THE DEVELOPMENT OF THE HYPOPHYSIO-PORTAL SYSTEM IN MAN

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IN recent papers Popa and Fielding (1,2) have described in the human subject a system of vessels running in the stalk of the pituitary which they call the hypophysio-portal veins. The development of this system is the subject of this paper.

MATERIAL AND METHOD

I have had the advantage of being able to study two early embryos, one of 11·9 mm. and the other not measured but probably about 5 weeks from conception, placed at my disposal at Oxford by Prof. Goodrich, for whose kindness in allowing me to examine and photograph them I am most grateful. I have also made use of three later specimens of about 2, 4, and 5 months, generously given to me by medical practitioners. These pituitaries were sectioned at 10 μ together with all the surrounding structures after fixation in mercury formol soon after death. The sections were stained with Mallory's connective tissue stain, modified for certain sections to show particular points. The series were then examined, the courses of the chief vessels determined, and the most important sections were photographed.

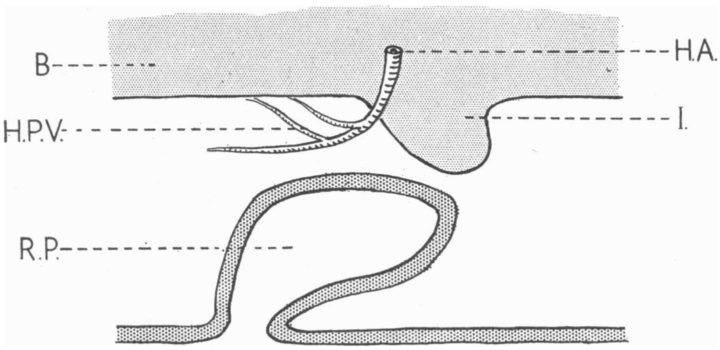
OBSERVATIONS

Plate I, fig. 1, shows a transverse section of an 11·9 mm. embryo at the region in which the carotid arteries are bent to conform with the flexure of the embryo. The arteries therefore lie in the plane of the section. The mesoderm immediately surrounding the brain, richly supplied with blood vessels, is about to form the meninges. Vessels are carried into the substance of the brain by this tissue growing in. When, later on, the different membranes can be distinguished, the vessels can be seen to be accompanied into the brain by pia mater and by arachnoid tissue. Each vessel comes in this way to be surrounded by a small diverticulum of the sub-arachnoid space—the space of Virchow-Robin.

According to the observations of Hughson (3,4) upon the adult dog and cat and the embryo pig, the pituitary complex in these forms lies wholly within the dura mater which covers the floor of the sella and is reflected to form the diaphragma sellae. The cord of cells from the buccal epithelium marking the closed tube of the original buccal invagination (Rathke's pocket) breaks down before the completion of the meninges, so that this total enclosure of the complex is developmentally comprehensible. The arachnoid membrane also encloses the complete organ. There is inside this and separated from it by a part of the sub-arachnoid space, a layer of pia mater. Hughson demonstrated this by injecting a medium into the sub-arachnoid space of his subject and observing that it appeared all round the pituitary and that it entered the pars anterior round the vessels leading to and from it. That is to say it was forced into the buccal analogues of the spaces of Virchow-Robin.

This description of the relations of the parts differs from the account by Parker (5) of the condition in *Trichosurus* and *Perameles*. Here, while the whole complex lies within the dura mater, the pars nervosa and the isolated pars tuberalis are alone within the pia mater.

Since the parts of the pituitary complex appear when the brain is surrounded by undifferentiated tissue, the nervous portion pushes down into formless mesoderm and the buccal portion pushes up into the same substance. The mesoderm which is trapped between the pars nervosa and the pars intermedia, bearing blood vessels, may, if it seems desirable, be termed pia mater, but since the membranes are formed as such out of undifferentiated mesoderm after the



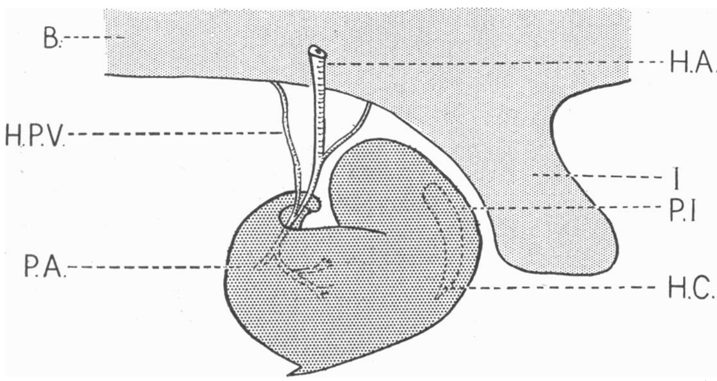
Text-fig. 1. A diagrammatic representation of the relations of the hypophysial artery, the infundibulum, Rathke's pocket, and the brain.

pituitary complex is established it is not surprising that difficulties are experienced and apparent anomalies found in efforts to trace their actual continuity.

A branch of a vessel supplying the brain can be seen invading it at ***S.A.B.*** in Plate I, fig. 1. Actual invasion of the substance of the brain is less advanced ventrally than laterally, though ventrally the closely applied mesoderm is very vascular. At ***H.A.*** in the same figure a conspicuous branch is seen springing from the carotid and running medially and forward in this connective tissue between the developing hypophysis and the brain. The same thing can be seen on the other side. These relations are indicated diagrammatically in text-fig. 1. The same vessels are seen again in Plate I, figs. 2–4. These sections are taken further forward where branches (***H.P.V.***) run from the vessels to the ventral surface of the brain. There is thus an arterial link from this tissue to the brain established even at this early stage.

The great venous sinuses beneath the brain surround the developing pituitary, and some connection is maintained between them and the vascular system of the organ, the connections penetrating the capsule when this is formed through actual discontinuities in it. These connections remain small at the ages which are here considered, and the definite hypophysial veins described by Popa and Fielding cannot be demonstrated in my material. It has proved impossible also to confirm the suggestion of Brander (6) that the hypophysial cleft becomes confluent with the venous system. The vessel which he describes as running back from the point where the buccal cord enters the sella to the ventral end of the cavity of the pituitary can be clearly seen in the later stages but remains outside the capsule. Venous spaces are beginning to appear in the mesoderm beneath the brain at the stage shown in Plate I, fig. 1, and at *H.V.* one can be seen entering the head vein.

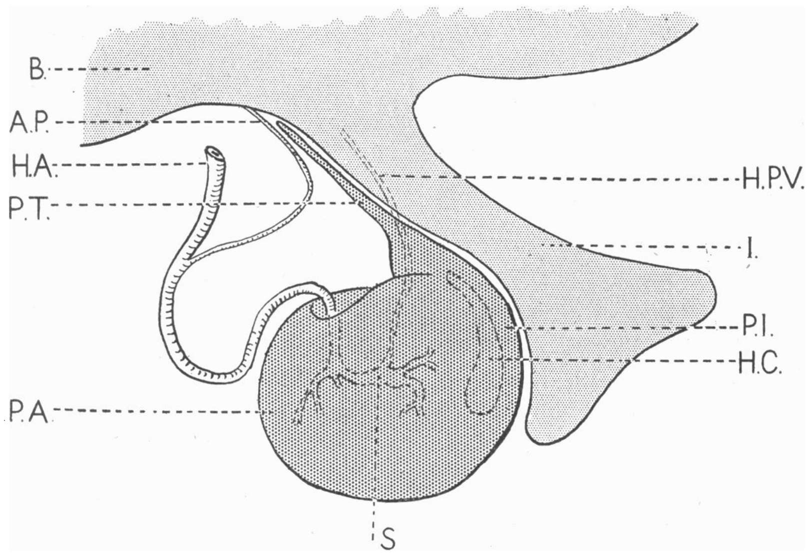
Plate II, fig. 5, shows a later stage, in which the invasion of the brain by vessels is further advanced laterally (*S.A.B.*), though still slight ventrally. The artery previously described as running forward between the brain and the



Text-fig. 2. A diagrammatic representation of the relations of the hypophysial artery, the infundibulum, the pars anterior, and the brain. The pars anterior is lapping round the hypophysial artery and its branches to the brain. The left side only is shown.

pituitary can be clearly seen leaving the carotid, and can now be identified with the hypophysial artery (*H.A.*). The connective tissue in which it runs is by now becoming surrounded by the upgrowing lateral horns of the pars anterior, as can be seen in Plate II, fig. 6 (*C.T.*), and as is indicated diagrammatically in text-fig. 2. This growth leads to the conspicuous core of connective tissue seen in ordinary transverse sections of the human pituitary, and is thus seen to be part of the layer of connective tissue which forms the pia mater elsewhere all round the central nervous system. This core comes on each side to be almost completely built in by glandular tissue, but it remains in continuity with the rest of the connective tissue of the region at one point, and it is here that the hypophysial artery enters the pituitary (see text-figs. 2 and 3 and Plate II, figs. 7 and 8).

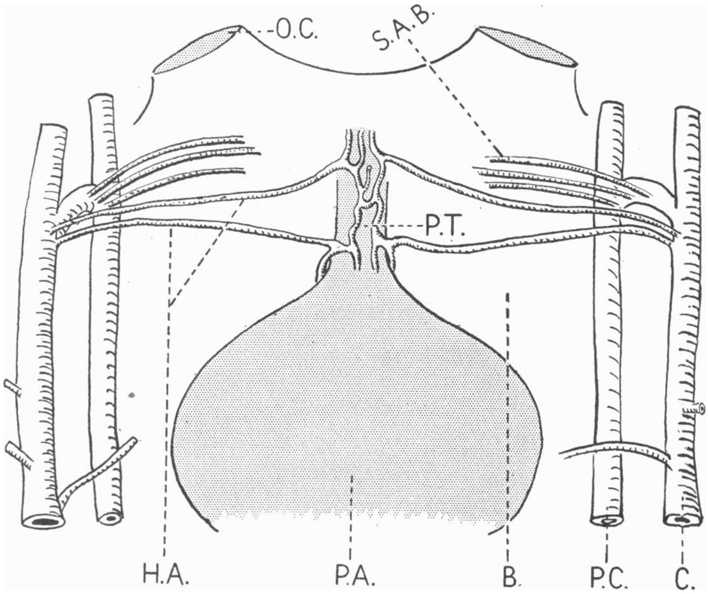
Within this core of connective tissue the artery, which may be single or double, or reduced or absent on one side, enlarges to form the sinusoids commonly described and seen in Plate III, fig. 9, at *S*. These sinusoids are large thin-walled vessels with an endothelium probably complete, though extremely attenuated. They ramify and anastomose in all directions, bringing the blood into the most intimate contact with the outer side of the acini of the glandular portions of the pituitary. The secretory cells are arranged so that the basiphil elements are towards the connective tissue and vessels, while the acidophil elements are towards the acini—unlike the condition found by de Beer in *Scyllium* (7). There is a very intensely acidophil area in the pars intermedia whose cells line the cleft. The cavities of the acini are derived from the original hypophysial cleft by a process of folding and the nipping off of evaginated portions.



Text-fig. 3. A diagrammatic representation of the relations of the hypophysial artery, the infundibulum, the pars anterior, the pars tuberalis, and the brain.

Part of the blood which reaches the pituitary by the hypophysial artery makes its way back into the general circulation by way of the venous connections previously described, but part of it must, it seems, be carried on from the earliest stages here studied by the vessels seen in Plate I, figs. 3 and 4, to a site beneath the brain. The heavy invasion of the ventral portion of the brain in this region is accomplished by branches of the pituitary vascular system. Such a branch is seen in Plate III, fig. 12. This is a hypophysio-portal vessel.

Further evidence about the nature of the portal vessels of the pituitary can be obtained from a study of the manner in which the vascular system of the pars tuberalis develops. The pars tuberalis pushes up the rostral aspect of the stalk, closely applied to the brain, and between the nervous tissue and the pia mater. This may be seen in Plate III, figs. 10 and 11. In doing so it interferes with a part of the arterial supply of this region of the brain, which is provided by invading twigs from a network confluent with the carotids and comparable with the network described by David (8) in other forms. In Plate III, fig. 10, this network is cut several times, and at *A.P.* an artery of the pia mater is seen actually in process of being involved in this upgrowing glandular tissue. These relations are indicated diagrammatically in text-fig. 3, and a reconstruction of this network in one embryo is shown in ventral view in text-fig. 4. In Plate III, fig. 11, a vessel from the sinusoids of the pars tuberalis is seen invading the brain. While the vessel seen in Plate III, fig. 10, does not invade the brain as a whole, its branches do, and it seems that these two vessels are to be inter-



Text-fig. 4. A squared-paper reconstruction of the relations of the arteries, the pituitary, and the brain in one embryo of 4½ months. Seen from the ventral side.

preted as showing two stages in the establishment of a part of the hypophysio-portal system. The colloid described by Popa and Fielding in these vessels has not been found in my material. Possibly it does not appear till later.

DISCUSSION

It is suggested that the hypophysio-portal vessels are morphologically branches of the carotid destined originally to supply the brain and quite secondarily involved in the pituitary complex simply because of the proximity of the pituitary to their path. On this view they are comparable to any other vessels bringing blood to the brain, and are really arterial in origin. They become sinusoid on being appropriated by the pituitary, but regain something of their original form when they reach their proper destination—the brain. In the tissue of the floor of the brain they break up into capillaries just as any other supplying vessels might. From these capillaries—the secondary distribution net of Popa and Fielding—the blood is removed by the ordinary systemic veins of this part of the brain.

The vessels have been termed by Popa and Fielding the hypophysio-portal *veins*, indicating their function of removing blood and secretions from the pituitary. While it is obviously very difficult to distinguish usefully between veins and arteries in this region, since both may be thin-walled and since anastomosis is so free that some reversal of flow may well occur, yet it is not easy to see why, if these vessels are to be regarded as veins, and a vein is taken to be a vessel normally conveying blood towards the heart, they should run to the brain. The analogy of the hepatic-portal vein does not help to make this clear, since, there, a pre-existing vein is appropriated by a developing gland and continues afterwards on its way to the heart as a vein still. Here the topography of the parts makes it almost impossible to imagine a vein from the pituitary to the heart becoming involved in the brain. Even if such a pituitary vein were so involved it is hard to see what developmental factors would be likely to cause it to break up into capillaries in the brain. The violent rearrangement of tissue which takes place in the liver hardly has an analogy in the brain.

If the vessels are veins coming from the brain and involved on their way in the pituitary, then their function must be quite different from that envisaged by Popa and Fielding, unless a reversal of flow and indeed of function has occurred to an extent difficult to understand. These authors have described colloid which has been thought to travel up these vessels from the pituitary to the brain. Moreover, the venous connections from the pituitary seem quite inadequate in my material if the hypophysio-portal vessels are considered as bringing additional blood to the pituitary.

These difficulties seem to be lessened if the hypophysio-portal vessels are regarded as part of the arterial supply of the brain. While the concept of a portal artery is not commonly employed, yet it may be argued that the carotid artery of the frog is nothing less. Here blood is conveyed from the capillary system of the carotid gland to the capillaries of the head. In the fish the whole arterial system is broken down in the gills and re-collected by the efferent arteries. In the eel, Woodland (9) has described an artery to the air bladder breaking up into the rete mirabile, the strands of which are re-collected, to break up into capillaries further on their course.

Concerning the ways in which this system could effectively transport material from the pituitary to the brain, the interesting suggestion of David (8) may be noted: that the pulse of the adjacent carotids might be communicated to the pituitary so as rhythmically to expel its contents.

While Hughson (3, 4) has shown that the vessels entering the pars anterior are accompanied by these spaces of Virchow-Robin, it has been held by Basir (10) that in the dog the hypophysio-portal vessels are not so accompanied, though the systemic vessels in the brain are. While it is extremely difficult to be sure of a point of this kind from microscopical examination without injection, it may perhaps be added that I have not been able to recognise arachnoid tissue round these vessels in my material. It seems probable that vessels growing from the pars anterior to the brain would not carry with them any recognisable arachnoid tissue, since, on the view I have suggested, they could be regarded as starting from the pia mater.

CONCLUSIONS

1. The hypophysio-portal vessels are a part of the arterial supply of the brain.
2. This part of the arterial supply has been secondarily involved and enclosed by the upgrowing wings of the buccal part of the pituitary when it was close to the under-surface of the brain.
3. As the infundibular stalk lengthens, the vessels assume their distinctive form.

I wish to thank Prof. A. C. Hardy, in whose Department most of the work was done, for his encouragement, and Dr G. R. de Beer for reading the paper in typescript and making many helpful suggestions.

EXPLANATION OF LETTERING

A.	Acini.
A.P.	Artery of pia mater.
B.	Brain.
C.	Carotid.
C.T.	Connective tissue core of pars anterior.
H.A.	Hypophysial artery.
H.C.	Hypophysial cleft.
H.P.V.	Hypophysio-portal vessel.
H.V.	Head vein.
I.	Infundibulum.
III.	Third ventricle.
O.C.	Optic chiasma.
P.A.	Pars anterior.
P.C.	Posterior communicating artery.
P.I.	Pars intermedia.
P.M.	Pia mater.
P.T.	Pars tuberalis.
R.P.	Rathke's pocket.
S.	Sinusoid.
S.A.	Sub-arachnoid space.
S.A.B.	Systemic artery of brain.

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EXPLANATION OF PLATES

Plate I.

Fig. 1. Transverse section through the pituitary of an 11·9 mm. embryo, showing the origin of the hypophysial artery from the carotid on each side. ×48.

Fig. 2. Same as fig. 1, but further forward, showing course of hypophysial artery. ×48.

Fig. 3. Same as figs. 1 and 2, but further forward, showing connection between hypophysial artery and brain. ×48.

Fig. 4. Same as figs. 1, 2 and 3, but still further forward, showing a similar connection on the other side. ×48.

Plate II.

Fig. 5. Transverse section through the pituitary of a later embryo, showing the origin of the hypophysial artery from the carotid on each side. ×30.

Fig. 6. Same as fig. 5, but further forward, showing enclosure of core of connective tissue with vessels by the upgrowing lateral lobes of the pars anterior. ×30.

Fig. 7. Para-median section of a 4-months' embryo, showing hypophysial artery approaching the pituitary. ×28.

Fig. 8. Similar to fig. 7, but showing the hypophysial artery cut twice, once inside and once outside the pituitary. ×28.

Plate III.

Fig. 9. An enlarged view of part of the connective tissue core, showing sinusoids and acini. ×130.

Fig. 10. Para-median section of the pituitary of a 4-months' embryo, showing artery of the pia involved by developing pars tuberalis. ×28.

Fig. 11. Para-median section of the pituitary of a 4-months' embryo, showing a hypophysio-portal vessel from the pars tuberalis entering the brain. ×28.

Fig. 12. Para-median section of the pituitary of a 4-months' embryo, showing a hypophysio-portal vessel well established, with thick glial sheath. ×28.

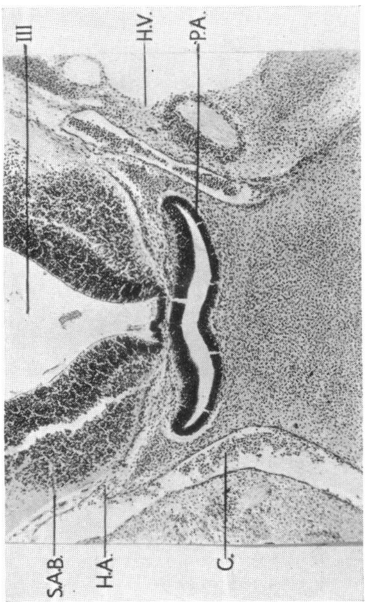


Fig. 1.

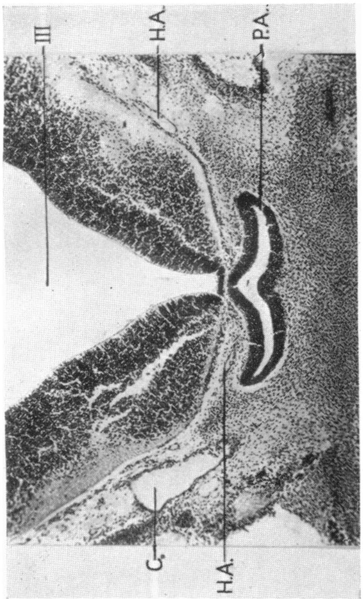
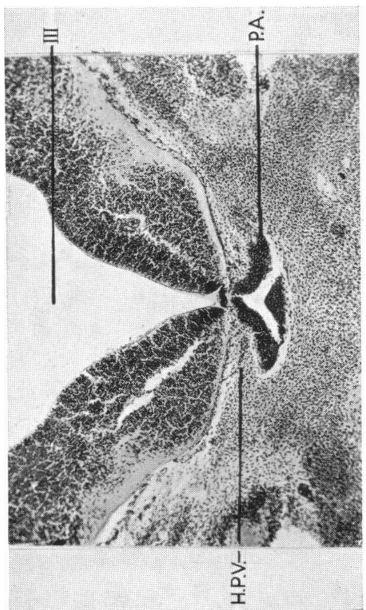


Fig. 2.



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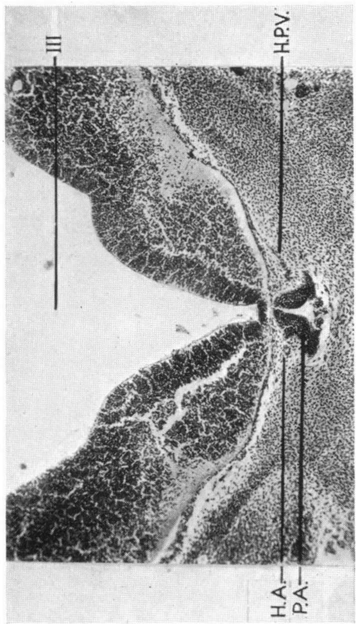

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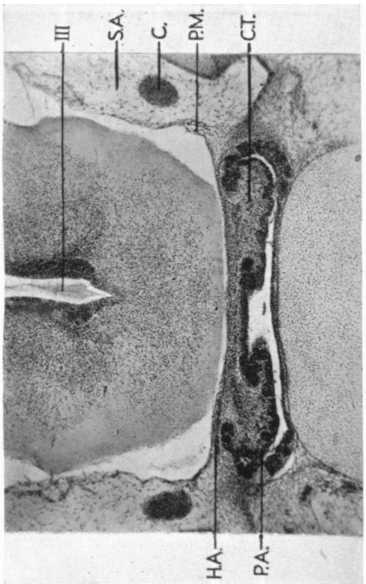
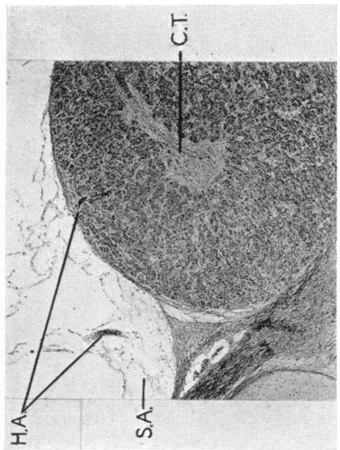


Fig. 6.



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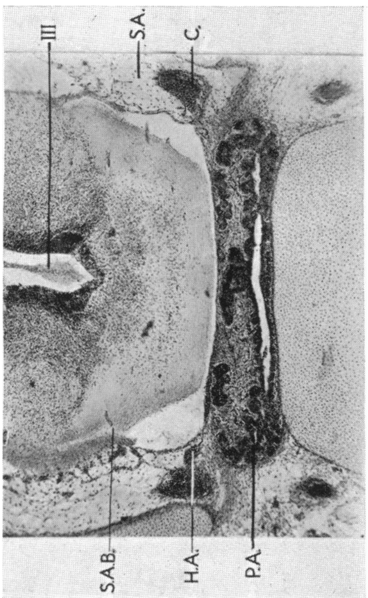

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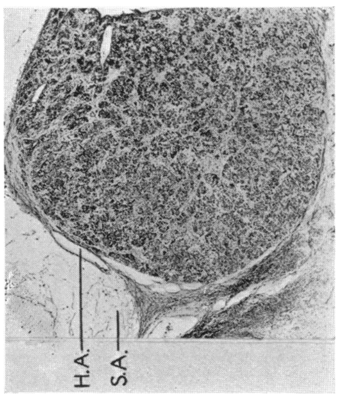

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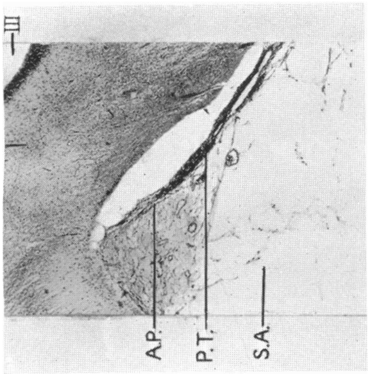

Fig. 10.

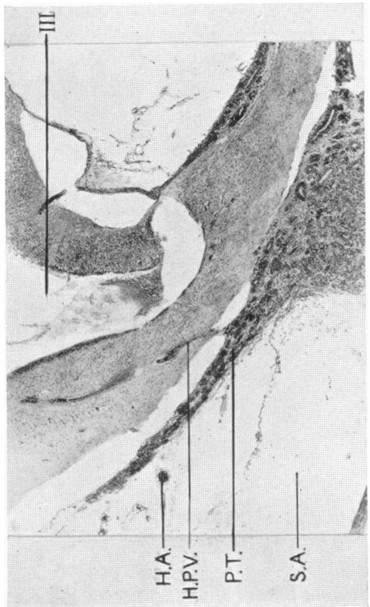

Fig. 12.

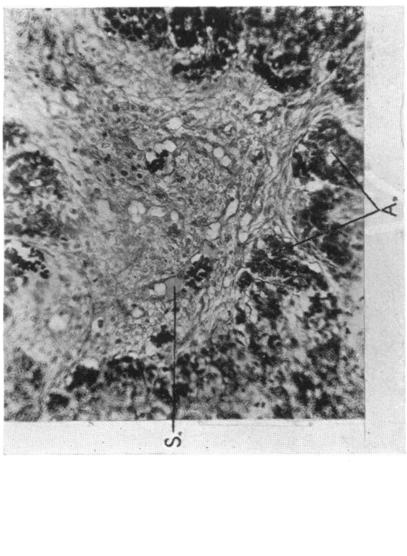

Fig. 9.

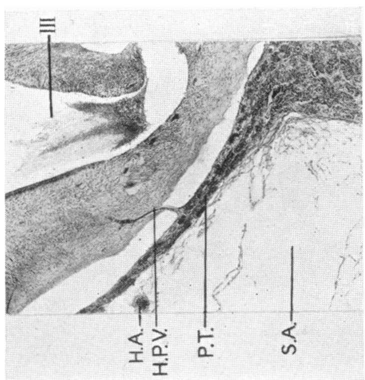

Fig. 11.