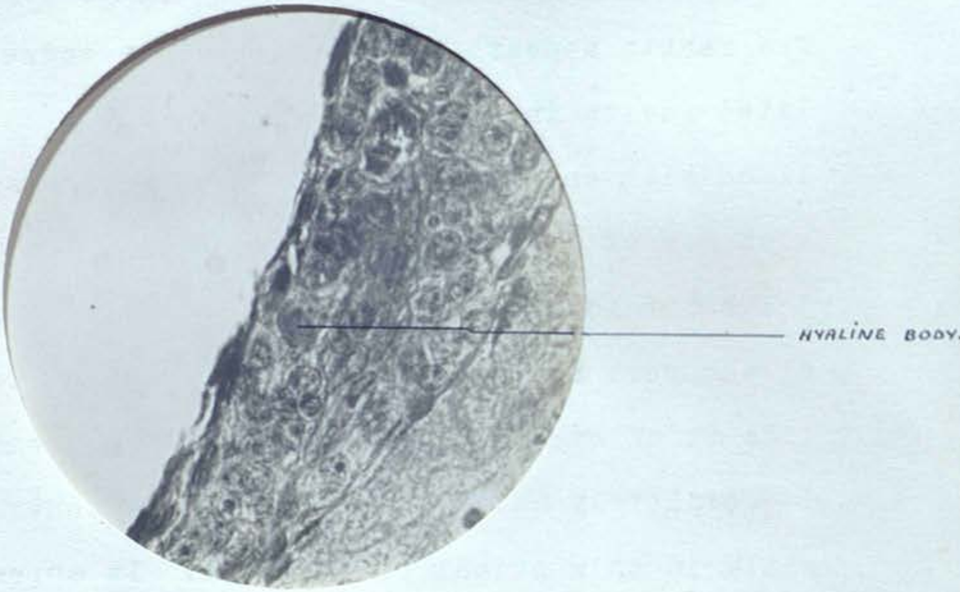


FIG. 21. THE "PARS TUBERALIS" ON THE ANTERIOR ASPECT OF THE STALK. A HYALINE BODY IS VISIBLE BETWEEN THE CELLS.

IRON HAEMATOXYLIN + EOSIN. X 710.

significance will be dealt with in considering the process of secretion.

In some animals, notably the cat and the opossum, there is a cavity communicating with the third ventricle and lined with ependyma cells; but in man and most mammals this portion of the pituitary is solid. The rabbit appears to be unique in possessing an isolated cavity in the pars nervosa (Fig.23). It is lined with ependyma and undoubtedly represents a persistence of a portion of the original cavity of the posterior lobe. It occupies the upper third or more of the pars nervosa and varies in shape from a slit-like to an ovoid space with rounded extremities. It is completely cut off from the third ventricle, the stalk in this animal being solid. It appears to be a constant feature - at least in pregnant animals - and shows very definite variations as to its shape and contents in different conditons of functional activity. The only reference to this feature that I have met with in the literature is a remark of Herring's, in referring to the pituitaries of the ox, pig, and rabbit, that "Traces of a central cavity are sometimes found in the neck of the posterior lobe". The appearances of this space in different states of physiological activity are described below.

The question as to whether the nervous portion of/

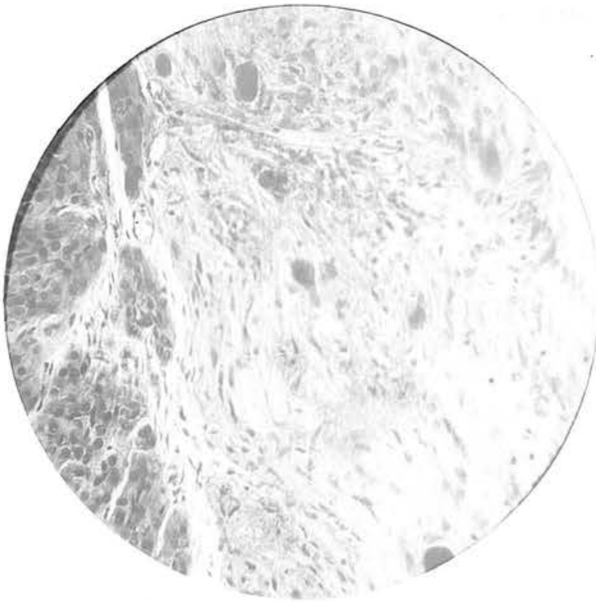


FIG. 22. HYALINE BODIES IN THE PARS NERVOSA OF THE RABBIT. THE PARS INTERMEDIA IS ON THE LEFT.

IRON-HAEMATOXYLIN + CONGO RED. X 210.

of the hypophisis contains nerve cells has formed the subject of repeated investigations. Both Krause and Berkley describe true nerve cells and nerve fibres. According to Berkley, the true nerve cells are situated chiefly in the lower and anterior part of the pars nervosa. This author has divided them into two groups - those having one dentrite and those having more than one. Ramon y Cajal found cells of an undefined kind in young rats, together with delicate fibres which were certainly nervous and which proceeded from nerve cells situated at the base of the brain behind the chiasma; these nerve fibres descended through the infundibulum, formed a plexus in the pars nervosa, and terminated in free branches. Kolliker, Caselli, and Herring deny the existence of true nerve cells in the pars posterior. They believe that the nervous elements consist entirely of neuroglial and ependymal tissues. Gentès discovered a considerable net-work of nerve fibres by Golgi's method, and this finding was confirmed by Thaon. With regard to the ependymal cells, these are found in the neighbourhood of the neck, and sometimes there are inclusions in the centre of the pars nervosa in those animals in which the central cavity has been obliterated in the process of development.

No evidence has yet been adduced to show that the/

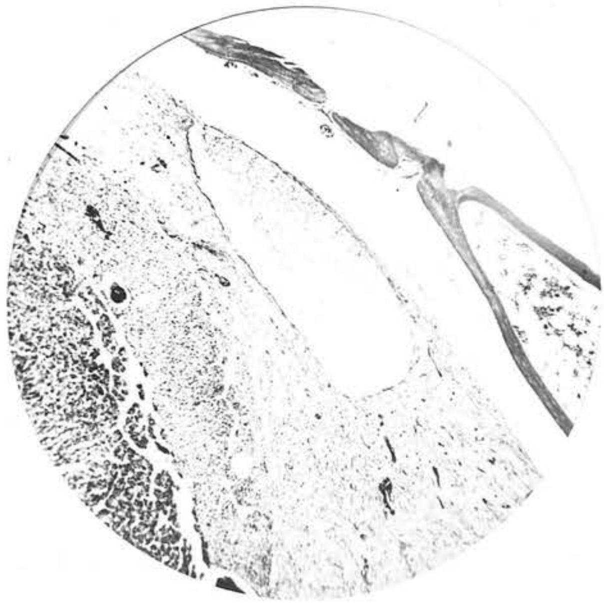


FIG. 23. THE CAVITY IN THE PARS NERVOSA OF A PREGNANT RABBIT. IT IS LINED WITH EPENDYMA AND CONTAINS A QUANTITY OF COARSE GRANULAR MATERIAL.

IRON HAEMATOXYLIN + EOSIN X 42.

the sympathetic nerves leave the blood-vessels in the pars nervosa as in the case of the pars anterior. It has been suggested, however, that such fibres may reach the pars intermedia from the pars anterior. The blood-vessels of the pars nervosa are comparatively few in number, so that in this respect there is a marked contrast between the anterior and the posterior lobe.

Special attention has been directed by Kohn and others to a peculiar pigment which has long been known to exist in the neuroglial fibres of the pars nervosa. The composition and origin of this pigment has not been discovered, but, according to Biedl, it has been shown to be neither a fat nor a lipochrome. Clunet & Jonnesco have also made a careful study of this material. They have found that it is possible with the naked eye to observe the pigment in unstained sections held up to the light; it is chiefly seen in the posterior part of the pars nervosa, although it may be distributed throughout. The granules are described as being more or less spherical and brownish-yellow or greenish in colour. It was found by these investigators that neither hydrochloric acid nor acetic acid has any effect on the pigment, but that sulphuric acid turns it black without dissolving it. It is insoluble in alcohol, xylol, benzene, chloroform, ether, and cedar-wood oil. Strong solutions of ammonia and of/

of caustic potash and caustic soda will only affect this substance after prolonged contact - that is to say, after twenty-four or more hours - when it may be completely dissolved.

The pigment does not give the iron reactions. It is not turned brown by osmic acid, nor coloured red by Sudan III or Scharlack R.; and it is not stained by haematoxylin, haematin, or safranin, but it is changed to an intense black by iron-haematoxylin, and blue by Giensa's stain. It is tinted also by a few of the rarer dyes.

Livon & Peyron look upon the pigment as a product elaborated by the neuroglial elements from the secretion of the glandular portion of the pituitary; but whether this is effected by a process of assimilation or deposition they were unable to discover. Fischer considers that this substance is the result of degeneration in old age. I have not met with the pigment in either the rabbit or the guinea-pig, so that it cannot be regarded as an essential element in the pars nervosa. Laboratory animals usually fail to attain to old age, so that the absence of the pigment in the animals examined may, perhaps, be taken as supporting Fischer's view that the presence of the pigment is a senile change.

THE/

THE HISTOLOGICAL EVIDENCES OF SECRETORY ACTIVITY In the PITUITARY.

It is well-known that the pituitary undergoes a remarkable enlargement during pregnancy. Erdheim & Stumme found that in nulliparous women the maximum weight during the reproductive period was 0.75 gramme, while in multiparae at the end of pregnancy, the average weight was 1.06 gramme. Attention has hitherto been mainly directed towards the anterior lobe and this part of the gland has been regarded as the seat of the principal changes in pregnancy. It becomes apparent, however, from the examination of a considerable number of pituitaries that the remainder of the gland shows very definite evidence of increased activity, and it is highly probable that the increase in size and weight of the pituitary is in part due to these changes and also to the capacity for the storage of secretion which the gland possesses to a striking degree.

PARS ANTERIOR.

The work of Erdheim & Stumme aroused great interest in connection with the changes which take place in this part of the gland in pregnancy. These authors attributed the enlargement entirely to changes in the anterior lobe. They describe , in the human female,/

female, the appearance in enormous numbers of a new kind of cell which they termed "pregnancy cells". The cells are large chromophobes; they have large, light, irregular nuclei, with abundant plasm which is distinctly granular. The eosinophil cells are as numerous as in the quiescent gland but are now largely out-numbered by these new pregnancy cells. The basophils also are unaffected. Launois & Mulon have described the different types of cell met with in pregnancy and observed that the cells sometimes showed a syncytial arrangement. Their observations were made on only two pituitaries from human females immediately <u>after</u> confinement. They mention the possibility of some of the appearances being due to post-mortem changes and do not discuss the relative proportions of the different types of cell.

Siguret observed in rabbits a diminution in the number of chromophobe cells and an increase in the number of eosinophils, the opposite change to that described by Erdheim & Stumme. This author also found that the change was as marked at the beginning as at the end of gestation. It is evident that, although all observers agree as to the increase in size of the anterior lobe in pregnancy, opinions are divided as to the relative proportions of the different types of cell. Blair Bell is impressed with the variations during/

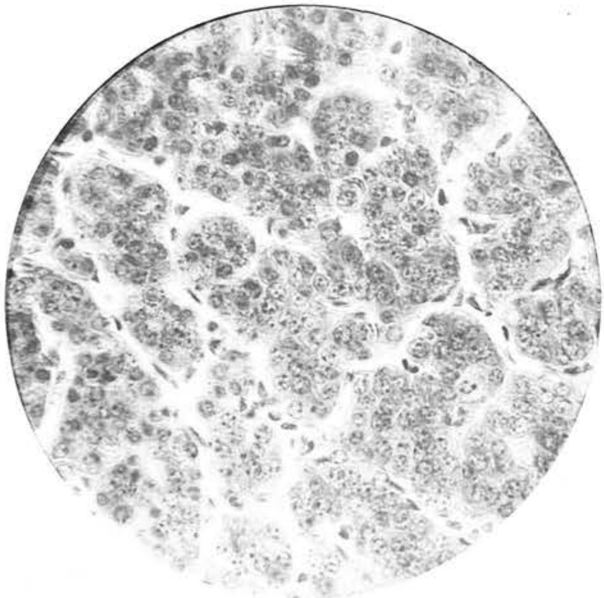


FIG. 24a. LOBULATION OF THE PARS ANTERIOR OF THE GUINEA-PIG.

IRON HAEMATOXYLIN & EOSIN X 390.

during pregnancy, both in animals and in women. Usually in rabbits he finds an increase in the degree of eosinophilia - that is to say, the lightly-staining eosinophil cells, which predominate in the pars anterior of this animal, stain more deeply. But he has also found pronounced chromophobia in this situation during pregnancy in the rabbit. In women, he states that the chromophobe cells are usually plentiful in pregnancy, but this is not always the case. He beleives that the essential change in the pars anterior of all animals during pregnancy is towards greater activity, and this may be represented by increased eosinophilia of the eosinophil elements or by chromophobia. In his opinion the large chromophobes of pregnancy are active cells in which the secretion is passed into the blood-stream as soon as produced, so that there is no time for it to accumulate in the cell and give the eosinophil reaction. Blair Bell also describes the lobulated or adenomatous arrangement of the cells which is commonly seen in pregnancy (Fig. 24a). This lobulated appearance of the cells frequently occurs in non-pregnant guinea-pigs and cannot be regarded as characteristic of the pregnant condition.

The conflicting statements as to the condition of the cells of the pars anterior during pregnancy are probably dependent on two facts - first, that there has been/

been no uniform method of sectioning the gland, and, second, that in the human pituitary there is always delay between the time of death and the fixation of the tissues. With regard to the first source of error, there is no doubt that the different type of cell vary in amount in different parts of the gland, so that, for example, a paramedian section might reveal a relatively larger number of chromophobe cells than a median. For purposes of comparison, as Cushing has emphatically declared, only median sagittal sections should be utilised. The second source of error, in the case of the human subject, can hardly be obviated. In the interval between death and fixation of the tissue, secretion products, probably more labile than in the resting gland, tend to disappear from the cell. The pituitaries of the lower animals, in which the tissue can be fixed immediately after death, are therefore of greater value in the investigation of this question.

In the animals examined the principal changes in pregnancy in the pars anterior of both the rabbit and the guinea-pig were an increased eosinophilia and an increased vascularity of this part of the gland. The increase in the eosinophilia was due, not only to an increase in the number of the chromophil cells, but also to an increase in the intensity of staining. There seems/

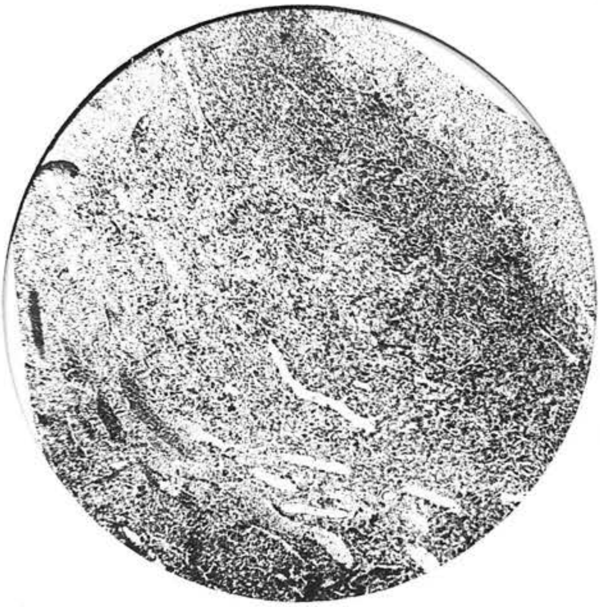


FIG. 24. THE PARS ANTERIOR OF A RABBIT 23 DAYS PREGNANT, SHOWING THE EXTREME VASCULARITY.

IRON HAEMATOXYLIN + EOSIN X 42.

seems to be little doubt that eosinophilia is the characteristic condition in functional activity of this part of the gland, although it is possible that too much stress has been laid on the staining reactions of the secretion granules. It has been pointed out that the acid-staining granules stain with iron-haematoxylin just as well as, or even better than, with eosin. In pregnant animals, the cells containing abundant granules are increased in number whether the stain used is iron-haematoxylin or eosin.

The increased vascularity of the pars anterior is a very striking feature, especially towards the end of pregnancy, as may be seen from an examination of Figs. 24 & 31 . The dilatation of vessels affects not only the sinus-like capillaries but also the larger vessels.

With regard to the disposal of the secretion of the anterior lobe, there can be little doubt that for the most part it is carried away in the blood-channels. Thaon and others have drawn attention to the fact that granular secretion may actually be seen in the blood-sinuses; but it seems certain that the secretion is chiefly taken into the blood-stream in infinitesimal quantities.

Storage of Secretion: The anterior lobe is large/

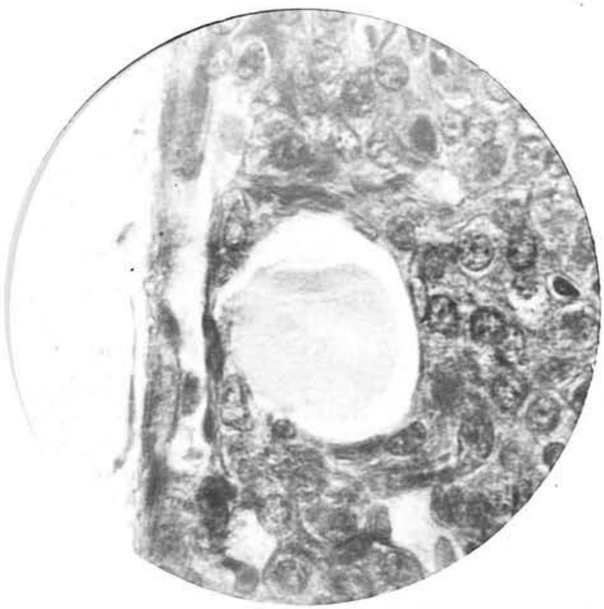


Fig. 25. A vesicle containing colloidal material from the pars anterior of a rabbit 23 days pregnant.

Iron haematoxylin + congo red X 710.

large in comparison with the posterior, and permeated everywhere by a net-work of vessels, so that a large amount of secretion can be rapidly produced and quickly passed into the blood-stream. Therefore, storage of secretion is hardly necessary to provide for the majority of physiological requirements. In the human pituitary it is not uncommon to find the eosinophil cells arranged in a tabular or vesicular manner with masses of granular, acid-staining secretion in the centre. In other cases basophil colloid material is seen surrounded by chromophobe cells. Storage of secretion is rarely met with in the rabbit or guinea-pig. Herring states that it does not occur in the pituitary of the rabbit, but I have found vesicles occasionally towards the end of pregnancy. Fig. 25 shows a vesicle from the pars anterior of a rabbit 23 days pregnant. It contains eosinophil colloid substance and is lined by flattened cells. These vesicles have not been met with in non-pregnant rabbits, and in pregnant animals only towards the end of the gestation period. In the guinea-pig two types of vesicle have been met with in the pars anterior of pregnant animals. Fig. 26 shows a type of vesicle which is sometimes seen in the upper part of the anterior lobe. It contains acid-staining colloid material, and resembles that seen in the rabbit, except that the cells are less/

Fig. 26. Vesicle from upper part of pars anterior of a pregnant guinea-pig.

Safranin X 710.

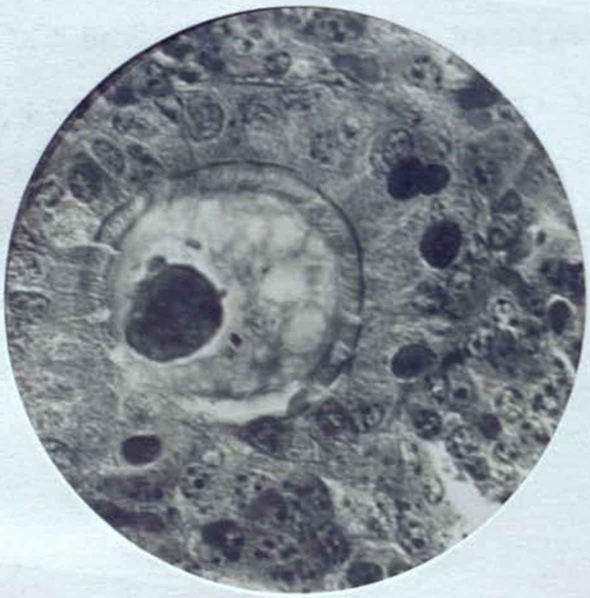


Fig. 27. Vesicle from pars anterior of guinea-pig towards the lower end of the cleft. It is lined with ciliated columnar epithelium.

iron haematoxylin X 710.

less flattened. The second type (Fig. 27) occurs near the lower end of the intra-glandular cleft. It contains a little granular material and is lined with ciliated columnar epithelium. It is probable that this second form represents a developmental "rest" from the primitive pouch of Rathke and possesses no physiological significance. From the pathological aspect such inclusions are of considerable importance; Erdheim and Cushing have emphasized the fact that they may form the source of epithelial growths or cysts. In non-pregnant guniea-pigs vesicle formation was only met with in one instance. In this animal the vesicles were surrounded by active eosinophil cells and contained acid-staining secretion (Fig. 28). They presented a very distinct resemblance to glandular acini. This animal was regarded as being aged, and this supposition was borne out by the presence of numerous pigment granules in the cells of the thyroid and the suprarenal cortex. If this is the case, the formation of vesicles supports the opinion of Thaon - that the pituitary remains an active organ in old age.

<u>The Significance of the Staining Reactions of the Cells of the Pars Anterior.</u>

There has been much discussion as to the relationship of the differently-staining cells of the anterior lobe. Some authorities - Gemelli, Scaffidi, Erdheim,/

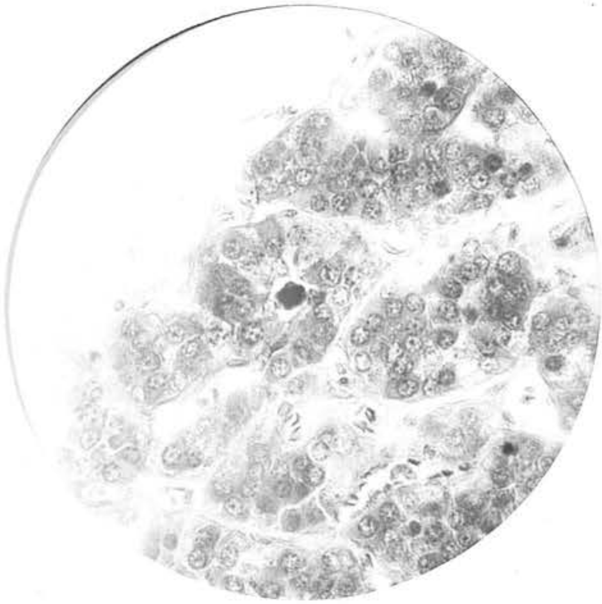


Fig.28. Vesicles in active pars anterior of non-pregnant guinea-pig. They resemble glandular acini.

iron haematoxylin + acid fuchsin X 390.

Erdheim, Friedman, and others, believe that the chromophils and the chromophobes represent two distinct types of cell, while Saint-Rémy, Pirrone, Thaon, Guerinni, Launois, Joris, Herring, Blair Bell, and others, regard the two forms of staining reactions as indicating different stages of activity of the same type of cell.

In support of the former view, Erdheim has pointed out that the adenoma-like formations found in pathological affections may consist, in some cases, entirely of eosinophils, in others, entirely of chromophobes, as if the conditions arose from groups of one or other type of cell. Cushing, however, has shown that an eosinophil adenomatosis or hyperplasia is associated, at least in the earlier stages of the disease, with the condition of acromegaly, this being a state of hyperpituitarism, while a chromophobe struma is invariably accompanied by signs of hypopituitarism. Thus, in twelve cases in which a chromophobe struma was present, there were signs of glandular insufficiency in every instance. These observations of Cushing lend very strong support to the view that the eosinophils are the active cells, charged with secretion, while the chromophobes are empty or exhausted cells.

Friedman, who supports the view that the two types/

types of cell are different forms, believes that the "pregnancy cells" have for their function that of inhibiting uterine contractions and preventing premature labour. He points out that in Grave's disease , in which condition, according to Fry, the pituitary presents a state of chromophilia, miscarriages are very frequent when pregnancy does occur. Whereas, in myxoedema, where the gland, according to the same observer, shows a condition of chromophobia, premature labour is very uncommon. This last observation, however, cannot be accepted without reserve. McCarrison states that miscarriage is frequent in myxoedematous patients. In any case, chromophobia in myxoedema can be equally well explained by regarding it as a state of hypoactivity of the pars anterior, corresponding to that which is seen in hibernating animals or, as shown by Blair Bell, in brooding hens, and corresponding also to the state of under-activity of the majority of the vital processes in that affection. It is probably to be regarded, not as a condition in which there is an increase of one type of cell, but as a state of underactivity of the majority of the cells of the pars anterior.

The observations of Erdheim & Stumme with regard to a state of chromophobia during pregnancy in the human/

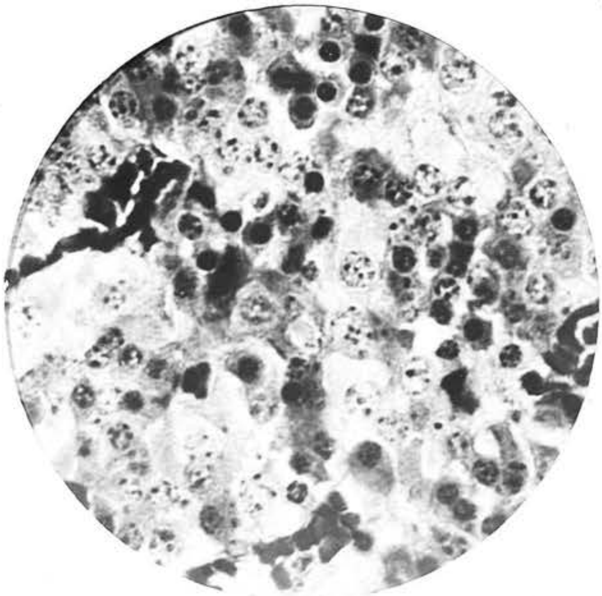


FIG. 29. THE CELLS OF THE PARS ANTERIOR STAINED WITH THE COMBINATION OF IRON HAEMATOXYLIN AND EOSIN. THE DISTINCTION BETWEEN CHROMOPHILS AND CHROMOPHOBES IS WELL-MARKED.

X 710.

human subject are generally accepted. It must be remembered, however, that a fallacy exists here owing to the delay in the preservation of the specimen; the cells which appear chromophobe may have been originally eosinophil. Blair Bell explains the existence of these large chromophobe cells by assuming that in conditions in which there is immediate and urgent demand for the secretion of the pars anterior,as in pregnancy, the small chromophobe cells, and even some of the young eosinophils, increase in size but remain chromophobe, and yield up their secretion as soon as it is formed.

In the pregnant animals examined, as mentioned above, the striking feature in the appearance of the cells of the pars anterior has been that of increased eosinophilia as compared with those of the pars anterior of non-pregnant animals. The chromophil cells are not only more numerous but show a greater intensity of staining, so that there is a much more distinct differentiation between the two types of cell in pregnant animals. The active state of the gland in the two animals examined is therefore associated with eosinophilia. This observation strongly supports the view that the chromophils are the active cells of the pars anterior, while the chromophobes are cells which have become emptied of secretion, the two forms being essentially/

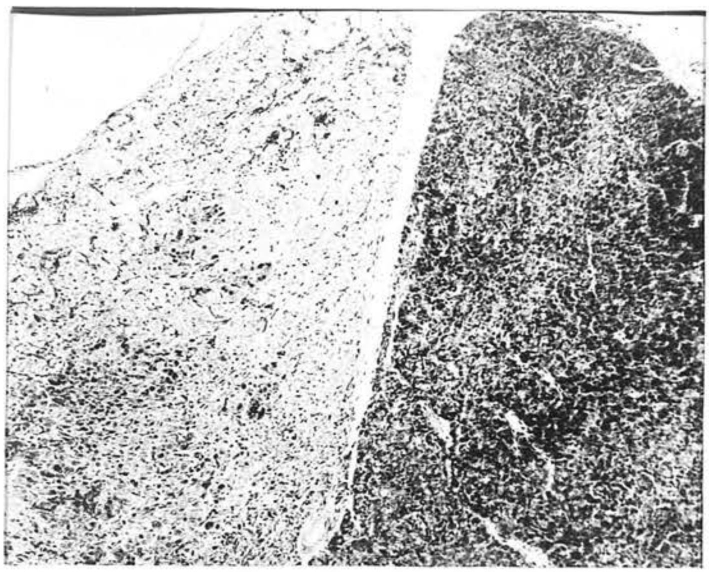


FIG. 30. THE SUBDIVISION OF THE ANTERIOR PORTION OF THE PARS ANTERIOR OF THE RABBIT INTO A ZONE OF CHROMOPHOBES — TO THE LEFT — AND A ZONE OF CHROMO--PHILS — TO THE RIGHT — BY A SEPTUM OF CONNECTIVE TISSUE.

IRON HAEMATOXYLIN + EOSIN X ~~150~~. 82.

essentially the same.

The only appearance supporting the opposite opinion is the localisation of groups of the two main types of cell to special regions of the anterior lobe. The condition in the rabbit is especially striking, in which the area in front of the vertical connective tissue septum is occupied by chromophobes, almost to the complete exclusion of chromophils (Fig. 30). This arrangement can perhaps be explained by supposing that the vascular mechanism in the anterior part of the gland facilitates the more rapid escape of secretion from the cells,; this part of the gland is certainly very vascular in the pregnant animal (Fig 31)

Speaking generally, the state of the pars anterior in pregnancy in the animals observed - that of eosinophilia and increased vascularity - corresponds to the condition of the thyroid in pregnancy in presenting an appearance of a general increase in the activity of the secretory processes.

THE POSTERIOR LOBE.

In considering the process of secretion in the pars intermedia and the pars nervosa, it is necessary to examine these two parts together. The relationship which they present is extremely intimate, not only anatomically/

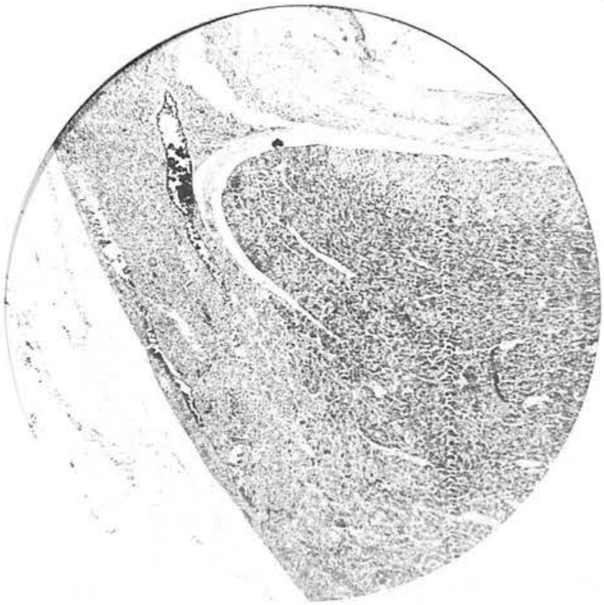


Fig. 31. To show the extensive vascularity of the chromophobe zone — to the left of the connective tissue septum.

Iron haematoxylin + Congo red X 42.

anatomically but physiologically. Since the discovery in 1895, by Oliver & Schäfer, of the action of extract of pituitary on blood pressure, and by Howell, in 1898, of the limitation of this action to the posterior lobe, much progress has been made in the knowledge of the functions of this part of the gland. There seems to be no question but that the hyaline and granular bodies described by Herring represent the secretion of the posterior lobe. This view receives strong support from the fact that these bodies are generally much more abundant in pregnant than in non-pregnant animals. It is generally believed also that they are derived from the epithelial cells of the pars intermedia; the absence of true secreting cells in the structure of the pars nervosa seems to render some such hypothesis necessary. The structure of this part of the gland presents a marked contrast to the known physiological activity of its secretion.

There is still considerable doubt as to the exact origin of the hyaline and granular bodies. Herring pointed out the resemblance which they present to cells which have undergone hyaline degeneration. He described also the frequent occurrence of these bodies in the neighbourhood of the wedges and groups of pars intermedia cells which invade the pars nervosa. He concluded that, although the secretion from the pars intermedia/

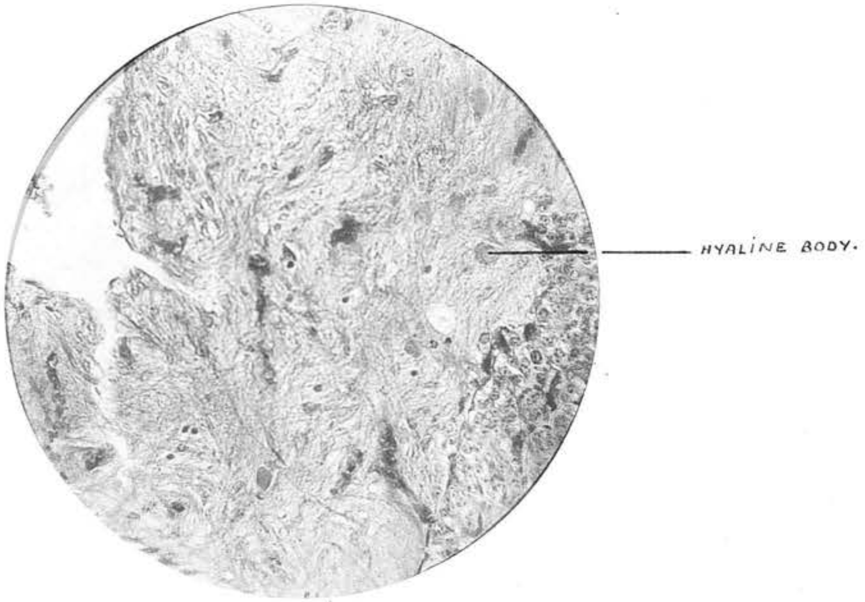


FIG. 32. HYALINE BODIES IN THE NEIGHBOURHOOD OF THE INFUNDIBULAR RECESS IN THE GUINEA-PIG.
THEY ARE ROUNDED FAINTLY-STAINING BODIES IN THIS SPECIMEN.

IRON-HAEMATOXYLIN + EOSIN. X 200.

intermedia is sometimes passed from the cells into the lymphatics of the pars nervosa, it is frequently derived from the breaking down and destruction of the whole cell. He considers that this is the probable fate of the incursions of pars intermedia cells in the pars nervosa. Blair Bell regards these hyaline bodies as being entirely derived from degenerated pars intermedia cells which have wandered into the pars nervosa. He says the very fact that some so-called "hyaline" bodies are without nuclei and others contain them indicates the true nature of these bodies. They are cells undergoing degeneration, which may in the process disperse their contents. He states also that it is a fact of some importance that one rarely sees many of these bodies in normal circumstances, but with this observation I do not agree, since they can be demonstrated abundantly in pregnant animals. This author also describes a marked degree of invasion of the pars nervosa by the cells of the pars intermedia after excision of the suprarenals. Herring described the presence of many nucleated bodies - as well as an increase in the amount of hyaline and granular material - after thyroidectomy. Mott has described similar appearances in cases of subthyroidic insanity.

With this idea of a degenerative process as the source of a physiological secretion it is difficult to agree/

FIG.33. HYALINE BODIES IMMEDIATELY BEHIND THE PARS INTERMEDIA OF THE GUINEA-PIG LYING IN WHAT APPEAR TO BE LYMPH SPACES.

SAFRANIN X 330.

agree. The conditions after excision of the thyroid and the suprarenals are abnormal and cannot be regarded as affording a true picture of the normal mode of secretion. They are probably the result of an exaggerated activity on the part of the posterior lobe of the pituitary in response to unusual stimuli and possibly in the endeavour to compensate in some way for the loss of the endocrine which has been removed. Rogowitsch and many subsequent observers have described the enlargement which the pituitary undergoes after thyroidectomy.

The appearances seen in pregnant animals are of value in the endeavour to trace the normal manner of production of the secretion of the posterior lobe; they represent the conditions which exist in physiological hyperactivity of this part of the gland. It may be mentioned, in the first place, that hyaline bodies possessing nuclei have not been encountered in either of the two animals examined. No example of nucleated hyaline bodies was detected either in pregnant or in non-pregnant animals. It is an important fact in the consideration of this question that in the rabbit the pars intermedia is separated from the pars nervosa by a well-developed layer of connective tissue. It is true that a certain number of the pars intermedia cells are present on the posterior aspect of this septum/

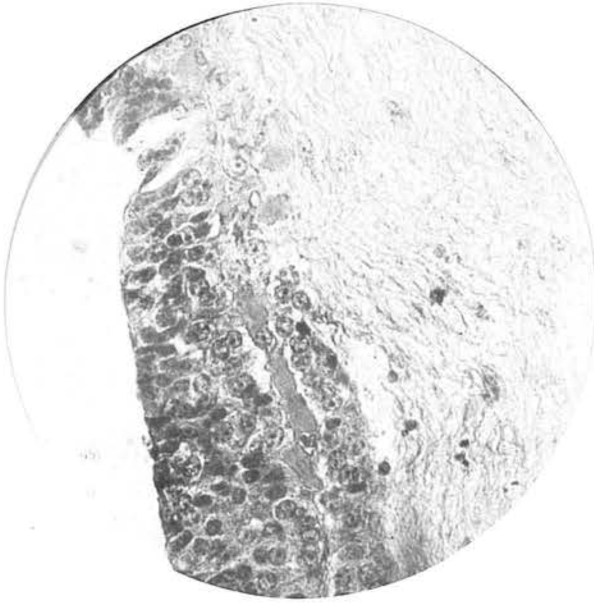


Fig.34. Hyaline bodies in the pars intermedia of the guinea-pig. The bodies are seen between the cells and are passing into the pars nervosa.

Iron haematoxylin + eosin X390.

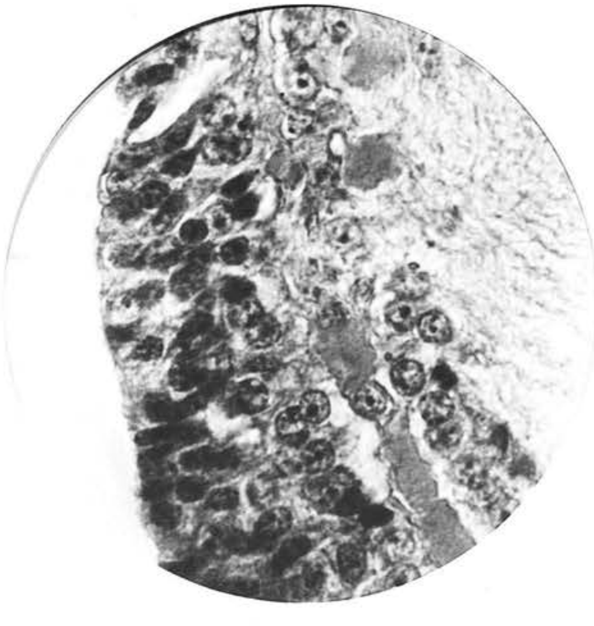


Fig.35. A higher power view of the same. The secretion bodies show no evidences of nuclei.

X710.

septum, but these are few in number, and it would appear that such a well-marked layer of connective tissue must act as a barrier, to a considerable extent, to the migration of the cells from the pars intermedia to the pars nervosa.

The hyaline bodies are readily seen in pregnant animals after staining deeply with acid fuchsin,congo red, or safranin, provided there has been no delay in the fixation of the specimen (Fig.32). They are found scattered throughout the whole of the pars nervosa, but are always most abundant in two definite regions - immediately behind the thick part of the pars intermedia which bounds the cleft posteriorly and in the neighbourhood of the neck of the gland, where the pars nervosa becomes continuous with the stalk. In some positions they lie in what look like lymph spaces lined by endothelium (Fig.33). In the guinea-pig the hyaline bodies are readily found in the substance of the pars intermedia. They lie between the cells and can be traced in the various stages of their progress from the substance of the pars intermedia into the pars nervosa (Fig.34). They are most abundant in the guinea-pig in that part of the pars intermedia which lies behind the upper part of the cleft, but they occur in all parts of the pars intermedia, and even, as has been already mentioned, in the "pars tuberalis"/

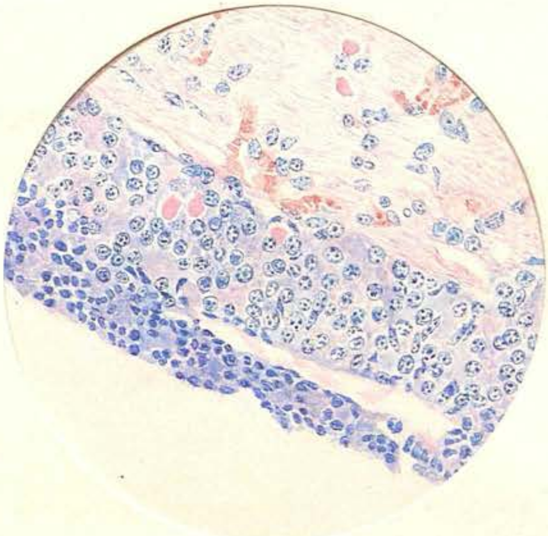


FIG.36. A DRAWING OF THE PARS INTERMEDIA BEYOND THE LOWER END OF THE CLEFT. HYALINE BODIES LIE BETWEEN THE CELLS; THEY ARE ALSO SEEN IN THE PARS NERVOSA.

ACID TOLUIDIN BLUE X330.

tuberalis." Fig. 36 shows a portion of the pars intermedia beyond the lower end of the cleft, and Fig. 37 is a camera lucida drawing of the epithelial investment of the posterior aspect of the pars nervosa, with hyaline bodies between the cells in both situations. They are also met with in relation to the thickening of the pars intermedia around the neck of the gland (Fig. 38).

Hyaline bodies are occasionally seen in the immediate neighbourhood of the wedges and islets of pars intermedia cells which occur in the pars nervosa, but they are relatively infrequent and scanty in amount in such situations, and their comparatively rare occurrence does not suggest that these inclusions form an important source of the secretion. It is certainly the case that isolated cells appear occasionally to undergo degeneration, so that the protoplasm disintegrates and the nuclei stain more faintly and ultimately disappear. The usual result of this process, however, is that the cell leaves no trace behind, or at least nothing resembling the appearance of the hyaline bodies.

Cushing believes that the hyaline bodies are largely derived from the colloid vesicles of the pars intermedia. He says "the pars intermedia cells are capable of forming acini which discharge a semi-fluid, soluble product into the spaces of the pars nervosa, many/

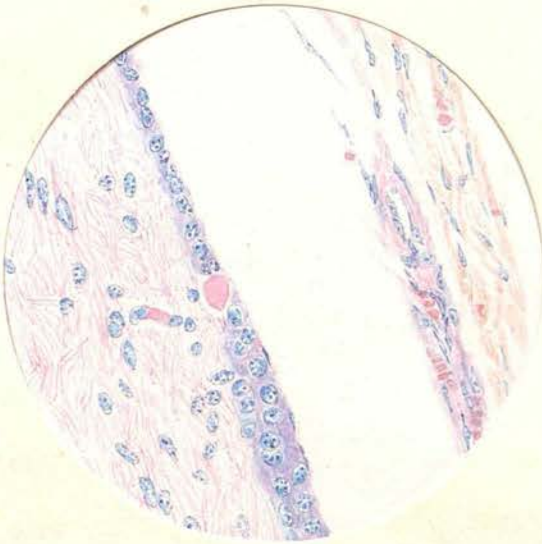


Fig. 37. A portion of the pars intermedia lining the posterior aspect of the pars nervosa.
The dura mater is on the right. There is a hyaline body between the cells.

Acid toluidin blue X 330.

many pars intermedia cells actually wandering into the tissue spaces". This view is not supported by the appearances in the two animals examined. In the guinea-pig, vesicles do not occur in the pars intermedia and therefore, in this animal at least, they cannot be the source of the hyaline bodies. As described above, these bodies occur frequently between the cells. In the rabbit, although colloid vesicles are abundant in the pars intermedia in the later stages of pregnancy, secretion globules are not seen in the neighbourhood of these vesicles, and the vesicles are usually situated well away from the edge of the pars intermedia in contact with the pars nervosa, so that they are not in a favourable position for passing on their contents into the pars nervosa (Fig.42). In the dog, on which animal most of Cushing's work has been done, the vesicles are often in direct contact with the pars nervosa, so that the possibility that the contents might pass directly into the pars nervosa is suggested by this relationship. From the appearances in the rabbit, it seems probable that the colloid vesicles represent an apparatus for the storage of secretion, and that the hyaline bodies are derived under normal conditions, from the epithelial cells which make up the bulk of this part of the gland.

In both the rabbit and the guinea-pig, as the result/

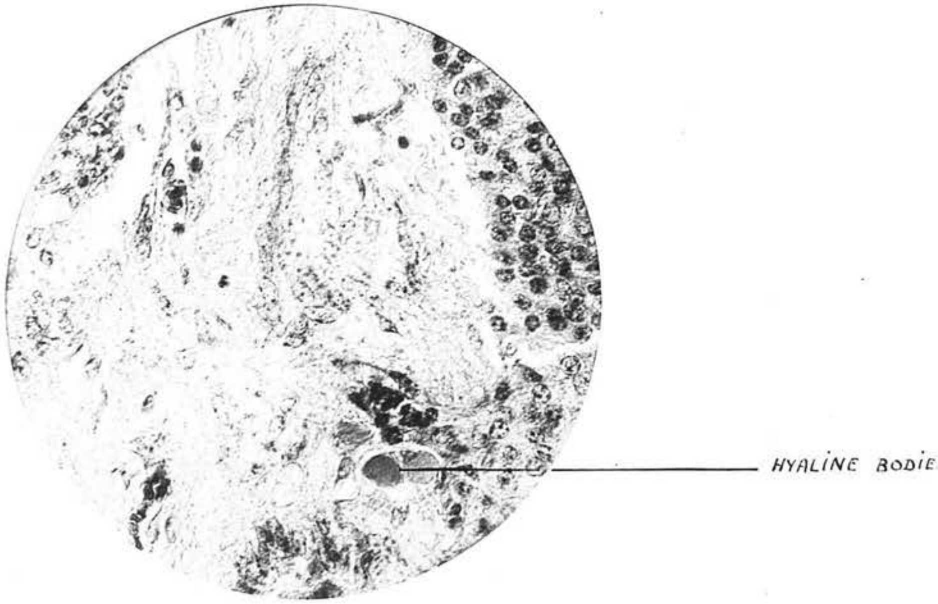


FIG. 38. HYALINE BODIES IN RELATION TO THE THICKENING OF THE PARS INTERMEDIA ON THE POSTERIOR ASPECT OF THE NECK

IRON HAEMATOXYLIN + EOSIN X 380.

result of the investigation of the posterior lobe in pregnant animals, there is little doubt that the hyaline secretion bodies, which are abundant in the pars nervosa, are derived, under normal circumstances, from a process of active secretion on the part of the pars intermedia cells. The material then passes on into the lymph spaces of the pars nervosa.

The Destination of the Secretion of the Posterior Lobe.

Herring, in 1908, brought forward the view that the hyaline bodies of the pars nervosa pass upwards in the infundibulum to the third ventricle and so into the cerebro-spinal fluid. If this view is correct the posterior lobe may be regarded as possessing an external secretion. Cushing & Goetsch investigated the question later and on the main points they agree with Herring. They found in the cerebro-spinal fluid an active substance resembling pituitrin in its physiological actions in producing similar effects on blood pressure, kidney volume, and urinary secretion. From this they concluded that it is proved beyond doubt that the active principle of the posterior lobe is passed directly into the third ventricle.

Although this view as to the fate of the secretion has been accepted by many authorities, it has recently been subjected to severe criticism. Carlson & Martin object to the observations of Cushing and Goetsch/

Goetsch regarding the passage of pituitrin directly into the cerebro-spinal fluid. These authors say: "It is obvious that the conclusions drawn by Cushing & Goetsch from their experiments are open to a number of grave objections. The cerebro-spinal fluid used in most of the experiments was pathological, and was concentrated 20-25 times, and the intravenous injections were made into another species. Finally, no control experiments were reported on blood or serum from the same individual yielding the cerebro-spinal fluid." Carlson & Martin found that the haemodynamic action of the cerebro-spinal fluid was solely due to the quantity injected, as is the case with defibrinated blood or Ringer's solution; there is, in fact, no evidence of a specific pressor or depressor effect.

These observers are careful to state, however, that their negative results do not prove that the cerebro-spinal fluid is free from pituitary secretion; but they say that we have as yet no satisfactory test for this secretion in the fluids of the body. When such tests have been worked out, Carlson & Martin think that the distribution of pituitary secretion in body-fluids will prove to be similar to that of all the other internal secretions so far studied, the concentration being greatest in the blood and least in the cerebro-spinal fluid.

Miller/

Miller, Lewis, & Matthews found that it was impossible to obtain pressor effects from an extract of the stalk, and they conclude that "there is, therefore, a distinct interruption in the path of secretion of the pressor substance from the pars nervosa to the ventricle". This is opposed to Herring's view concerning the passage of secretion from the pars nervosa to the third ventricle. Atwell also disagrees with Herring and feels that to accept the view that the secretion of the pars nervosa enters the cerebro-spinal fluid to gain the blood-stream is to believe an incredibly round-about process to which there is no parallel in the animal economy".

Blair Bell believes that the secretion of the posterior lobe is taken up by the blood-stream and that there is no evidence to show that it passes directly into the cerebro-spinal fluid. In support of this view he calls attention to the morphological facts that there is a net-work of blood-vessels beneath the pars intermedia, and that in some animals, such as the ox, the pars nervosa has a very rich internal blood-supply. He believes that the secretion of the posterior lobe is absorbed by way of these vessels.

Herring, in his most recent work, has failed to detect the presence of pituitrin in cerebro-spinal fluid removed from the fourth ventricle of the cat. He examined 3 series of 6 animals, comprising 3 males and/

and 3 females in each group. The animals were healthy adults of as near a weight and age as possible. One set of 6 animals was fed with large quantities of fresh ox thyroid for from two to three weeks in addition to their ordinary diet. In the second set thyro-para-thyroidectomy was performed on each animal. The cats of the third group were utilised as normal controls. The cerebro-spinal fluid was collected from the fourth ventricle of each cat under anaesthesia. It was then evaporated and dried at 37 C. The dried cerebro-spinal fluid was tested physiologically, by Dale's method upon the uterus of the virgin rat, by Elliott's method upon the blood pressure of a pithed cat, which Herring finds to be a good method for revealing small differences in the strengths of weak solutions of pituitrin, and by their action upon the blood-pressure, kidney volume, and secretion of an anaesthetised cat.

The extracts from the cerebro-spinal fluid of the 3 groups were practically inactive. A slight increase in the uterine contractions was observed after immersion of the uterus in the cerebro-spinal fluid of the thyro-parathyroidectomised cats, but was not a constant phenomenon. None of the extracts showed any effect upon blood-pressure, kidney volume, and urinary secretion other than that which is produced by a similar amount of Ringer's solution alone. Herring concludes that/

that there is no appreciable amount of pituitrin in the cerebro-spinal fluid taken from the fourth ventricle, whether from normal, thyroid-fed, or thyro-parathyroidectomised cats. He points out, however, that this does not exclude the possibility that pituitrin is occasionally liberated into the cerebro-spinal fluid in the third ventricle. If such takes place, he points out, one would expect rapid absorption to occur, and the probablity is against the material reaching the fourth ventricle.

In support of Herring's original hypothesis - that the secretion of the posterior lobe passes directly into the cerebro-spinal fluid of the third ventricle - attention may be directed first to the fact that any mechanical interference with the stalk of the pituitary is followed by symptoms of hypopituitarism. Cushing has shown that infundibular tumours are always associated with signs of glandular insufficiency, though the value of this observation is perhaps diminished by the fact that tumours in the region of the stalk are liable to cause compression of the gland itself and so to interfere with its function. Marienesco & Goldstein were the first to draw attention to the fact that hydrocephalus may be associated with evidences of hypopituitarism, and this observation has been confirmed by Cushing, Babonneux & Poisseau, and other workers. The/

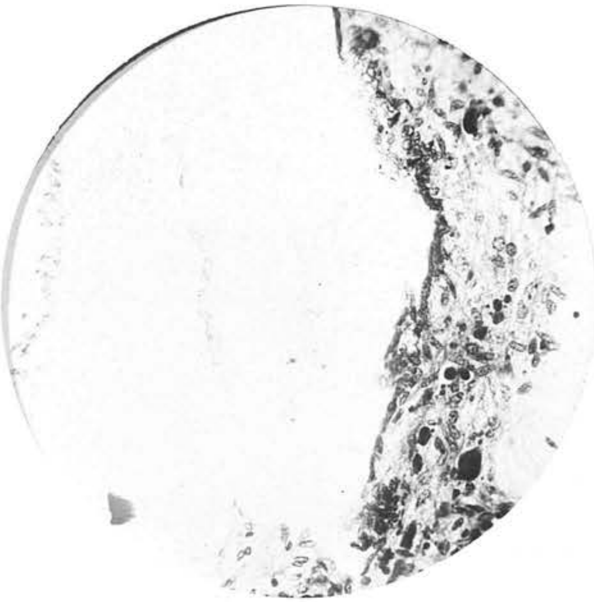


Fig. 38a. Hyaline bodies alongside the infundibular recess of the third ventricle in the guinea-pig. They are stained darkly with safranin.

x 210.

The stasis of the cerebro-spinal fluid and the increase in the intra-ventricular tension are believed to interfere with the free escape of posterior lobe secretion.

Blair Bell has obtained very definite results after compression or severence of the stalk. After this operation in the dog there has occurred a remarkable increase in weight from deposit of subcutaneous fat, one animal increasing in weight from 3000 to 5050 grammes in 51 days. Atrophy of the genital organs may also occur after this procedure, but this result is not invariable. It is generally believed that the autacoid which is concerned in carbohydrate metabolism is derived from the posterior lobe, and the experiments mentioned appear to afford striking evidence in favour of the belief that the secretion from this part of the gland passes upwards by way of the stalk to the third ventricle. Blair Bell, however, explains the result of interference with the stalk as due to damage to the blood-vessels supplying the pituitary. He appears to have over-looked the fact that the artery supplying the posterior lobe enters on the postero-superior aspect and - in the guinea-pig and the rabbit at least - this vessel enters below the level of the diaphragma sellae and would not necessarily be injured in operations on the stalk.

Cow has contributed an important observation in this/

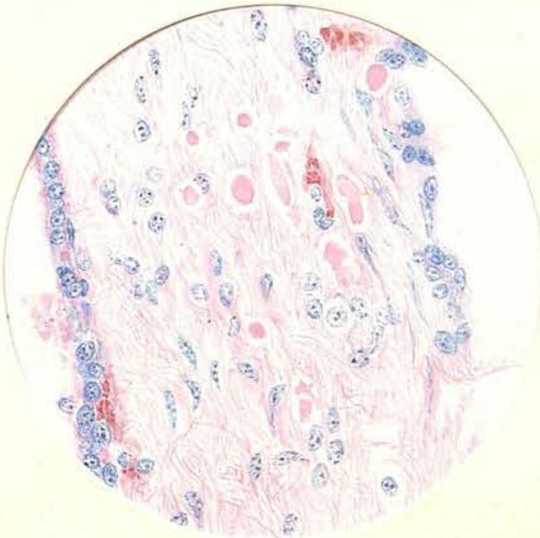


FIG. 39. ACCUMULATION OF HYALINE BODIES ALONGSIDE THE INFUNDIBULAR RECESS—ON THE RIGHT— IN THE PREGNANT GUINEA-PIG. IN THE UPPER PART OF THE FIGURE A HYALINE BODY IS IN THE PROCESS OF ENTERING THE VENTRICLE.

ACID TOLUIDIN BLUE. X 330.

this connection. He has been able to discover, after intravenous injections of extracts of the duodenal mucous membrane, definite evidences of pituitrin in cerebro-spinal fluid removed from the fourth ventricle. He found that apart from such stimulation of the pituitary the amount of pituitrin in the cerebro-spinal fluid was very minute.

The appearances seen in the pregnant animals examined have furnished evidence which is strongly in favour of Herring's view with regard to the fate of the posterior lobe secretion. It has been mentioned that in both rabbit and guinea-pig the hyaline bodies are generally most abundant in the region of the neck, where the infundibulum joins the pars nervosa. The neuroglia fibres of the pars nervosa are arranged so that their general trend is towards the neck and it is difficult, from this grouping of the hyaline bodies, to avoid the conclusion that they have ascended in the lymph spaces between the fibres to this region. In the guinea-pig these bodies are seen in greatest number in the immediate neighbourhood of the infundibular recess of the ventricle (Fig. 38a), and it is possible in some cases to see a hyaline body actually in the process of passing through the ependyma lining the ventricular cavity. (Fig. 39)

The appearances in the rabbit seem to be conclusive. The hyaline bodies can be traced upwards throughout/

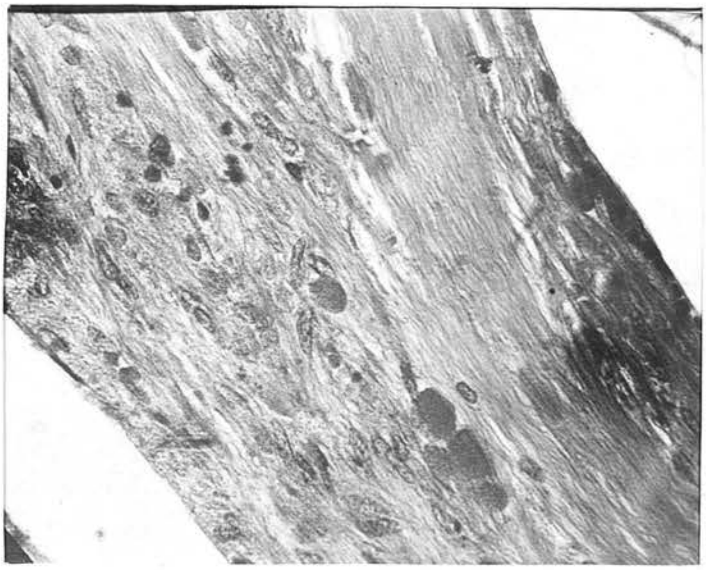


FIG. 39A. A HIGH POWER VIEW OF THE STALK IN THE RABBIT SHOWING ABUNDANT HYALINE BODIES. THERE IS NO INVESTING EPITHELIUM SO THAT THESE BODIES MUST HAVE COME FROM BELOW.

IRON HAEMATOXYLIN + CONGO RED X 710.

throughout the whole length of the stalk (Fig. 39a). In this animal the stalk possesses no epithelial investment, so that the hyaline bodies in this region can only have come from below - from the pars nervosa. The secretion bodies are much more numerous in the stalk than in the pars nervosa generally, which shows that the local accumulation in this region must be due to migration from elsewhere. The stalk in this animal is of considerable length, and from the abundance of these bodies throughout the whole extent there can be little doubt that this arrangement represents no accidental diffusion of the hyaline bodies, but an orderly progression from the pars nervosa to the third ventricle above. The most vascular part of the pars nervosa in both the rabbit and the guinea-pig lies some little distance below the level of the neck and, if the hyaline bodies are mainly absorbed into the blood-stream - as Blair Bell & Atwell believe - we should expect very few of these bodies to pass beyond this vascular area.

From a consideration of these various facts, and especially the marked accumulation of hyaline bodies around the infundibular recess of the ventricle in the guinea-pig and from the aggregation of the bodies throughout the whole length of the stalk in the rabbit, it seems impossible to avoid the conclusion that, in the/

the functionally active state of the gland in pregnancy, they are progressing towards and into the cerebro-spinal fluid of the third ventricle. The absence of pituitrin from the cerebro-spinal fluid of the fourth ventricle, demonstrated by Herring, may perhaps be explained by absorption from the vessels of the choroid plexus of the third, and possibly of the lateral ventricles. The circulation of cerebro-spinal fluid throughout the ventricular system, as the work of Dandy has shown, is normally a slow process, and there must be abundant opportunity for the absorption of pituitrin from the cerebro-spinal fluid during the time which it takes to diffuse from the higher ventricles to the lower.

The Physiological Relationship of Pars Intermedia and Pars Nervosa.

Extracts of the whole posterior lobe of the pituitary produce their most marked effects in the form of stimulation of plain muscle generally and of the secretion of the mammary gland and the kidney. The effect on plain muscle is most striking in the case of the vascular system, producing a great rise of blood pressure with constriction of vessels and increase in the force of the heart beats. There is a marked action also on the plain muscle of the uterus, the bladder/

bladder, the stomach, and the intestine. The effect on the mammary gland causes milk which has accumulated in the gland to be immediately poured out, and a sufficient dose will produce complete emptying of the alveoli. It has been shown by Schäfer that this action also is probably due to stimulation of plain muscle fibres which lie between the basement membrane and the secreting cells. The action on the kidney shows a striking difference from the effects produced elsewhere. The renal vessels undergo dilatation instead of constriction, as in the other parts of the body, and the secretion of urine is increased. It has been proved by Schäfer and Herring that the increase in secretion is not merely the result of the dilatation of vessels; they showed that diuresis occurred even when the arteries in the kidneys failed to dilate, and when the general vasoconstriction was absent after repeated does of extract. They concluded that there must be direct stimulation of the secretory cells of the kidney by the autacoid concerned, and compare the action on the kidney cells to that of the secretion of the duodenum on the cells on the pancreas.

Various attempts have been made to differentiate between the physiological properties of the secretion in the pars intermedia and the pars nervosa. Osborne and/

and Swale Vincent found that by careful dissection they could separate the central portion of the posterior lobe from the epithelial investment, and that whereas an extract of the former gave the typical effects of pituitrin, an extract from the epithelial portion gave much less definite results. These authors showed also that extracts of other nervous tissues do not possess the same physiological activity as an extract of the posterior lobe.

Herring has shown that both pars intermedia and pars nervosa of the ox pituitary contain an active principle which stimulates uterine muscle, but extracts of the two parts are not equally active. The pars nervosa is from two to five times more powerful than the pars intermedia in its action. Herring also found that an extract of pars intermedia in strengths of 0.5 per cent and less has no specific action on the blood pressure or renal excretion; whereas an extract of the pars nervosa in so low a strength as 0.005 per cent produces the characteristic pressor and diuretic effects. Extracts of pars nervosa alone produce the characteristic effects of posterior lobe extracts on blood pressure and kidney secretion, as well as on milk secretion and the plain muscle of the uterus. He believes that these facts are suggestive of there being two separate active/

active principles in the posterior lobe. From the differences in the action of extracts of pars intermedia and pars nervosa he concludes that the active material of the posterior lobe is a product of the epithelial cells of the pars intermedia and that the substance acting on the uterus is formed at an early stage in the cells of the pars intermedia, whereas the substance acting upon blood pressure and the kidney is a later product, the secretion from the pars intermedia undergoing some kind of alteration in character in the substance of the pars nervosa. His view is that a process of ripening or maturation of the secretion takes place as it passes through the pars nervosa and it then becomes capable of producing the effects on blood pressure and kidney secretion.

The histological appearances in the pregnant animals do not throw much light on this question . The hyaline or colloid material which is seen between the cells of the pars intermedia shows no difference in appearance or staining reactions from those of the hyaline bodies seen in the substance of the pars nervosa and in the stalk. Dale believes that it is not necessary to postulate the existence of two active substances in posterior lobe extracts; from a comparison with the action of drugs he believes that the same/

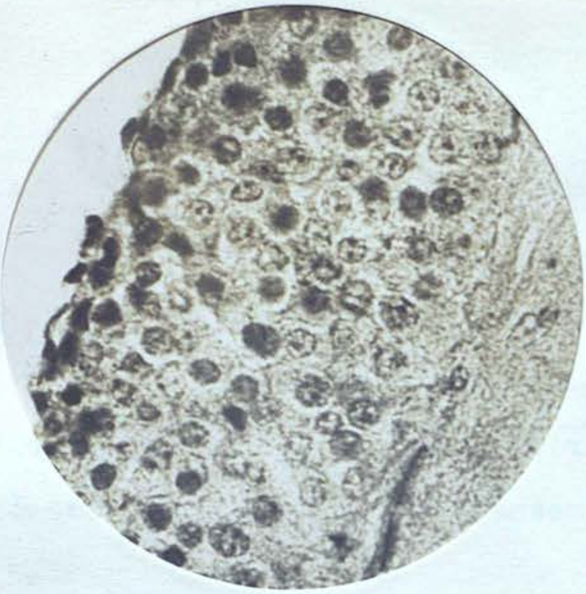
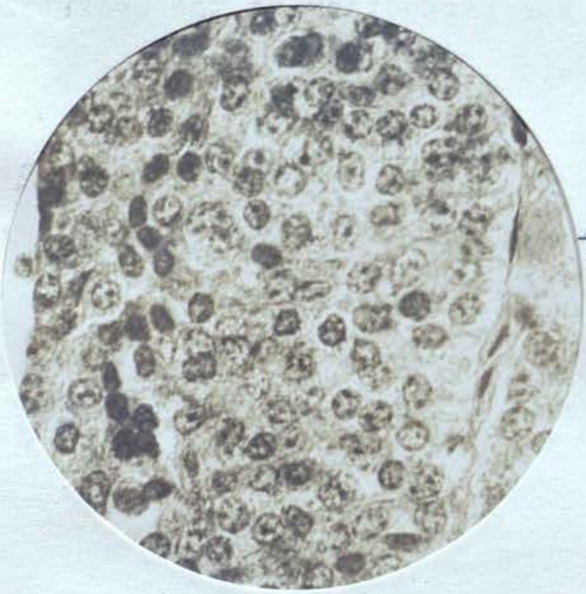


FIG. 40. THE PARS INTERMEDIA OF A NON-PREGNANT GUINEA-PIG BEHIND THE CLEFT. THE REGION IS COMPARATIVELY NARROW.

IRON HAEMATOXYLIN + EOSIN X 710.



HYALINE BODY.

FIG. 41. THE PARS INTERMEDIA OF A PREGNANT GUINEA-PIG. THE REGION IS WIDER; THE CELLS AND THE NUCLEI ARE LARGER AND STAIN MORE UNIFORMLY. THERE IS A HYALINE BODY IN THE ADJACENT PARS NERVOSA.

IRON HAEMATOXYLIN + EOSIN X 710.

same active substance may produce a double result. It may be that the active substance in the pars intermedia is merely a weak and immature stage of the posterior lobe secretion.

The contents of the vesicles of the pars intermedia do not appear to represent the active material of the posterior lobe; it seems more probable that they form a means of storage of the secretion in an inactive state. Cushing and Goetsch tested the contents of these vesicles with negative results, though Lewis, Miller, and Matthews, finding two cysts in the pars intermedia in 1200 ox pituitaries examined, ascertained that they contained a pressor substance. As already mentioned, vesicles do not occur in the pars intermedia of the guinea-pig and are therefore not essential to the production of the secretion of the posterior lobe.

Cellular Changes In The Pars Intermedia.

An interesting observation has recently been made by John Fraser in connection with the pars intermedia in children. Limiting himself to that part of the pars intermedia which forms the posterior boundary of the cleft, he distinguishes between an "active" and a "resting" stage of the gland. In the adult human pituitary this part forms a very thin layer. In the child/

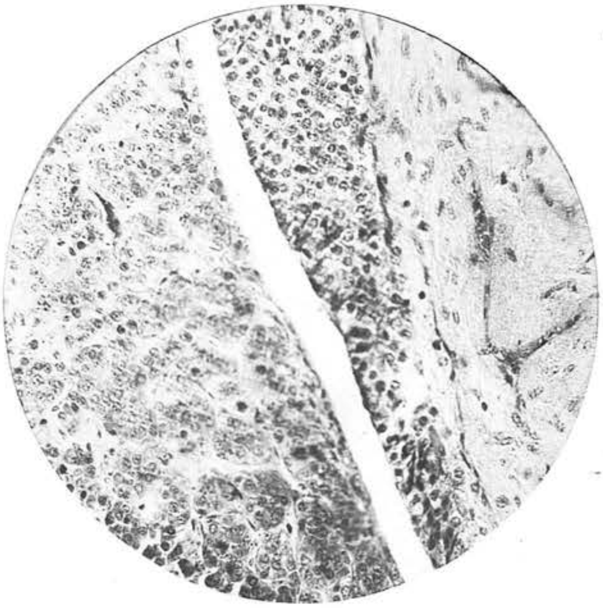


Fig. 41[a]. The pars intermedia and the cleft in a non-pregnant guinea-pig.

Iron haematoxylin + Congo red. 210.

child, Fraser describes two types of pars intermedia:-

(1) There is a single layer of cubical epithelium which lies in contact with the cleft; deeper, there is a thin layer of fibrillar tissue carrying blood-vessels, and among the fibrillar tissue there may be groups of cubical cells similar to those which lie on the surface.

(2) The space may be occupied by a zone of rounded, finely granular cells: the zone may be ten or twelve cells in depth, the numbers varying considerably in different parts. There is no trace of a distinct limiting band of cubical epithelium, such as exists in type (1).

He regards the first condition as representing the active stage and the second as the resting stage of the pars intermedia. He finds that the second condition is synchronous with a marked eosinophilia of the pars anterior, and suggests that the active condition of the pituitary in children is related to the periods of active growth of bone, especially to the epiphyseal changes which result in growth in length of the bone.

Other observations with regard to cellular activity in the pars intermedia - apart from formation of secretion - appear to be very scanty. In the pituitary after thyroidectomy, Herring finds that the cells/

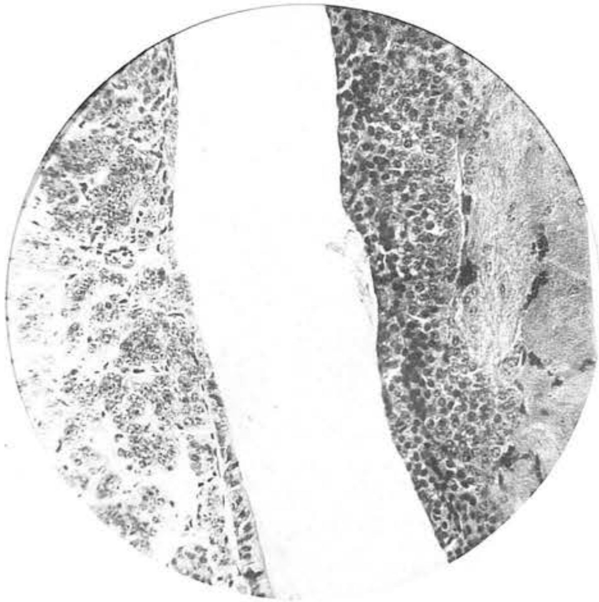


FIG. 41^B. THE PARS INTERMEDIA AND CLEFT IN A PREGNANT GUINEA-PIG.

IRON HAEMATOXYLIN + CONGO RED X210.

cells of the pars intermedia are distributed as usual, but are somewhat increased in amount and stain more deeply.

In pregnant animals there is not the striking difference in this respect from the non-pregnant as that described by Fraser between the active and resting stages of the pituitary in children, but in pregnancy certain definite signs of increased activity can made out. In both the rabbit and the guinea-pig the pars intermedia forms a well-marked layer behind the cleft in the non-pregnant as well as in the pregnant state, but, as a general rule, this portion tends to be distinctly thicker in pregnancy. The difference is most evident towards the lower end of the cleft (Fig.40+41). The cells are larger in pregnancy, they stain more readily, and are distinctly more granular. These appearances are indicative of increased activity and correspond to the condition of the rest of the gland.

Storage of Secretion in the Posterior Lobe.

The severe and sustained muscular effort of parturition and the establishment of active secretion of milk immediately afterwards must bring about a sudden and clamorous demand for an increased supply of pituitary secretion, especially for that of the posterior/

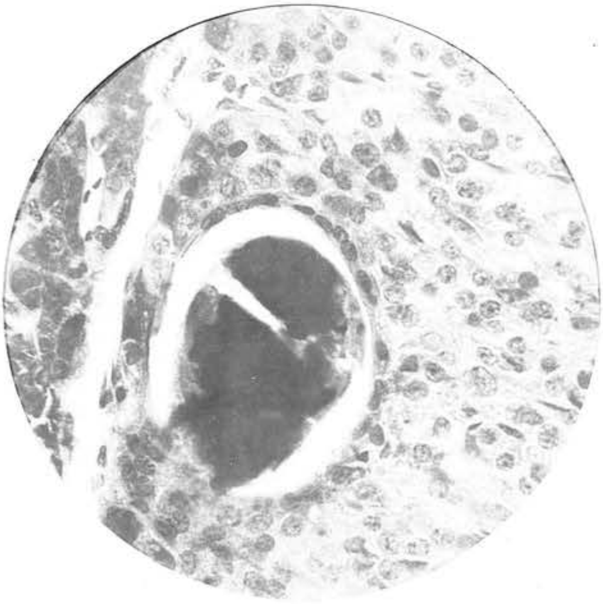


FIG. 42. VESICLE IN THE PARS INTERMEDIA OF THE PREGNANT RABBIT. IT CONTAINS COLLOIDAL MATERIAL AND IS LINED BY FLATTENED CELLS WITH DARKLY--STAINING NUCLEI.

IRON HAEMATOXYLIN & EOSIN X 390.

posterior lobe. The thyroid is provided against such a sudden demand on its activities by the power of storage of secretion which it possesses to a remarkable degree. It is natural to look for a similar storage function on the part of the pituitary.

Attention may be directed, in the first instance, to the colloid-containing vesicles which are sometimes a well-marked feature of the pars intermedia. The colloid substance is regarded by Benda, Gemelli, and others as a product of degeneration. Erdheim considers it to be rudimentary and reminiscent of a time when the organ possessed an external function. By many authors, particularly those of the French school, the colloid substance is believed to be the product of normal secretion.

The appearance of these vesicles is seen in Figs. 42 & 43 . They are lined by flattened cells with darkly-staining nuclei. These cells resemble those which line the thyroid vesicles in the resting state of the gland. In certain circumstances the resemblance of this part of the pituitary to thyroid tissue is sometimes remarkably close, and attempts have been made to show that the pituitary may function vicariously for the thyroid after removal, or in diseased conditions of, the latter. Rogowitsch stated that in rabbits and other animals which can survive the/

the operation of thyroidectomy the functions of the thyroid are maintained by increased activity on the part of the pituitary. Other observers - Gley, Pisenti & Viola, and Schöneman, have found changes in the pituitary consequent on removal or disease of the thyroid. Fry reports that in myxoedema colloid formation is very marked in the pars intermedia and the material is contained in large dilated alveoli. Kojima states that after partial thyroidectomy in the dog - about two-thirds of the gland was removed by Sir Edward Schafer, the parathyroids being left undisturbed - the pars intermedia contains many vesicles of variable size, but mostly larger than those normally found.

It therefore seems to be established that in cases of thyroid insufficiency there is an increase in the amount of colloid in this part of the gland. That this is an attempt to compensate for the absence or diminution of thyroid secretion is unlikely. Simpson & Hunter report that complete removal of the thyroid in lambs does not lead to the appearance of iodine in the pituitary. Kendall has shown that iodine is an essential element in the thyroid secretion, so that the observation of Simpson & Hunter disproves the theory that the pituitary may act vicariously for the thyroid/

thyroid . In thyroid insufficiency, as shown by Plummer, and others, there is a remarkable diminution in the basal metabolic rate, with a falling-off in the amount of energy production in the body. There must be a corresponding falling-off in the demand for pituitary secretion, and the vesicle formation in the pars intermedia is probably to be regarded as the result of accumulation and storage of secretion consequent on the diminished demand.

Vesicle formation in the pars intermedia is a striking feature in certain other circumstances. In a specimen recently exhibited by Sir Harold Stiles, the pituitary from a case of hydrocephalus associated with well-marked clinical evidences of hypopituitarism, showed a remarkable degree of vesicle formation in this situation. In hydrocephalus there seems to be little doubt that the increased tension in the ventricular system interferes with the discharge of secretion from the posterior lobe; the accumulation of colloid in the pars intermedia in this condition is probably due to the hindrance to its escape into the third ventricle. The secretion is held up in the pars intermedia and stored in the form of colloid

Mention has already been made of the fact that Cushing & Goetsch failed to obtain any physiological action/

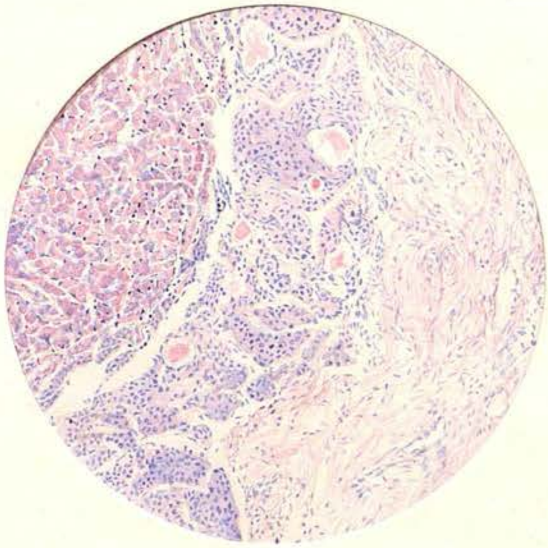


FIG. 43. THE PARS INTERMEDIA OF A RABBIT 23 DAYS PREGNANT SHOWING ABUNDANT COLLOID-CONTAINING VESICLES.

ACID TOLUIDIN BLUE X ~~330~~ 72.

action from the contents of the vesicles, though Lewis, Miller, and Matthews believed that they obtained a pressor effect.

In the pregnant animals examined, vesicle formation in the pars intermedia was found only in the rabbit; they do not occur in the pars intermedia of the guinea-pig. Vesicles are alsomet with in non-pregnant rabbits, but are relatively infrequent; in a sagittal section it is unusual to see more than a single vesicle. In pregnant animals, on the other hand, vesicles are frequently met with in great abundance. This is especially the case towards the end of pregnancy (Fig. 43). They are most abundant in the region beyond the lateral margin of the cleft, but occur also throughout the whole of the pars intermedia behind the cleft. The increase in the vesicles during pregnancy indicates that the colloid material which they contain possesses an important physiological significance; it is not the result of a degenerative process nor is it merely a developmental remnant, as has been suggested by the authors quoted above. It seems reasonable to conclude from the appearances in pregnant animals that the vesicles of the pars intermedia represent a mechanism for the storage of posterior lobe secretion - possibly in an immature form - against the/

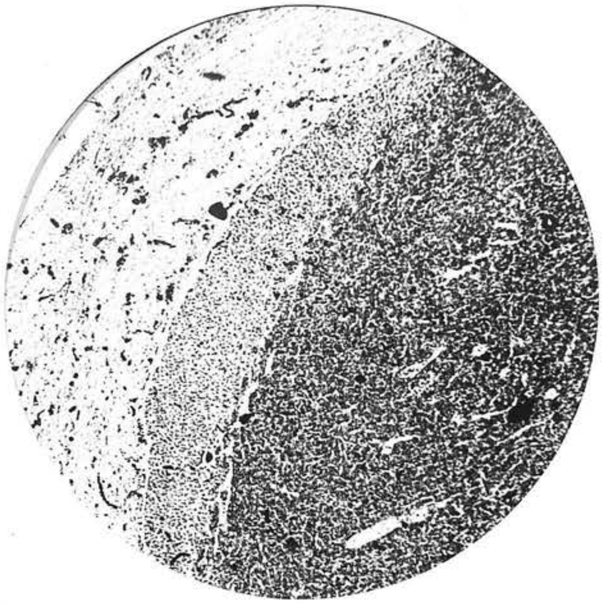


FIG. 44. THE PARS INTERMEDIA OF A NON-PREGNANT RABBIT. IT FORMS A NARROW STRIP AND CONTAINS ONLY ONE VESICLE.

IRON HAEMATOXYLIN X ~~43.~~ 79.

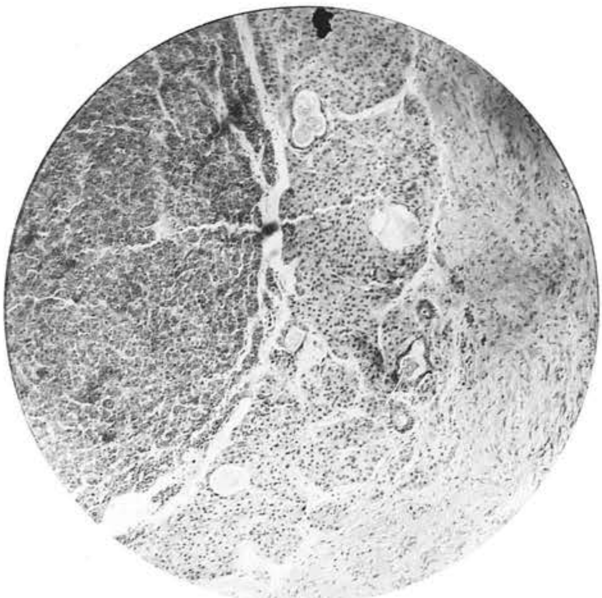


FIG. 45. THE PARS INTERMEDIA OF A RABBIT 23 DAYS PREGNANT. IT FORMS A BROAD STRIP CONTAINING ABUNDANT VESICLES. ACID TOLUIDIN BLUE X ~~43.~~ 79.

THE SPECIMENS ARE FACING IN DIFFERENT DIRECTIONS.

the sudden and severe demands in pregnancy and during the puerperium. The failure of Cushing & Goetsch to obtain any physiological action from the contents is, perhaps, to be explained by assuming that the secretion is stored in an inactive condition.

The demands on the pituitary of the rabbit - in view of the numerous offspring of this animal - must be especially great, and the rabbit appears to be provided with a second apparatus for the storage of posterior lobe secretion. Mention has already been made of the cavity which has been found in the pars nervosa of the pregnant animals. Herring expressed the view that the hyaline bodies of the posterior lobe appear to be stored, especially around the capillaries of the lobe. In the guinea-pig there is usually a well-marked accumulation of hyaline bodies in the stalk around the infundibular recess of the ventricle, and this may represent such a method of storage as is suggested by Herring. No other suggestion appears to have been made with regard to a storage of secretion in this part of the gland; so far as I am aware, the cavity in the pars nervosa of the rabbit has not been previously described.

This cavity shows a very definite lining of ependyma and almost certainly represents a portion of the original/

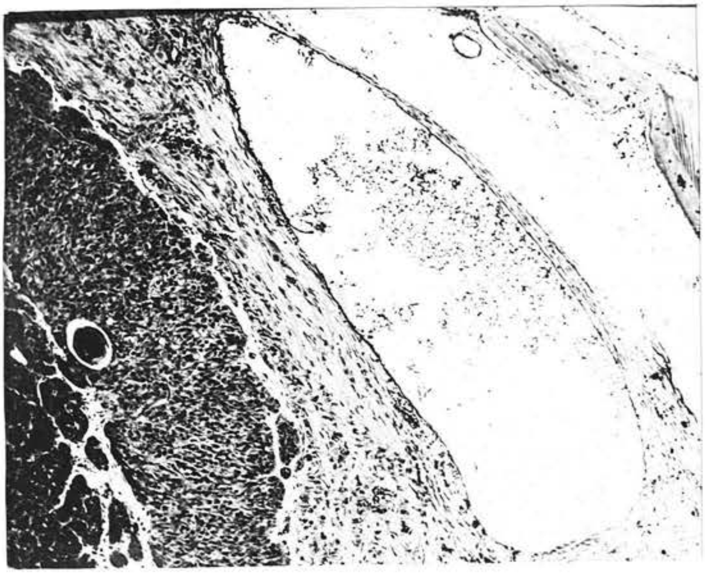


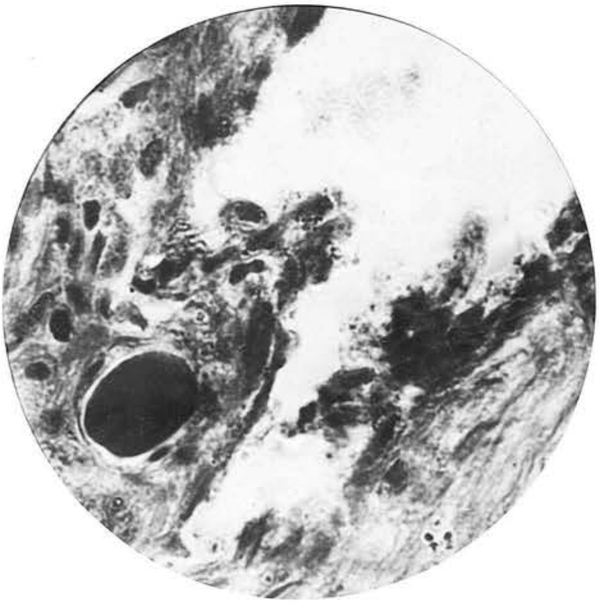
FIG. 46. THE CAVITY IN THE PARS NERVOSA OF A PREGNANT RABBIT. IT IS LINED WITH EPENDYMA AND APPEARS TO BE DISTENDED WITH SECRETION.

IRON HAEMATOXYLIN + EOSIN X ~~150~~ 82.

original lumen of that part of the cerebral vesicle from which the pars nervosa is derived. It presents interesting varieties in its appearance during the course of pregnancy. It attains to its maximum development towards the end of the gestation period (Fig. 46). At this time it is an ovoid space occupying the upper third or so of the pars nervosa. The walls appear tense and the cavity seems distended. It approaches very close to the surface of the posterior aspect of the pars nervosa. The contents at this stage of pregnancy consist, in part at least, of a coarse granular substance which stains darkly with iron-haematoxylin. It appears to contain a considerable quantity of unstained fluid material in addition.

In the earlier stages of pregnancy, there is less evidence of tension in the cavity; the walls are more flattened and are more closely approximated. Hyaline bodies are numerous in the pars nervosa around, and it is possible to trace the passage of these bodies into the cavity in the same manner as they pass into the infundibular recess of the third ventricle. Figs. 47 + 48 show hyaline bodies on the seventh day of pregnancy in the immediate neighbourhood of the cavity and in the process of passing through the lining ependyma.

The appearance of the space a week after parturition /



Figs. 47 & 48 Hyaline bodies in the process of entering the cavity in the pars nervosa in a rabbit 7 days pregnant.

Iron haematoxylin & acid fuchsin X 710.

parturition - seen in Fig. 50 - is especially suggestive. The walls of the cavity are relaxed and thrown into folds, and are in much closer apposition than at the end of pregnancy. The cavity does not approach so closely to the surface of the pars nervosa; in part at least, it is separated by a well-marked layer of neuroglia. The contents stain much less distinctly in this specimen. The appearance of the space at this time suggests a state of diminished tension as the result of the removal of a considerable proportion of the contents.

It is justifiable to conclude from these appearances that this cavity in the rabbit's pituitary represents an apparatus for the storage of the secretion of the posterior lobe, represented by the hyaline bodies. This stored secretion is utlised for the supply of posterior lobe secretion in response to the increased demands of parturition and the puerperium.

The Intraglandular Cleft.

The intraglandular cleft has been usually regarded as being mainly of developmental interest as the persistence of the original lumen of Rathke's pouch. Recent observations have shown, however, that it may be of physiological as well as of embryological importance. The mere fact that the cavity persists and/

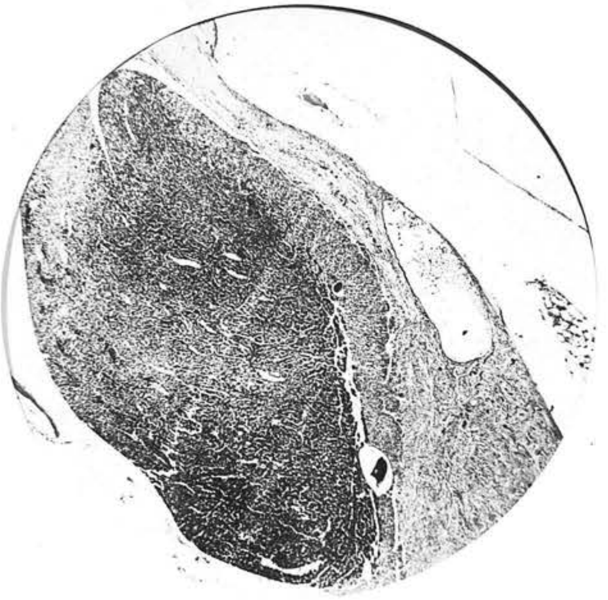


Fig.49. The cavity in the pars nervosa in a pregnant rabbit. It is distended with secretion.

Iron haematoxylin + Congo red X 23.

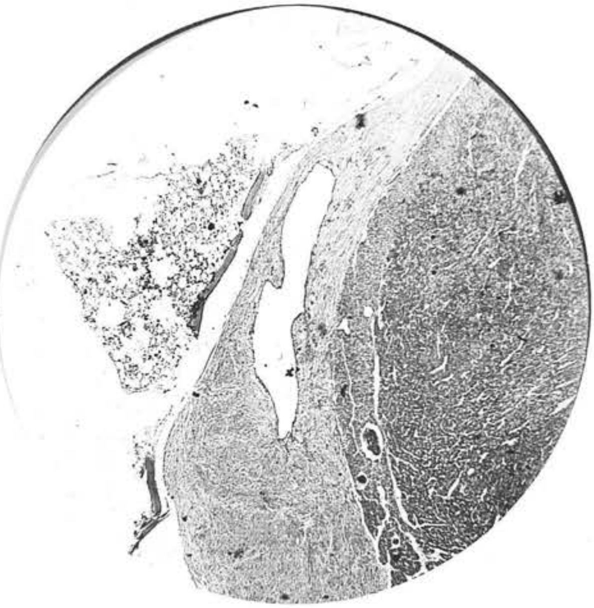


Fig.50. The cavity in the pars nervosa a week after parturition. It appears empty and the walls are relaxed and thrown into folds.

and does not undergo obliteration suggests that it may possess a functional significance. In the guinea-pig it remains as a well-marked space separating the pars intermedia from the pars anterior, except towards the lateral aspect and in the region of the neck of the gland. In the rabbit, although it undergoes partial obliteration, there are always one or more definite cavities containing colloid material in the line of the original cleft.

Herring finds that in the ox the cleft is usually empty, but occasionally contains a thin fluid of a yellowish colour; at other times a viscous or hard, transparent yellow, solid material is present, the latter being moulded into the shape of the distended cleft. He finds that the contents of the cleft produce little or no effect on blood-pressure - at most a slight fall. He agrees with Hamburger that the solid contents of the cleft, when present, are often insoluble, The soluble material was not tried upon the uterus, so that he cannot state whether it stimulates uterine muscle or not.

Blair Bell states that colloidal material is sometimes seen in the cleft in the human pituitary and most frequently in the female during and just after pregnancy and in old age in both sexes. The obser-vation/

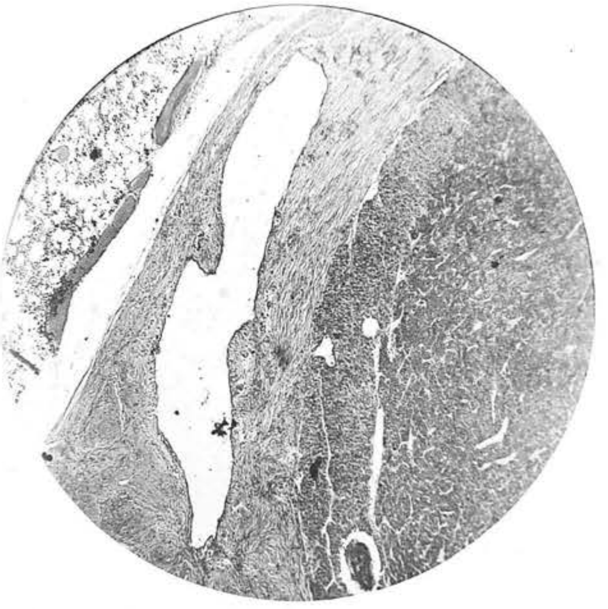


FIG. 51. A HIGHER POWER VIEW OF THE CAVITY A WEEK AFTER PARTURITION. THE WALLS ARE RELAXED. THE VESICLES IN THE PARS INTERMEDIA ALSO APPEAR EMPTY.

IRON HAEMATOXYLIN + EOSIN X 23.

observation that the material is most abundant during pregnancy suggests that it is a physiological secretion and not a developmental remnant or a product of degeneration. The second observation supports the view - apparently correct - that the activity of the pituitary is well maintained in old age.

Fraser has described very remarkable variations in the condition of the cleft in young children. He finds that in the resting stage of the pituitary it may exist as a practically empty slit, while during the active phase it may undergo a distension so great as to occupy a third,or even more, of the gland. He finds that the state, as regards distension, is closely related to the condition of the pars intermedia; when the pars intermedia is in an active state the cleft is distended with content, while a pars intermedia in the resting state is accompanied by a slit-like or empty space. He believes that the contents are mainly derived from the pars intermedia, but has also found a certain amount of eosinophilic secretion in the form of rounded globular-like bodies, which he believes to be derived from the pars anterior. He regards the cleft in children as the reservoir of the pituitary secretion. In his specimens, the pituitary was cut <u>in situ</u>, the bone having been previously decalcified/

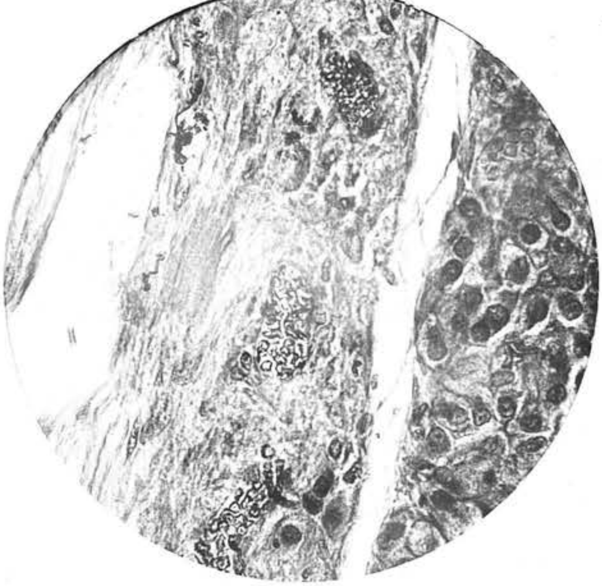


FIG. 52. A SMALL SPACE IN THE PARS NERVOSA OF A NON-PREGNANT RABBIT WHICH PROBABLY REPRESENTS THE LARGE CAVITY SEEN IN PREGNANT ANIMALS.

IRON HAEMATOXYLIN + ACID FUCHSIN X380.

decalcified, and there can be no doubt as to the remarkable distension of the cleft in some cases. The patients died from a great variety of causes, none of which had any direct bearing on the condition of the cleft, so that he does not regard the state of this cavity as being dependent on pathological conditions.

In the animals examined the cleft never attains to the degree of distension described by Fraser, but they afforded definite evidence in support of his view that the cleft is a means of providing, to a certain extent, for the storage of secretion. In the guinea-pig, it is usually almost or quite empty in the non-pregnant animal, but in pregnancy it is common to find a little colloid secretion in the space. It is difficult in this animal to express a definite opinion as to the state of the distension of the cleft, since the boundary at the lower end is very thin and apt to give way a little in the handling of the specimen. Fig. 53 shows the pituitary of a non-pregnant animal, and Fig. 54 that of a pregnant; in the second case the cleft appears distinctly distended. The cells which limit the cleft in front are often cuboidal in appearance in pregnancy, but this condition of the cells is soometimes seen in non-pregnant animals also. The area covered by ciliated columnar epithelium, described/

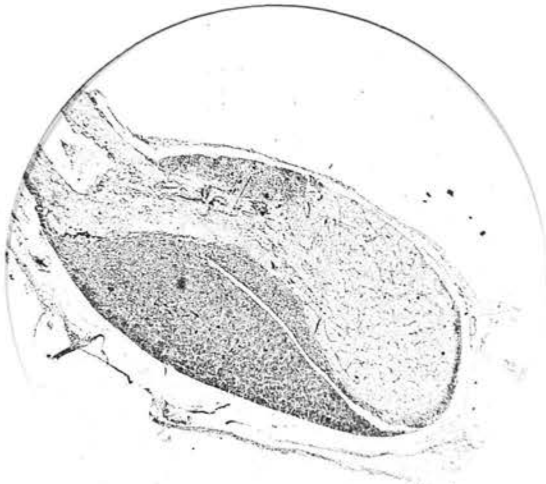


FIG. 53. THE PITUITARY OF A NON-PREGNANT GUINEA-
-PIG. THE CLEFT IS A NARROW SLIT-LIKE SPACE.

IRON HAEMATOXYLIN + CONGO RED. X23.

described previously lining about the lower third of the cleft in front, appears to be more extensive in pregnant than in non-pregnant guinea-pigs.

In the rabbit, colloidal material is present in the cavities which represent the cleft in non-pregnant as well as in pregnant animals, but it is common to observe a more distended appearance of the cavities in the pregnant state, (Fig. 57). The lining of these spaces consists of ciliated columnar epithelium in both the pregnant and the non-pregnant condition.

The Significance of the Signs of Activity in Pregnancy.

It has been shown that in pregnant animals the pituitary shows signs of increased activity in all parts - in the posterior lobe as well as in the anterior. In the anterior lobe the evidences are well-marked and consist of a condition of increased vascularity and of eosinophilia as regards the staining reaction of the cells. This condition agrees with the appearances in acromegaly, which disease is believed to be due to an excess in the secretion from this part of the gland. It is generally accepted that the anterior lobe is intimately concerned in the development of the skeletal, sexual, and other structures /

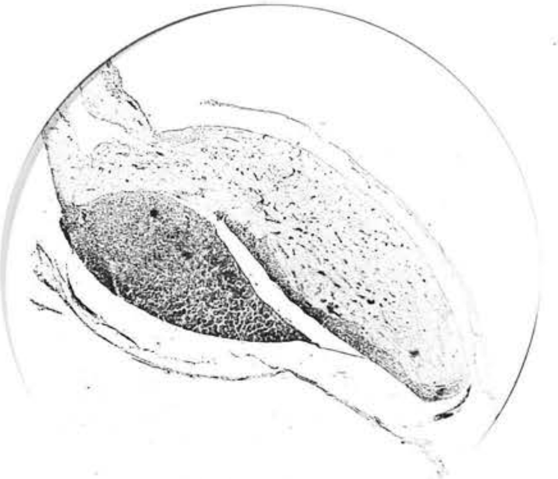


FIG. 54. THE PITUITARY OF A PREGNANT GUINEA-PIG. THE CLEFT CONTAINS A LITTLE SECRETION AND APPEARS DISTENDED.

IRON HAEMATOXYLIN + EOSIN. × 23.

structures in the growing animal and also with the maintenance of these in a normal state of activity in the adult subject. These beliefs are the result, to a large extent, of the observation of the effects of artificial hypopituitarism, demonstrated by Cushing, Biedl, and other workers. They have shown that after partial removal of the anterior lobe in young animals, these animals fail to grow properly; the epiphyses do not ankylose, the sexual organs fail to develop, and the milk teeth and lanngo are retained.

Feeding experiments also provide strong evidence in support of this view of the functions of the anterior lobe. Among the most conclusive of these are the experiments reported recently by Uhlenhuth of the Rockefeller Institute. He has shown that when anterior lobe is fed to metamorphosed salamanders of the type Amblystoma tigrinum, there is a well-marked increase in the rate of growth and the size, the animals becoming larger than those fed on other substances. If the animals are given anterior lobe, they grow at a higher rate than those which are given earthworms. Moreover, they attain a size far in excess of that reached by worm-fed or liver-fed animals and surpass the largest known normal animal of the species. The largest hypophysis-fed animal was 19% heavier than the largest/

FIG. 55. THE CLEFT IN A NON-PREGNANT GUINEA-PIG. THE CELLS FORMING THE ANTERIOR BOUNDARY ARE FLATTENED.

IRON HAEMATOXYLIN + CONGO RED. X 710.

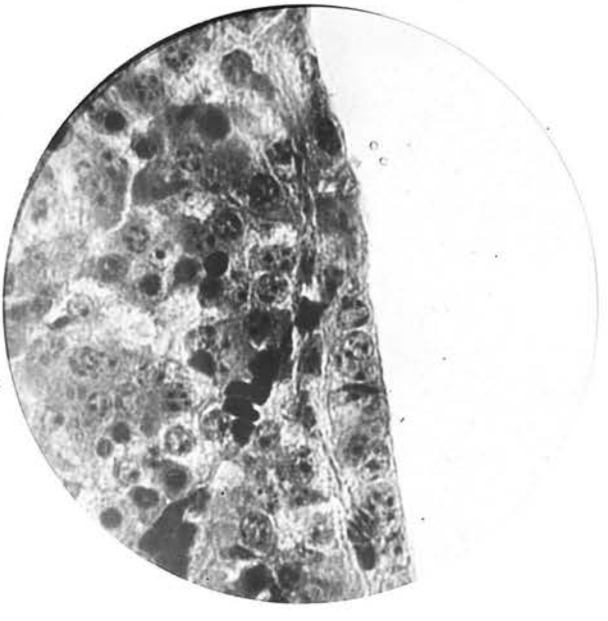


FIG. 56. THE ANTERIOR BOUNDARY OF THE CLEFT IN A PREGNANT ANIMAL. THE CELLS ARE CUBOIDAL.

IRON HAEMATOXYLIN X 710.

largest liver-fed animal, 25% than the largest known normal animal, and 37% than the largest worm-fed animal. Liver-feeding causes a rate of growth higher than that resulting from an earth-worm diet and equal to that produced by anterior-lobe feeding. But the liver-fed animals stop growing at a size at which anterior-lobe fed animals of the same age continue to grow vigorously. Liver-fed animals may grow larger than worm-fed animals and may exceed the size of the largest known animal of the species by as much as 47%, but they do not reach the size of the hypophysis-fed animals.

Brailsford Robertson has recently succeeded in isolating from the anterior lobe a substance which he has called <u>tethelin</u>, which accelerates growth in young animals and is thought to have a possible value in hastening the healing process in wounds. The effects on growth of mice are in every particular like those of the adminstration of anterior lobe, and consist in retardation of the first portion of the third growth cycle - that occurring about six weeks after birth - followed by acceleration of the latter portion of this cycle.

The relationship of the anterior lobe to the activities of the reproductive system was strikingly illustrated by the experiments of Clerk. He fed pituitary/

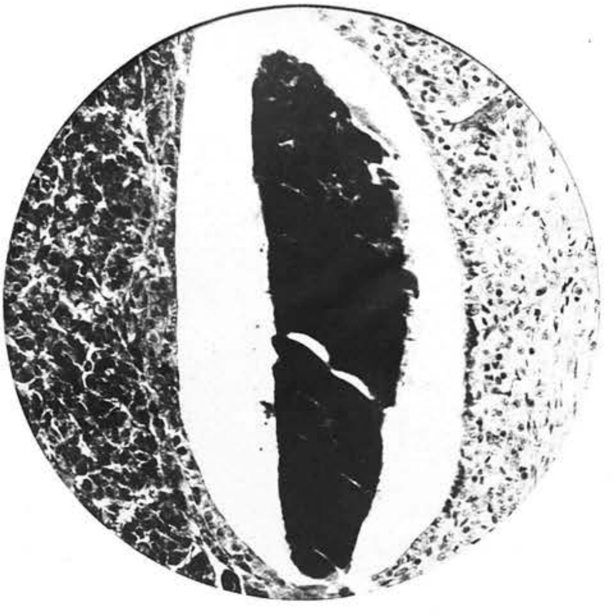


FIG. 57. THE CLEFT IN A PREGNANT RABBIT.
IT APPEARS DISTENDED WITH SECRETION.

IRON HAEMATOXYLIN + EOSIN. X 150.

pituitary ~~xxxxxxxxx~~ gland to laying hens. By giving to one-year-old hens, in addition to their usual food, 20 milligrams of fresh pituitary substance for four days, it was found that the average daily number of eggs laid by a batch of 655 hens was raised from 273 during the four days preceding the pituitary feeding to 352 during the four days of the adminstration, these results being obtained at a time of year when the natural egg-production of the hen was diminishing. It was found also, that the fertility of the eggs was greatly enhanced.

The enlargement and increased activity of the anterior lobe in pregnancy is probably in part the result of the increased activity of the reproductive apparatus. It is reasonable to suppose that it is due in part also to the presence of the growing foetuses and to the supply to these from the maternal blood of the autacoid responsible for the proper development of bone and other tissues. In the earlier stages of development, at least, the foetal endocrines can take little part in the production of the essential autacoid. In the anencephalic foetus, in which the pituitary is completely absent, the formation and ossification of the long bones, as Browne has recently shown, are entirely normal. The autacoid in this case can only have/

have come from the maternal blood.

The posterior lobe also presents well-marked signs of increased activity in pregnancy. It has been shown, in addition, that there are good grounds for believing that this part of the gland possesses the power of storing secretion and that this secretion is utilised especially in connection with the stimulation of uterine muscle during parturition and of milk secretion during the puerperium.

It has been proved by the workers previously mentioned that the secretion of the posterior lobe is concerned in the stimulation of plain muscle, of urinary secretion, and of milk secretion. It is believed, also, that it is intimately concerned with carbohydrate metabolism. After intravenous or subcutaneous injection of posterior lobe extract, a marked lowering in the tolerance for sugar is observed, usually to such an extent that glycosuria becomes established. Cushing and his pupils have concluded that the posterior lobe contributes an autacoid which stimulates the utilisation of sugar in the body. In cases of pituitary disease associated with other signs of hypopituitarism, it is usual to find an increased sugar tolerance. Confirmatory evidence for this view is furnished by the observation that mechanical stimulation of the posterior lobe, such as is produced by puncturing/

puncturing it with a needle, is followed by a temporary glycosuria, which is said to be as pronounced as that following puncture of the diabetic centre, provided glycogen is present in the liver. The production of this carbohydrate autacoid would appear to be under the control of the sympathetic nervous system, for it has been found by Cushing, and others, that stimulation of the superior cervical ganglion, which has been known for many years to be frequently followed by glycosuria, has this effect only provided the posterior lobe of the pituitary is intact. Even surgical manipulation of the pituitary may excite a hypersecretion of pituitrin, which would account for the glycocosuria often observed after experimental excision or partial destruction of the pituitary. A similar irritation may be set up in disease of the gland.

The increased activity of the posterior lobe in pregnancy may be partly due to increased production of the autacoid which stimulates carbohydrate metabolism as well as to the other causes already mentioned.

CONCLUSIONS.

1. The pituitary of the guinea-pig and that of the rabbit illustrate the two common types of mammalian pituitary.

2. In both animals there are well-marked signs of/

of increased functional activity in pregnancy. The activity is apparent in the posterior lobe as well as in the anterior.

3. In the anterior lobe the signs of increased activity are mainly in the form of eosinophilia of the cells and a marked increase in the vascularity . In the rabbit there is an area of chromophobe cells constantly present in the anterior region of the pars anterior, partly separated by a connective tissue septum from the remainder. The chromophobe condition of the cells in this region is probably to be explained by its extreme vascularity, the secretion escaping into the blood-vessels without accumulating in the cells so as to give the eosinophil reaction.

There is occasionally evidence of storage of secretion in the pars anterior of pregnant animals.

4. There are no sufficient grounds for considering that the epithelial investment of the stalk and its prolongation towards the base of the brain differ physiologically from the rest of the pars intermedia. Hyaline bodies can sometimes be seen between its cells. It differs from the rest of the pars intermedia in being very vascular.

5. The posterior lobe, consisting of pars intermedia and pars nervosa, shows well marked signs of increased/

increased activity in pregnant animals. The hyaline bodies which it contains are increased in pregnancy. These appear to be mainly derived by a process of active secretion from the cells of the pars intermedia. Isolated pars intermedia cells or groups of cells in the pars nervosa play little or no part in their production.

6. The appearances in pregnant animals afford strong evidence in favour of the belief that the hyaline bodies pass up the stalk into the cerebro-spinal fluid of the third ventricle. The appearance of the stalk in the pregnant rabbit is especially convincing on this point.

7. The colloid vesicles of the pars intermedia are increased in pregnancy in the rabbit; they do not occur in the guinea-pig. They probably represent an apparatus for storing the secretion of the pars intermedia.

8. The rabbit appears to be unique in possessing an isolated cavity in the pars nervosa. This is lined with ependyma and probably acts as a reservoir for the storage of posterior lobe secretion.

9. The intra-glandular cleft contains a greater amount of secretion in pregnant than in non-pregnant animals and may, possibly, also act as a reservoir for/

for secretion.

10. The appearances of the pituitary in the active state are in accordance with the belief that acromegaly is sometimes associated with an excess of the pituitary secretion. Eosinophilia of the cells of the anterior lobe is characteristic of both conditions. They support the belief also that interference with the escape of secretion into the cerebrospinal fluid results in a state of hypopituitarism.

FIG. 58. THE PINEAL BODY OF THE RABBIT.

IRON HAEMATOXYLIN + ACID FUCHSIN. X 82.

THE PINEAL BODY.

Although the function of the pineal is still in doubt, evidence is accumulating to show that it is possessed of an internal secretory function.

Morphology.

In man, the pineal body is a small, conical, reddish grey body which lies in the depression between the superior corpora quadrigemina. It is placed beneath the splenium of the corpus callosum, but is separated from this by the tela chorioidea or velum interpositum of the third ventricle, the lower layer of which envelopes it. It is described as measuring about 8 m.m. in length, and its base, directed forwards, is attached by a stalk of white substance. The stalk divides anteriorly into two laminae, a dorsal and a ventral, separated from one another by the pineal recess of the third ventricle.

In the rabbit and the guinea-pig the pineal occupies a similar position to that in man. In the rabbit it is ovoid in shape and somewhat flattened from above downwards (Fig. 58). The stalk in this animal is long and its inferior lamina is commonly folded on itself in a slightly convoluted manner.

In/

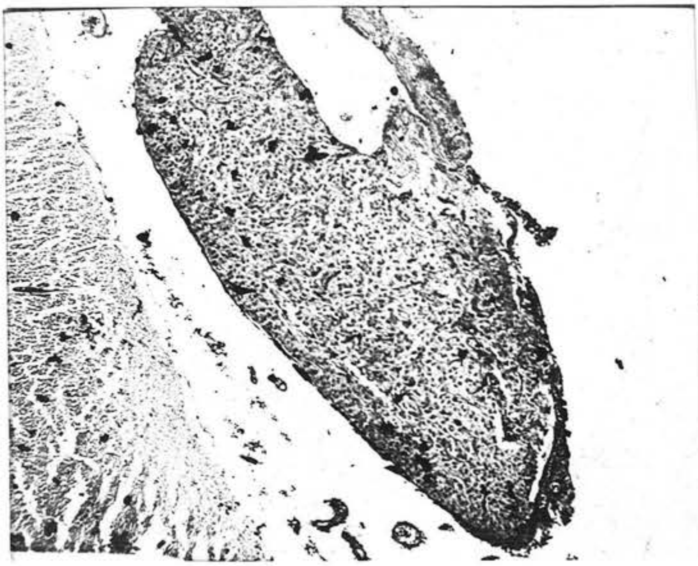


FIG. 58a. THE PINEAL OF A GUINEA-PIG.
THE ORGAN IS ENTIRELY CELLULAR.
THE SPECIMEN SHOWS THE PINEAL RECESS OF THE THIRD VENTRICLE.

IRON HAEMATOXYLIN + ACID FUCHSIN X 82.

In the guinea-pig, the pineal is decidedly conical (Fig. 59), tapering off rapidly towards the tip. The stalk in this animal is short and is hollowed out by the presence of the pineal recess of the third ventricle. In both animals the pineal is very closely related to the pia mater, and if this membrane is removed the pineal is certain to be torn away. Large blood-spaces are always present in close relationship to the gland.

Development.

The pineal body arises as a bilateral evagination of the roof plate immediately in front of the mid-brain; in vertebrates, only the left portion persists, and it becomes solid, with the exception of its proximal part, which forms the recessus pinealis. The pineal body consists essentially of (a) a distal part representing a rudimentary eye, and (b) a proximal part which is glandular in nature; only this latter portion is represented in man. In lizards it is elongated into a stalk, and its peripheral extremity is expanded into a vesicle, in which a rudimentary lens/

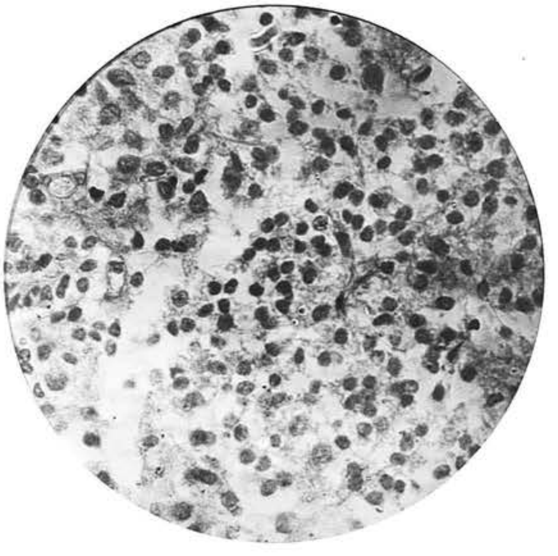


FIG. 59. THE PINEAL CELLS IN A CHILD OF SIX MONTHS.
SPECIMEN LENT BY PROFESSOR ROBINSON.

ACID TOLUIDIN BLUE X 380.

lens and retina are formed; the stalk becomes solid and nerve-fibres make their appearance in it, so that in these animals the pineal body forms a rudimentary eye.

Histological Anatomy.

The appearance of the pineal varies with the stage of functional activity of the gland. At birth, the human pineal consists of irregular lobes held together by a small quantity of connective tissue. The lobes are composed of cells arranged irregularly and croweded together in the interior of the organ (Fig.59) According to the careful investigations of Krabbe, the pineal parenchyma consists of cells of three main varieties, namely, (1) pineal cells, (2) glia cells, and (3) nerve cells. The pineal cells form the bulk of the parenchyma, and are of rounded shape, with irregular nuclei poor in chromatin; at birth they exactly resemble the neuroblasts of a foetal brain. The cell-protoplasm stains only faintly. The glia-cells are relatively few in number, and give rise to a net-work of glia fibres. The nerve cells have scanty protoplasm and angular nuclei rich in chromatin; from the first year of life onward, they develop increasing numbers of out-running nerve-fibres with knobbed endings, and appear to have no connection with/

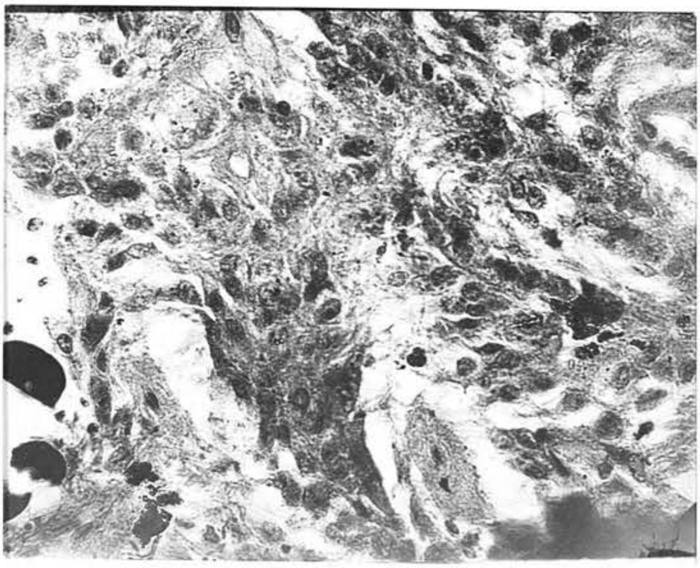


FIG. 60. THE ADULT HUMAN PINEAL.
THERE ARE ABUNDANT EPITHELIAL CELLS IN THE SPECIMEN.

IRON HAEMATOXYLIN + EOSIN X 380.

with the sympathetic fibres that accompany the blood-vessels. Connective tissue cells and fibrils appear in the pineal body during the first year of life, and habitually increase in quantity year by year, converting it into a pseudo-alveolar organ by the age of six or eight; the rate at which this fibrosis takes place is very variable. There is a connective tissue capsule which is apparently free from unstriped muscular fibres in man. Calcareous concretions may be found in the pineal body at any age, and are constant after the seventeenth year, occurring mainly in the parenchyma and representing debris of the pineal cells. Spaces or cysts also occur normally in the pineal body and may be either included portions of the embryonic pineal recess of the third ventricle and lined with ependyma, or due to degeneration of parts of the pineal parenchyma. Biedl points out that even in extreme old age, glandular cells are encountered which are intact and, apparently, still functionally active.

In a specimen obtained from a middle-aged man, who died as the result of an accident, pineal cells were found to be abundantly present (Fig. 60). The specimen showed a large amount of interstitial tissue which was arranged in places so as to present a follicular-like appearance. In the substance of the thicker bands of interstitial tissue there were occasional particles of "brain-sand". These did not invariably consist/

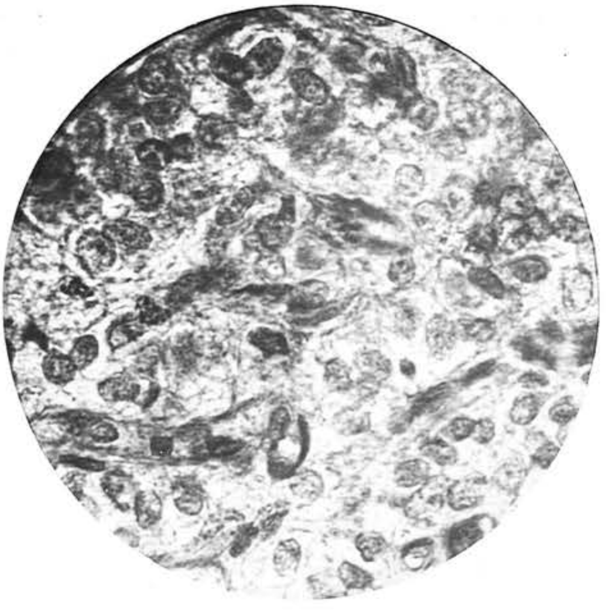


Fig. 61. A high power view of the cells of the pineal in a pregnant rabbit.

Iron haematoxylin & congo red. X 710.

consist of calcareous material as is usually stated, but frequently presented a hyaline appearance. The persistence of apparently active epithelial cells in adult life may be of considerable significance from the functional point of view.

Cosantini describes the presence of definite granules in the protoplasm of the pineal cells and concludes from these that the pineal must be possessed of an internal secretion. Galasescu & Urechia also emphasise the importance of the granules, which are oxyphil in their staining reactions, and they also conclude that the granules are indicative of a secretory function.

In the rabbit the histological appearances resemble very closely those in the human subject. The pineal cells have large nuclei with scanty chromatin and a small amount of faintly staining protoplasm. In some cases fine oxyphil granules are distinctly evident. The cells towards the surface may show a follicle-like arrangement. In the guinea-pig the appearances are similar, except that the nucleei tend to be larger and contain still less chromatin. In both animals the degree of fibrosis is commonly very much less than in the human subject; the gland remains highly cellular and presents the appearance of an actively functioning structure (Fig. 61).

Evidences/

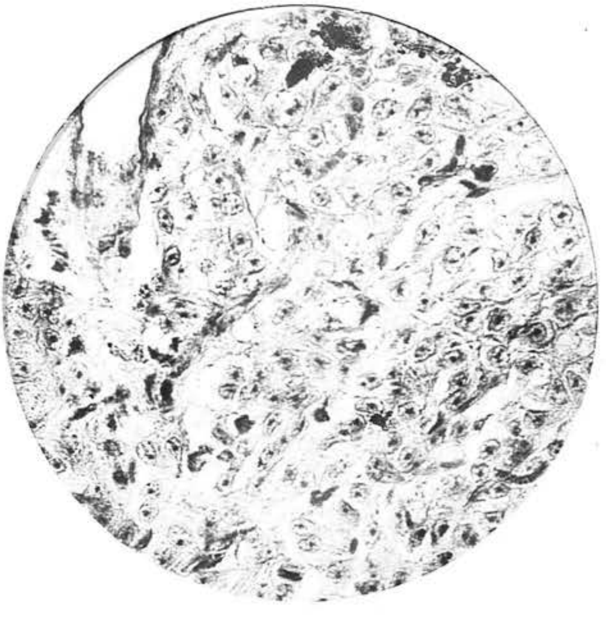


FIG. 62. THE PINEAL CELLS IN THE GUINEA-PIG.

IRON HAEMATOXYLIN & EOSIN X 380.

Evidences of Secretory Activity.

The evidence with regard to the nature of the function of the pineal body is most conflicting. The gland is commonly believed to possess a relationship to the development of the sex organs and also to body growth. Some authorities believe also - largely as the result of clinical observations - that it is related to the metabolism of carbohydrates (Barker). Lyon has suggested, as the result of experiments in which he directly stimulated the pineal, that it is concerned in the regulation of the flow of cerebro-spinal fluid from the third ventricle, and Krabbe is of the opinion that it remains an active organ throughout life and that its activities are dependent upon variations in the pressure of the cerebro-spinal fluid.

Park makes the statement that "it seems probable that a mass of experimental literature will develop about the pineal body like that which has sprung up around the thymus and the spleen. It can now be said that the experimental work on the pineal up to the present time has failed to prove that it possesses a function".

The results of injecting extracts of pineal are not impressive. Fenger, after a careful study of the/

the physiological properties, came to the conclusion that the gland is essentially inactive. Schäfer, however, reports that intravenous injection produces a marked but temporary fall of blood-pressure accompanied by a diminution in volume of the kidney. The latter effect he considers to be passive, since there is no change in the rate of the flow of urine.

Feeding experiments have produced varying results Sisson & Finney, and also Hoskins, who employed the albino rat in their investigations, came to the conclusion that pineal feeding produces no effect on growth or sexual development. McCord, however, after administering pineal by feeding and by subcutaneous injection, believes that it contains some substance which is capable of stimulating growth.

Tumours of the pineal are believed to be accompanied, in some cases at least, by characteristic symptoms. Marburg reported in a young girl, the subject of a pineal tumour, the occurrence of extreme obesity. Ogle, Gutzeit, Oestrick-Slawyk, and Frankl-Hochwart have reported characteristic symptoms in pineal teratomata in young boys. In addition to symptoms of cerebral tumour and disease of the corpora quadrigemina, these authors observed abnormal growth in height, abnormal growth of hair, premature development of the genital organs and of sexual instinct, and/

and mental precocity. These symptoms were associated with a diminution of pineal tissue. From these observations the organ is believed to exercise a definite and apparently inhibitory influence upon the development of the sexual glands and probably to produce a secondary effect on mental development.

Sir John Bland-Sutton, on the other hand, is very sceptical with regard to the effects of pineal tumours. He points out that the total number of recorded cases is very small and that, except for the fact that the tumours lie upon the corpora quadrigemina, there is nothing to indicate definitely that many of them were tumours of this body. He believes that the majority of the tumours in this region are developed from the membranes and that if these are carefully excluded, tumours arising from the pineal body are exceedingly rare. He considers that effects on the sexual organs - and possibly adiposity - may be due to secondary effects on the pituitary, which result from hydrocephalus produced by pressure on the acqueductus cerebri. The increased pressure in the cerebro-spinal fluid of the third ventricle is believed to interfere with the escape of pituitary secretion.

Timme believes that early involution of the pineal/

pineal in the human subject is associated with premature development of the gonads and with muscular asthenia. He states that the condition of the pineal can be estimated by the shadow which it gives on X-ray examination.

Extirpation of the pineal has been followed by varying results. It has been definitely established that the organ is not essential to life. Dandy, whose experimental work is generally excellent, found that removal produced no effect on body growth or sexual development. Horrax, on the other hand, employing the same technique, concluded that both growth and sexual development were accelerated after extirpation of the pineal. The work of Foà in this direction has been followed by interesting results. After removal of the pineal in chickens he came to the following conclusions:-

1. Complete extirpation in the earlier months of life gives rise to a retardation of development during the first two or three months after operation; afterwards the development of the body becomes normal.

2. In cockerels there occurred an earlier development of both primary and secondary sexual characters in the operated than in the control animals.

3. In cocks examined eight to eleven months after operation/

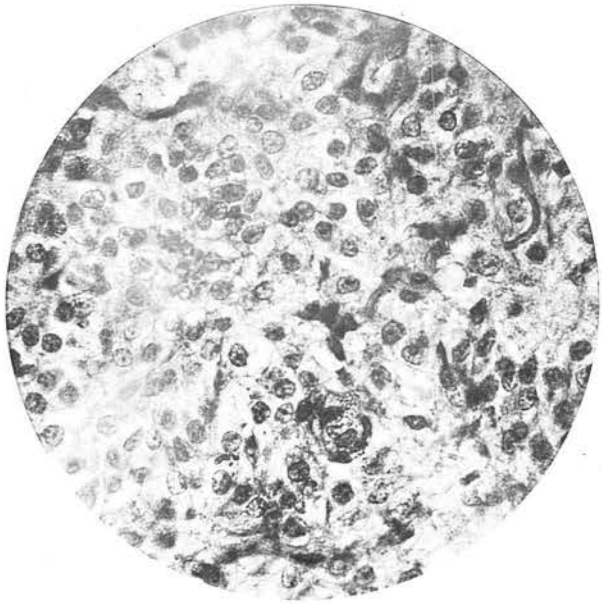
operation there is marked hypertrophy of comb and testes.

4. There are no corresponding changes in pullets.

The work of Foà has been confirmed by Sarteschi. This observer found that in young rabbits and dogs, the male animals, after extirpation of the pineal, showed hypertrophy of the testes, bodily overgrowth, and sexual precocity.

In a recent report of further work, Foa states that removal of the pineal produces no effect on female chickens or female rats. In male rats the same results ensue as in cockerels, namely, rapid increase in bodily weight and in the size of the testes. He found advanced development both of spermatozoa and the interstitial tissue of the testes in both rats and cockerels. The premature increase of the interstitial tissue corresponds to the precocity of the secondary sexual characters - the growth of the comb in the cock and the increase in body weight of the rat.

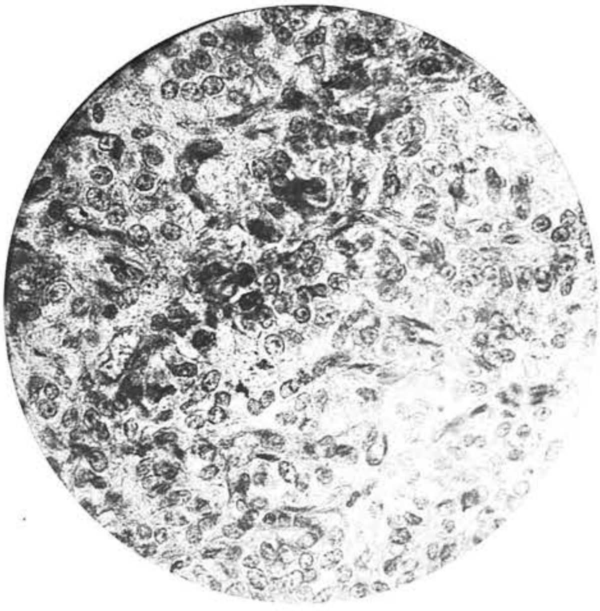
In the animals examined the pineal presented the appearance of an actively functioning organ, both in the pregnant and the non-pregnant animals. In some cases there was a zone of interstitial tissue in one part of the gland, but in most cases the greater portion was occupied by well-developed epithelial cells. In/



Figs. 63. 64. The upper photograph shows the pineal cells in a non-pregnant rabbit. They appear active and resemble closely the cells in Fig. 59.

The lower photograph is from the pineal of a pregnant rabbit. There is no apparent difference between the cells in the two conditions

X 380.



In the rabbit and the guinea-pig the organ does not undergo the degree of fibrosis which is seen in the human subject. Fig. 58 shows the pineal of a pregnant rabbit. There is a patch of interstitial tissue towards the superior aspect, but the ramainder of the gland consists of epithelial cells with a small amount of supporting stroma.

The fact that the organ remains active in pregnancy does not support the belief that in the adult animal it exercises an inhibitory effect on the reproductive apparatus. Certain observers, indeed, have reported that feeding with pineal has a stimulating effect on the growth of the sexual organs - exactly the opposite to that which one would expect from a consideration of the extirpation experiments of Foà and others and from the reported effects of tumours.

The persistence of the organ in an active cellular condition in both pregnant and non-pregnant animals suggests that it is possessed in the adult animal of some additional function besides the regulation of sexual development, a function as yet unrecognised, and apparently of more importance in these animals than in man. I have not been able to recognise any essential difference in structure between the pineal of pregnant and that of non-pregnant animals.

CONCLUSIONS/

CONCLUSIONS.

1. In the adult rabbit and guinea-pig the pineal body persists as an active epithelial organ.

2. The persistence in adult animals and the active state of the gland in pregnancy point to the existence of some other function than that of inhibition of the activity of the genital organs.

THE THYROID.

The thyroid apparatus includes the parathyroids as well as the thyroid, but it is more convenient here to consider the two parts separately. The thyroid will be considered first.

Morphology.

The comparative anatomical studies of Mrs. Thompson and of Marine & Lenhart have shown that the gland presents indentical features in all mammals. In the rabbit and the guinea-pig the structure resembles closely that of man. The gland consists of two lateral lobes lying on the side of the larynx and the trachea, connected, as a rule, by a slender isthmus. In the rabbit the isthmus is always present; in the guinea-pig it is occasionally absent. The guinea-pig appears to be almost unique as regards the large size of its thyroid. There is a correspondence in this respect to the state of the suprarenals in this animal. The more minute details of structure are readily examined, and the guinea-pig forms a very suitable subject for the investigation of structural changes in the thyroid.

The blood-supply of the thyroid is remarkably abundant; in proportion to its size it receives more than/

than ~~than~~ five times as much blood as the kidneys. The vessels form a rich anastomosis on the surface, their smaller branches penetrating with the connective tissue framework between its lobules. Each follicle is surrounded by a close net-work of sinus-like capillaries with which the vascular epithelium is in direct contact. The veins are correspondingly large and numerous, intercommunicating freely.

The lymphatics of the thyroid are very abundant. Lymph spaces lie outside the peri-vesicular capillaries. These drain into interlobular vessels which ultimately open into a large plexus on the surface of the gland. The lymph drains from this in the human subject by two sets of vessels, an upper, which accompanies the superior thyroid artery and enters the superior deep cervical lymph glands, and a lower, which runs partly to the pretracheal lymph glands and partly to the small paratracheal lymph glands which accompany the recurrent nerves.

The nerve-supply is derived from the superior and inferior laryngeal branches of the vagus and from the superior cervical ganglion of the sympathetic. Fibres are distributed to the secreting epithelium as well as to the muscle cells of the vessels. The secreting fibres reach the cells from the cervical sympathetic/

sympathetic, so that the secretion of the gland is directly under the control of the sympathetic impulses. Cannon states that as the result of experimental stimulation the secretion issues as promptly as in five to seven seconds.

Development.

The thyroid develops from an evagination of the floor of the pharynx between the first and second branchial arches. In an embryo of 10 m.m. there is a median duct - the ductus thyreoglossus - which opens on the tongue at a spot which corresponds to the foramen caecum of the adult. At the lower end of the duct there is a well-marked lateral expansion on each side, and at this stage the whole structure consists of a bilateral epithelium vesicle connected by a slender hollow pedicle with the surface of the tongue. In amphioxus and others of the lower animals, the connection of the duct with the alimentary tube is retained, but in man it is obliterated by about the eighth week of foetal life.

The bilateral expansions branch and re-branch, ultimately forming groups of small epithelial masses in which little closed epithelial lined cavities are formed; these constitute the vesicles or secretory units of the organ. These vesicles are formed by the breaking/

breaking down of the central cells of a given epithelial mass to form the colloid-content of the cavity, the peripheral cells of the mass forming the vesicular lining.

As in the case of the anterior lobe of the pituitary, cysts or tumours may be derived from persistence of a portion of the primitive duct - thyroid tumours of the posterior part of the tongue, thyroglossal cysts, and median fistula of the neck are the commoner pathological sequelae. Occasionally a few of the developing cell masses become detached from the main rudiment and these may give rise to an accessory thyroid; such a structure may be found in any part of the area lying between the root of the tongue and the aorta. An accessory thyroid in the lower part of this area may give rise to a retro-sternal goitre.

Mention may also be made, in connection with the development of the thyroid, of the ultimobranchial body. This structure is believed to be derived, in the human subject, from the fifth branchial pouch. According to Howden, it is enveloped by the lateral prolongations of the median thyroid rudiment; it does not, however, form true thyroid tissue and no trace of it can be found in the human adult. Mrs. F.D. Thompson described the post-branchial body in elasmobranchs, urodela, frogs, reptiles, and birds. In birds this is/

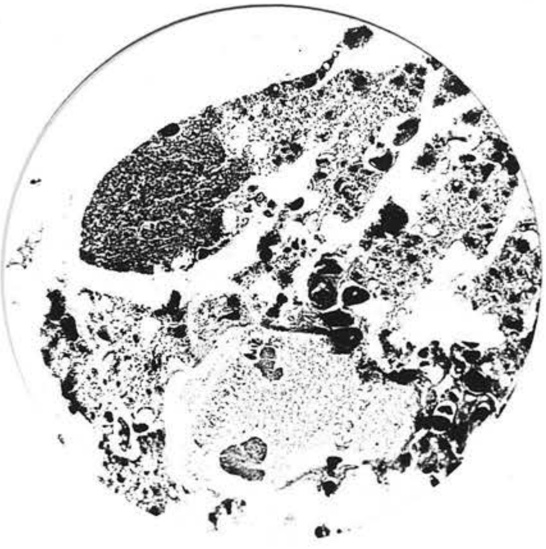


Fig. 65. A cystic cavity in the thyroid of the rabbit — probably the post-branchial body. The cellular area is an internal parathyroid — parathyroid IV

iron haematoxylin & eosin X 79.

is a most complicated structure/consisting of three parts - the first composed of compact epithelial cords, the second of spherical vesicles lined with cubical epithelium which may be ciliated, and the third of true para-thyroid tissue and thymus. Dr. Madge Robertson, in investigating the material used by Noël Paton and Findlay in their investigation on Tetania parathyreo-priva, discovered a structure closely corresponding in character with this post-branchial body. It was found in the thyroid of dogs and cats as a structure, cyst-like in some of its forms, and duct-like in others. According to Dr. Robertson, the space has its origin in the breaking down of epithelial cells of a type quite distinct from those of the parathyroid and thy-roid and easily recognisable in the midst of either of these. The epithelial cells are larger than those of the thyroid or parathyroid, they stain as a rule more faintly, and they are sometimes peculiarly clear and almost refractile in appearance. The cavity contains a large amount of homogeneous necrotic material, obvi-ously derived from broken down epithelial cells, and differing, as a rule, in its staining properties from the colloid of the thyroid vesicles. When haemalum and eosin are used this material usually takes a dark bluish black colour.

A similar body to that described by Dr Robertson was/

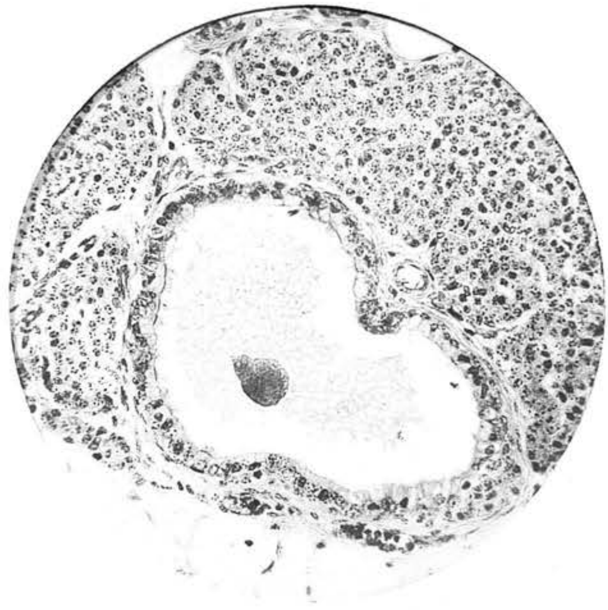


Fig. 66. A cystic cavity in the parathyroid of the guinea-pig lined with ciliated columnar epithelium.

Iron haematoxylin X200.

was found in the thyroid of the rabbit and in the para-thyroid of the guinea-pig. In the rabbit (Fig65) there is a cystic cavity, lined partly with cubical and partly with flattened cells, in the substance of the thyroid, not far from an internal parathyroid. The contents consist of granular necrotic-looking material. In the guinea-pig (Fig.66) the cavity in the parathyroid was lined with ciliated columnar epithelium and contained a substance resembling that seen in the rabbit.

Morphological studies have shown that the thyroid apparatus, from the earliest stage of its evolutionary history, has been an essential part of the digestive tract, and so intimately related with the genital organs as at one time to have formed an integral part of them.

Histological Anatomy.

The thyroid gland is surrounded by a thin capsule of connective tissue from which processes run into the interior of the organ, subdividing it into smaller and smaller lobules. The ultimate lobules are irregularly circular or oval on section and have a diameter of .5 to 1 m.m. It has been shown conclusively that the glandular substance is composed of closed vesicles, which are separated from one another by a very fine and/

and highly vascular fibro-elastic covering and a variable amount of intervesicular cellular tissue. Most of the vesicles are more or less rounded, but may be long, ovoid, or polyhedral. They vary much in shape and size, being small in the glands of the newly-born and young, while in the adult they are smaller towards the periphery. In the adult, their size varies from 45 to 300μ. Each vesicle is surrounded by a very abundant net-work of capillaries.

The capsule of the organ and the connective tissue stroma are made up of bundles of white fibres with numerous elastic fibres. The connective tissue comes into direct contact with the epithelium lining the vesicles; Lagendorff & Schmid have shown that there is no basement membrane, the vesicle being enclosed by very fine bundles of connective tissue fibres, outside of which is the endothelium of the lymph spaces.

The epithelial cells lining the vesicles vary in height from low cuboidal to columnar, according to the state of secretory activity of the gland. When examined in normal saline, the cells of the thyroid in both man and animals show a number of granules of varying sizes. They are chiefly aggregated in the free end of the cells next to the lumen of the follicle; they /

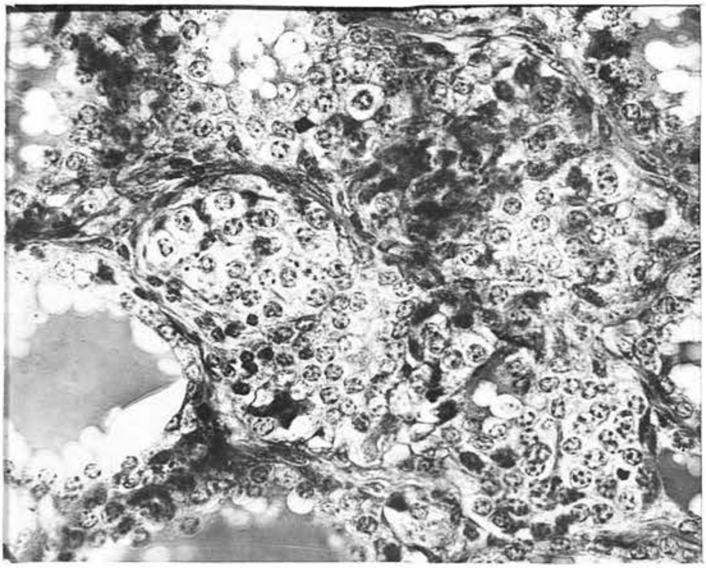


FIG. 67. THE INTERVESICULAR TISSUE OF THE THYROID OF THE GUINEA-PIG. THE CELLS RESEMBLE THOSE LINING THE VESICLES.

IRON HAEMATOXYLIN & ACID FUCHSIN X 380.

they are highly refractive and show a characteristic greenish tinge. They are believed to consist of fat in combination with oleic acid. Lagendorff, in osmic acid preparations stained by the Ehrlich-Biondi method, endeavoured to distinguish beteen principal cells and colloid cells, the former being unstained, while the latter appear red with green nuclei. Subsequent observers have failed to support this distinction. According to V. Ebner, these do not represent two distinct varieties of element; McCarrison states that the appearances merely represent different stages of the cell's activity.

The cell protoplasm shows a retiform structure, with frequent longitudianl striation. The nuclei are spherical and show a very fine chromatin net-work. Lying between the vesicles and filling up the spaces left by the approximation of the more or less rounded vesicles is the intervesicular parenchyma. The cells in this situation bear a close resemblance to those which line the vesicles (Fig. 67). The intervesicular tissue is more abundant in the young and developing thyroid; with advancing age the gland becomes less cellular and more vesicular. The amount also varies with the state of functional activity of the gland, as will be shown later. Vincent has directed attention to the resemblance between the intervesicular cells and those of the parathyroid. He believes that/

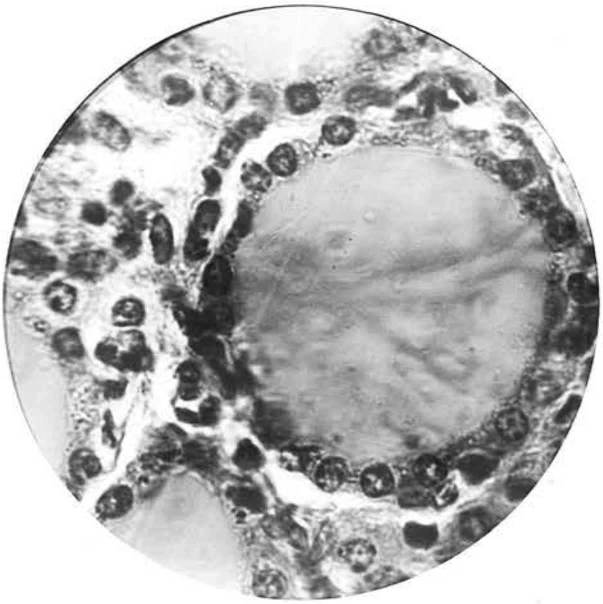


FIG. 68. A VESICLE IN THE THYROID OF THE GUINEA-PIG.
THE COLLOID FILLS THE VESICLE COMPLETELY.

IRON HAEMATOXYLIN + EOSIN X 710.

that this tissue is in all essential respects of the same nature as that forming the parathyroids. This view received support from the work of Mrs. Thompson, but the point has not yet been definitely settled and will be referred to later, after the changes of functional activity have been considered.

The intervesicular tissue may, in addition to its parenchyma cells, contain portions of thymus tissue or of parathyroid tissue. Many small cells may be found scattered through it or arranged in masses. Some of these are lymphocytes, others, found in more compact masses, are the "foetal rests" from which "foetal adenomata" are said to arise.

The contents of the vesicles consist of the so-called colloid material. Morphologically, this is a colloidal substance, though chemically it is not. It varies in consistence and is insoluble in water, alcohol, ether, and diluted acids. It stains with acid aniline dyes and most readily with eosin. In preparations which are fixed with those agents which coagulate proteins without change of form, such as osmic acid mixtures, the colloid is found to fill the vesicles completely (Fig.68). It lies in close contact with the follicular epithelium and, as a rule, has a perfectly homogeneous aspect in the resting gland. The outstanding/

outstanding characteristic feature of the colloid material is that it contains iodine, which exists in combination with a non-protein nitrogenous base, and it is usually called iodothyrin. E. C. Kendall has recently succeeded in isolating a pure crystalline substance of perfectly constant composition and containing over 60 per cent of iodine. He has named this substance "thyro-oxy-indol" or "thyroxin" for every-day reference. It has been identified as an indol compound and has been made synthetically. Kendall believes this substance to be the active constituent of the thyroid and to be associated with the metabolism of amino acids.

The Histological Evidences of Secretory Activity.

The examination of a number of thyroids demonstrates the fact that different specimens show considerable variation as to their minute anatomy. Some specimens show well-marked signs of secretory activity, while in others these signs are almost or entirely absent. Chalmers Watson has shown that it is possible by variations in the diet to produce in rats all transitions from an active or hyperactive organ with highly developed columnar epithelium and irregular large vesicles, and without any great accumulation of colloid, to a gland with flattened epithelium and vesicles greatly distended/

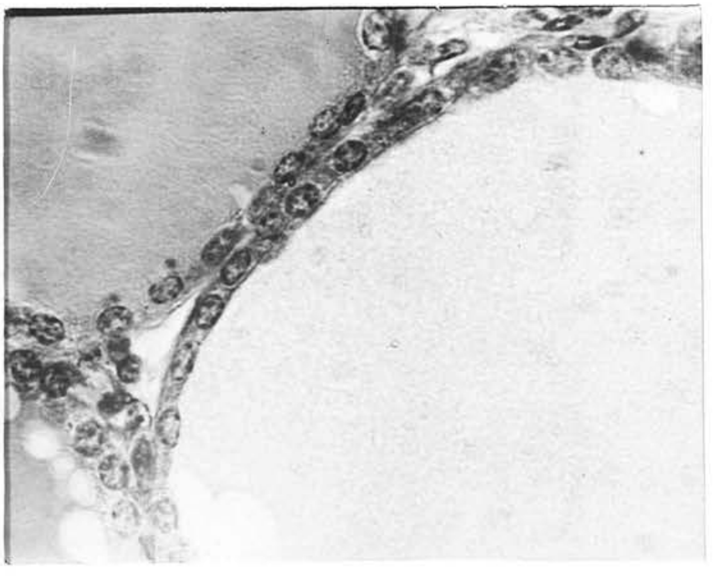


Fig. 69. Vesicles from a resting thyroid.
The lining cells are markedly flattened. The vesicles are large and distended with colloid.

Iron haematoxylin & eosin. X 710.

distended with colloid. In order to come to a conclusion as to what features constitute what may be called the "normal" signs of functional activity, it is essential that the animals examined should be under the same conditions as to feeding, general health, and invironment generally. The same remarks which have been made in the case of the pituitary as to the unsuitability of human material apply to the thyroid. The thyroid responds very quickly to toxic conditions, the effects being exhibited in varying degrees of hyperplasia, hypertrophy, and cell destruction, so that specimens from patients who have died from such causes are of no value in attempting to obtain a picture of the normal signs of secretory activity. Even in the case of healthy subjects who have died from injury, degenerative changes are apt to take place in the cells owing to delay in fixation.

The animals examined were in good health and under the same conditions as to feeding and general surroundings. As in the case of the pituitary, the thyroid shows well-marked signs of activity in the pregnant state. The enlargement of the thyroid in pregnancy is a well-known clinical fact. Ripmann recently found, in the Queen Charlotte Hospital in London, that about 50 per cent of pregnant women showed/

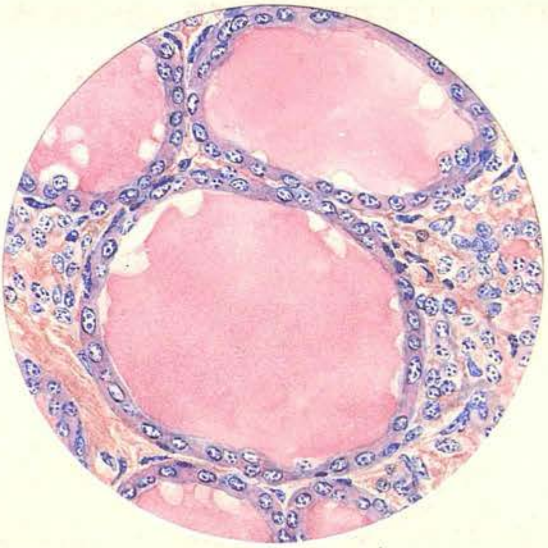
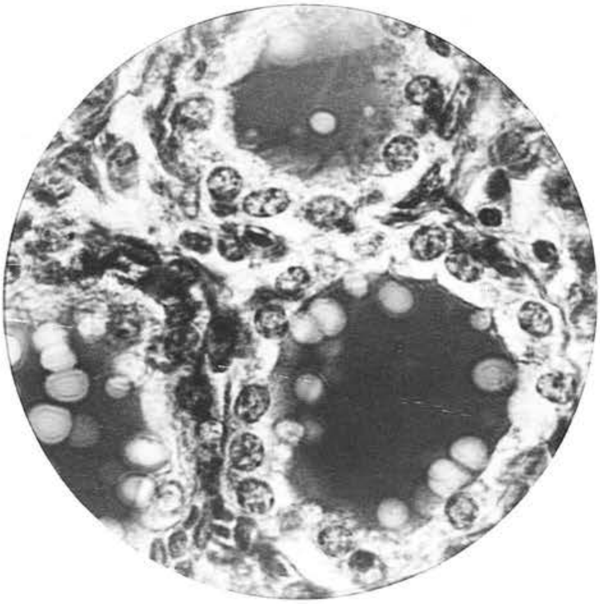


FIG. 70. A DRAWING OF A RESTING THYROID.
THE DISTENDED VESICLES ARE LINED WITH FLATTENED CELLS. THERE IS ABUNDANT INTERVESICULAR TISSUE.

IRON HAEMATOXYLIN + EOSIN X 330.

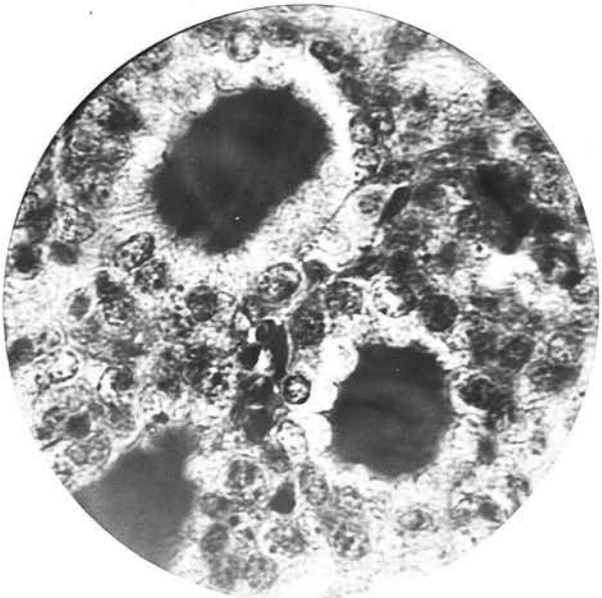
showed slight thyroid enlargement which had originated during pregnancy. Primaparae showed such swellings to a surprising extent. The gland is most likely to enlarge during the fifth and sixth months of pregnancy. Von Graff found that of 633 pregnant women who had no swelling prior to pregnancy, 49 per cent presented thyroid enlargement. The thyroid of the healthy pregnant animal therefore provides good material for the investigation of the gland in the active state. On comparing the thyroids of pregnant and non-pregnant animals, it is possible to distinguish between an "active" and a "resting" stage of the gland.

Appearances in the Resting Phase. In non-pregnant animals the vesicles of the thyroid are usually distended with a granular or perfectly homogeneous colloid. This substance lies closely applied to the lining epithelium unless a fixative has has been used which causes shrinkage in addition to coagulation. In this event indentures at the edge of the colloid are to be seen. It shows few, if any, vacuoles. It stains freely with all basic dyes, and, as a rule, uniformly; occasionally, however, a denser area may be seen towards the centre. The cells which line the vesicles are markedly flattened (Fig. 69). The protoplasm stains uniformly and the granules are few in number/



Figs. 71-72. Vesicles from the active thyroids of pregnant animals. In the upper photograph the lining cells are cuboidal in shape; in the lower some of the cells are columnar.

Iron haematoxylin + eosin x 710.



number . The nucleus is placed either at the centre or at the base and may almost fill the flattened cells. The nuclei tend to be smaller in the resting phase. They are spherical or oval in shape, according to the degree of flattening of the cell. The vessels and capillaries of the organ are not distended.

In this stage the colloid has become thick owing to its gradual admixture with the elements of cellular disintegration, when iodine has been fixed by the colloid and the consistency of this substance has been altered by the salts of the body tissues.

<u>Appearances in the Active Phase.</u> In pregnant animals the thyroid usually shows well-marked evidences of secretory activity. The epithelium lining the vesicles becomes heightened. It is commonly of a cuboidal or low columnar appearance (Fig. 71), but in some cases may even be tall columnar. The protoplasm shows abundant granules. The granules appear to be discharged as a thin secretion into the vesicle or directly into the lymph spaces. After the escape of secretion the protoplasm may appear pale and vacuolated. The nucleus is centrally placed and does not fill the cell. It is distinctly larger than in the resting state. The edge of the epithelium towards the acinar cavity is usually uniform, but in some cases it becomes ragged/

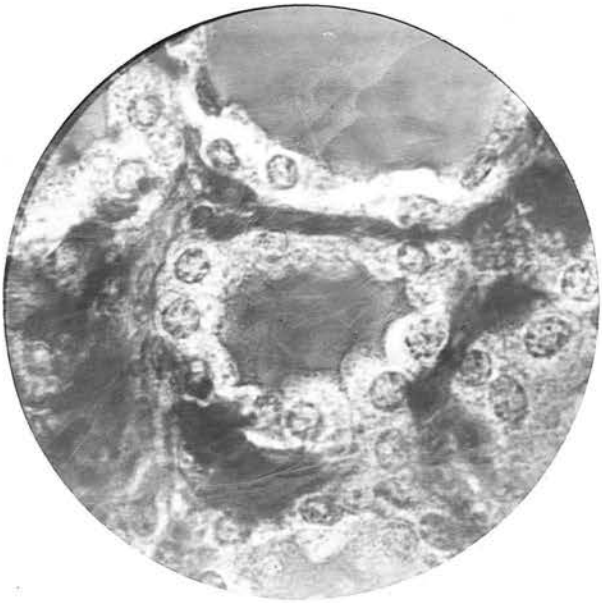


FIG. 73. ANOTHER SPECIMEN SHOWING THE APPEARANCE OF ACTIVELY SECRETING CELLS.

IRON HAEMATOXYLIN & EOSIN X 710.

ragged and irregular, merging into the colloid substance. The colloid becomes vacuolated (Fig. 76) as the clear fresh secretion accumulates in the vesicle, and gradually becomes absorbed. The absorption is more rapid at the periphery of the colloid mass, so that a crenated appearance may result. There is no increase in the stroma, but the blood-vessels and the capillaries are distinctly dilated. The changes in the intervesicular tissue will be discussed later.

Cowdry has recently made an interesting observation on the behaviour of the reticular material in secretory activity in the thyroid of the guinea-pig. He finds that the reticular material (i.e., Golgi apparatus, canalicular apparatus, etc.) is not invariably found between the nuclei and the follicular lumen, as is generally supposed; but in some cases undergoes an active migration to the opposite pole of the cell, which, together with other evidence at hand, indicates the existence, in his opinion, of a reversal in physiological polarity whereby the secretion is absorbed directly, instead of being first stored within the follicles.

In the active state the clear fresh secretion readily finds its way into the lymph spaces, though the manner in which it is transmitted is not quite certain. Hürthle believes that the secretion passes out/

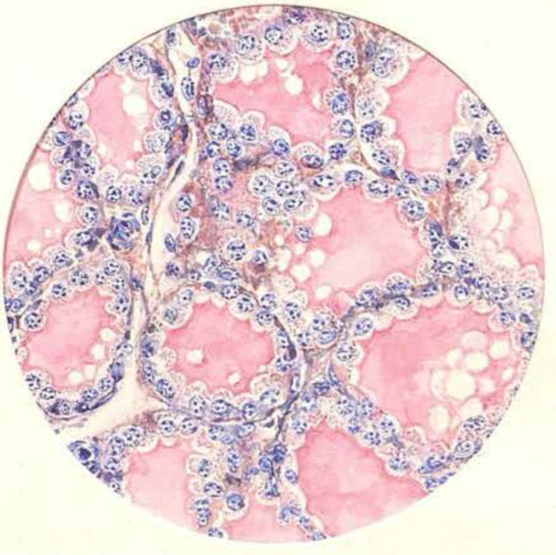


Fig. 74. Drawing of vesicles of an active thyroid. The cells are cuboidal and contain numerous secretion granules. The colloid appears vacuolated owing to the presence of fresh secretion.

Iron haematoxylin + eosin X 330.

out by way of the intercellular passages, while Lewandowski is of opinion that the process is osmotic. In any case, there is no doubt that the secretion enters the lymphatic vessels. Apparently, it is only the thin fresh secretion that makes its way into the lymphatics, the store of colloid substance being used up by a process of solution and absorption. Towards the end of the active phase the secretion from the vesicular cells begins to accummulate in the vesicles, where it becomes intermingled with portions of disintegrated cells and increases in viscosity in consequence, probably, of chemical change. This change is well seen in the thyroid of the rabbit killed one week after parturition. Rounded globules of fresh secretion can be seen in the midst of the denser colloid towards the epithelial lining of the vesicle (Fig. 79). The newly-formed colloid substance then becomes impregnated with iodine in organic combination. Thus the gland returns to the resting phase until a fresh demand is made for a large supply of iodine-containing secretion. In the thyroids of healthy animals the process stops short of total expenditure of the stored-up colloid, so that frequently small masses of this material are left behind in the vesicle around which the new colloid is deposited.

McCarrison/

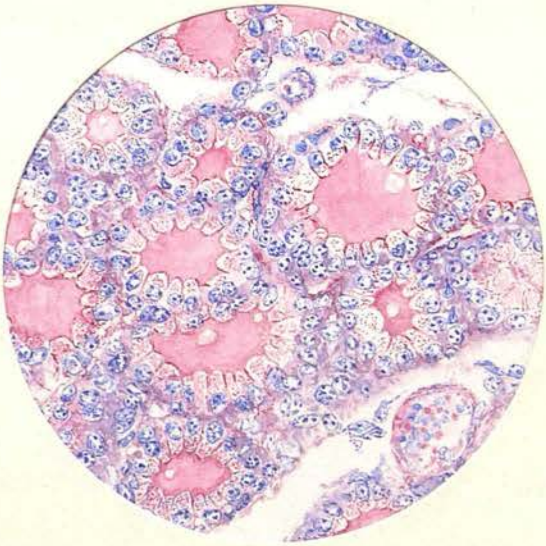


FIG. 75. A THYROID FROM A PREGNANT ANIMAL SHOWING AN EXTREME DEGREE OF SECRETORY ACTIVITY. THE CELLS ARE COLUMNAR AND RESEMBLE THOSE OF EXOPHTHALMIC GOITRE. THE VESICLES ARE SMALL.

IRON HAEMATOXYLIN + EOSIN. X 330.

McCarrison regards the colloid as a substance designed to contain an emergency reserve of iodine, a reserve which is not ordinarily called upon in the daily routine of the body demands. The thyroid cells elaborate the specific hormone for the daily needs, probably from substances supplied to them in the blood, without calling upon this reserve. The reserve store of iodine is only called upon under certain conditions, excessive sympathetic excitation, as in rage or fright, pregnancy, and so on. A distinction is to be drawn between the "thyroid secretion" and the"colloid"; the latter term ought to be restricted to the reserve store of the iodine-containing material. It is necessaey to realise that the stored-up colloid is no measure of the state of the activity of the gland at the time of its examination. This activity is indicated by the degree of parenchyma hyperplasia and by the amount of "secretion" lying between the cells and in the lymph spaces.

The secretory activity of the thyroid is very closely under the control of nerve impulses, the secretory fibres being derived from the cervical sympathetic. Cannon has shown that when the phrenic nerve is joined to the peripheral portion of the cervical sympathetic in the cat, and the thyroid is thus continuously/

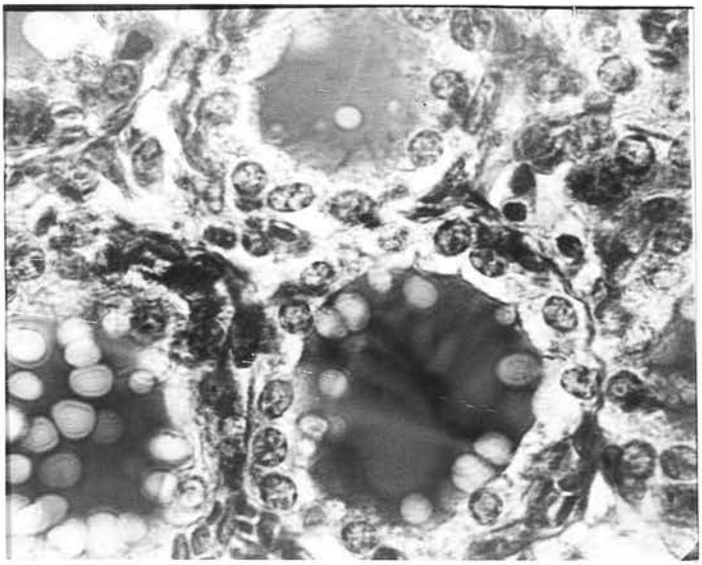


FIG. 76. GLOBULES OF FRESH SECRETION IN THE MIDST OF THE COLLOID.

IRON HAEMATOXYLIN & EOSIN X 710.

continuously stimulated as the animal breathes, this operation results in tachycardia, increased excitability, loose motions, exophthalmos on the operated side, great increase in the metabolism, and in some cases an increase in size of the adrenals. The superior and inferior laryngeal nerves seem to be concerned with trophic impulses; Exner found that after resection of these two nerves the amount of iodine in the gland remains unchanged, and Katzenstein reports the occurrence of histological degeneration after this procedure.

The Relationship between the Histological Appearances in the Healthy Active Gland and those of Pathological Affections associated with Toxic Symptoms.

It is becoming customary, especially in America, to subdivide cases of goitre into two main groups - the "simple" and the "toxic". In the latter group there occur symptoms resembling those of hyperthyroidism, while in the former group these are absent and the harmful effects of the thyroid enlargement are almost entirely local. Greenfield, in 1893, was the first to describe the pathological findings in exophthalmic goitre and to ascribe the clinical symptoms to a state of hypersecretion of the thyroid. It has been shown chiefly owing to the work of Plummer, that the group of/

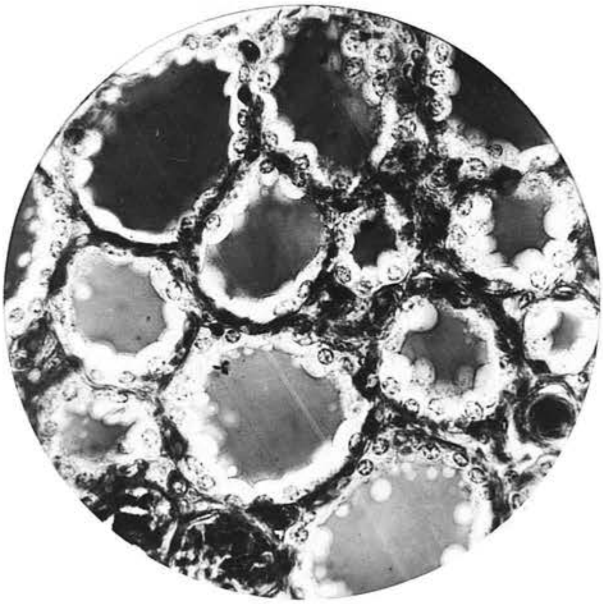


Fig. 77. A specimen showing the increased vascularity in pregnancy. The red blood cells are stained black with iron haematoxylin and form almost a complete circle round each vesicle.

Iron haematoxylin & eosin. X390.

of toxic goitres includes not only cases of exophthalmic goitre but also a second group consisting of cases of adenomata with toxic symptoms. Plummer has shown that cases of toxic adenoma constitutes about one fifth of the cases formerly included under the heading of exophathalmic goitre. The characteristic features of toxic adenomata are that, although in this condition there is a general resemblance to the symptoms of exophthalmic goitre, exophthalmos is absent, the symptoms generally are milder, they appear later in life, and supervene on a thyroid enlargement which has existed for ten or twenty years.

L. B. Wilson has recently made the following statement from a study of 1208 thyroids removed from patients of the Mayo Clinic, diagnosed clinically as having exophthalmic goitre, and of 2356 thyroids removed from patients diagnosed clinically as having simple goitre:-

"(a) The pathology of the thyroid in true exophthalmic goitre is essentially a primary parenchymatous hypertrophy and hyperplasia, that is, an increased amount of functioning parenchyma associated with increased absorption. The process is an acute one.

(b) The pathology of non-toxic/simple goitre is marked essentially by atrophic parenchyma, decreased function, and/

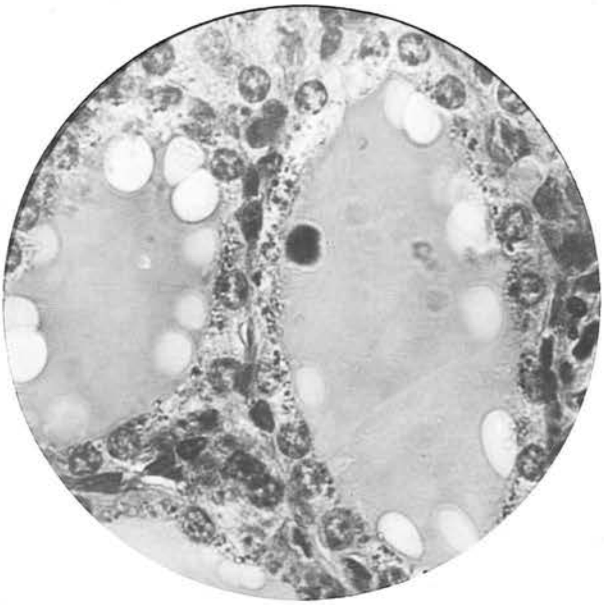


FIG. 78. A SPECIMEN SHOWING COARSE PIGMENT GRANULES IN THE CELL PROTOPLASM — PROBABLY AN OLD ANIMAL.

IRON HAEMATOXYLIN X 710.

and decreased absorption. The process is a chronic one. It is parallel in stages of development and regression with similar stages of development and regression of symptoms.

(c) The pathology of the thyroid in toxic non-exophthalmic goitre in cases most resembling ordinary exophthalmic goitre is probably one of increased parenchyma though regenerative processes in atrophic parenchyma, or the formation of new parenchyma of foetal type with an increase in each instance of secretory activity and absorption. The new parenchyma of foetal type may be diffuse or in definitely walled adenomas. The process is a chronic one.

(d) The above pathological evidence points to a constant relative association of increased secretion and increased absorption from the thyroid proportional to the degree of toxicity on the part of the patient. We have as yet no absolute proof that such secretion and absorption is the cause of the symptoms rather than co-ordinate with them, but the evidence presented strongly points to that conclusion".

Toxic goitre is almost universally claimed to be due to hypersecretion of the thyroid, because,(1) the symptoms of the disease are not unlike those produced by excessive adminstration of thyroid to a normal individual/

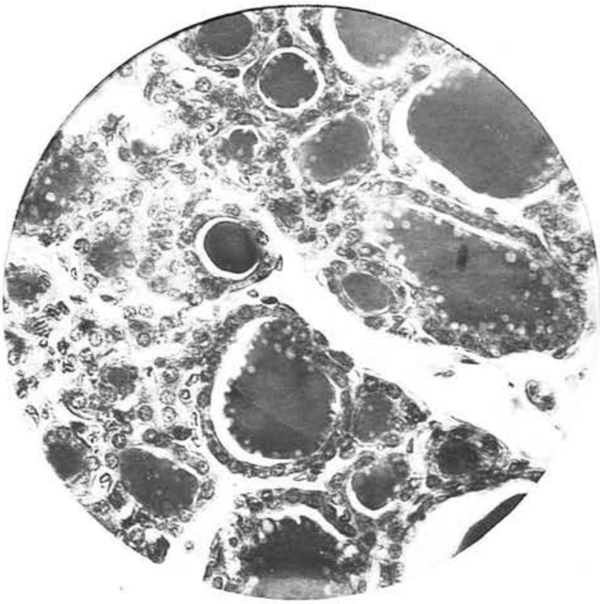


Fig. 79. A thyroid from a rabbit 7 days after parturition.
Globules of fresh secretion are present in the colloid.

iron haematoxylin & acid fuchsin X380.

individual; and (2) they are in general opposite in character to the symptoms found in cases where the thyroid gland is atrophied. Certain investigators, however, deny that it has been conclusively proved that toxic goitre is due to hypersecretion of the thyroid. They believe that the changes in the thyroid are the result of some obscure toxic condition which effects not the thyroid alone but initiates disturbances of the whole endocrine system. They hold that many of the symptoms in toxic goitre are due to derangements of other organs than the thyroid and that the secretion of the thyroid, although frequently increased in amount, is deficient in quality from the outset. In the consideration of this question it is of importance to ascertain how the histological appearances of the thyroid in toxic goitre compare with those of the normal active gland; if the condition in toxic goitre is purely one of hypersecretion, we should expect to find a close resemblance between the two histological pictures. It is necessary first to review the evidence in favour of one or the other opinion.

In addition to the facts already mentioned as supporting the theory of hypersecretion, mention may be made of the experiments of Reid Hunt, who showed that/

that the blood from a patient suffering from exophthalmic goitre when injected into mice increases their resistance to the toxic action of acetonitrile, this being also the case after thyroid extract has been injected.

Further evidence in support of this view is afforded by the resemblance in the effects on metabolism in toxic goitre and after administration of thyroid extract. It has been shown by Magnus-Levy, Salomon, Benedict, Boothby, and others that the metabolism in toxic goitre is characterised by an increased expenditure of energy. The respiratory interchange of gases shows an increase of 50 to 80 per cent in the amount of oxygen consumed. The increased consumption and the increased and remarkably fluctuating caloric production is partly the result of the augmented cardiac and respiratory activity; in part, and to an even greater degree, it is due to the nervous excitement and motor unrest, more particularly the tremor. But even in complete muscular repose there is still a large increase in the interchange of gases. For clinical purposes the increased energy production has been expressed by the estimation of the "basal metabolic rate". This is defined by Meakins & Davies as the rate of energy exchange, i.e., the number of calories/

calories per unit of time and per unit of body surface, under basal or resting conditions. The result is conveniently expressed as percentage increase or decrease, as compared with the known standard for the average normal individual of the same sex and age as the subject. Patients with complete atrophy of the thyroid have a basal metabolic rate about 40 per cent. below normal; in exophthalmic goitre the average metabolic rate is 57 per cent. above normal.

It has been shown that after the experimental administration of thyroid extract the metabolic rate is affected in exactly the same way as in exophthalmic goitre. It is an interesting fact that the active substance isolated by Kendall - thyroxin - affects the metabolic rate in the same way as thyroid extract. Thyroxin produces quickening of the pulse only when protein food is also taken; Kendall believes that this is to be explained by an association between the thyroid hormone and the metabolism of amino acids. He has shown that it relieves completely the symptoms of myxoedema.

The correspondence between the effects on the metabolic rate of administration of thyroid extract and the conditions in toxic goitre appear to prove that the increased energy production, at least, in toxic/

toxic goitre, is due to excess of thyroid secretion. The degenerative changes in the myocardium and also in the skeletal muscles - which Wilson has recently shown to be marked - the mental symptoms, the blood changes, and other features are less easily explained.

The results of surgical treatment have an important bearing on the nature of the essential lesion in toxic goitre. In toxic adenomata, at least, the results are striking. Barker of Baltimore says - "the results of surgical therapy for thyroid adenoma are particularly gratifying. One of the most striking things that a physician has opportunity to observe is the obvious relief that patients with outspoken hyperthyroidism experience within a few days after partial thyroidectomy". C. H. Mayo found that after removal of toxic adenomata the basal metabolic rate falls from 35 per cent. to 7 per cent. above normal usually within two weeks. Judd obtained 80 per cent. of cures in this condition. The results of partial thyroidectomy in true exophthalmic goitre are less striking but are frequently satisfactory. The beneficial effects of removal of a part of the thyroid in these conditions furnishes support for the opinion that the symptoms in toxic goitre are mainly due to an excess of thyroid secretion.

The/

The work of Durante & Wilson on the nerve cells and fibres of the cervical sympathetic is also of considerable significance in the consideration of this question. They have demonstrated very definite changes in cases of exophthalmic goitre. These changes consist of various stages of degeneration, namely, (a) hyperchromotisation, (b) hyperpigmentation, (c) chromatolysis, and (d) atrophy or granular degeneration of the nerve cells. All of these, according to Wilson, are but successive steps in degeneration, which, if uninterrupted, proceed to the complete destruction of the ganglion cells affected. Not all of the ganglion cells in any of the ganglia examined were so completely destroyed as to render improbable their return to normal under favourable conditions. Accompanying the more advanced changes in the ganglion cells are similar degenerative changes in the nerve fibres, and an increase of connective tissue throughout the ganglion, but especially in the outer and middle coats of the vessels and in the periganglionic tissue. The degree of hyperpigmentation, the amount of granular degeneration, the atrophy, and the reduction in the number of ganglion cells are approximately in direct relation to the continuation and subsequent remission of the toxic symptoms. The perivascular connective/

connective tissue and the connective tissue stroma generally through the ganglion are increased in direct ratio to the time during which the toxic symptoms had continued. These changes in the ganglion cells are quite distinct from those due to senility or to other prolonged wasting diseases.

There are two possibilities with regard to these changes in the ganglia. It is possible they result directly from the generally toxic condition in exophthalmic goitre, or, on the other hand, they may be due to a specific primary infection of the ganglion itself.

Experimentally, Wilson has been able by direct inoculations into the cervical sympathectic ganglion of goats to produce histological pictures within the ganglion and in the thyroid which resemble those found in exophthalmic goitre in man. He believes that these experiments, though few and far from conclusive, support the suggestion that in exophthalmic goitre the thyroid receives its stimulus through its nerve supply and as a result of over-stimulation of the cervical sympathetic ganglion.

The main facts supporting the hypersecretion theory - to recapitulate - are (1) the resemblance between the symptoms of toxic goitre and those of administration of large doses of thyroid extract or thyroxin/

thyroxin, (2) the contrast which the clinical picture presents to that of myxoedema, (3) the similar changes in the basal metabolic rate in toxic goitre and after administration of thyroid extract, and (4) the beneficial results of surgical therapy. The observations of Wilson & Durante appear to show that in toxic goitre the thyroid is stimulated by way of the cervical sympathetic, but they do not prove that the main factor in the disease is an excess of the normal secretion of the thyroid. If the ganglion changes are due to a toxic irritant, as Wilson suggests, the toxin involved may affect other tissues as well as the thyroid and the symptoms may be partly due to lesions elsewhere, particularly in the other endocrines.

Marine & Lenhart, McCarrison, and other investigators deny that it has yet been conclusively demonstrated that exophthalmic goitre is due to hypersecretion of the thyroid. Some authorities believe that the essential cause of the symptoms is the production of a preverted thyroid secretion - a condition of dysthyroidism; others believe that the thyroid changes are only a part of a widespread lesion involving especially the other endocrines and the lymphoid tissue throughout the body, and probably resulting from the presence of a toxic irritant.

McCarrison/

McCarrison emphasises the distinction between true hyperthyroidism and the symptoms of exophthalmic goitre. He believes that there is no sufficient evidence, either from experiments on animals or observations on man, that hyperthyroidism, that is to say, excess of the normal secretion of the thyroid gland, is the direct cause of the tachycardia, nervousness, or exophthalmos which characterise exophthalmic goitre. The symptoms of true hyperthyroidism are loss of weight, gastro-enteritis, diarrhoea, and an increase in the pulse rate proportionate to the increase in metabolism. His own view is that under pathological conditions the system is rarely flooded with a chemically unaltered secretion, but that the bio-chemical balance of the secretion may be so changed as to render it deficient in some respect or to impart to it a toxic quality. In the vast majority of cases, the excitation which determines the gland's derangement is toxic, and is one which initiates disturbances of the whole endocrine system.

There can be no doubt that, as McCarrison points out, in exophthalmic goitre the majority of the other endocrines may show profound alterations. Simmonds has shown that the thymus is persistent and hyperplastic in 75 per cent. of cases. Fry has described evidences/

evidences of over-activity with chromophilia in the anterior lobe of the piruitary. Marine & Lenhart have concluded that the facts that exophthalmos may be present either with the thyroid normal or with any degree of thyroid hyperplasia, and that there may be a marked thyroid hyperplasia without exophthalmos, weigh heavily against the view that thyroid hyperplasia is etiologically related to exophthalmos and towards the view that both phenomena are parallel, though often not synchronous manifestations of a fundamental and more obscure nutritional disturbance. Exophthalmos cannot be produced experimentally in animals by thyroid feeding. Gley records a case in which exophthalmos developed slowly in a rabbit from which he had removed the whole thyroid apparatus. Maurice of Lyons has shown that exophthalmos is due, not to excessive action of the thyroid, but to excessive action of the suprarenals. To the activity of the suprarenals is probably also to be attributed the "frightened facies" of exophthalmic goitre, as is suggested by the observations of Cannon. The occurrence of extensive pigmentation of the skin justifies the assumption that the suprarenals may ultimately be injured, and actual atrophic changes have been observed in these organs by Ratman. The lymphocytosis, often amounting to as much as 50 per cent., the nervousness, and/

and the occasional mental derangements are difficult of explanation on a basis of simple hyperthyroidism. The infiltration of the thyroid, the liver, and other organs with lymphocytes is very suggestive of a condition of chronic toxic irritation as the underlying factor of the disease.

It is believed that in the early stages of exophthalmic goitre an initial hyperplasia occurs in the thyroid which results in the flooding of the bloodstream with a secretion which at first is excessive in quantity, but from the commencement is deficient in quality. It is uncertain to what extent the initial increase in quantity makes up for the deficiency in quality; at all events, symptoms which might reasonably be attributed to hyperthyroidism form part of the clinical picture in the majority of cases during the earlier stages of the malady. But as the morbid change proceeds, exhaustion of the secreting cells occurs, and normal secretion is produced in gradually diminishing amount. Ultimately, the symptoms of myxoedema in major or in minor degree are added to the clinical picture. At a comparatively early stage in the disease-process there may be deficiency in some one or all of the chemical ingredients. Such symptoms as nervousness, tremor, and mental/

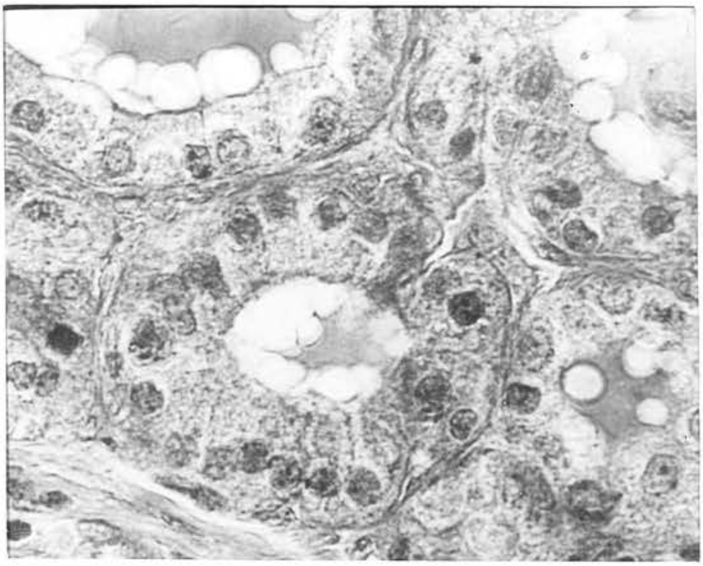


FIG. 80. EXOPHTHALMIC GOITRE. THE VESICLES ARE LINED WITH TALL COLUMNAR EPITHELIUM.

IRON HAEMATOXYLIN + EOSIN X 710.

mental derangements may be in some measure the consequence of these finer nutritional disturbances in the cells of the nervous system which this deficiency entails.

The changes in the quality and in the quantity of the thyroid's secretion in this disease are believed to be primarily the outcome of toxic irritation of the gland itself and of the sympathetic nerves controlling its secretion. Whether or not the secretion is so chemically altered during the course of the morbid process as to acquire a high degree of toxicity is still not proven. But in either event it is believed that it is the intervention of chemical substances derived from sources outside the thyroid gland which determines the result and imparts to Grave's disease its toxic character.

The principal facts which weigh against the hypersecretion theory are - (1) many of the symptoms of exophthalmic goitre, notably the exophthalmos and the mental symptoms, are not reproduced by the administration of thyroid extract, (2) hyperplasia of the gland may occur without producing exophthalmos, (3) the hypersecretion theory does not account for the persistence of the thymus, the tendency to fatty degeneration of the myocardium and the skeletal muscles, the blood/

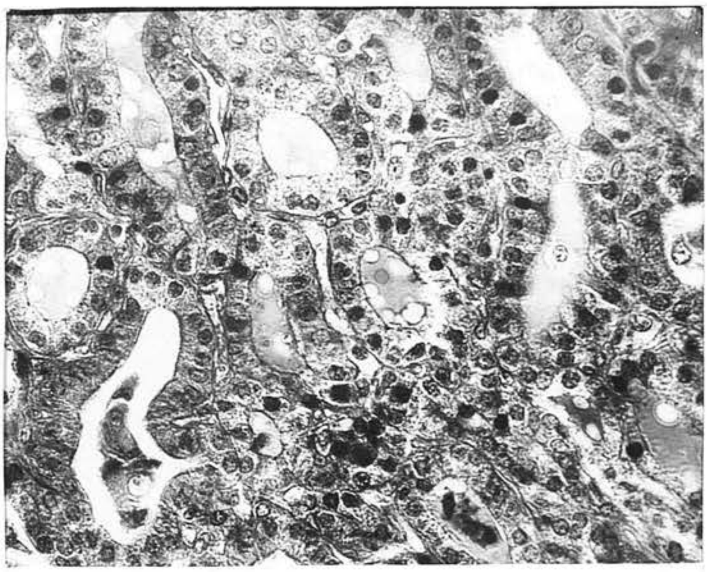


FIG. 81. ASYMMETRY AND CROWDING TOGETHER OF THE ALVEOLI IN EXOPHTHALMIC GOITRE.

IRON HAEMATOXYLIN + EOSIN X 380.

blood changes, the lymphocytic infiltration of the organs, and certain other features.

The injection into animals of blood from patients suffering from exophthalmic goitre does not appear to produce symptoms similar to those following the injection of thyroid extract; the results of such experiments, at least, have been confusing and indecisive. If the blood from these patients contained an excess of normal thyroid secretion, one would expect to obtain evidences of this by such injections.

The Histological Picture in Exopthalmic Goitre.

A specimen of the thyroid in this condition was obtained, for purposes of comparison, from a typical case operated upon by Mr. Lewis Beesly in Chalmers Hospital. The specimen was treated in the same way as the healthy thyroids, being fixed in Zenker's solution while still warm and stained in a similar manner.

The parenchyma in this specimen showed the signs of cellular activity to an extreme degree. The cells, instead of being cuboidal or low columnar as in the normal active gland, are almost uniformly tall columnar (Fig. 80). McCarrison states that tall columnar epithelium is never met with in the healthy thyroid, but with this statement I do not agree. In some cases/

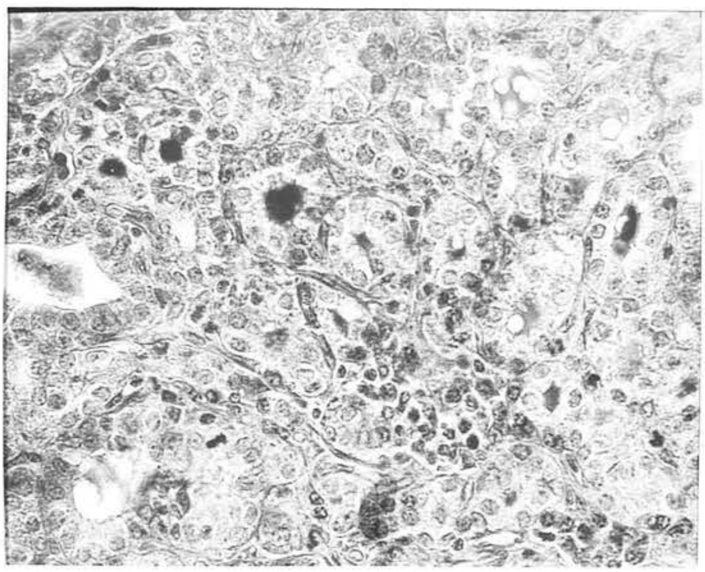


Fig. 82. A region of small newly-formed acini in exophthalmic goitre. These are derived from the intervesicular tissue.

Iron haematoxylin + eosin x 380.

cases this condition of the epithelium was met with in the guinea-pig in excessively active thyroids from pregnant animals (Fig. 75). The height of the epithelium affords a fair index to the state of activity of the gland. The cell protoplasm shows abundant granules. The nuclei in most cases are large and spherical with a distinct chromatin net-work, but in some regions they show considerable variations in appearance. Where the cells are closely crowded in the very active alveoli they tend to be small and darkly staining and may be slightly flattened. In some parts of the gland the cells lining the alveoli are several layers thick, and groups of cells or single cells may become desquamated and lie loose in the vesicle. The free edge of the tall columnar cells sometimes presents the slightly ragged appearance that may be seen in the cells of healthy active glands after a period of prolonged activity.

The alveoli show the greatest irregularity in shape (Fig. 81). In some regions they are small and rounded and more or less symmetrical, these represnting new forms developed in the intervesicular tissue (Fig. 82), but in most cases they are distorted and compressed. The most striking departure form the normal consists in the development of buds and papil-lary/

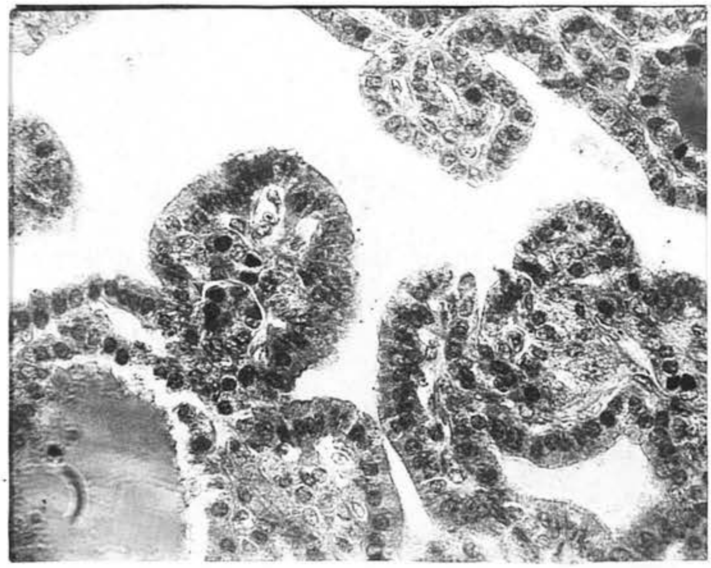


FIG. 83. PAPILLARY PROJECTIONS OF THE ACINAR WALL IN EXOPHTHALMIC GOITRE. THEY ARE COVERED WITH HYPERPLASTIC COLUMNAR EPITHELIUM.

IRON HAEMATOXYLIN + EOSIN X 380.

papillary projections of the acinar wall, such as are seen in Fig. 83 . These are developed in order to accomodate the hyperplastic epithelium, and they add to the asymmetry in the appearance of the vesicles. The contents of the vesicles stain only faintly in many regions, and in some parts appear to consist of clear newly-formed secretion. Occasionally the wall of a vesicle breaks down and the contents may escape into the surrounding connective tissue (Fig. 84).

In addition to these evidences of parenchyma hyperplasia, the thyroid in exophthalmic goitre presents certain other features which do not always receive sufficient consideration. In many regions there is an abundant infiltration with small lymphocyte-like cells (Fig. 85). Roussy & Clunet consider that unless this lymphoid proliferation is present, the condition cannot be considered to be one of true exophthalmic goitre. This feature cannot be explained by any theory of hypersecretion alone. It suggests strongly a response to the action of some toxic irritant and corresponds, to a certain extent, to the reaction on the part of the tissues in response to such toxins as those of syphilis and tuberculosis.

Another feature in which the thyroid of exophthalmic goitre differs from the normal active thyroid consists/

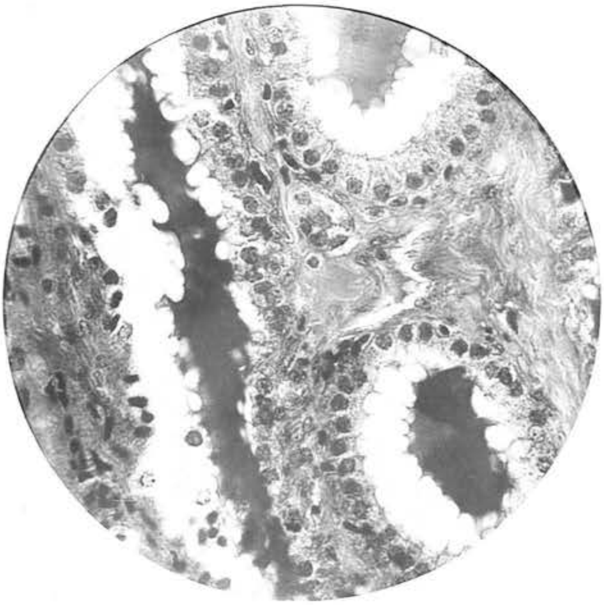


FIG. 84. RUPTURE OF A VESICLE IN EXOPHTHALMIC GOITRE. THE ESCAPING COLLOID IS IN DIRECT RELATION TO THE CONNECTIVE TISSUE STROMA — — ON THE LEFT.

IRON HAEMATOXYLIN + EOSIN X 380.

consists in the very marked thickening of the connective tissue framework which takes place. The trabeculae of connective tissue which separate the lobules from each other are enormously thicker and coarser than in the healthy gland. There is a resemblance in this respect to the changes which occur in the mammary gland in chronic mastitis, or in the pancreas in chronic pancreatitis in response to chronic toxic irritation. The vessels show in places a very definite condition of obliterative enderteritis (Fig 87)

The histological picture in exophthalmic goitre is therefore one of a state of frenzied activity on the part of the parenchyma, combined with changes in the stroma and vessels of the gland which correspond to those seen elsewhere as the result of a toxic irritant. The parenchyma changes are an exaggeration of those seen in the healthy gland in a state of active secretion.

The Histological Picture in Toxic Adenoma.

Toxic adenoma is the most common type of toxic non-exophthalmic goitre. A specimen of this condition was obtained at operation from a case operated on by Mr. F. E. Jardine. Portions were fixed in Flemming's solution and in Zenker's solution and stained in the same way as the others. According to Plummer, the symptoms/

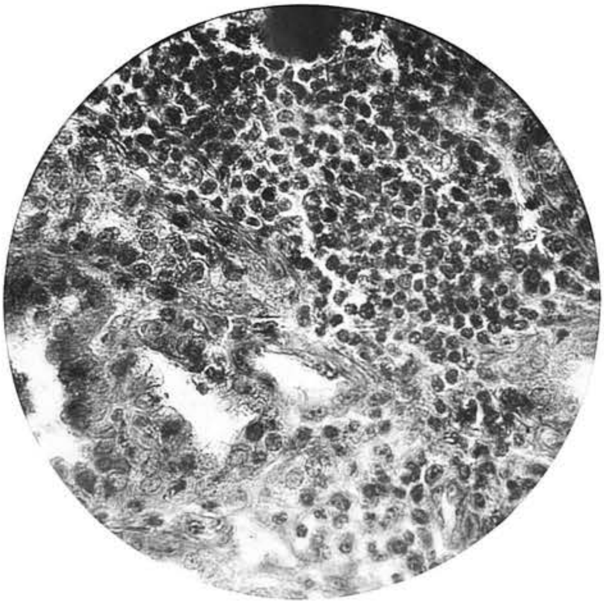


FIG. 85. INFILTRATION WITH LYMPHOCYTE-LIKE CELLS IN EXOPHTHALMIC GOITRE.

IRON HAEMATOXYLIN + EOSIN X380.

symptoms of toxaemia in patients with toxic adenomata appear in patients who have had goitres on an average of fourteen and a half years, and the patients come for operation on an average of three years later. They do not have exophthalmos, but have tachycardia, tremor, loss of weight, and nervousness, which appear when the patients are from five to ten years older than the average patient is when the symptoms of exophthalmic goitre develop. Boothby, Meakins & Davies, and others have shown that the basal metabolic rate is increased in much the same way as in exophthalmic goitre.

In the patient from whom the specimen was obtain- a thyroid swelling had been present for some ten years, and toxic symptoms had appeared about six months previous to operation. It was an interesting feature in this case that a similar swelling in a sister of the patient had followed exactly the same course. The development of nervousness, irritability of temper, and other symptoms were readily recognised, and, operation in the first sister having been followed by the most satisfactory results, the second patient came for surgical treatment sooner than she would otherwise have done. The tumour was a definite adenoma and was readily shelled out from a well-marked capsule.

Mr. J. M. Graham kindly lent another specimen of this/

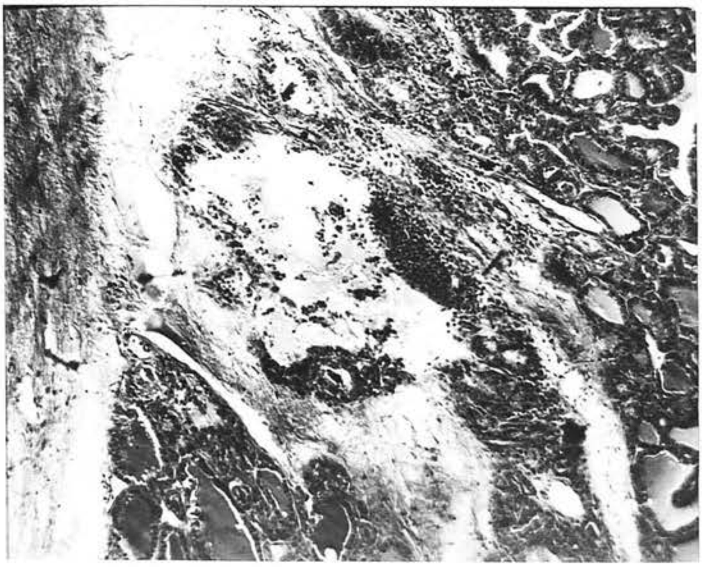


FIG. 86. EXOPHTHALMIC GOITRE. THIS SHOWS A PART OF THE THICKENED CONNECTIVE TISSUE STROMA WITH LYMPHOCYTIC INFILTRATION. NEAR THE CENTRE THERE IS SOME LOOSE COLLOID DERIVED FROM A RUPTURED VESICLE.

IRON HAEMATOXYLIN + EOSIN X 82.

this condition and an example of simple goitre for comparison.

Wilson has shown that in toxic adenomata of the "adult" type the appearance of toxic symptoms is due to regeneration in previously atrophied parenchyma. In the specimen obtained at operation evidence of the old-standing retrogressive changes were well-marked in the form of extensive calcification, and also in the presence of numerous large spaces lined with flattened atrophied cells and distended with colloid which was often basic staining. Areas of regeneration were abundantly present. The newly-formed alveoli are frequently small, they are markedly asymmetrical, and present a close resemblance to those of exophthalmic goitre (Fig. 88). The lining parenchyma cells are mostly cuboidal in shape, though here and there columnar epithelium is present. They do not generally attain to the height of the cells in exophthalmic goitre but resemble rather, in this respect, the cells of a healthy gland in a moderately active state. This difference in the height of the cells corresponds to the difference in the acuteness of the symptoms in the two forms of goitre; those of toxic adenoma are always milder and progress more slowly than in exophthalmic goitre. The resemblance between the cells of toxic adenoma/

FIG. 87. ENDARTERITIS OBLITERANS IN EXOPHTHALMIC GOITRE.

IRON HAEMATOXYLIN & EOSIN X 150.

adenoma and those of a normal active gland suggests that the secretion may not be excessive in amount in this condition - not necessarily greater than in a state of physiological activity, such as pregnancy. If such is the case, then the toxic symptoms must be due, not to excess of secretion, but to the production of a secretion which is abnormal in character - a condition of dysthyroidism.

Budding and plication of the epithelial lining of the acini was met with in the toxic adenoma, but to a less extent than in exophthalmic goitre. The same may be said with regard to desquamation of epithelium. The vesicles generally contained abundant densely-staining colloid, though the smaller and more active alveoli frequently contained only clear secretion. The specimen lent by Mr. Graham, from which Fig. is taken showed the same combination of old retrogressive changes with recent hyperplasia. The specimen of simple goitre (Fig. 90) shows no similar proliferative changes but consists almost entirely of large colloid spaces lined with atrophied parenchyma. These spaces are similar to those observed in the old-standing areas of the toxic adenoma.

Lymphocytic infiltration occurred in the toxic adenoma (Fig.) to an even greater degree than in exophthalmic/

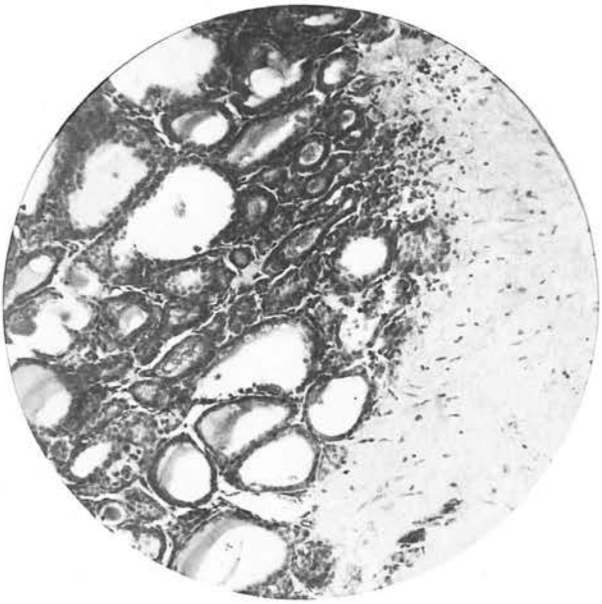


FIG. 88. Mr GRAHAM'S SPECIMEN OF TOXIC ADENOMA. MANY OF THE NEWLY-FORMED ALVEOLI ARE SMALL AND IRREGULAR IN SHAPE.

X ~~150~~ 82.

exophthalmic goitre. This fact has received very little attention in the literature and appears to be a point of considerable significance. It suggests again a reaction to some toxic agent which has not yet been recognised. It may be that this toxic substance is also the prime factor in causing the hyperactivity of the parenchyma cells - possibly through the agency of the cervical sympathetic, as the work of Wilson & Durante affords grounds for believing. The connective tissue stroma shows the same hyperplasia as in exophthalmic goitre.

The principal conclusions that suggest themselves after the examination of the histological picture in the two main types of toxic goitre and a comparison with the signs of activity in the healthy gland are - (1) the pathological changes in the two forms of toxic goitre are essentially the same, though the parenchyma changes differ in degree; (2) they show a marked deviation from the appearance of a healthy active gland; (3) they do not support the view that the symptoms in toxic goitre are due to hypersecretion pure and simple; (4) they strongly support the view that there exists in cases of both exophthalmic goitre and toxic adenoma some circulating poison, which causes a reaction in the gland corresponding to that seen in chronic toxic conditions/

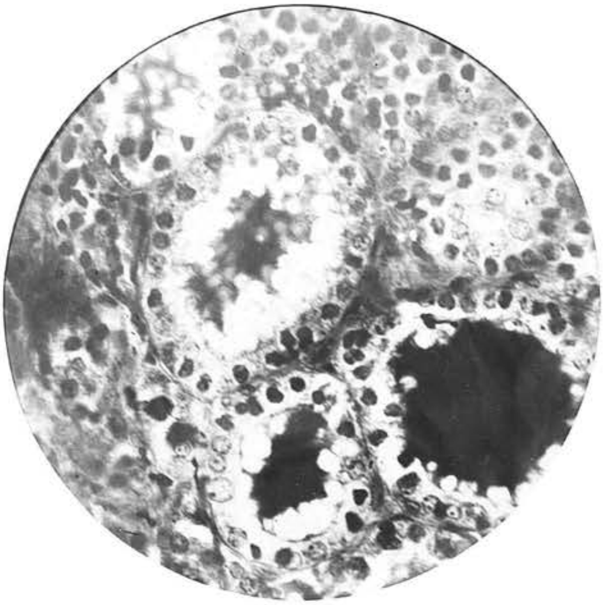


FIG.89. TOXIC ADENOMA. THE CELLS LINING THE ALVEOLI ARE CUBOIDAL IN SHAPE.

IRON HAEMATOXYLIN + EOSIN X380.

conditions elsewhere. It may be that this circulating toxin is the essential cause of the disease.

The Nature of the Intervesicular Tissue of the Thyroid.

The spaces between the vesicles of the thyroid are filled up by groups of cells which form the intervesicular parenchyma. The physiological significance of these cells has been the subject of much discussion. Swale Vincent & Jolly have attempted to show that these cells are essentially the same as those of the parathyroid, and their views have been supported by Halpenny, Forsyth, and the late Mrs. F. D. Thompson. The last investigator considered the subject from a widely comparative standpoint. Clinical observers, on the other hand, notably Wilson & McCarrison, consider that the intervesicular tissue is made up of cells which are similar to those lining the vesicles and that its sole function is to provide a reserve store of parenchyma from which new vesicles can be formed when an increased demand is made upon the functions of the gland. Kohn, Vassale, Generali, and other observers have also urged the view that the thyroids and the parathyroids are entirely distinct, both morphologically and physiologically.

An examination of the intervesicular parenchyma in/

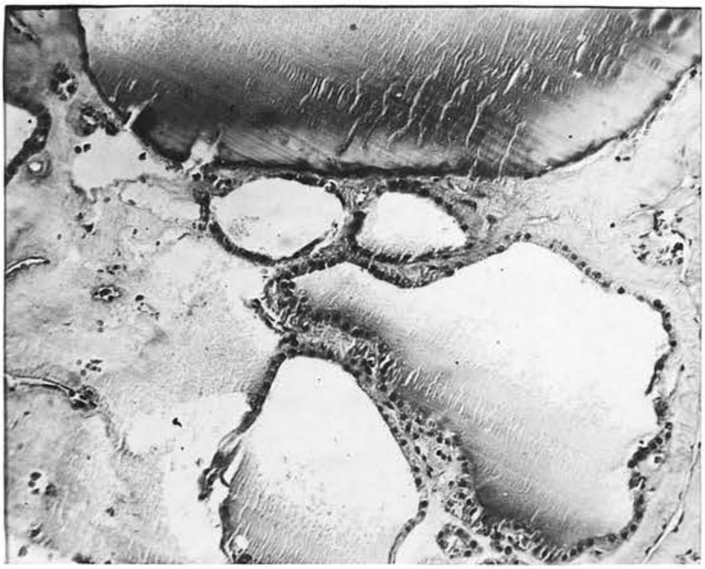


FIG. 90. A SPECIMEN OF NON-TOXIC SIMPLE GOITRE FOR COMPARISON WITH TOXIC ADENOMA. THE ALVEOLI ARE LARGE AND DISTENDED WITH COLLOID. THEY ARE LINED WITH FLATTENED CELLS.

M^c GRAHAM'S SPECIMEN. X ~~150~~ .82.

in pregnant and non-pregnant animals is very enlightening in the investigation of the essential nature of this tissue.

Vincent has laid stress upon the fact that the thyroid and the parathyroids are derived from very similar sources, and even in the fully developed state there is no fundamental difference between the constituent cells. He believes that the intervesicular tissue is to all intents and purposes identical with that of the parathyroids, and states that the instances of tissue continuity and gradual transitions and intermediate types from thyroid to parathyroid are described. In perhaps the majority of cases the transition forms are best seen between thyroid and internal parathyroid, though in the ox and the human subject such transitions are shown to exist between thyroid and external parathyroid.

Halpenny & Thomson state that after removal of all the parathyroids there is a multiplication of the intervesicular cells of the thyroid which they believe to be of the same nature as the cells of the parathyroids; Vincent & Jolly found that, on microscopic examination of parathyroids left _in situ_ after thyroidectomy, vesicles containing colloid material were met with which presented a close resemblance to the vesicles/

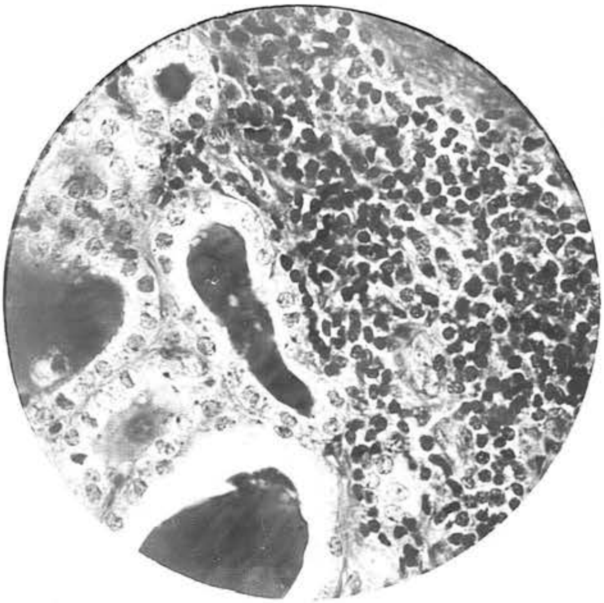


FIG. 91. LYMPHOCYTIC INFILTRATION IN TOXIC ADENOMA. THIS RESEMBLES THE CONDITION REFERRED TO IN EXOPHTHALMIC GOITRE.

IRON HAEMATOXYLIN + EOSIN X 380.

vesicles of the thyroid. These workers believe that the one kind of tissue can function vicariously for the other. It has been suggested by the opponents of this view that the last-named workers were dealing with portions of thyroid tissue undergoing hyperplasia, possibly in the form of accessory thyroids.

Mrs. Thompson, as the result of her comparative anatomical studies, expressed the view that, while in the lower vertebrates, the thyroid and the parathyroids are completely separate, both developmentally and structurally, in birds and mammals the tissues of the two organs are largely intermixed. It is certainly the case that in normal animals colloid-containing vesicles resembling those of the thyroid are sometimes found in the parathyroid. These vesicles, however, are very infrequent; I have met with no example in the parathyroid of the guinea-pig. They are probably to be regarded as accidental inclusions of thyroid tissue during development, corresponding to the parathyroid inclusions that are commonly seen in the thymus.

Wilson looks on the thyroid as "a congeries of a great number of groups of cells which may be found even in the adult in any stage of development from masses of unarranged embryonic cells (Wölfler's rests) through tightly packed, concentrically arranged groups of/

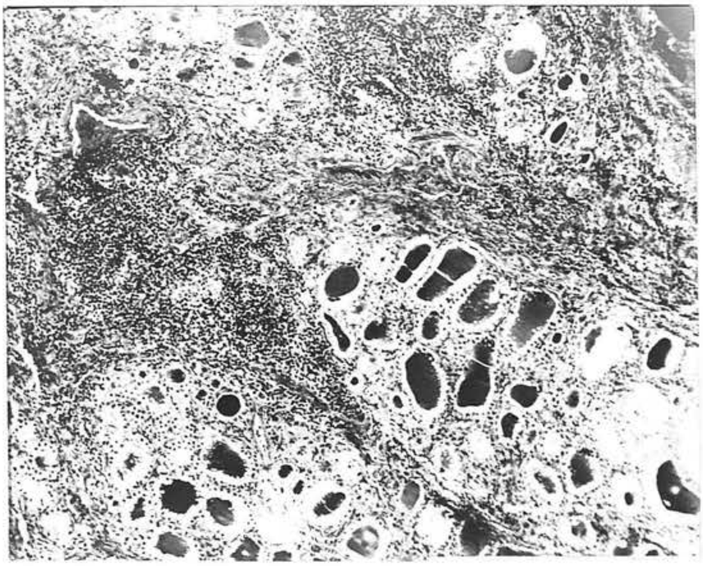


FIG. 92. TOXIC ADENOMA. THIS SHOWS THICKENING OF THE STROMA WITH A MARKED DEGREE OF LYMPHOCYTIC INFILTRATION.

IRON HAEMATOXYLIN + EOSIN. X 79.

of embryonic epithelial cells, to well-developed follicles lined with epithelium, evidently capable of secreting into the well-marked central cavity". He has shown that in toxic goitre the solid clumps of cells are transformed into new vesicles. In exophthalmic goitre the Wolfler's rests may have entirely disappeared. These facts are of the greatest significance in relation to the question under discussion.

McCarrison believes that all parenchyma cells, whether lining the vesicles or not, may, if occasion demands, form themselves into new vesicles and take part in the formation of the gland's secretion.

The guinea-pig forms a good subject for the examination of the intervesicular tissue. The cells are large and the details of their structure can be readily investigated. Fig. 93 shows groups of intervesicular cells under a high power in an actively secreting thyroid. These cells resemble very closely in appearance those which are lining the adjacent vesicles. The nuclei are similar in shape and size and the staining reactions are the same. It is true, as Swale Vincent claims, that there is a superficial resemblance between the intervesicular cells and those of the parathyroid. The resemblance, however, is only superficial and the two types of cell can be readily/

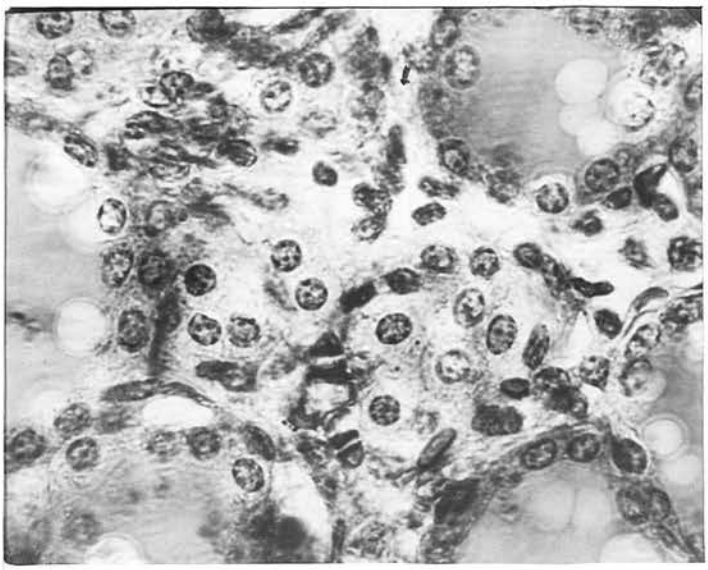


FIG. 93. THE INTERVESICULAR TISSUE OF THE THYROID OF THE GUINEA-PIG. THE CELLS RESEMBLE THOSE LINING THE ALVEOLI.

IRON HAEMATOXYLIN + EOSIN. X 710.

readily distinguished. Fig. 94 shows an internal parathyroid in the guinea-pig at the junction with the thyroid tissue. There is no encapsulation of the parathyroid cells, but the line of demarcation is quite definite. The parathyroid cells are distinctly more darkly stained than the intervesicular thyroid cells, both as regards the nuclei and the cell protoplasm. The ease of differentiation here suggests comparison with the region in the pituitary at the side of the cleft where the cells of the pars anterior and pars intermedia intermingle. In both cases the two types of cell are readily distinguished from each other.

In pregnant animals it is possible to show that the intervesicular cells undoubtedly undergo transformation into actively secreting vesicles. It is important, in relation to this question, to keep in mind the original mode of development of the thyroid vesicles. In the embryo the original epithelial outgrowth forms groups of small epithelial masses in which vesicles are formed by the breaking down of the central cells of a given epithelial mass. When an increased demand is made upon the functions of the gland, as in pregnancy, this process is repeated in relation to the intervesicular tissue. The various stages in the transformation/

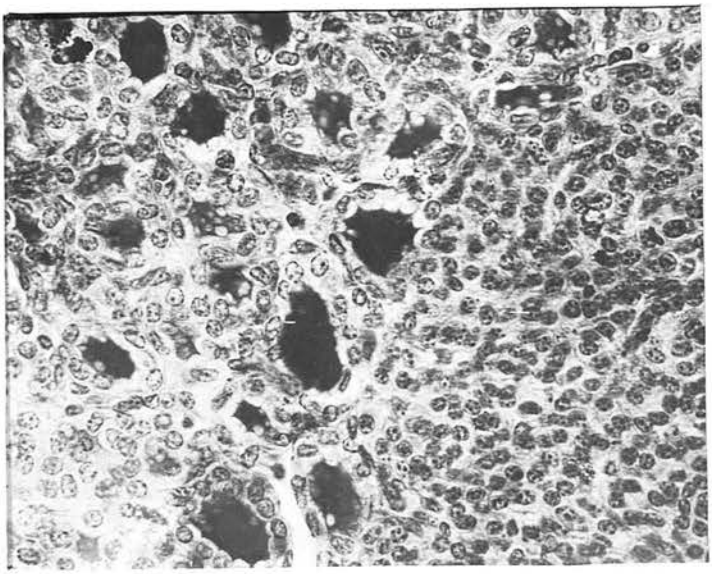


Fig. 94. An internal parathyroid in the thyroid of the guinea-pig. The cells stain more darkly than those of the adjacent intervesicular tissue of the thyroid.

Safranin X380.

transformation from solid groups of cells to secreting vesicles are seen in Figs. 95 to 99 . Fig 95 shows the appearance of the intervesicular tissue in the resting thyroid of a non-pregnant animal. The cells are arranged in solid clumps in a more or less concentric fashion. In pregnant animals these groups become transformed from solid clumps into small actively -secreting vesicles. The stages in the process of transition are, firstly, the appearance of faintly-staining colloid material in and between the cells; the nuclei of the central cells become indistinct and disappear; ultimately the central cells become completely disintegrated and mingle with the colloid, though the cell-outlines may remain visible after all trace of nucleus and cell protoplasm have vanished. The cells at the periphery of the group remain as the lining epithelium of the newly-formed vesicle. Appearances such as those of the transition groups in Figs. 95-97 might suggest that they are due to the vesicles being cut towards their extremities, but this is not the case since the outlines of disintegrating nuclei are plainly visible. Moreover, these transition forms show a very marked increase in number in pregnancy, while they are rare in the thyroids of non-pregnant animals.

The/

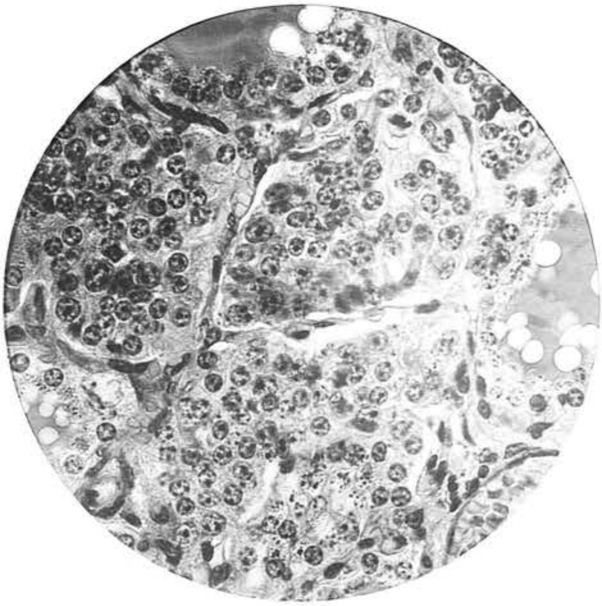


FIG. 95. THE INTERVESICULAR TISSUE IN A NON-PREGNANT GUINEA-PIG. THE CELLS ARE ARRANGED IN SOLID CLUMPS.

IRON HAEMATOXYLIN + EOSIN X380.

The examination of the series of pregnant and non-pregnant animals affords strong evidence in support of the view that the intervesicular tissue constitutes a reserve store of parenchyma from which new vesicles can be formed when an increased demand is made upon the functions of the gland, as in pregnancy. The pathological observations of Wilson and the manner of development of the vesicles are also in favour of this belief. The only observation suggesting an intimate physiological relationship to the parathyroids has been the occasional occurrence, in the rabbit only, of thyroid vesicles in the midst of the parathyroid tissue. This appearance is probably the result of an accidental developmental inclusion.

The Significance of the Signs of Increased Thyroid Activity in Pregnancy.

The relationship between the thyroid and the activities of the reproductive system is well known. This is illustrated by the increased activity of the gland at puberty, menstruation, and in pregnancy, and also by the depression of the sexual functions which occurs in myxoedema and in cachexia strumipriva. In pregnant animals the gland almost invariably shows well-marked signs of secretory activity, sometimes to an/

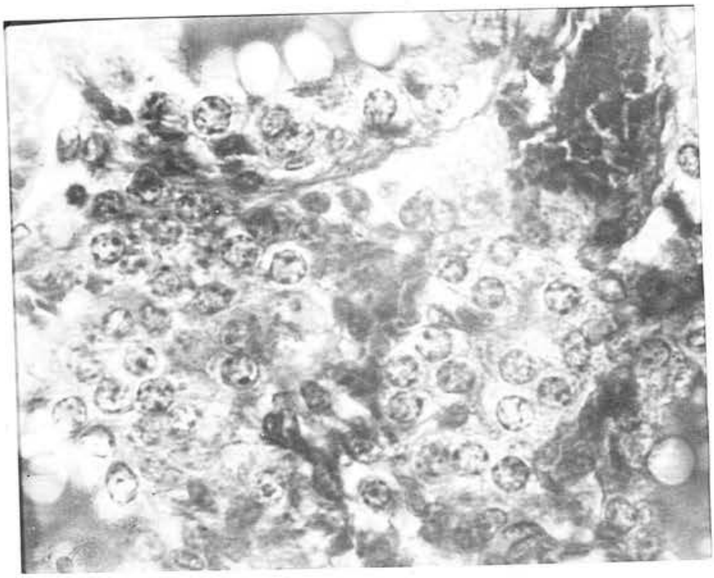


FIG. 96. THE INTERVESICULAR TISSUE IN A PREGNANT ANIMAL. COLLOID IS BEGINNING TO APPEAR BETWEEN THE CELLS.

IRON HAEMATOXYLIN + EOSIN. X 710.

an extreme degree (Fig. 75). The intervesicular tissue undergoes a gradual transformation into vesicles and towards the end of pregnancy, in the guinea-pig, may have become very scanty in amount (Fig. 101).

The increased activity of the thyroid in pregnancy is to be attributed in part to the hyperactive state of the sex organs and in part also to the increase in the maternal metabolism. The increase in metabolism is evidenced by the rise in the basal metabolic rate as described by Meakins & Davies. There is little doubt that the thyroid hyperplasia is dependent also on the demand by the tissues of the developing embryos for thyroid secretion. The thyroid of the foetus and of the newly-born child is in a relatively inactive state; it contains little or no iodine, the vesicles are smaller and fewer in number, so that the intervesicular tissue is increased in comparison, and they contain less colloid than in later years. In the early stages of its career, therefore, the organism is dependent to a large extent on the maternal thyroid secretion, transmitted by the blood-stream and placental circulation during the intra-uterine period, and by the maternal milk in the early weeks or months of extra-uterine existence. It has been shown that subthyroidism in the mother may retard infantile development.

That/

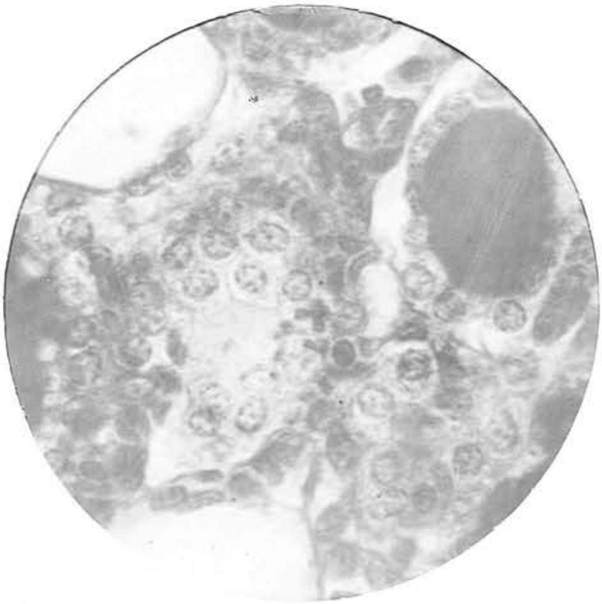


FIG. 97. THE TRANSITION OF THE INTERVESICULAR TISSUE IN A PREGNANT ANIMAL. THE CELLS IN THE CENTRE OF THE GROUP ARE BEING TRANSFORMED INTO COLLOID.

IRON HAEMATOXYLIN & EOSIN X 710.

That the thyroid's secretion is essential to the developing and growing tissues is certain. The feeding experiments carried out by Gundernatsch and subsequently by Rogoff & Marine, indicate that the thyroid hormone has a powerful influence on the development of the body. Tadpoles fed upon thyroid substance showed a striking acceleration of the normal metamorphosis. Those fed with the glandular material grew less rapidly than the controls fed upon ordinary diet, but the tails of the former showed more rapid involution and the arm buds developed prematurely. In cretinism, where the thyroid is atrophied at birth, the effects on growth of bone, especially the failure at the epiphysial junctions, the derangement of the nutrition of the muscular and connective tissues, and the defective development of the repropductive and nervous systems are well known.

The relationship between the thyroid and the maintenance of the constituents of the blood-red cells, white cells, haemaglobin, and salts - at a proper level may also have a bearing on the hyperplasia of pregnancy. It has been shown that the functional activity of the gland appears to increase with residence at increasing heights above sea-level. This increased action is necessitated by the gland's influence in/

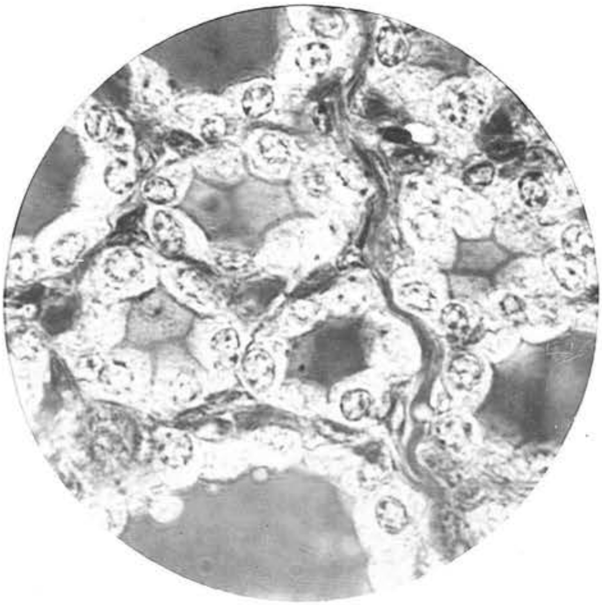


Fig. 98. Small newly-formed alveoli derived from the intervesicular tissue. The cell outlines and, in some cases, the disintegrating nuclei are still visible.

Iron haematoxylin + acid fuchsin X 710.

in maintaining the red cells and haemoglobin at a level appropriate to the altitude. The effect of altitude being to call for a rapid rise in the blood's red cell and haemoglobin-content, the thyroid responds to this call by increased action. In pregnancy the the thyroid's activity in this respect must be called upon in connection with the increased blood-supply to the developing uterus and to the maternal tissues generally - in accordance with the increased metabolic rate - and also, no doubt, in connection with the establishment and maintenance of the foetal circulation.

CONCLUSIONS.

1. A cyst-like space resembling the post-branchial body of the lower animals is sometimes met with in the thyroid of the rabbit and the parathyroid of the guinea-pig.

2. The thyroid of pregnant animals shows well-marked signs of secretory activity. The increased activity is probably dependent on the increased metabolic rate of pregnancy, the state of the reproductive system, the increased blood-supply to the rapidly-growing uterus and the maternal tissues generally, and also on the demands of the developing foetal tissues.

3. The principal evidences of secretory activity are/

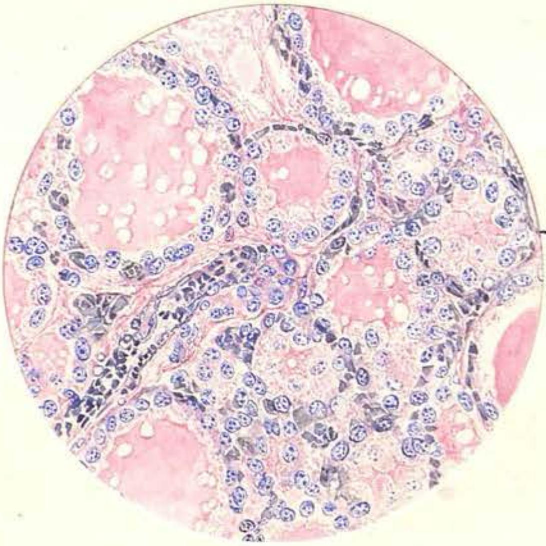


FIG. 99. TRANSITION OF THE INTERVESICULAR TISSUE IN A PREGNANT ANIMAL. THE CELL OUTLINES AND THE NUCLEI ARE STILL VISIBLE BUT ARE BEING TRANSFORMED INTO COLLOID.

IRON HAEMATOXYLIN + ACID FUCHSIN X 330.

GLOBULES OF CLEAR NEWLY FORMED SECRETION ARE SEEN IN THE VESICLES.

are (a) an increase in the height of the follicular cells to a cuboidal or low columnar shape: (b) the appearance of clear fresh secretion in the vesicles and in the lymphatics of the gland; (c) a gradual solution and absorption of the colloid; and (d) an increased vascularity.

4. The colloid probably represents a substance containing an emergency reserve of iodine. Under normal conditions the thyroid secretion passes directly from the cells into the lymphatics or blood-vessels without entering the lumen of the vesicles.

5. A comparison between the active gland of healthy pregnant animals and the thyroid in toxic goitre shows that (a) in toxic goitre the parenchyma changes are an exaggeration of those seen in the healthy gland in a state of active secretion; (b) in both forms of toxic goitre there is a marked degree of infiltration with lymphocytes; (c) the connective tissue framework shows considerable hyperplasia; (d) in exophthalmic goitre there is frequently well-marked endarteritis obliterans. The parenchyma changes are in accordance with a theory of hyperthyroidism as the explanation of the symptoms in toxic goitre, but the last three conditions named are difficult of explanation on such a theory. They present a close resemblance to the reaction seen in other/

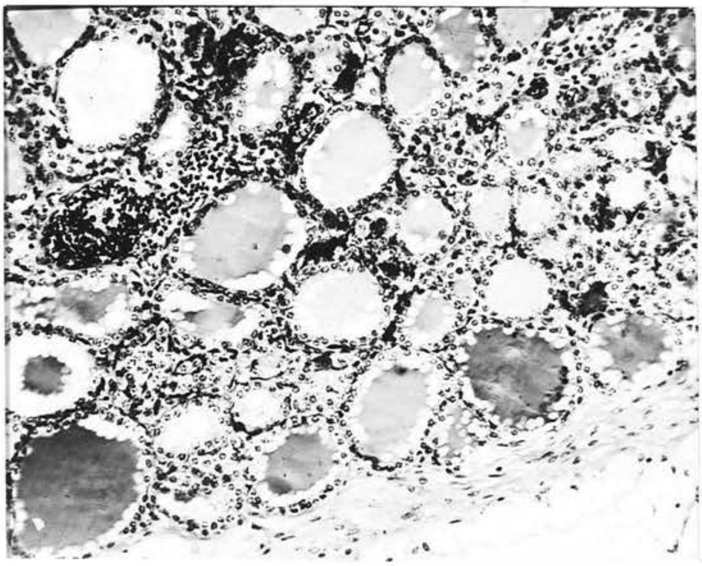


FIG. 100. A THYROID FROM A NON-PREGNANT ANIMAL SHOWING THE RELATIVELY LARGE AMOUNT OF INTER-VESICULAR TISSUE.

IRON HAEMATOXYLIN & EOSIN X 79.

other organs as a response to chronic toxic irritation.

6. The parenchyma changes are less marked in toxic adenoma than in exophthalmic goitre. This corresponds to the milder character of the symptoms in the former condition.

7. The intervesicular cells of the thyroid present a superficial resemblance to those of the parathyroid, but differences in their staining reactions can be detected. In pregnant animals the intervesicular tissue can be traced in its transformation from solid groups of cells into newly-formed alveoli. It is to be regarded as reserve parenchyma which can be transformed into vesicles when an increased demand is made on the functions of the gland. This view is supported by the original method of development of the vesicles and by the appearances seen in toxic goitre.

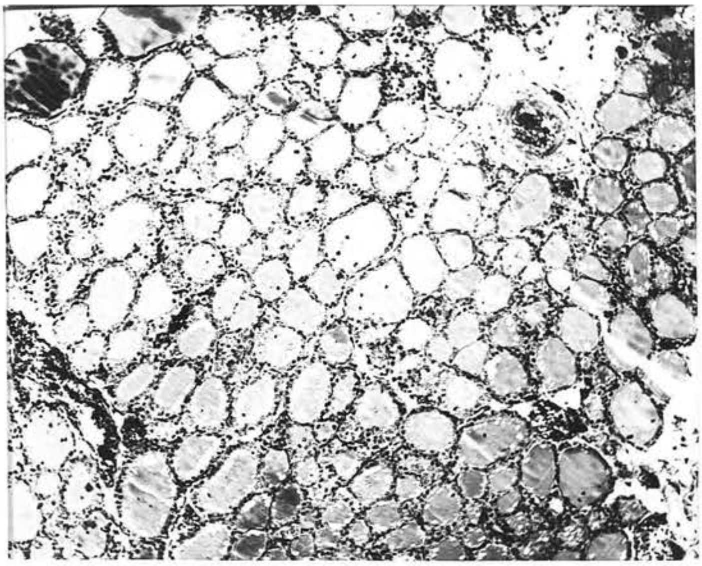


FIG. 101. A THYROID FROM A GUINEA-PIG AT AN ADVANCED STAGE OF PREGNANCY. THE INTERVESICULAR TISSUE IS SCANTY, HAVING BEEN TRANSFORMED INTO ACTIVE VESICLES.

IRON HAEMATOXYLIN X 79.

THE PARATHYROIDS.

That there is an increased demand on the functions of the parathyroids during pregnancy is proved by the observation that after partial parathyroidectomy in the dog, tetany may develop only when the animal becomes pregnant. Vassale observed this condition for the first time in a bitch from which three parathyroid glands had been removed. Adler & Thaler found that when animals, which appear perfectly sound after the removal of two or three parathyroids, become pregnant, pregnancy is heralded by an outbreak of tetany. After partial parathyroidectomy the animal is regarded as being in a state of potential tetany, the fits only developing when the conditions of pregnancy bring about an increased demand on the functions of the organs.

Morphology.

The number and arrangement of the parathyroids vary considerably in different species and also in different members of the same species. In the rabbit they are usually four in number, and in this animal, parathyroid IV, from the fourth visceral pouch, is an "internal" parathyroid, being situated in the substance of the thyroid, while parathyroid III, from the third/

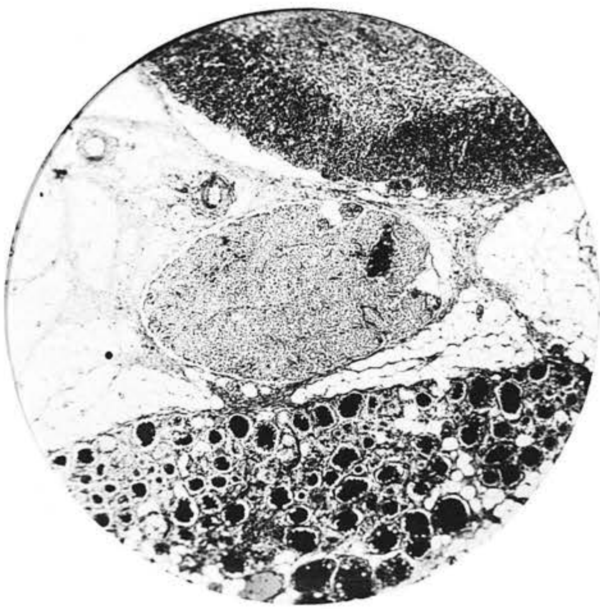


FIG. 102. AN EXTERNAL PARATHYROID IN THE GUINEA-PIG.
IT LIES ON THE LATERAL SURFACE OF THE THYROID.
A PORTION OF THE THYMUS IS ALSO SEEN IN THIS SPECIMEN.

IRON HAEMATOXYLIN + ACID FUCHSIN. X 79.

third pouch, remains outside the thyroid as an "internal" parathyroid. In the guinea-pig, according to Schäfer, only parathyroid III is ordinarily present and this varies greatly in position relatively to the thyroid. In my experience it is nearly always an external parathyroid lying superficial to the thyroid on the surface of the lateral lobe (Fig.102); it may be either towards the anterior or the posterior part of the surface. Occasionally an internal parathyroid is present in addition (Fig.103). One specimen showed two external parathyroids lying close together. In some cases the parathyroid of the guinea-pig lies immediately under the capsule of the thyroid (Fig.104) so that it is intermediate in position between an "external" and an "internal" parathyroid.

C. H. Mayo emphasises the variability in number and position in the human subject. In 125 autopsies Berkeley found about an average of two and a half parathyroids per person; in 138 autopsies by Verebely, four parathyroids were found 108 times. It is common to find thyroid nodules, portions of thymus, or lymph nodes in the neighbourhood of the usual site of the parathyroids. In 263 specimens selected as resembling parathyroids, Rogers & Ferguson found that 111 proved to be thyroid tissue in large part. Ginsburg emphasises/

FIG. 103. A SPECIMEN SHOWING BOTH AN EXTERNAL AND AN INTERNAL PARATHYROID IN THE GUINEA-PIG.

SAFRANIN. X 23.

emphasises the difficulty in differentiating parathyroids from closely allied lymphatic nodes. The omission of a histological examination probably explains in some cases the conflicting statements on the subject. Mayo finds that the parathyroids are nearly always in relation to the "channel" of anastomosis between the superior and inferior thyroid arteries. Accessory and aberrant parathyroids are not infrequent. Small cellular accumulations have been described by Muller & Erdheim. These are sometimes sufficient in amount to defeat the object in attempted complete parathyroidectomy.

Halstead & Evans describe the human parathyroids as flattened, ovoid, or reniform bodies, each covered by a thin fibrous capsule, beneath which a fine anastomosis can be seen. The surface presents an exceedingly fine, barely visible, granular appearance, probably due to the blood-vessels. The colour is reddish-yellow, or brownish red. Each glandule has invariably its special artery which Halstead & Evans designate the superior and inferior parathyroid artery - right and left. The vessel is large in proportion to the organ supplied, and this aids in the body's identification. The glandules are quite free and hang from the artery which enters the hilum. Both parathyroid/

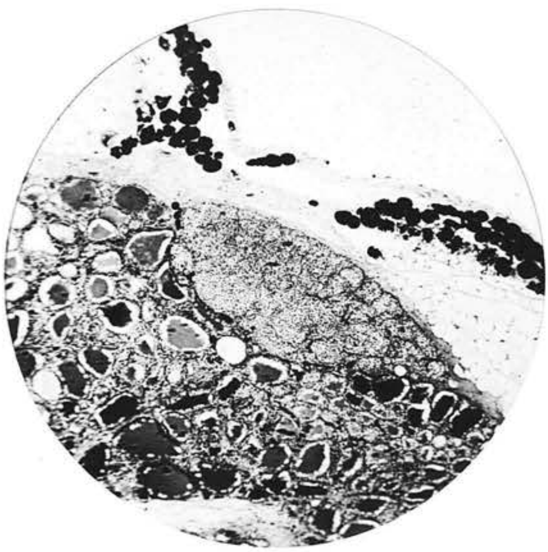


FIG. 104. A PARATHYROID IN THE GUINEA-PIG LYING IMMEDIATELY UNDER THE CAPSULE OF THE THYROID.

IRON HAEMATOXYLIN + ACID FUCHSIN X 79.

parathyroid arteries usually arise from the inferior thyroid, but frequently they take origin from the anastomosing channel between the inferior and superior thyroid vessels.

Development.

The parathyroids appear as epithelial thickenings from the dorsal parts of the third and fourth visceral clefts.The thymus arises from the ventral portion of the same clefts, and it is not unusual to find parathyroid tissue included in the thymus. Falta states that embryological investigations up to the present support the view that the relation of the parathyroids to the thyroid is purely topographic.

Histological Anatomy.

The parathyroid possesses a thin capsule of connective tissue. This is filled with parenchyma which is subdivided into columns of epithelial cells by delicate septa which proceed from the envelope. These septa covey the capillary vessels, and they unite to form a kind of net-work, in the vessels of which the parenchyma is enclosed. Kohn distinguishes in man and different mammals, three different arrangements of the epithelial cells - (1) a compact cell mass; (2) a retiform/

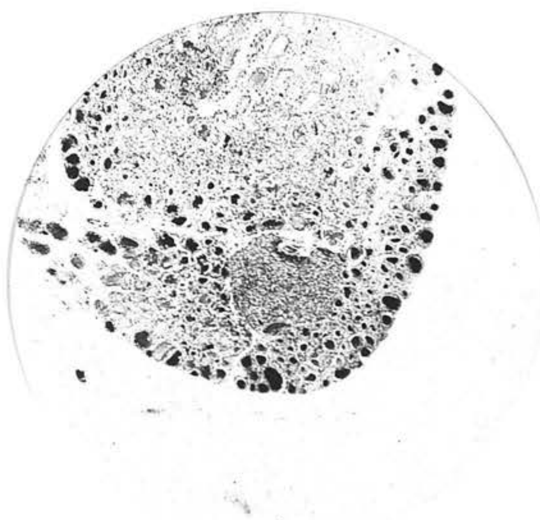


FIG. 105. AN INTERNAL PARATHYROID IN THE GUINEA-PIG.

SAFRANIN X 43.

retiform tissue; and (3) a lobular conformation. These different arrangements are not characteristic of any species or any age, but may be found side by side in the same glandule. In the rabbit, the parathyroid is often of the compact type; in the guinea-pig it may be either compact or lobulated (Fig. 107). There was no constant arrangement in this respect in either pregnant or non-pregnant animals.

Welsh has classified the parathyroid cells into two principal types - (1) the "principal" cells, which greatly predominate; (2) the "oxyphilic" cells. The principal cells are usually small with protoplasm which does not stain readily. In the guinea-pig they appear to be larger than is generally the case, and the protoplasm may be fairly abundant (Fig. 108). The protoplasm contains fine granules which stain with iron haematoxylin. The nuclei, which stain well, are about the size of red blood cells; they are furnished with a regular net-like chromatin framework, and have several nucleoli. The oxyphilic cells have a relatively large body with fine, strongly eosinophilic granules. The nucleus is small, deeply-staining, and with chromatin closely arranged. In Schäfer's opinion, these oxyphilic cells probably represent a functional stage of the ordinary cells, since transitional/

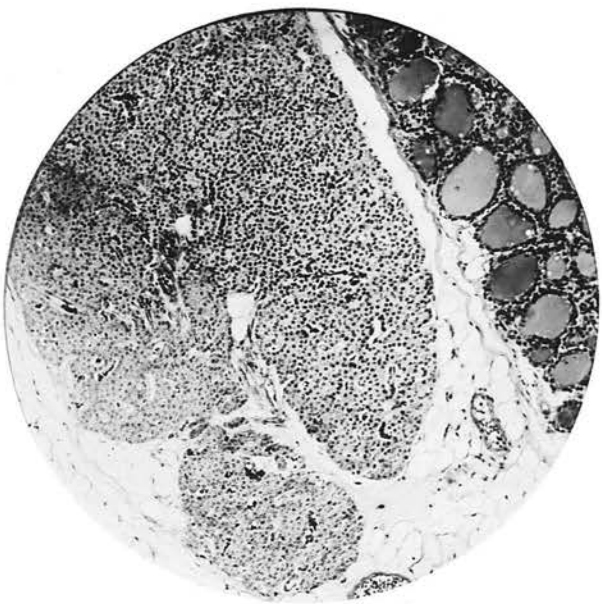


FIG. 106. THE HILUM OF THE PARATHYROID.
THIS FORMS A CLEFT THROUGH WHICH THE VESSELS ENTER.

IRON HAEMATOXYLIN & EOSIN X 150.

transitional forms occur. One type of these oxyphilic cells is believed by some authors to represent a separate cell-form. It is intimately associated with the connective tissue of the capsule and appears as a cubical or cylindrical cell with an epithelial nucleus. These cells unite to form palisade-like rows, which are arranged either radially or perpendicularly to the direction in which the septa run. In the rabbit and the guinea-pig the cells are entirely principal cells; the oxyphilic cells do not appear to occur.

Fatty granules are found in both types of cell. They occur during the first month of life and increase in number with age, but, according to Biedl, are not affected by the general nutritional conditions. They are regarded as furnishing evidence as to the secretory activity of thee parenchyma cells. Petersen found glycogen in the parathyroid glands of man at all ages; its distribution was irregular, the principal cells containing much, the oxyphilic cells little. It is also present in the connective tissue and the blood-vessels. Petersen's view is endorsed by Guizetti, Verbely, and Yanase. H. Koenigstein considers that upon histological gounds glycogen may be regarded as a secretory product of the parathyroid glands.

Colloid/

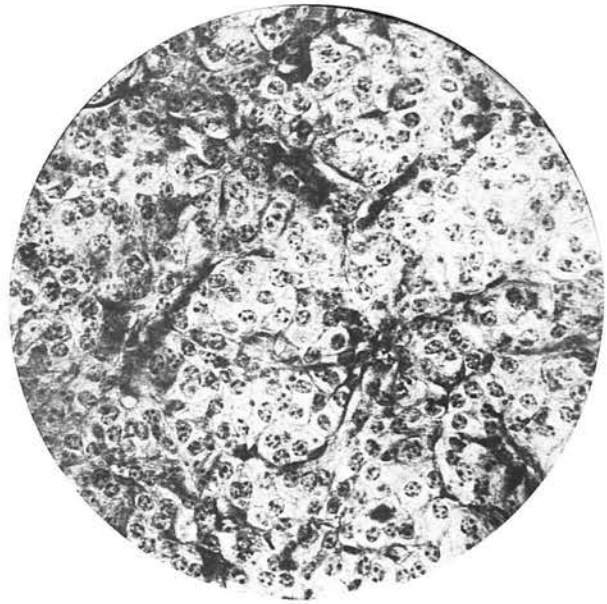
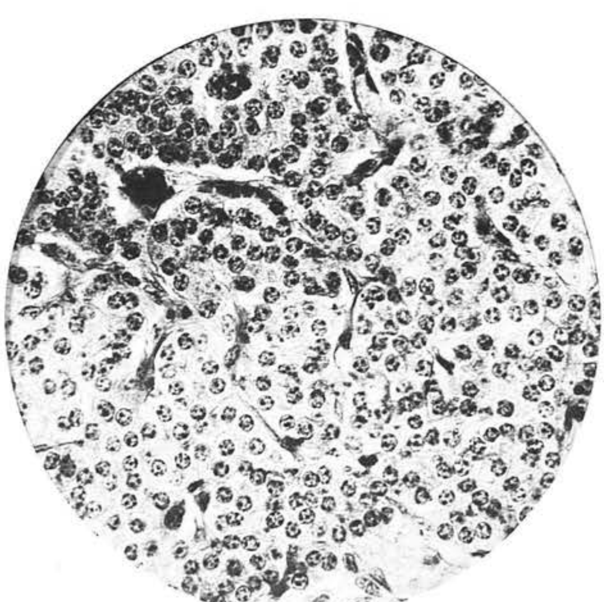


FIG. 107. THE UPPER PHOTOGRAPH SHOWS A PARATHYROID FROM A NON-PREGNANT GUINEA-PIG — THE LOWER A PARATHYROID FROM A PREGNANT ANIMAL. THE STRUCTURE IS SIMILAR IN THE TWO CASES. THE UPPER SPECIMEN SHOWS A SLIGHTLY LOBULATED ARRANGEMENT OF THE CELLS.

IRON HAEMATOXYLIN + ACID FUCHSIN X380.



Colloid vesicles, as already mentioned, are sometimes met with in the parathyroid. They do not ocurr in the parathyroid of the guinea-pig and are therefore not an essential part of the gland.

The internal blood-vessels of the parathyroid are very abundant. The numerous sinus-like capillary vessels unite to form a close net-work. Their endothelial cells, in some cases, rest on the epithelial cells and in others are covered with a delicate sheath of connective tissue. Occasionally, and more particularly in old age, the arteries are accompanied by large lymphatics. According to Sacerdotti & Anderson, the vessels in the interstitial tissue are accompanied by nerve fibres, by which they are enclosed as in a net-work, and which may also penetrate between the epithelial cells.

The Evidences of Secretory Activity.

Views as to the nature of the physiological activities of the parathyroids are still largely hypothetical. No hormone, if such a chemical substance exists, has been isolated, and theories as to the function of the glands are largely based, as yet, on the results of experimental parathyroidectomy. It seems to be established, that if all four parathyroids/

parathyroids are removed, provided that no accessory parathyroidal structure is present, fatal tetany results. If two or three glandules are removed, the animal is in a state of latent tetany, the condition only developing when some additional strain is thrown on the vital activities, such as pregnancy and various intercurrent diseases. A similar observation has been made in the human subject by Haberfeld. In a patient in the Shauta clinique, Vienna, tetany developed during pregnancy, the patient having previously manifested no signs of the condition. In this case all four of the parathyroids showed pathological changes. Two presented large scars, in the regions of which there were parenchymatous atrophy and small cysts. In one gland round-celled infiltration was present, and in the fourth such extensive atrophy, that scarcely any epithelial cells remained.

In the human subject parathyroidectomy was occasionally performed accidentally in the early days of thyroid surgery, before the importance of the parathyroids was recognised. Thus, in 52 cases of thyroidectomy in the Billroth clinique, tetany occurred 12 times, and was fatal in 9 cases. At the present day it is a very rare event. C. H. Mayo reports that in a series of 8,500 operations for goitre in the Mayo clinic/

Clinic, one case presented manifestations of tetany. The condition subsided, leaving doubt as to its true nature. Halstead, Biedle, and others have shown that after removal of a part of the parathyroidal substance, the remaining portion undergoes hypertrophy. Halstead has also shown that when tetany is the result of a complete extirpation of all parathyroid tissue, the symptoms can be combated by a successful transplantation or graft of parathyroid tissue made from an animal of the same species. Indeed, it has been found that the success of a graft of parathyroid is assured only when the graft is derived from the same kind of animal as that from which the parathyroid has been removed. With regard to the treatment of tetany in the human subject by means of grafting, C. H. Mayo states that the resuls have been divergent, but that the history of this phase of the subject contains successes sufficiently supported to stimulate encouragement and painstaking research.

These observations are sufficient to show that the parathyroids are structures of vital importance. Apart from tetania parathyreopriva, there is considerable doubt that other forms of tetany are dependent upon parathyroid deficiency, but there are many observations supporting this view. The case of tetania gravidarum/

gravidarum, reported by Haberfeld, has already been referred to. In infantile tetany, it is believed by Erdheim, Yanase, Haberfeld, and others that the condition is dependent on intra-parathyroidal haemorrhages. Such haemorrhages are assumed tò occur during intra-uterine life or at the time of labour, and to the occurrence of these haemorrhages are also attributed tetanic attacks of later childhood and even adult life. In such cases, a lymphatic condition of the parathyroids has been observed, and the only indication of the early bleeding may be the presence of haematogenous pigment, together with evidence of inhibited growth of functional tissue. The existing, limited parathyroidal material suffices to maintain a state of equlibrium in the presence of normal conditions, but with the advent of some intercurrent disturbance, such as the common gastro-intestinal diseases of the young, pregnancy, etc., the glandules become relatively insufficient for the increased demand.

There are at the present time two principal views as to the cause of the symptoms in tetany - (1) the absence of some substance which checks the activity of the nervous system, and (2) the appearance of a specific poison, acting on the nervous system, appearing in parathyroid absence or deficiency. It was previously/

previously thought by Macallum that the essential cause was a deficiency of calcium salts in the body. Voegtlin & Macallum showed that the adminstration of calcium salts, either intravenously or by the mouth, stops very promptly the tetanic symptoms. There is no doubt also, that, as Leopold & von Reuss have shown, in young animals after partial parathyroidectomy the total amount of calcium in the body is diminished and the teeth and the bones fail to calcify properly.

It is pointed out, however, that no view can be correct which takes as its basis the absence or deficiency of some one or other substance which is supposed, normally, to influence the activity of nervous tissues, since copious blood-letting or transfusion with normal saline immediately removes the symptoms, and keeps then in abeyance for some time. The most probable explanation of the beneficial effect of calcium upon the nervous symptoms is that it behaves merely as a sedative, reducing the excitability of the nervous system, an action which it is known to possess. It has been shown that other cations - magnesium, barium, and strontium - have a similar action.

Noel Paton, Findlay, and Watson believe that the essential cause of tetany is an intoxication by guanidine. They point out that - (1) Guanidine or methyl guanidine administered to normal animals produces symptoms/

symptoms that are identical with those following parathyroidectomy; (2) no drug, other than guanidine, which can effect a decided increase in the excitability of the motor nerve endings to the constant current, as exists in tetany, has been found; there is a marked increase in these substances in the blood and urine of parathyroidectomised dogs, and in the urine of children suffering from idiopathic tetany; and (4) in certain cases the serum of parathyroidectomised dogs acts upon the muscles of the frog similarly to weak solutions of guanidine.

The question, however, must still be regarded as unsettled. Howland & Marriott have shown, after extensive analytical work, that the blood of children suffering from tetany shows a reduction of calcium, to the extent of 40 per cent. in many instances. It is possible that neither of these factors - guanidine formation or calcium deficiency - is the primary cause of tetany, but that one or perhaps both may be secondary to some condition as yet unrevealed.

Histologically, the parathyroids are among the most enigmatic of the endocrines. The increased demand on these organs during pregnancy is undoubted, as shown by the onset of tetany in women or animals with parathyroid deficiency, there having been no manifestations of the disease under normal conditions. C. H. Mayo/

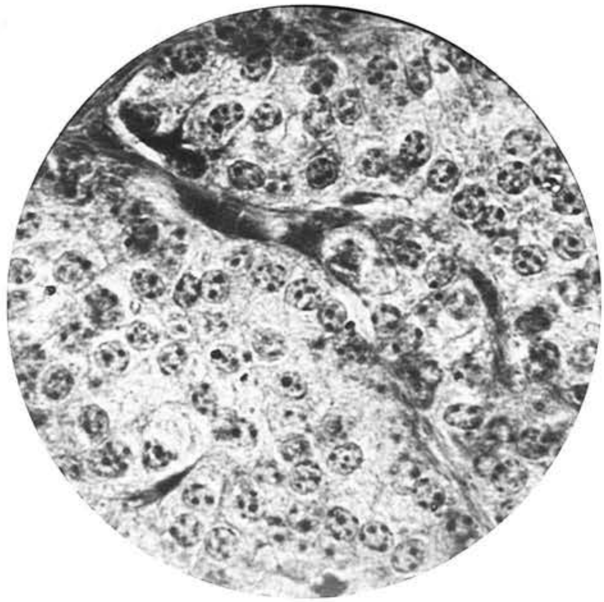
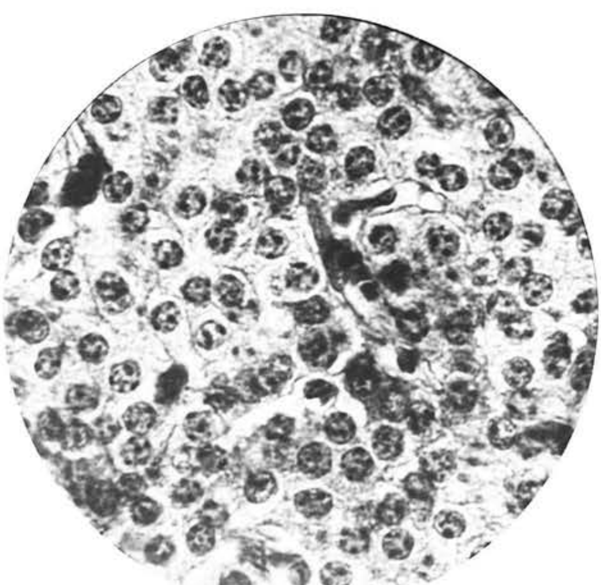


FIG. 108 A HIGH-POWER VIEW OF THE CELLS OF THE PARATHYROID. THE UPPER IS FROM A NON-PREGNANT ANIMAL – THE LOWER FROM A PREGNANT. THE CELLS OF THE NON-PREGNANT SPECIMEN APPEAR TO CONTAIN MORE GRANULES, BUT THIS APPEARANCE IS NOT CONSTANT.

IRON HAEMATOXYLIN + ACID FUCHSIN. X 710.



Mayo states that no manifestations of hyperactivity of these glandules, even in the presence of hypertrophy or adenoma, have been observed.

The one positive statement that can be made from an examination of the parathyroid in the pregnant animals is that in pregnancy the parathyroids are distinctly more vascular as compared with the condition in non-pregnant animals. The vaso-dilatation affects the larger vessels. The cells present the same appearance in pregnant and in non-pregnant animals (Fig. 108). The granules which are demonstrated by iron haematoxylin do not show any constant relationship to one or the other condition.

CONCLUSIONS.

(1) In the guinea-pig, only parathyroid III is commonly present and it usually lies on the lateral aspect of the thyroid. Occasionally an internal parathyroid is present in addition.

(2) The cells are arranged, in the guinea-pig, sometimes in a "compact" and sometimes in a "lobulated" manner; the arrangement of the cells has no functional significance.

(3) Histological evidences as to functional activity/

activity are very scanty, the one definite feature being an increased vascularity in the gland of pregnant animals as compared with that of non-pregnant.

THE THYMUS.

The thymus is generally regarded as a "puberty gland". In the human subject it attains its maximum development about the time of puberty and thereafter undergoes retrogressive changes. In animals it frequently exisists in a well developed state in the adult.

Morphology.

In man, in its most active stage the thymus consists of two lateral lobes placed in close contact in the middle line, situated partly in the thorax and partly in the neck, and extending from the fourth costal cartilage upwards as high as the lower border of the thyroid gland. It lies in front of the pericardium and trachea and partly behind the sternum. The two lobes generally differ in size; they are occasionally united so as to form a single mass; and sometimes separated by an intermediate lobe. The thymus is of a pinkish-grey colour, soft, and lobulated on the surface.

In the rabbit it occupies the same position and presents much the same appearance as in man, except that the lobulation is more distinct. In the guinea-pig it forms two flat lobes; these are situated in the/

the neck on each side of the trachea and do not extend into the thorax.

Development.

The thymus appears in the form of two diverticula arising from the ventral portions of the third visceral pouches. These extend laterally and backwards into the surrounding mesoderm in front of the ventral aortae. Here they meet to become joined to one another by connective tissue, but there is never any fusion of the thymus tissue proper. The pharyngeal opening of each diverticulum is soon obliterated, but the neck persists for some time as a cellular cord. By further proliferation of the cells lining the diverticulum, buds of cells are formed which become surrounded and isolated by the invading mesoderm. In the latter, numerous lymphoid cells make their appearance, and are aggregated to form lymphoid follicles. The original epithelial organ ultimately develops into a structure resembling the lymph glands. Thymus rudiments appear to develop from the fourth pouches, but these play little, if any, part in the development of the thymus proper.

There are two views as to the nature of the fully developed thymus. Hammar, Stöhr, Pappenheimer, and others believe that the organ remains essentially an epithelial/

epithelial structure - that the epithelial cells of which it originally consists divide and subdivide, becoming smaller and smaller so as to resemble lymphocytes. Other observers believe that the epithelial beginning of the thymus is, with the exception of a small portion, entirely replaced by mesodermal elements.

Involution. Hammar has shown that, in the human subject the organ reaches its greatest development between the fourteenth and sixteenth years. From that time onwards it gradually loses in weight, but microscopical investigation shows that it still functions. A true atrophy of parenchyma, with elimination of function, comes on about fifty to sixty years of age.

In Rabbits the organ attains its greatest development about the fourth month, while the organism is preparing for spermatogenesis. In guinea-pigs it increases in size until the weight of the animal is about 300 grammes, which occupies about two months. At this age the animal becomes sexually mature and retrogressive changes in the thymus begin to take place.

Histological Anatomy.

A thymus lobule shows a subdivision into a cortical and a medullary portion. The cortex presents a close resenblance in its structure to lymphoid tissue/

tissue, being crowded with lymphocyte-like cells and incompletely separated into nodules by trabeculae of connective tissue. The medulla stains less darkly than the cortex and is more ~~is more~~ open in its structure. It contains three different cellular elements. Its reticulum is made up of large, transparent, branched cells, which are sometimes arranged in an epithelioid manner. In the meshes of the reticulum are a certain number of lymphoid cells, but these are less abundant than in the cortex. The most characteristic elements are the concentric corpuscles of Hassal. These structures present a certain resemblance to the cell nests of a squamous epithelioma. They consist of groups of epithelial cells arranged in a concentric fashion around a nucleus, which consists, apparently, of cells which have undergone degeneration. It has been suggested that these bodies are the remains of the original epithelium, but evidence is accumulating against this view. Hammar and Bell appear to have shown that they are derived from hypertrophic reticular cells. It has been shown by Wallisch that the total volume of the Hassal's corpuscles in a young child exceeds that of the whole thymus of a three months embryo, so that it is unlikely that these bodies are merely developmental remnants/

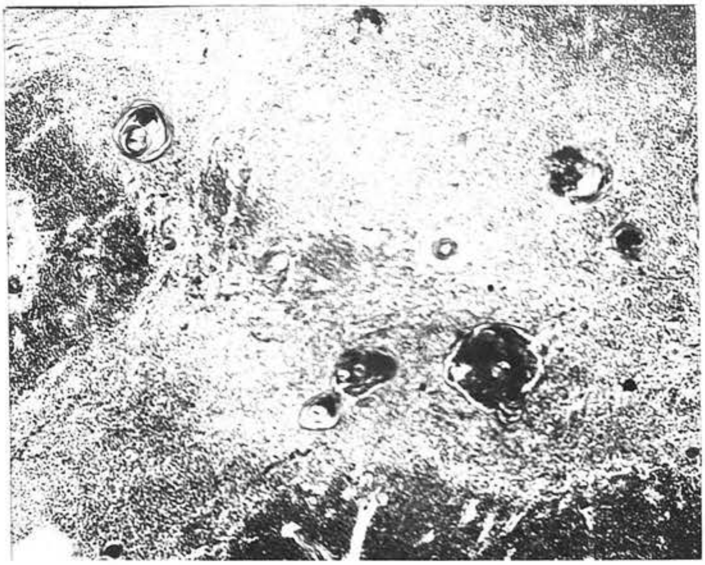


FIG. 109. THE THYMUS OF THE YOUNG GUINEA-PIG SHOWING ABUNDANT HASSAL'S CORPUSCLES.

IRON HAEMATOXYLIN + EOSIN X 82.

remnants. They form a very striking feature in the thymus of the young guinea-pig (Fig. 109).

The Evidences of Functional Activity.

The theory of the possession of an endocrine function by the thymus has not yet been firmly established. Wiesel makes the statement that "the problem of the functional importance of the thymus gland is almost completely unsolved". In the large amount of experimental work which has been done there has been a striking lack of uniformity in results. The divergence in the results of experimental extirpation are probably to be partly explained by the diversity in periods of thymic existence at which operation has been performed.

Some authorities hold that there is no sufficient evidence to prove the existence of an endocrine function, and regard the organ merely as a lymphoid structure. There seems to be little doubt that in early life the lymphoid elements in the thymus are concerned with the formation of lymphocytes for the circulating blood. Lymphocyte counts from infancy to puberty show a declining curve, the gradient of which follows closely that of thymic involution. Hoskins believes that the main function of the thymus is to act/

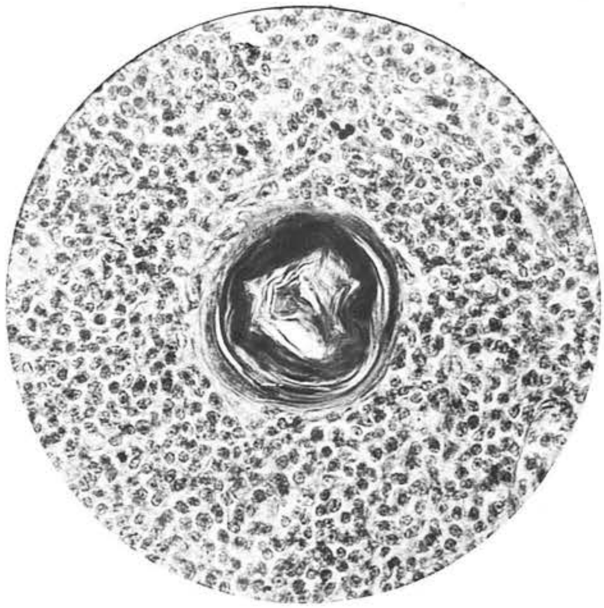


FIG. 110. THE ACTIVE HASSAL'S CORPUSCLE OF THE YOUNG GUINEA-PIG.

IRON HAEMATOXYLIN + EOSIN X 380.

act as a lymphoid organ in infancy and childhood when a large number of lymphoid cells and leucocytes are needed to combat infection. The possession of such a blood-forming function does not, however, exclude the possibility of the production of an autacoid substance in addition.

There is now a large body of evidence in favour of the belief that the thymus is related to the development of the sex organs and probably also to the regulation of metabolism, especially to the development of the skeleton. The work of Basch has also suggested that the thymus is concerned in the causation of tetany, as well as the parathyroids, and this view has recently received considerable support from the observations of Uhlenhuth.

The evidence in favour of a relationship to the development of the sex organs is considerable. It is well-known that castration in animals prevents the normal involution of the thymus. Noel Paton has shown that removal of the thymus in guinea-pigs before they reach the age of puberty is followed by a rapid development of the testicles. Klose and Vogt also report more rapid development both of testicles and ovaries after thyrectomy. Adler reports that destruction of the thymus by means of the electric cautery/

cautery in the larvae of Rana temporaria was followed by increase in the rate of the growth of the gonads. It has been shown recently that the thymus is exceedingly sensitive to X-ray irradiation, and attempts have been made to destroy the organ by this means. The rsults of the procedure have been conflicting; Hewer reports interference with the function of the testes, but the findings of Regaud and Cremien have been negative in this respect.

Many observers, including Hammar and Fischl, have reported entirely negative results after removal of the thymus, but the weight of the experimental evidence, in association with the fact that involution of the thymus corresponds to the time of attaining sexual maturity, suggests that the thymus exercises an inhibitory influence on the development of the sex organs, and the appearances seem to show that the involution of the thymus is consequent upon the maturity of the sexual glands. That this, however, is not the only factor in producing involution of the thymus is shown by the fact that the thymus sometimes persists in a fully developed state in pregnant animals.

The relationship of the thymus to regulation of metabolism is still extremely debatable. Gudernatsch found thymus-fed larvae delayed their metamorphosis, although/

although the animals grew on this diet, and Uhlenhuth has recently confirmed this observation. Allen, however, reports that no effect on the time of metamorphosis is produced by extirpation of the thymus. Klose and Vogt, Basch and Lucien and Parisot have reported interference with the growth of the skeleton and other metabolic symptoms after extirpation of the thymus. These are manifested especially by a diminution in the length and weight of the bones, and also by a pronounced softness and pliability, so that deformities tend to develop. The undissolved calcium is diminished by one half. A lethargic mental condition is also described. Shimizu has recently endeavoured to destroy the thymus by the use of a strong thymolytic serum. He reports a marked retardation of bone growth in young dogs, with extensive atrophy of the medullary portion of the thymus. He concludes that the medullary portion has a different function from the cortical portion, and that the endocrine function of this gland with its influence upon the growth of animals must be ascribed to the medullary portion only.

Many observers, however, report entirely negative results on metabolism after removal of the thymus Noël Paton and Goodall were unable to discover any harmful/

harmful effects after thymectomy in guinea-pigs. Swale Vincent found that removal of the thymus in frogs produced no result. Pappenheimer, Park, and others have come to similar conclusions. Regand and Cremien, after destruction of the thymus by means of X-ray irradiation, observed no deleterious effects on the health of the animals. Surgical removal in the human subject has rarely been followed by harmful results; König has reported one case which he believed to present signs of insufficient thymic function following thyrectomy. C.H. Mayo considers it advisable to leave a portion of thymic tissue behind at operation.

Many authorities believe that the harmful effects of thymectomy on metabolism, when they do occur, are due to the trauma of the operation and, in some cases, to sepsis. Noël Paton has made an interesting observation in this connection. He found that removal of the thymus alone, or of the testicles alone, has no effect on the rate of growth of the guinea-pig, whereas removal of both thymus and testicles produced a marked delay in the rate of growth. This observation seems to suggest that the thymus furnishes a hormone of some kind which ministers to the needs of the economy before the reproductive organs are fully developed. If the thymus is removed or destroyed, the development/

development of the reproductive organs is hastened and they are able to furnish the necessary substance.This view is supported by the effects of castration on the thymus.

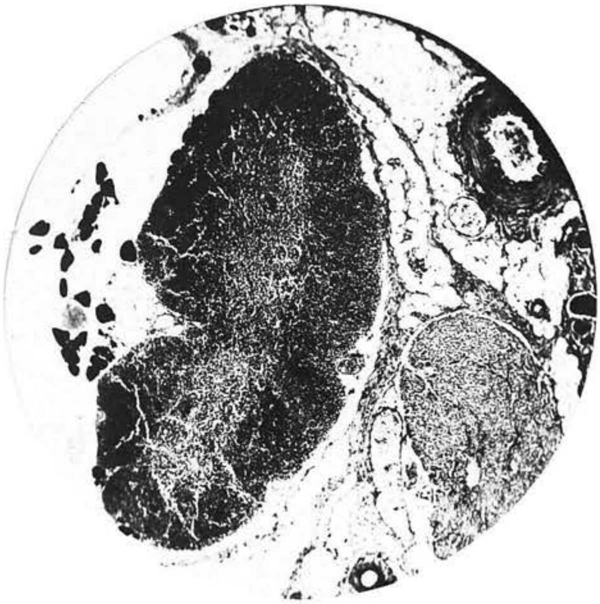
The "status thymicus" of the human subject throws very little light on the functions of the thymus. The essential nature of this condition is still imperfectly understood. According to Hart, the hyperplasis of the thymus is almost invariably accompanied by enlargement of the lymphoid tissue throughout the body and the condition is practically always one of status thymico-lymphaticus. The swelling of the lymphatic apparatus appears to represent a tissue reaction dependent on the thymus. Mayo believes that the mechanical theory of thymic death is untenable, except, perhaps, in isolated cases in helpless infants. Bartel has described, in addition to the hyperplasia of the thymus and the lymphoid tissue, a remarkably small heart and also hypoplasia of the aorta and peripheral vessels, with altered sex characteristics, and hypoplasia of other structures, for example, the chromaffin system. The defect in the chromaffin system has been emphasised by several authors. Hedinger found that, out of fifteen cases of Addison's disease, seven presented a marked degree of status thymico-lymphaticus.

Wiesel/

Wiesel believes that the cause of sudden death in this condition is a deficiency in adrenalin, so that the blood pressure is not maintained and slight causes may bring about heart failure.

The present tendency is to regard the status thymico-lymphaticus as a manifestation of an abnormal constitution with a disturbance in the polyglandular system of endocrine organs. The importance of the thymic hyperplasia is doubtful. According to Biedl, it may be merely a secondary condition, depending on disturbance of one or more of the endocrines. In this view, the condition of the thymus in status thymico-lymphaticus is analagous to the hyperplasia which is seen in exophthalmic goitre. Hart believes that the hyperplastic thymus produces a toxic effect on the heart, but there is no direct evidence as to this action. In any case, there is no proof of hyper-activity on the part of the thymus and no indication as to the function of the normal thymus secretion. A toxic effect on the heart, if it exists, is more likely to be due to an abnormal secretion than to excess of the normal.

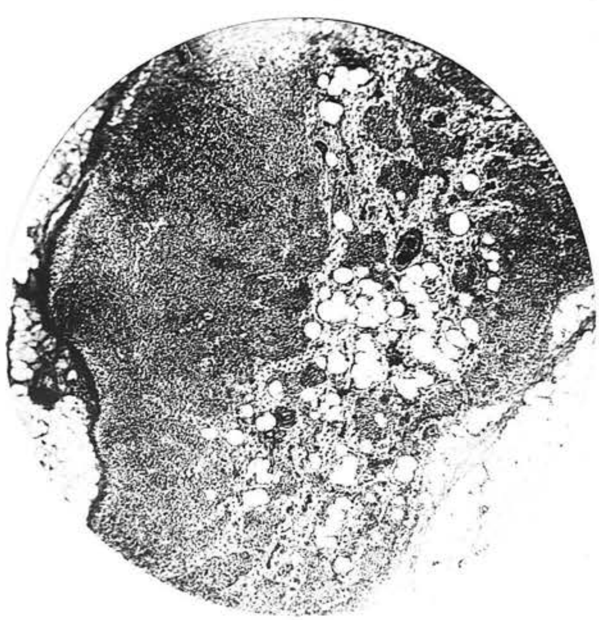
It was found, in the animals examined, that the thymus was commonly present in the pregnant, as well as in the non-pregnant state. I did not realise to begin/



FIGS. 111-112. THE UPPER PHOTOGRAPH SHOWS THE THYMUS FROM A PREGNANT GUINEA-PIG. IT IS A COMPACT CELLULAR STRUCTURE.

THE LOWER SPECIMEN IS FROM A NON-PREG--NANT ANIMAL. IT SHOWS A MARKED DEGREE OF INFIL--TRATION WITH FAT.

IRON HAEMATOXYLIN + ACID FUCHSIN. X79.



begin with, that the thymus is so frequently persistent in adult animals, and obtained only three specimens from the guinea-pig, one in a pregnant animal and two in non-pregnant. In the rabbit, thymic tissue can practically always be identified, and a fully developed thymus was found in both pregnant and non-pregnant animals. Where a complete gland was not present, smaller portions of thymic tissue were found embedded in the mediastinal fat.

In the guinea-pig the condition of the gland seemed to show a distinct relation to pregnancy. In the adult non-pregnant guinea-pig the gland showed a considerable degree of infiltration with fat; this involved both cortex and medulla, though there was abundant tissue of both varieties in existence (Fig. 112) In the pregnant animal, which weighed 640 grammes, the thymus had the appearance which is seen in young animals (Fig. 111); it was a compact, highly cellular structure with no sign of infiltration with fat. The most striking difference between the pregnant and non-pregnant animals related to the Hassal's corpuscles. In the non-pregnant animal these were exceedingly scanty and presented a markedly atrophic appearance, being small in size and ill-defined in structure (Fig. 113). In the pregnant animal, on the other hand, Hassal's/

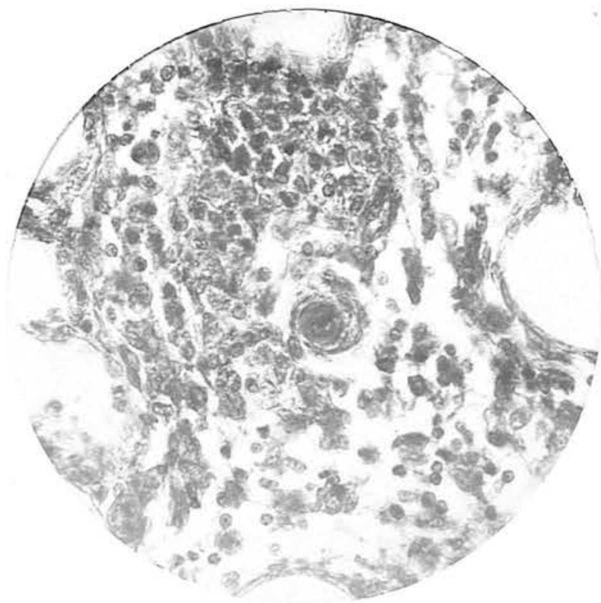


FIG. 113. A HASSAL'S CORPUSCLE FROM AN ADULT NON-PREGNANT GUINEA-PIG. IT HAS AN ATROPHIED APPEARANCE.

IRON HAEMATOXYLIN + CONGO RED X 380.

Hassal's corpuscles were comparatively abundant, though not so plentiful as in the young animal. They were large and well developed and the details of their structure were plainly visible (Fig. 114). The appearances in these animals suggest that regeneration may take place to a certain extent in pregnancy. Rudberg has observed regeneration after exposure to the X-rays.

In the rabbit's thymus Hassal's corpuscles do not appear to be a prominent feature. They were few in number in both pregnant and non-pregnant animals. Fig. 115 shows a corpuscle from a pregnant animal with a fairly well-defined structure. The transparent reticulum cells are sometimes particularly in evidence in pregnant animals. The most impressive feature in the rabbit was the remarkable degree of development which the thymus frequently presents in adult animals; it was found as a large, fleshy organ, in both the pregnant and non-pregnant conditions, filling up a large part of the anterior mediastinum.

CONCLUSIONS.

1. Since a fully-developed thymus may exist in a pregnant animal, the maturity of the sexual organs is not the only factor in producing involution of the thymus.

2. /

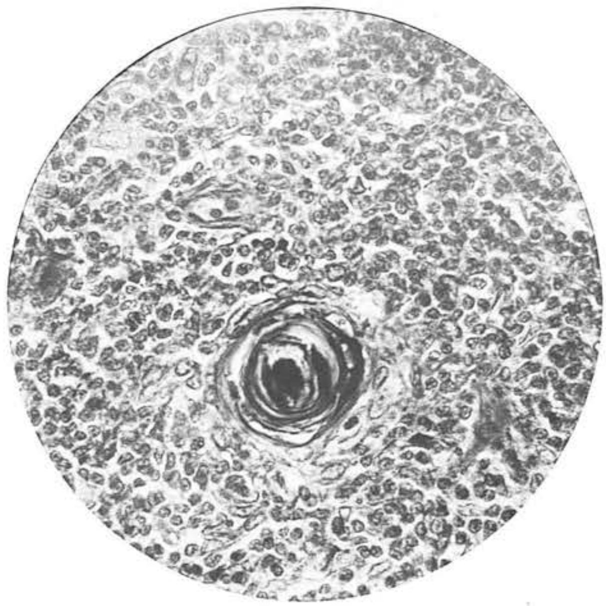


FIG. 114. A HASSAL'S CORPUSCLE FROM A PREGNANT GUINEA-PIG. IT PRESENTS A WELL-DEVELOPED APPEARANCE, LIKE THAT OF THE YOUNG ANIMAL.

IRON HAEMATOXYLIN + EOSIN X 380.

2. Thymic tissue is practically always present in adult animals, both non-pregnant and pregnant; therefore, it probably continues to exercise its function throughout the whole of life.

3. Hassal's corpuscles are well-developed in pregnant animals. This fact is in favour of the view that it is the medullary portion of the thymus which is concerned in its endocrine function.

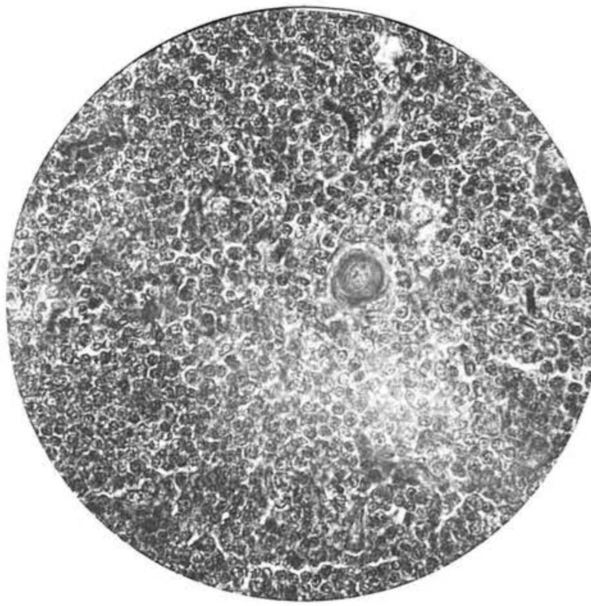


FIG. 115. A HASSAL'S CORPUSCLE IN THE THYMUS OF A RABBIT 11 DAYS PREGNANT.

IRON HAEMATOXYLIN + ACID FUCHSIN X 380.

THE SUPRARENALS.

The suprarenals correspond to the majority of the endocrines in showing increased activity during the period of gestation. The relationship between the cortex and the activities of the reproductive system is believed to be close, but Elliott & Tuckett have shown, by careful observations of the weight and the actual mass of the two parts, that the medulla also undergoes enlargement during pregnancy.

Morphology.

In all mammals the suprarenals consist of two parts - the cortex and the medulla. The arrangement, however, represents the fusion of the two organs which, developmentally and morphologically, are widely different. In fishes, the two kinds of tissue appear as two different organic systems, anatomically separate from one another and known as the interrenal and adrenal. The interrenal system includes all the structures which, like the suprarenal cortex, are composed of cells with lipoid contents; the adrenal system comprises all tissues, the cells of which, like those of the medullary portion of the suprarenal, are characterised by the chromaphil reaction, i.e., they present a bright yellow to dark brown staining with chromium/

chromium salts and with chromic acid. Comparative anatomy shows that the two fundamental tissues are present in all vertebrates, and are therefore to be regarded as structures which are component parts of the vertebrate body.

In mammals, the amalgamation of the two systems is complete. This is the result of the topographical arrangement by which the adrenal system becomes the medullary portion, while the interrenal system becomes the cortical portion of the suprarenal capsules. But even here, a considerable portion of the adrenal system remains independent. It is distributed along the sympathetic system, partly in the form of isolated chromaphil cells, and partly in the form of larger structures, invariably found at the bifurcation of the common carotid artery and at the division of the abdominal aorta, and named respectively the carotid gland and Zunkerkandl's accessory organs of the sympathetic system. The greater number of what are usually called accessory suprarenal organs are rather free portions of the interrenal system. They are found in the neighbourhood of the suprarenals, in the substance of the kidneys, and distributed through the whole of the retroperitoneal space and extending downwards into the pelvis, chiefly in the broad ligament in women and in/

in the vicinity of the spermatic cord and testis in men.

The guinea-pig is conspicious among mammals by the huge development of its suprarenal, the growth being chiefly of cortex. Elliott & Tuckett have shown that, relatively to body weight, its medulla is slightly less than that of the dog, both, however, being high for mammals; but its cortex is tenfold as great as the dog's. Mammals generally, are characterised by the great development of the cortex, whereas in birds the medulla shows a marked development. It appears that the lower the animal in the scale of vertebrates the larger is its stock of chromaffin tissue. The suprarenal of the rabbit shows certain differences from that of the guinea-pig, especially in the arrangement of the cells of the cortex, and forms a useful standard for comparison with the suprarenal of the latter animal.

Development.

The cortex and medulla of the suprarenal of mammals develop from entirely different sources. Balfour expressed the view that "in Elasmobranch fishes we have (1) a series of paired bodies derived from the sympathetic ganglia, and (2) an unpaired body of mesoblastic origin. In the ammiota these bodies unite to/

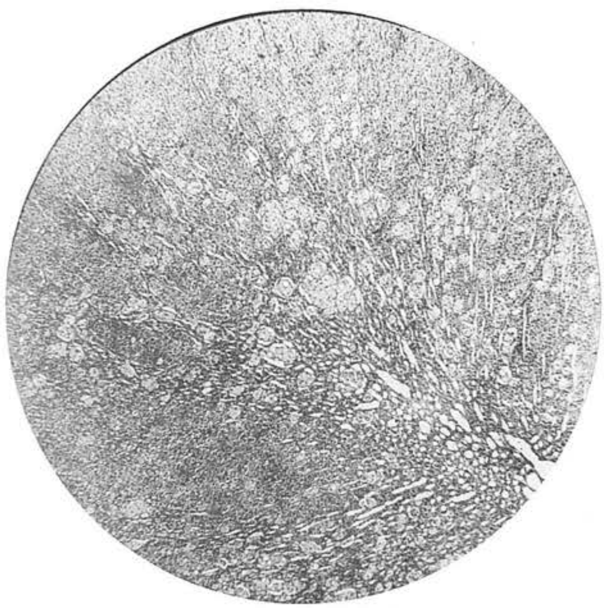


FIG. 115a. INTERMINGLING OF CORTEX AND MEDULLA SOMETIMES SEEN IN THE RABBIT. THE ISLETS OF PALE CELLS ARE MEDULLARY CELLS. X 43.

to form the compound suprarenal bodies, the two constituents of which remain, however, distinct in their development. The mesoblastic constituent appears to form the cortical part of the adult suprarenal body, and the nervous constituent the medullary part" This hypothesis has been fully supported, and the observations leading to it have been completely confirmed by all subsequent work upon the embryology of the suprarenals.

The cortex of the suprarenal is the direct descendant of the mesoderm. It is developed from the coelomic epithelium in the so-called interrenal zone.

It becomes first recognisable about the beginning of the fourth week as a series of buds from the coelomic cells at the root of the mesentery. These buds appear about the same time as the sex glands. Later, the cortical portion becomes completely separated from the coelomic epithelium and forms a suprarenal ridge projecting into the ceolom between the mesonephros and the root of the mesentery.

The medullary portion of the suprarenal is derived from the ectoderm, presenting a close relationship to the sympathetic system and developing as part of it. In mammals, at the time when the cortical portion has become clearly defined and histologically differentiated/

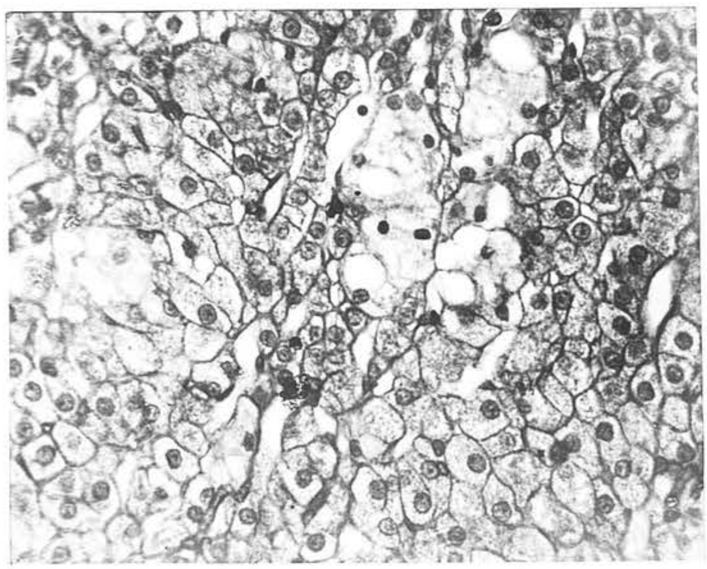


FIG. 115B. THE INTERMINGLING OF MEDULLA AND CORTEX WHICH SOMETIMES OCCURS IN THE RABBIT.
THE ISLETS OF PALE CELLS ARE GROUPS OF MEDULLARY CELLS EMBEDDED IN THE CORTEX.

IRON HAEMATOXYLIN + ACID FUCHSIN X 380.

differentiated, undifferentiated sympathetic elements wander from the principal mass of the abdominal plexuses to the cell-columns of the interrenal bodies. These cells migrate along the line of the central vein and make their way between the cell agglomerations and columns of the interrenal tissue. This intrusion of sympathetic elements is continued during the whole of foetal life, the interrenal system becoming entirely interwoven with these elements, as is seen in the complicated suprarenal of birds. In the rabbit, also, the intermingling of medullary and cortical elements sometimes presents in adult life (Fig. 115a). At about the beginning of the fourth month, the cells of the medullary portion acquire the chrome-brown colour which is their chief characteristic.

Histological Anatomy.

Structure of the Cortex: The connective tissue capsule of the suprarenal is connected with the centre of the organ by means, partly of thickish strands conveying the nerves and blood-vessels, and partly by delicate connective tissue lamellae which radiate from the periphery to the centre. The arrangement of these lamellae subdivides the cortex roughly into the three zones originally described by Arnold. A short distance from the capsule, the vertical lamellae are connected/

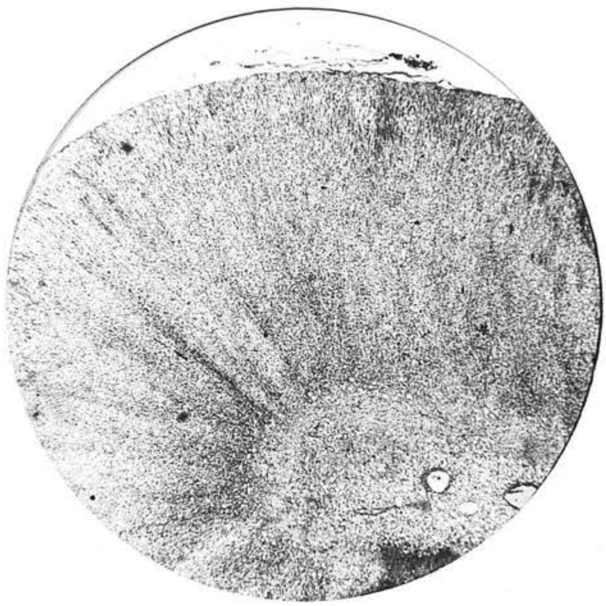


FIG. 116. THE SUPRARENAL OF THE RABBIT.
THIS SHOWS THE LARGE SIZE OF THE ZONA FASCICULATA.

IRON HAEMATOXYLIN + SAFFRANIN X23.

connected by oblique and transverse strands and by this means the outer cortical zone is defined - the zona glomerulosa. Beyond this the radial arrangement of the connective tissue strands becomes more open, enclosing parallel spaces in which isolated connective septa conveying capillaries are arranged transversely and diagonally. In this region of parallel lamellae are the cells of the zona fasciculata. This zone is particularly well developed in the rabbit. In the innermost part of the cortex, the connective tissue processes become still more delicate and, in the neighbourhood of the medulla, they break up into a fine net-work of delicate connective tissue threads, in the meshes of which single parenchyma cells are situated - the cells of the zona reticularis.

The cells of the cortex are mainly arranged in solid cell columns without a cavity - the cortical columns of Kölliker. These cell columns are usually composed of a single row of polygonal cells, though occasionally of two or three. The columns are best seen in the zona fasciculata. In the zona glomerulosa they end in rounded and sometimes hollowed-out terminations. The cells of this zone are polygonal in the guinea-pig (Fig.129) and in the rabbit - not columnar as is frequently the case. The question as to whether the/

the cells of the zona glomerulosa encloses a definite lumen has been carefully investigated by Stoerk. He showed that, under normal conditions, there is no free space within the loop-like arrangement of the cell-cylinders, although the appearance of these sometimes closely simulates a lumen. Where, for instance, owing to the overfilling of the suprarenal vessels, there is extravasation of blood into the external cortical layer, the cell columns become detached from the connective tissue by which the vessels are converged; thus, appearances are produced which, where the intra-vascular blood is not demonstrable as such, bear a misleading resemblance to transverse and oblique sections of glandular acini. This affect is heightened by the fact that compression of the cell contents produces an apparently basal position of the nuclei. From the nature of his findings, Stoerk is convinced that the suprarenal does not assume the formation of a true gland either under normal or pathological conditions.

The cells of the zona fasciculata are also polygonal and occasionally elongated in the direction of the column. In the rabbit and the guinea-pig they are frequently larger than in either the zona glomerulosa or the zona reticularis. In the zona reticularis the cells/

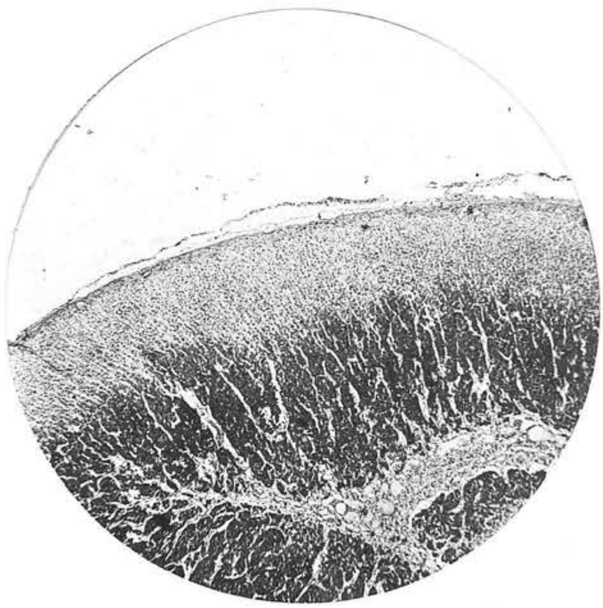


FIG. 117. THE SUPRARENAL OF THE GUINEA-PIG SHOWING THE MARKED DEVELOPMENT OF THE PIGMENT ZONE.

X 23.

cells are arranged in branching trabeculae. The cells in this zone tend to be somewhat oblong in the rabbit, but are generally rounded in the guinea-pig.

The most striking characteristic of the cortical cells in most animals consists in the presence of the lipoid granules which they contain. The granules are soluble in fat solvents, but differ from ordinary fat by their extreme solubility in essential oils. When xylol is used in the preparation of sections the granules disappear and leave behind a vacuolated appearance of the protoplasm. They do not stain with fuchsin, methylene blue, or other similar colouring agents, but stain vividly with the specific stains for fat.

The cells of the suprarenal cortex also contain pigment. The pigment-containing cells form a much wider zone in the guinea-pig than in the majority of other mammals. Elliott & Tuckett state that the guinea-pig is almost unique in their possession, but I have found a similar zone in the rabbit, and Browne and Flint describe similar granules in the suprarenal of the human foetus. In the guinea-pig the pigmented cells form a well-marked strip in the region adjacent to the medulla (Fig. 117). They can be readily seen in the unstained specimens and show up well after staining with iron haematoxylin. They stain with/

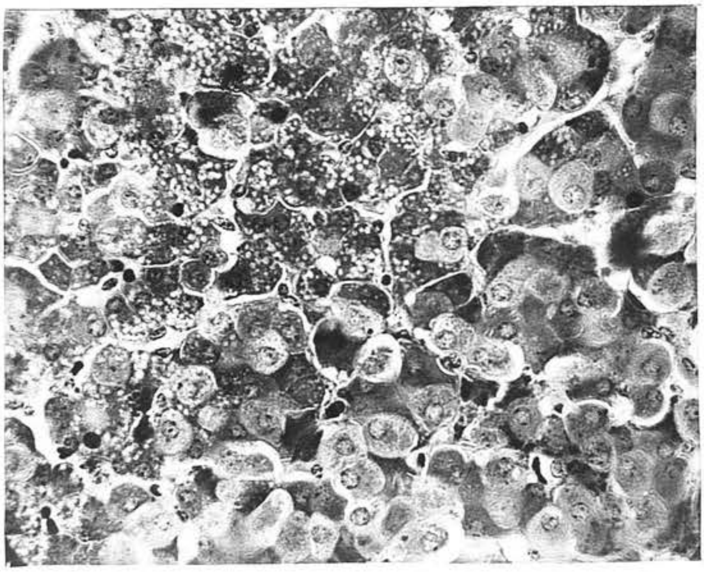


FIG. 118 THE JUNCTION BETWEEN THE PIGMENT ZONE AND THE LIPOID ZONE IN THE GUINEA-PIG.
THE PIGMENT CELLS – BELOW AND TO THE RIGHT – ARE SPHEROIDAL IN SHAPE; THE DARKER CELLS ARE PACKED WITH GRANULES. THE LIPOID-CONTAINING CELLS – ABOVE AND TO THE LEFT – PRESENT A VACUOLATED APPEARANCE.

IRON HAEMATOXYLIN X 380.

with eosin and other solid dyes. In many cases the individual granules are exceedingly small and may be almost ultra-microscopic, so that the cells may be tinted brownish-black by their presence, though the granules themselves may be barely visible (Fig. 118).

These granules do not give the chromophil reaction and are quite distinct from those of the cells of the medulla. They differ from the granules in the medullary cells also in being much finer and of a brownish hue. In Fig. 119 is seen a high power view of adjacent portions of the cortex and medulla. The cells of the medulla contain well-marked coarse granules; the granules of the adjacent cortex are much more numerous, so that they completely fill the cell, and are very much finer than those of the medullary cells. The distinction between cortex and medulla in this way is sharply defined.

Browne and Flint have described similar granules in the zona reticularis of the human suprarenal. Browne states that they are not only found in the cells of the zona reticularis but commonly extend into the zona fasciculata and sometimes to the surface of the gland.

The breadth of the pigmented zone in the guinea-pig depends partly on the age of the animal and partly, as will be shown later, on the state of functional activity/

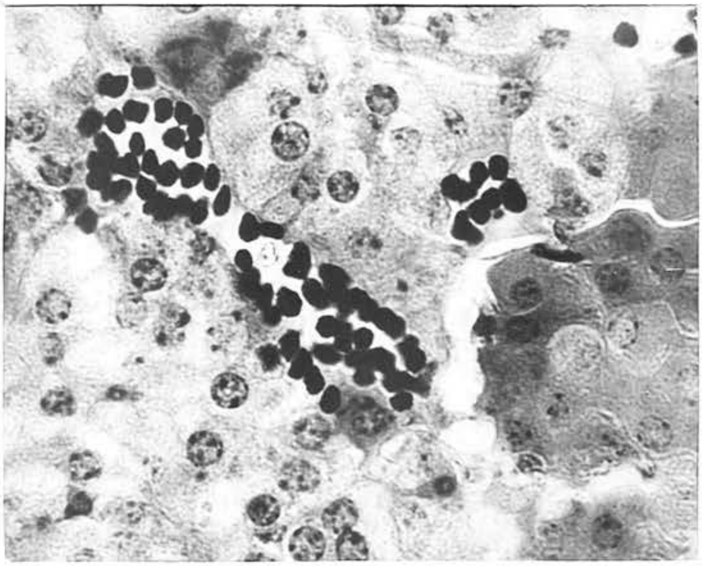


FIG. 119. THE JUNCTION BETWEEN THE PIGMENT ZONE OF THE CORTEX AND THE MEDULLA. THE PIGMENT CELLS - TO THE RIGHT - ARE DENSELY PACKED WITH FINE PIGMENT GRANULES. THE MEDULLARY CELLS ARE PALER AND CONTAIN COARSE GRANULES.

IRON HAEMATOXYLIN X 710.

activity of the suprarenal. The zone certainly does not correspond to the anatomical zona reticularis. It commonly includes the whole of the zona reticularis and may extend back for a varying distance into the zona fasciculata.

Elliott & Tuckett have also described in the cortex a doubly refractive substance which is soluble in ether. This differs from the lipoid granules in its distribution. In the guinea-pig the lipoids are usually most abundant in a heavily-loaded belt in the outer half or third of the cortex, while the doubly refractive substance is described as being scattered very lightly over all.

In connection with the suprarenal cortex, mention must be made also of the so-called "boundary zone" of the human foetus. Elliott & Armour have stated that the relatively large size of the suprarenal of the foetus is due to a marked development of the inner part of the cortex. The cells of the boundary zone are said to differ from those of the rest of of the cortex, in having no lipoid granules. After birth, the zone gradually disappears and is no longer visible after the first year. At birth, the portion representing the adult cortex forms a thin strip towards the surface of the gland. These observers found that in/

in the anencephalous foetus the boundary zone is absent; it must be noted, however, that this observation was made on a single specimen.

Browne has recently re-investigated the condition of the suprarenal in the normal and in the anencephalous foetus, five specimens of the latter being examined. He denies the existence of a "boundary zone", but finds that in the normal foetus the zona reticularis is relatively much wider than in the adult suprarenal. He states that lipoid granules are abundantly present in all the layers of the cortex, an observation which traverses that of Elliott and Armour. Browne regards the diminution of the thickness of the zona reticularis during the first year of life as merely a re-arrangement of the cells, and finds that the pigment granules which are limited to the zone reticularis before birth become abundantly present in the zone fasciculata afterwards. He believes that a further ingrowth of the bundles of fibrous tissue separating the columns of the zona fasciculata takes place, and transforms the net-work of the outer portion of the zona reticularis of the foetus into parallel columns. In the anencephalous foetus he finds that the zona fasciculata is relatively thicker than in the normal foetus, and that the zona/

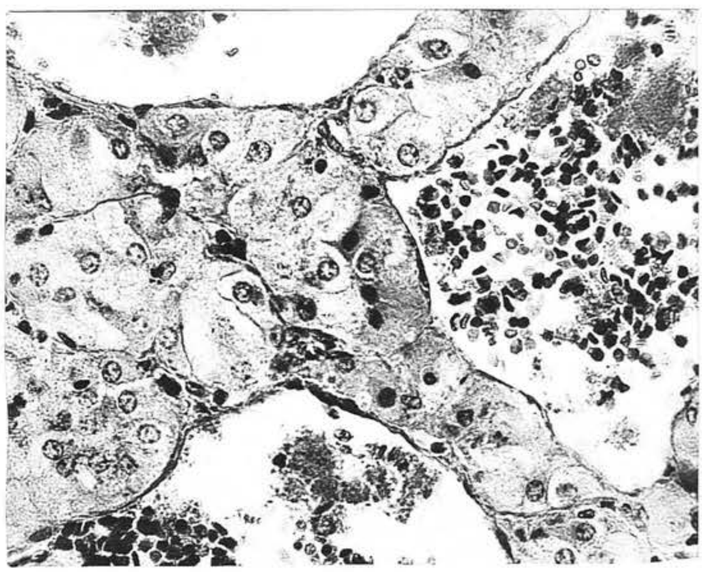


FIG. 120. THE MEDULLA OF THE SUPRARENAL IN THE GUINEA-PIG. THE CELLS ARE SEPARATED FROM THE BLOOD SPACES BY A VERY THIN LAYER OF ENDOTHELIUM.

IRON HAEMATOXYLIN X 380.

zona reticularis forms about one half of the cortex. The latter zone is relatively narrower than in the normal foetus, but is not the mere strip described by Elliott & Armour.

Structure of the Medulla: The medulla of the supra-renal is the most vascular structure in the body. It forms a solid cell-mass permeated by large sinus-like blood-vessels with the cells compactly arranged between and around them. The cells are supported by delicate strands of connective tissue. They are irregularly polygonal in shape, but when they abut on the sinuses they often assume a more columnar aspect. The cells are always placed close against the blood-vessels (Fig.120) and, as a rule, are separated by the endothelium only, though occasionally also by a delicate tissue sheath, from the lumen of the capillaries and the enlarged sinus-like veins. The cytoplasm contains numerous granules, which vary in size in different animals. In the guinea-pig they are comparatively coarse and are readily observed; they are more delicate in the rabbit. If the fixation has been satisfactory they are found to be scattered fairly uniformly throughout the cytoplasm. They are most readily observed in specimens stained with iron haematoxylin; they stain also with eosin.

Blood/

Blood-Supply and Nerve-Supply.

The blood-supply of the cortex is represented by fine arteries which run inwards from the capsule to the medulla in the connective tissue that lies between the columns of cortical cells. The vessels do not penetrate the cell columns of the zona glomerulosa and the zona fasciculata, but are restricted to the supporting connective tissue. On reaching the zona reticularis they become enlarged and come into close relationship with the cells. The vascularity of the medulla, as already mentioned, is one of its most striking features. The sinuses with which it is permeated are lined with a single layer of thin endothelial cells which are in direct contact with the cells of the medulla. Lymphatic vessels are present in the connective tissue of the cortex and these open into the lymph spaces of the medulla.

The nerves of the suprarenal are abundant. They are derived from a net-work of nerve fibres in the capsule of the organ, and the nerve supply of this plexus comes partly from the suprarenal plexus, formed by twigs from the coeliac, phrenic, and renal plexuses, and partly from the splanchnic nerve. The nerve fibres are partly distributed to the vessels and cells of the cortex, but the majority pass into the medulla where they form a dense plexus from which filaments pass to the secretory cells.

The/

The Histological Evidences of Secretory Activity.

In view of the different origin of the cortex and the medulla and the differences in structure, it is commonly believed that the functions of the two parts are quite distinct. Some observers, however, believe that there is a physiological relationship between the two regions, especially in view of the fact that the blood-vessels of the cortex pass directly into the medulla. It is convenient to consider the two parts separately, in the first instance.

Secretory Activity in the Cortex.

The evidences of secretory activity in the cortex which appear to be of most importance are the pigment granules and the lipoids. The doubly refracting granules described by Elliott & Tuckett are of doubtful significance. Aschoff adopts the view that they may represent only a modification of the ordinary lipoids - a special sort of storing up of fats. He believes that they are composed of cholesterine esters, and this view is endorsed by Biedl. In Biedl's opinion they are not to be regarded as products of secretion destined to be carried off by the blood-stream.

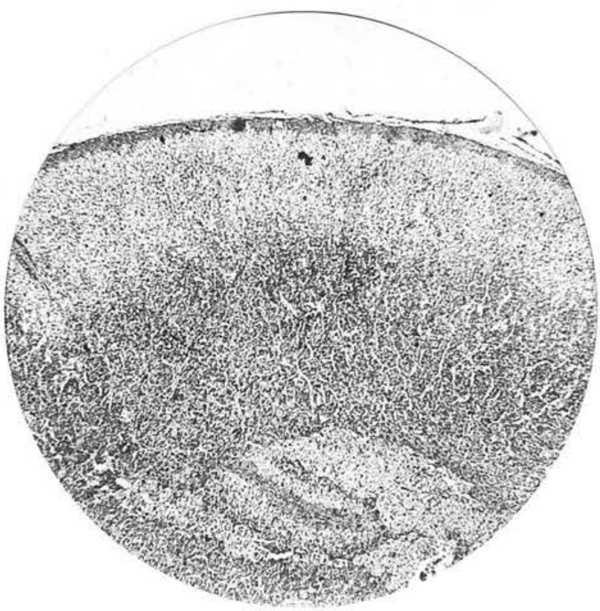
The pigment granules in the deeper part of the cortex appear to represent secretion products which can/

can be quickly utilised by the body. According to Elliott and Tuckett, they disappear rapidly with muscular work and re-accumulate with rest. In the young guinea-pig, the suprarenal contains no cortical pigment and the fat is distributed throughout the cortex. With growth the brown granules appear and may finally occupy more than three-fourths of the diameter, the dark ground so held being enveloped by a thin shell crammed with the fatty material. In view of the fact that the medulla does not grow after adolescence, it might be urged that the same is true of the fat-producing cells of the cortex; that the latter have simply been borne outward on the swelling mass of those required to produce the granules, and that the great specific enlargement of the guinea-pig's cortex is caused simply by the addition of these special cells. Elliott and Tuckett have shown that this is not the case. In conditions under which it may be assumed that the gland is exhausted, as in poisoning by diphtheria toxin, the fatty substance sweeps over the entire cortex and completely replaces the brown granules. Similarly, the granules may all disappear in a couple of days under the extra demand made on the remaining tissue when one half of the suprarenal has been removed.

An/

FIG. 121. THE UPPER PHOTOGRAPH SHOWS THE PIGMENT ZONE IN A NON-PREGNANT GUINEA-PIG —, THE LOWER THE VERY MUCH LARGER PIGMENT ZONE IN A PREGNANT ANIMAL.

X23.



An examination of the suprarenal of the guinea-pig suggests a subdivision of the cortex into three physiological zones, which differ to a certain extent from the familiar anatomical zones. The physiological zones appear to be (1) the zona glomerulosa, which seems to be distinct from the others, physiologically as well as anatomically, (2) the lipoid zone, and (3) the pigmented zone. The cells of the pigmented zone are quite characteristic, both in guinea-pigs and in rabbits. They are spheroidal in shape; the nucleus is generally eccentric in position; and the protoplasm contains abundant fine brownish granules. The number of the granules varies in different cells; some are so full as to appear almost black and individual granules cannot be identified; in others the granules are less numerous and the individual granules can be plainly seen (Fig. 118).

This zone shows variations in size under certain conditions. As already mentioned, the granules tend to disappear in states of exhaustion. Apart from such conditions, Elliott and Tuckett relate the size of this zone to the body weight of the animal.

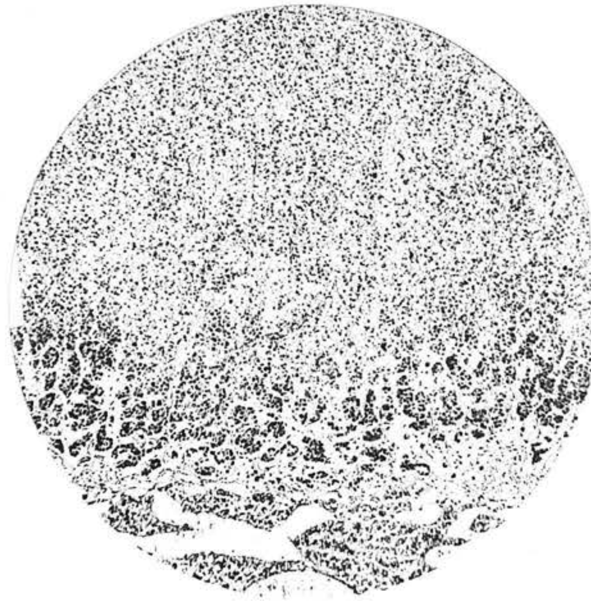
An examination of the series of pregnant and non-pregnant animals shows that this zone presents a distinct relationship to the activities of the reproductive/

FIG. 122. THE SUPRARENAL OF A MALE GUINEA-PIG.
THE PIGMENT ZONE OCCUPIES MORE THAN HALF OF THE CORTEX.

X 23.

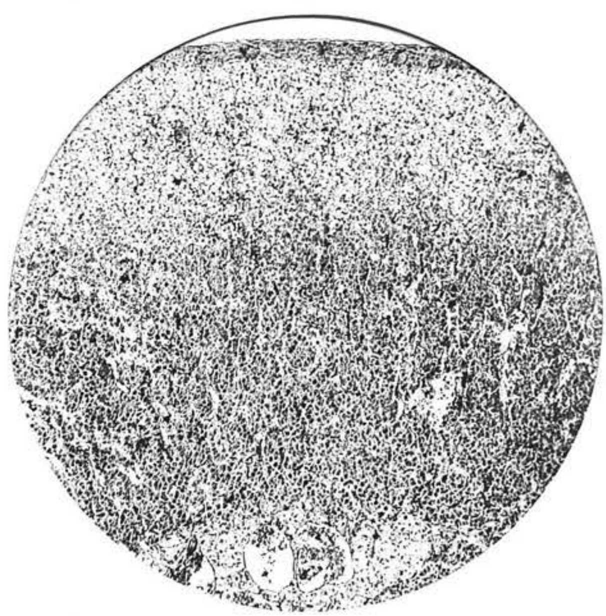
reproductive system. It can be shown in the first place that the size of this zone does not depend entirely on body weight, other conditions being normal. In Fig. 121 the upper illustration is taken from the suprarenal of a non-pregnant female guinea-pig of 560 grammes and shows a very narrow pigment zone; Fig. 122 shows a much wider zone in a male animal of only 325 grammes. A group of 5 male animals, varying in weight from 325 to 880 grammes, was examined, and in all cases the cortex showed a wide pigment zone, quite independently of the body weight. It has been shown by Noël Paton and Goodall that a guinea-pig of 300 grammes is sexually mature, so that the large size of the pigment zone seems to be dependent upon the attainment of an active state of the reproductive system rather than on the size of the animal. In the female this development of the pigment zone seems to be delayed until pregnancy is well established. At this period the size of the pigment zone corresponds to that seen in male animals. In the early stages of pregnancy in animals of a lighter weight, where the animal is presumably a primipara, the zone may still be small, resembling that of the non-pregnant animals.

It may be noted here that the suprarenal of the guinea-pig undergoes a very definite alteration in its external/



FIGS. 123. HIGHER POWER VIEWS OF THE PIGMENT ZONE IN A NON-PREGNANT AND A PREGNANT ANIMAL.

X43.



external shape in the course of a first pregnancy. In virgin animals it presents a triangular appearance on cross section, the surfaces being flattened and the borders well-defined. In the later stages of pregnancy the cross section is rounded or ovoid, the gland having become enlarged and the borders rounded off.

In non-pregnant guinea-pigs the pigment zone was usually a narrow strip in comparison with that of pregnant animals. Exceptions to this rule were present in three large females of approximately 600 grammes in weight. These showed a pigment zone of a size corresponding to that seen in the later stages of pregnancy. The condition in these large, probably multiparous, females presents a resemblance to the pituitary enlargement which occurs in a first pregnancy and which remains permanently, though to a slightly diminished extent. Comparison is suggested also with the areola of the mammary gland in the human subject; in the early months of pregnancy this becomes pigmented and never returns to the virgin condition, though the degree of pigmentation diminishes at the end of pregnancy.

The state of the pigment zone in guinea-pigs may be summarised:-

(1) In all sexually mature animals - over 300 grammes/

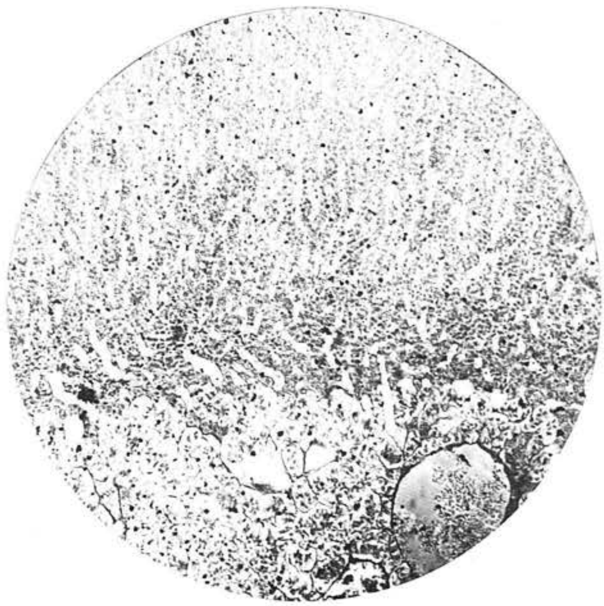
grammes in weight - there is, under normal physiological conditions, a large pigment zone. This zone, no doubt, becomes diminished in size by muscular work and other conditions causing expenditure of energy - as Elliott and Tuckett have shown - but a large zone represents the normal state. The early development of the pigment zone in males of light body weight - presumably young animals - suggests that the male gonads are more directly dependent on the activities of the endocrines than the female. The experiments of Foà on the pineal body support this view.

(2) The size of the zone does not depend on body weight alone. In fully-grown non-pregnant females it is sometimes a narrow strip.

(3) In the later stages of pregnancy it forms a large zone, corresponding to the condition in the sexually mature male animal.

(4) In virgin females the zone is generally small. In multiparous females which are non-pregnant, the zone is of considerable width, but the cells, in some cases at least, appear to contain less pigment than in pregnant animals.

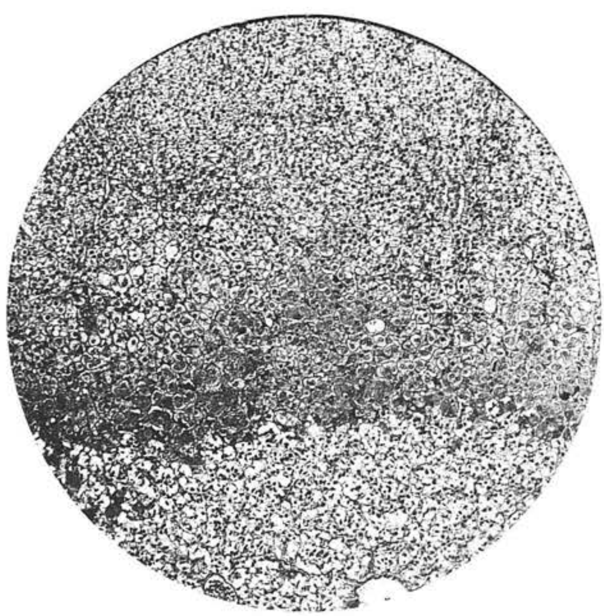
In the rabbit the pigment zone is much less developed than in the guinea-pig. In the non-pregnant animal it forms a very narrow strip, the cells of which/



FIGS. 124-125. THE UPPER SPECIMEN SHOWS THE PIGMENT ZONE IN A NON-PREGNANT RABBIT. THE ZONE IS NARROW AND RELATIVELY SLIGHTLY PIGMENTED.

THE LOWER REPRESENTS THE SAME REGION IN A RABBIT ON THE 15th DAY OF PREGNANCY.

X 79.



which contain only a small amount of pigment (Fig. 124) In pregnancy, however, it forms a fairly broad, deeply pigmented zone. In this animal also the development of the pigment zone appears to present a close relationship to the activities of the reproductive system.

It is generally believed that the lipoids of the suprarenal cortex are increased in amount in pregnancy, though a quantitative estimation does not appear to have been made. I have not been able to satisfy myself, from the histological appearances, that there is any constant relationship in this direction. In the guinea-pig the lipoids are contained mainly in a belt which lies between the pigment zone and the zona glomerulosa, though they extend into both the other regions. They are commonly abundant in pregnancy, but in some cases they are scanty in amount. On the other hand, they are sometimes plentiful in non-pregnant animals, especially in those of large size.

The zona glomerulosa also appears to undergo little alteration in pregnancy. In the guinea-pig the cells of this zone stain more darkly, both with basic and with acid stains, than those of the lipoid zone and the zona glomerulosa is quite sharply defined. It is never more than a thin strip at the surface/

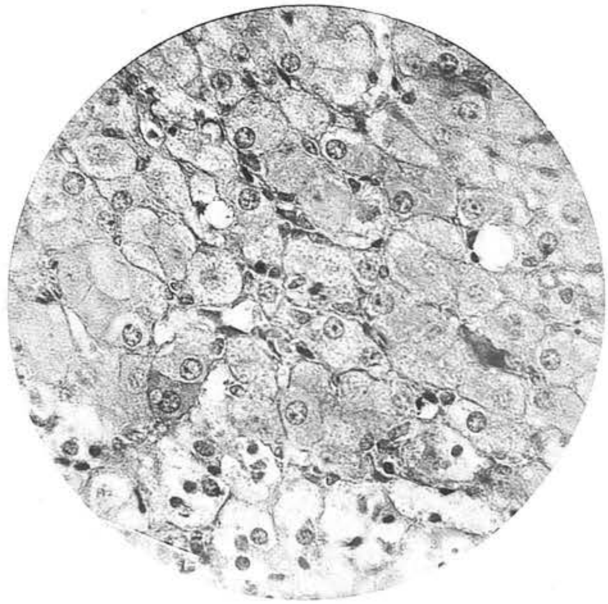


FIG. 125a. THE PIGMENT ZONE IN THE CORTEX OF THE PREGNANT RABBIT. THE PALE CELLS BELOW ARE THOSE OF THE MEDULLA.

IRON HAEMATOXYLIN X 380.

surface of the gland and does not appear to undergo any enlargement in pregnancy.

Secretory Activity in the Medulla.

It has been shown by Elliott and Tuckett that the medulla undergoes distinct enlargement in pregnancy, although to a much less degree than the cortex. The increase is probably partly due to increased vascularity, but it can be shown that cellular changes also take place. The cells of the medulla have been described as being generally polygonal in shape and as possessing granules in their protoplasm. The significance of these granules has been variously interpreted. Stoerk and v. Haberer have stated that the characteristic granules of the protoplasm of the suprarenal medulla are not cast out into the lumina of the blood-vessels. In their opinion these granules represent structural units which are possibly to be regarded as the seats of chemical action whose products are to be looked upon as the true secretion material of the medullary cells, which materials pass into the blood by some such process as diffusion. These authors believe that the fluid secretion product is the true bearer of the chromaphil reaction of the medullary cells, the granules having the reaction only in their secretory phase, when they are just forming/

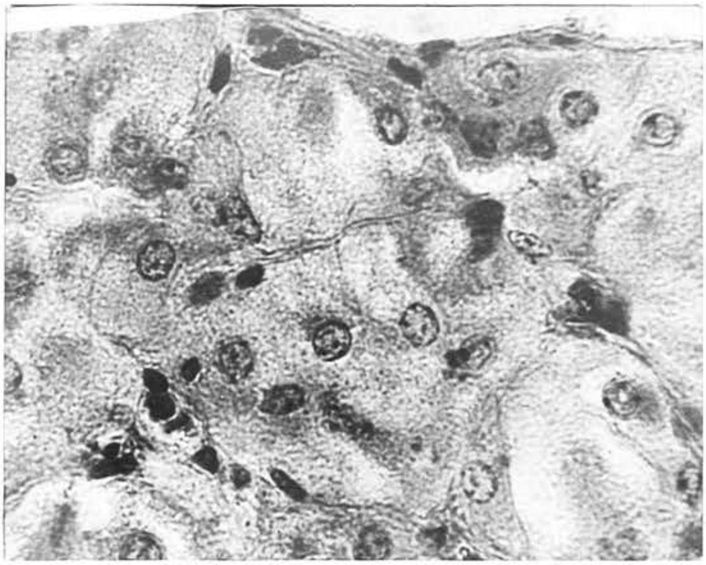


FIG. 126. THE MEDULLA OF A PREGNANT GUINEA-PIG.
THE CELLS ARE CROWDED WITH GRANULES.
IRON HAEMATOXYLIN X 710.

forming the chromaphil substance. They state that the fluid secretion can be recognised intracellularly in both the protoplasm and the nucleus, and extra-cellularly, in admixture with the serum of the capillary and venous blood. Besides the typically fine granules of the medullary protoplasm, they describe coarse structures which occur on the side of the cells turned towards the vessels and which reveal a different staining reaction from the granules. I have been quite unable to identify the coarse structures mentioned; the medullary granules are usually distributed uniformly throughout the entire cell.

Carlier, on the other hand, believes that he was able to observe the granules in the blood channels and in different stages of elimination from the cells. Hultgren and Andersson also believe that they observed the passage of the granules from the cells into the blood-vessels, and Félicine described the granules in the intercellular canals and lacunae.

Crile, in connection with his work on surgical shock, has described very strikingly variations in the appearance of the medullary cells. He finds that, under the influence of such causes as trauma, haemorrhage, loss of sleep, muscular exertion, or excessive emotion, the granules undergo a marked diminution in number/

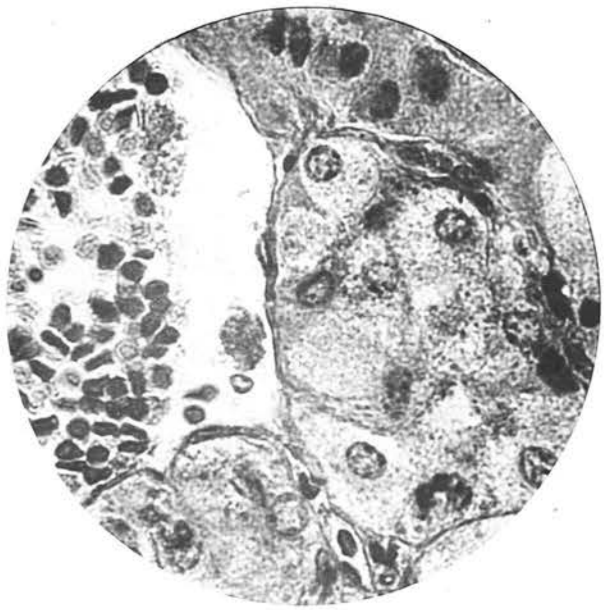


FIG. 127. ANOTHER SPECIMEN FROM A PREGNANT ANIMAL SHOWING ABUNDANT COARSE GRANULES IN THE CELL PROTOPLASM.

IRON HAEMATOXYLIN X 710.

number and a falling-off in distinctness of staining. The contrast was impressively demonstrated in the adrenals of salmon; one group was examined in the resting state at the mouth of the Columbia River and the other at the end of their 700 miles journey to the spawning grounds. In the second group the granules in the medullary cells had become much reduced.

In pregnant animals the medullary cells are, as a rule, more uniformly full of granules than in non-pregnant animals. Figs. 126 & 127 show the appearance of the cells in the pregnant condition. The cells are crowded with coarse granules distributed uniformly throughout the protoplasm. In Fig. 128 a portion of the medulla of a non-pregnant animal is shown. The granules are fewer in number and not sharply defined as in the other examples. The appearances vary, to a certain extent, in different parts of the medulla, but the general rule is that in pregnant animals the granules are more generally abundant than in non-pregnant.

The medullary cells also show a very constant difference with regard to their shape and size in pregnant and non-pregnant animals. In non-pregnant animals they are mostly polygonal and quite irregular in shape. In pregnant animals the cells are distinctly/

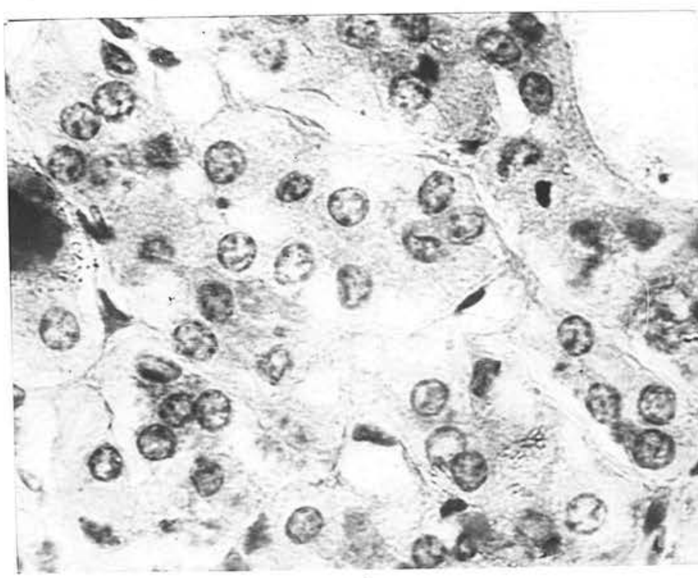


FIG. 128. A PORTION OF THE MEDULLA OF A NON-PREGNANT GUINEA-PIG. THE CELLS ARE SMALLER THAN IN FIG. 126 AND CONTAIN FEWER GRANULES.

IRON HAEMATOXYLIN X 710.

distinctly larger and they show a well-marked tendency to assume a columnar form (Fig. 126). In these elongated cells the nucleus usually lies towards the end of the cell which is away from the blood-channel, whereas in non-pregnant animals the nucleus is commonly central in position. The medullary secretion is often plainly visible in the blood channels, but I have not observed any constant difference in the amount of this secretion between pregnant and non-pregnant animals.

The appearances of the cells of the medulla in pregnancy, as compared with those in the non-pregnant state, support the belief that the granules represent the secretion products, and illustrate the condition of increased functional activity which exists in pregnancy.

Significance of the Signs of Activity in Pregnant Animals.

The difference in origin between the cortex and the medulla and the relationship of the two parts in fishes suggest that the function of the cortex is entirely different from that of the medulla. Evidence is accumulating, however, to show that the two parts are intimately related from the physiological point of view. The fact that the cortex and the medulla are united/

united to form one organ in man and the higher animals and the arrangement of the blood-supply, by which the blood reaches the medulla after having passed through the cortex, suggest that the anatomical relationship is necessitated by a physiological interdependence. Cramer has furnished convincing evidence to show that the cortex takes part in the functional activity of the medulla and that the two parts are not physiologically interdependent. Certain functions, however, have been assigned to the cortex alone. The relationship to the reproductive system seems to concern the cortex rather than the medulla. This is evidenced by the much greater increase in size of the cortex in pregnancy. The close relationship between the size of the pigment zone and the activities of the reproductive system, which has just been described, strongly supports this belief.

Further evidence of the relationship to the sexual functions is supported by the results of pathological affections of the suprarenals. Gallais has recently observed and collected a number of cases in which tumours of the suprarenals have given rise to striking abnormalities in the development of the reproductive organs. Barker describes three possible results of hyperactivity on the part of the suprarenal cortex/

cortex. (1) Pseudo-hermaphrodism. This condition is believed to be due to a congenital form of hyper-interrenopathy, commencing before birth. The true sex of the person depends upon the character of the internal sex organs. The external genital organs of the pseudo-hermaphrodite usually resemble those of the sex opposite to that to which the patient really belongs. (2) Premature puberty. This is believed to be an early postnatal form of hyperinterrenopathy. The patients appear normal at birth but soon become obese. The growth is abnormally rapid, and premature development of the secondary sexual characters takes place. Many of these cases suffer from tumours or hyperplasia of the suprarenal cortex. (3) Adult hirsutism or virilism. This is believed to be a late or adult form of postnatal hyperinterrenopathy. The condition usually affects women between sixteen and twenty. The patient tends to acquire masculine characters, the most characteristic feature being the change in the number and distribution of the hairs; a beard develops and hair appears on the chest, abdomen, and elsewhere. These patients commonly suffer from a tumour of the suprarenal cortex.

The feeding of young animals with suprarenal cortex appears to stimulate the growth of the testes, though/

though Hewer has recently described degenerative changes similar to those produced by exposure to the X-rays. Grafting experiments have usually been unsuccessful, but recent experience in the human subject seems to show that this affords a promising field for further research. Tanner transplanted a suprarenal removed from a foetus just before death into the testicle of a patient suffering from Addison's disease. The patient has improved considerably and the graft can be made out as a nodule in the testicle. Transplantation of the suprarenal into another organ appears to be more likely to be followed by success than merely grafting under the skin.

The significance of the pigment in the cells of the cortex has been the subject of repeated investigations. Elliott and Tuckett believed that the guinea-pig was almost unique in its possession, but Flint and others have described the pigment in the human suprarenal. As already mentioned, it forms a well-developed zone in the pregnant rabbit. Findlay has shown that it is abundant in infancy and also in chronic diseases, such as tuberculosis, syphilis, and carcinoma, which are associated with cell depression. Bauer has recently advanced the opinion that the cortex detoxicates the waste products of the intermediary/

intermediary metabolism which are present in the circulation even under physiological conditions. The chief product of the purin metabolism presents uric acid. The latter, according to Bauer, is also the mother substance of pigment. The melanin of the cortex, or oxidised uric acid, is elaborated into adrenalin by a process of destruction and by repeated processes of reduction in the medulla. The oxidation of uric acid in the cortex serves a double purpose; to keep the pigment in the cortex in equilibrium, and to oxidise the raw material for the medulla, He found the suprarenals much enlarged in patients who died from chronic nephritis, especially in those with contracted kidneys. Simultaneously with the large size of the suprarenal glands, the cortex was unusually broad and it showed a pronounced increase in pigment. He believes that the increase in size in these cases is due to the excess of uric acid, the result of the deficient kidney function. If the suprarenals are overworked and unable to deal with the excess of pigment, it becomes deposited in the skin, where it may become oxidised to pigment. He found that, after incubation, the skin from uraemic patients showed a marked brown colour. Bauer has demonstrated, by careful microchemical tests, the presence of uric acid in/

in the cortex. · Wolf and Thacher have shown that in Addison's disease there is a marked retention of purin bases in the blood. It appears from these observations that the pigment in the cortex is the precursor of the adrenalin in the medulla. The increase in the pigment zone in pregnancy, if this view is correct, may be regarded as possibly a preparation for the increased demand for adrenalin which must exist during parturition.

The significance of the lipoids is still extremely debatable. Many observers, and especially those of the French school, believe that the cortex represents the factory for lipoids; other authorities consider that the cortex acts rather as a storehouse for lipoids produced elsewhere and carried to the suprarenal by the blood-stream. Against this latter view is the observation of Federici that there was no diminution in the amount of the lipoids in animals which were starved to death. This observer also found no change in the lipoids of bats or dormice relative to hibernation. It has been mentioned that no constant relationship was found to exist between the amount of lipoids and the pregnant state, so far as could be made out by histological examination.

Few attempts have been made to assign a specific function to the zona glomerulosa. Browne, from his observations/

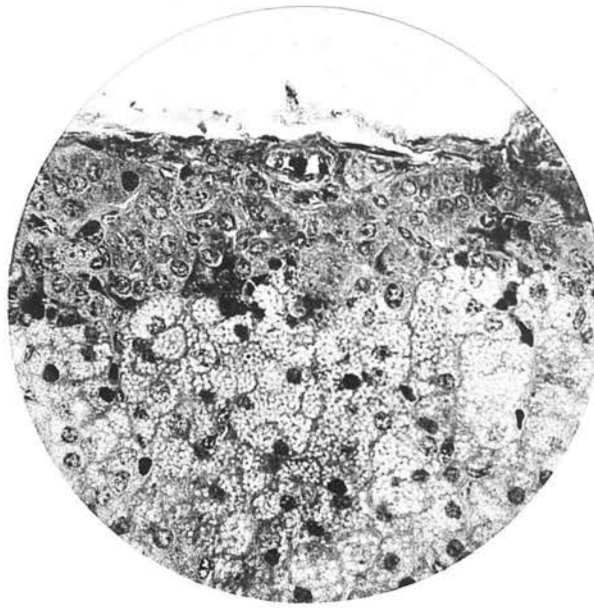


FIG. 129. THE ZONA GLOMERULOSA AND ADJACENT ZONA FASCICULATA IN THE GUINEA-PIG. THE CELLS OF THE ZONA GLOMERULOSA STAIN MORE DARKLY THAN THOSE OF THE ZONA FASCICULATA AND CONTAIN FEWER LIPOIDS.

IRON HAEMATOXYLIN X380.

observations on anencephalous and normal foetuses, has proferred the suggestion that it may present a relationship to the anterior lobe of the pituitary. He finds this zone increased in size in anencephalous foetuses, and thinks that this may represent an attempt to assume the function of the absent pituitary. He mentions, in support of this suggestion, the fact that there is a certain resemblance in appearance between the cells of the zona glomerulosa and those of the anterior lobe of the pituitary. Beyond the fact that the cells of the zona glomerulosa of pregnant animals stained readily with acid stains, the appearance of the zone in the animals examined furnished no evidence in support of this view. There was no indication of an increase in size such as takes place in the pars anterior of the pituitary in pregnancy.

The characteristic function of the medulla is the production of adrenalin. The manner in which this is utilised by the body is still under discussion. It was found by Oliver and Schäfer that even in the blood of the suprarenal vein there is not always enough of the autacoid to cause a rise of blood-pressure when a few cubic centimetres were injected into a vein. Stewart, Rogoff, and Gibson devised a method recently which shows that normally a small amount of adrenalin passes more or less continuously into the circulation. Blood/

Blood from the suprarenals was collected in a pocket of the inferior vena cava, which was made by applying clamps to this vein above and below the level of the suprarenal veins. An animal in which the iris had been sensitized towards the action of adrenalin by prior removal of the superior cervical sympathetic ganglion was employed. It was found that after the pocket had been allowed to fill with blood, removal of the upper clamp caused the pupil to dilate. It has been shown, however, that the amount in the suprarenal vein is normally very small - not more than one part in a million. No effects were observed on the general health or the blood pressure of animals in which the suprarenal of one side was removed, and the nerve control of the opposite gland severed, although it is evident that very little adrenalin could have been present in the blood. The amount under these conditions has been estimated at not more than one part in 400 million parts of blood.

Since a "tonus" hypothesis of the medullary function is untenable, an "emergency" hypothesis has been brought forward, chiefly owing to the work of Cannon. He believes that adrenalin is secreted into the blood in supernormal amounts when certain emergencies arise, such as asphyxia or conditions of extreme emotion, such as fright or fear. In his earlier researches a catheter was passed through a slit in the/

the femoral vein so as to lie in the inferior vena cava opposite the suprarenal veins. Blood was removed and tested for adrenalin by observing its effect on an isolated strip of intestine. The original experiments of Cannon were criticised by Stewart and Rogoff and these observers were unable to verify his conclusions. Cannon has repeated his earlier observations by a method which would not entail loss of blood, and employed a denervated heart as the test object. It has been shown by Levy, Gasser, and Meek that this responds to extremely small concentrations of adrenalin. He found that these later experiments verified his original conclusions in every respect.

The "emergency" hypothesis of the medulla bears an important relationship to death under anaesthesia. It has been suggested by Levy that death in the early stages of anaesthesia is sometimes due to the sudden liberation of a large amount of adrenalin. This is believed to act as an overdose to the heart and to bring about arrest in a state of "delirium cordis". The question is of importance also in relation to the operative risk in cases of toxic goitre. It has been shown that the suprarenals in this condition are in a state of hyperactivity and sudden death during operation may, in some cases, occur in the manner suggested.

The/

The observations of Crile, in his investigations into the nature of surgical shock, appear to have shown that the granules in the medullary cells are utilised by the body in conditions associated with expenditure of muscular energy. The accumulation of granules and the active state of the cells in pregnant animals, considered in relation to the views of Cannon and Crile, are probably to be interpreted as a preparation for the expenditure of muscular and other energy at the time of parturition and in the later stages of pregnancy. The medulla, therefore, may be regarded as possessing, to a certain extent, a storage function, such as is seen in a number of the other endocrine glands.

CONCLUSIONS.

1. The cells of the pigment zone of the suprarenal cortex are characteristic in their appearance in guinea-pigs and in rabbits. The zone is especially well developed in the guinea-pig, but is also present in the rabbit.

2. The size of the pigment zone does not depend on body weight alone. In fully-grown non-pregnant female guinea-pigs it sometimes forms a narrow strip.

3. The zone presents a close relationship in its development/

development to the activities of the reproductive system.

4. It reaches to full development at an earlier date in male animals than in female. This suggest that the male gonads are more directly dependent on the activities of the endocrines than the female.

5. In the later stages of pregnancy it forms a large zone corresponding to that seen in male animals. In non-pregnant virgin females and in the early stages of a first pregnancy it forms a small zone.

6. In non-pregnant rabbits the pigment zone is faintly marked; in pregnancy it forms a prominent feature of the cortex.

7. The lipoids of the suprarenal cortex present no constant relationship to the pregnant state. The zona glomerulosa undergoes no change in pregnancy.

8. The cells of the medulla show an increase in size and a tendency to a columnar shape in pregnant guinea-pigs. The granules which they contain are distinctly increased in pregnancy.

9. The increase of the granules in pregnancy lends support to the view that they represent the secretion products of the cells.

In/

In conclusion, I have to express my great indebtedness to Professor Robinson for the facilities placed at my disposal in the Anatomy Department for the carrying out of this work and for much instruction, encouragement, and advice.

I have also to thank Mr. Lewis Beesly, Mr. J.M. Graham, and Mr. F. E. Jardine for several operation specimens of pathological conditions, and Dr. W. A. Alexander for specimens of normal tissues from the Pathological Department of the Royal Infirmary.

I am indebted to my wife for the drawings which illustrate this thesis and for the mounting and labelling of the illustrations.

The rest of the work, including the preserving, cutting, and staining of the specimens, has been carried out entirely by myself. The photographs, also, are my own work throughout.

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