THE NUTRITION OF THE RETINA AND THE INNER EYE;
A THESIS PRESENTED FOR THE DOCTORATE OF
PHILOSOPHY OF THE UNIVERSITY OF GLASGOW BY
ISAAC CHESAR MICHAELSON.

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INTRODUCTION.

The purpose of this work is to review the developmental and adult condition of the blood vessels of the inner eye of the vertebrates and to consider the role of these vessels in the nutrition of the retina. In addition to a general summary of the vascular conditions in each class of the vertebrates, a more detailed description will be given of certain representative species including the eel, roach, frog, pigeon, horse, rabbit, cat, rat and man.

Later, emphasis will be laid on two aspects which emerge in the course of the study. The first is the role of the choroid in the nutrition of the retina; and the second is the presence in the developing retina of a factor or factors capable of affecting the growth of new vessels. Finally, an interpretation will be made of some features of the vascular pattern of the inner eye of vertebrates in terms of the choroid's capacity to nourish the retina and of the activity in the retinal tissue of the factor or factors affecting new-vessel growth.

Most of the anatomical features are based on the appearances of injected retinae, although where possible this has been preceded by an ophthalmoscopic examination of the live animal. For the injection, Indian Ink (Reeves') diluted 50% with water was given at determined pressures into the foetus or animal as shortly after death as possible. The injection mass was given through a canula under a head of pressure which was accurately measured by means of a mercury manometer. The pressure was maintained at a steady level by

means of a rubber hand pump with a balloon air-reservoir. The injections were made into the heart, the carotid artery, or the ophthalmic artery according to the size of the specimen and the experience obtained with each species. In man, however, in order to avoid the frightful appearance of Indian ink in the surface tissues of the corpse, the injected material used was sedimented red cells of citrated human blood mixed with a gelatine solution as detailed later in the description of the human retina.

In some cases attempt was made to help the filling of the vessels of the head by clamping the venous return after the injection had been in progress for some time. The efficacy of an injection was judged by the appearances of the skin, conjunctiva and tongue, although these were not invariably good criteria of the state of the retinal injection. The effect of the injection on the retinal vessels was frequently controlled by ophthalmoscopic examination of the dead animal for which purpose care was taken to keep the cornea moist with saline.

Following injection, the eyes were removed, placed in 10% formalin for a day and then opened by a coronal incision passing in front of the ora serrata. Unless the vessels were within the vitreous, this tissue was then most carefully mopped away with cotton wool as the transparency of the mount is greatly dependent on this procedure. Finally with the help of a blunt probe the retina was gently removed from its choroidal bed and mounted

in glycerine on a slide. Despite great care during this manoeuvre, the retina especially in an early foetus eye was occasionally torn and spoiled for our purpose. About one hundred satisfactorily injected and mounted retinae were obtained in this way. Where necessary portions of the mounted retinae were removed, embedded in paraffin or celloidin and sectioned for histological examination.

Observations were made only on retinae, or portion of retinae, completely injected. An area showing no injected vessels was not considered to be avascular unless found so with the use of the high power of the microscope.

Although the majority of the descriptions, ophthalmoscopic and microscopic, are based on personal observations some are derived from authorities to whom acknowledgement in each case is made; a dependence made necessary in most instances by the difficulty of obtaining certain specimens.

P I S C E S.

Material & Methods: Preparations of retinae were obtained from six eels varying in size from one to three feet. These were killed by means of a large dose of nembutal. The injections of Indian ink were made into the heart, 10 mls being used at a pressure of about 70 mm of mercury. The retina of the roach was successfully injected, 2 mls of the Indian ink preparation being given into the heart at a pressure of 40-50 mm of mercury. Much of the information regarding the pisces was derived from the works of Hans Virchow (1882-1901), de Waele (1900), v.Kittlitz (1907), and Franz (1913).

Adult Conditions: While the selachii including the chimaeridae do not possess vitreous vessels, such vessels are present in most of the teleostii (fig.1). In respect of vitreous vessels the ganoidei are intermediate to these orders, the cartilaginous ganoids possessing superficial vitreous vessels like the majority of the teleostii. In the dipnoids, inner ocular vessels are absent in the ceratodus, but in the protopterus Pincus (1895) has demonstrated a vessel passing from the disc for a short distance into the vitreous and Hosch (1904) has demonstrated fine vitreous branches coming from vessels lying on the inner surface of the eye. These vessels lie in a membrane which cannot be separated from the nerve fibre layer and which according to Hosch should therefore be considered as the internal limiting membrane of the retina.

Teleostii: The eel:. There are many teleostii in which there are no vitreous vessels. When present they form a vascular net containing the superficial vitreous vessels. These vessels arise from a branch of the internal ophthalmic artery which like the draining vein uses the disc as portal.

Among the teleostii the eel shows a unique and extraordinary extension of the superficial vitreous vessels into the retina as first demonstrated by Krause (1876). H.Virchow (1882) stated that "this single cold blooded animal possesses a retinal vasculature which excels that of mammals." After injection it is easy in this animal to distinguish between the retinal and the superficial vitreous vessels (fig.2). This is, however, possible only if the vitreous is not brushed away from the surface of the retina. Broad vessels with associated capillaries lie on the vitreous surface while narrower vessels with an associated double capillary net are situated within the retina (figs. 3 and 4). If a substance such as alcoholic shellac solution, which does not pass the capillaries is used for injection it can be seen that the larger retinal vessels are veins (Virchow 1882). The broader vessels lying on the surface of the vitreous are by the same criterion arterial. These latter vessels result from the dichotomous division of the large central artery coming from the optic disc. This central vessel forms nasal and temporal vessels which continue to divide as they pass on the surface of the vitreous towards the periphery of the fundus where they form

capillary loops. The capillaries which lie between these arteries form a very open reticulum. From these superficial vitreous vessels fine branches pass outwards through the inner limiting membrane into the retina and communicate with the vessels within that tissue (fig.4). If the vitreous is brushed away from the retina numerous torn vascular communications can be observed with a loupe. Virchow (1882) estimated that about 9600 such fine vessels pass from the vitreous into the retina. Many of them pass directly into retinal veins while others divide to form intra-retinal capillaries (fig.5). The retinal veins congregate into four main vessels which join to form a central vein in the optic nerve head (fig.2).

In sections Denissenko (1882) and Virchow (1882) demonstrated two vascular layers in the retina of the eel; the inner situated in the inner nuclear layer and consisting of larger vessels as well as capillaries, and the outer lying in the outer nuclear layer immediately in front of the external limiting membrane. Virchow noted that the average size of the capillary mesh in the outer net is smaller than that of the inner one, and that its diameter varies from 30 μ to many times that extent. The situations of these capillary nets are indicated in figs. 5 and 6. In the former figure the vessel, which passes from one lying outside the retina, can be seen dividing at two levels. At the level of the inner branch (the inner nuclear layer) there can be seen an un-injected large vessel which

is a vein filled with nucleated blood-corpuscles.

The circulation thus flows from the central artery in the optic disc into the superficial vitreous vessels and then through the retinal capillary nets from which it drains into the retinal veins.

A most notable feature of the fundus of the eel is the complete absence of a choroid (figs. 1 and 6). This figure represents a section of the globe from an eel which had previously been injected with Indian ink. The injected superficial vitreous system of vessels and the two retinal capillary nets can be clearly distinguished. A layer of large cells representing the hexagonal pigment layer lies directly on the sclera. The absence of a choroid has no doubt necessitated a retinal vascularisation which extends to the immediate vicinity of the rod and cone layer and which in that respect is to my knowledge unique among the vertebrates. There is no evidence of the absence of a choroid in any other vertebrate.

In the other teleostii, which possess vessels within the inner eye, there are no intra-retinal vessels. In these animals the arteries, capillaries and veins are situated in the vascular net lying on the surface of the vitreous, the arteries and veins alternating in position with capillary zones placed between them (fig.7). The veins drain anteriorly into an annular vein which leaves the inside of the eye through the ciliary body. A notable feature of the superficial vitreous

vascular net is the presence around each artery of a zone free from capillaries, an appearance not seen around the veins (figs. 7 and 7A). This phenomenon has been particularly noted by Virchow in the conger vulgaris (1882) and by Schultze in the carp (1892).

In the eel where the arteries and veins lie in entirely different planes it is difficult to determine whether there are fewer capillaries in the immediate vicinity of the arteries than in that of the veins; but there is no doubt that the great bulk of the capillaries are situated in the retina close to the veins.

Development: The development of the intra-ocular vessels of pisces has been studied in the selachii and the teleostii.

The selachii as already stated do not possess vitreous vessels at the definitive stage but de Waele (1900) has demonstrated in the embryo vessels which lie within the foetal fissure and later disappear.

In the developing trout at the 10 mm stage v.Kittlitz (1907) noted associated with the foetal fissure a processus falciformis with a contained vascular loop. The dorsal limb of this loop passes anteriorly between the margins of the fissure to the position where later the muscle of accommodation (lens muscle) will be formed. There it turns to pass once more between the margins of the fissure as the returning or

ventral limb of the vascular loop. From the dorsal limb there develops a complex of blood vessels which invades and later fills the vitreous chamber. These vitreous vessels are referred to by v.Kittlitz as the "vitreous glomerulus", although Virchow (1881 & 1885) preferred to describe them as the deep vitreous vessels in contra-distinction to the superficial vitreous vessels found in the fully developed eye of the trout and other teleostii. In the 12 mm trout these deep vitreous vessels begin to disappear, a process almost complete in the 27 mm fish. At the latter stage a bud from the vitreous vessels grow towards the disc and probably represents the anlage of the superficial vitreous vessels found in the definitive eye.

A M P H I B I A.

Material & Methods: Several adult frogs were examined ophthalmoscopically after the instillation of adrenalin into the conjunctival sac. Four frogs were killed with chloroform and the hearts injected with Indian ink at a pressure of 60 mm mercury. In this animal it is very difficult to separate the retina from the choroid. The tissues were therefore mounted together and the choroid depigmented with potassium permanganate and oxalic acid.

Adult Conditions: While the inner ocular vessels are absent in the urodela they are present in the form of a well developed net in the anura as first discovered by Hyrtl (1861). In the frog, which in this respect can be considered as typical of the anura, the inner vessels of the eye lie in the border zone between retina and vitreous, the retina itself having no blood vessels (figs.1,8 and 9). With the ophthalmoscope the vascular net can easily be seen to consist of arteries, veins, and capillaries. A broad vein runs from above downwards in front of but not on the disc, increasing in diameter as it passes downwards by access of vessels from either side. It forms the ventral root of the hyaloid vein and joins at the extreme periphery below with a vessel about half its breadth coming from the nasal side and with one coming from the temporal side - the

nasal and temporal roots of the hyaloid vein. At the place where these roots join, a broad artery - the hyaloid artery - divides into its nasal and temporal branches. The hyaloid artery is the terminal portion of the ophthalmic artery which entering the choroid just beyond the equator forms an arch out of which pass two vessels to supply the iris. The temporal branch of the hyaloid artery which is the larger, passes at first temporally, then upwards and to the nasal side. This vessel, because of its very peripheral situation in places, is not everywhere ophthalmoscopically visible. At its upper part it gives off 7 vertical twigs which pass towards the posterior pole of the globe. These twigs divide dichotomously without anatomoses. The nasal branch of the hyaloid artery likewise gives off twigs which pass towards the posterior pole. The temporal and nasal arteries thus form a peripheral arterial ring open only for a short space on the nasal side. The ventral root of the hyaloid vein in its downward passage receives from either side branches whose terminal twigs pass widely in the horizontal meridian and upwards. At the few arterio-venous crossings the artery is always over the vein. The capillary net which can always be seen ophthalmoscopically by sharp focussing, is thickest at the posterior pole and much thinner peripherally where there are many zones without capillaries. In all vessels the blood flow is visible and this is useful in differentiating between artery and vein,

the stream in the former passing from the broader to the narrower portion of the vessel. The visibility of the blood stream is due to two factors chiefly; the magnification with direct ophthalmoscopy in the frog is 70 times as compared to 14 times in man, and the size of a red blood corpuscle in the frog is 22 μ (Hirschberg 1882). The flow in the capillaries is visibly slower than in the arteries, while that in the veins is slowest of all. In the capillaries the corpuscles can be seen as glistening points which often are motionless for a long time. A striking feature of the circulation is that when two veins become confluent two streams can be seen in the resultant vein and if shortly a third vein joins the main vessel, three separate streams are visible.

The superficial vessels of the frog lie in a membrane which can easily be separated from the retina. It is however, very difficult to separate the retina from the choroid. Choroidal tissue was therefore depigmented with potassium permanganate in order to obtain satisfactory mounts showing the injected retinal vessels. The capillary mesh has an average diameter of 130 μ.

A notable feature is the presence of a capillary free zone around the arteries in contrast to the relatively dense capillary arrangement around the veins (figs. 8 and 9).

All the anuren amphibians have vitreous vessels similar to those of frog except in respect of details. As already stated the urodela on the contrary have no superficial vitreous vessels. Hyrtl (1861) did not find them in the salamandrina nor did Kessler in the larvae of Triton. Many of the urodela possess a pecten (fig. 1D).

Development: In the amphibian embryo a vessel passes through the middle of the vitreous to the lens (de Waele 1905). This vessel disappears later. No information could be obtained from the literature regarding the development of the superficial vitreous vessels of the adult eye.

REPTILIA.

Methods: There was no opportunity to inject the retina of an animal of this class. The circumstances of the adult conditions were derived from the contributions of Virchow (1883) and those of development from Kessler (1877).

Adult Conditions: The snakes alone of the reptilia possess superficial vitreous vessels. The hyaloid artery which proceeds from one or both common ciliary vessels passes through the sclera at its junction with the ventral aspect of the sheath of the optic nerve. At the disc the artery divides into nasal and temporal branches which divide and ramify in a zone between retina and vitreous, the resulting capillary net covering at least one third of the entire retinal surface. Close to the ora serrata there is an annular vein with temporal and nasal roots. There are no intra-retinal vessels, but Müller (1872) noted that if the vitreous be separated from the retina, the vessels cling to the latter tissue and in sections they are found to be tied to it by means of a fine connective tissue.

A well developed pecten is found in many of the reptilia including the lizards. It is also present in certain of the snakes (boa and viper) which do not possess superficial vitreous vessels.

Development: The early development of the intra-ocular vessels in the reptilia is similar to that found in many vertebrates. A vessel enters the globe below the optic nerve between the margins of the foetal fissure and passes across the vitreous. It leaves the globe anteriorly close to the ora serrata. With the closure of the fissure the anterior portion of the vessel is separated from its place of exit and the remaining portion may take part in the formation of the pecten (figs. 1 and 10). This organ has a pointed free end lying in the vitreous. There is no detailed information in the literature regarding the development of the superficial vitreous system of vessels found in many of the snakes; but it is probable that its development is similar to that found in the teleostii. Virchow (1883) has shown that this system appears later than the temporary vessel which grows from the disc into the vitreous.

A V E S.

Material & Methods: Two pigeons were injected with Indian ink and sections made of the posterior portion of the globe. The injections were made into the heart and contained 20 mls of the material. Much information regarding the inner ocular vessels of the birds was derived from contributions of Kessler (1877) and Franz (1913).

Adult Conditions: The pecten contains the only blood vessels of the inner eye of the birds (fig. 1D). The numerous vessels within it communicate with each other by means of loops while between them is a sparsely pigmented connective tissue (figs. 11 and 12). The course of the vessels is generally from the base of the pecten to the free end which is in the vitreous, and the single feeding artery, the arteria pectinis, enters the base of the organ close to the edge of the optic disc. It is a branch of the ophthalmic artery. The draining vessels enter a large choroidal vein which leaves the globe through a special opening in the sclera. The choroid is well developed and there are no intra-retinal blood vessels (fig.13).

Development: On the ventral side of the optic vesicle there is a vascular loop consisting of a dorsal and ventral limb. With the invagination of the vesicle the dorsal limb after lying within and then over

the margins of the optic fissure, is situated finally within the vitreous of the developing eye. The position of this vessel is indicated in fig.14 illustrating a 5 day hen embryo. This vessel is the anlage of the arteria pectinis of the developed eye. The ventral or returning limb of the primary vascular loop atrophies and disappears. In the hen the earliest development of the pecten can be noted on the fifth day and on the sixth day there is already atrophy of the ventral limb of the vascular loop.

M A M M A L I A.

In most of the mammalia the hyaloid supply of the inner eye although present in development is superceded in the definitive stage by special retinal vessels which enter the globe through the optic disc. The extent to which these vessels traverse the retina may vary from one species to another and accordingly the retinae of mammalia have been classified into four types; anangiotic, pseudoangiotic, angiotic, and euangiotic (Lindsay Johnson 1901).

Anangiotic Type: In these retinae no trace of vessels can be observed with the ophthalmoscope (figs.15 and 16). Animals of this type are echidna, hystrix, myopotamus, pteropus, and rhinocerus. They are representative of the lowest mammalian orders, monotremes, marsupials, edentata, and rodentia.

Pseudoangiotic Type: The visible retinal vessels are scarce and extend only as far as the edge of the disc or a short distance beyond it (fig.17). This is the case in the majority of marsupials, perissodactyla, edentata and rodentia, e.g., hyrax, tapirus, equus, myremecophaga, phalangista, petaurus, and capybara. In some of these animals the vessels are so few and slight that their retinae are almost of the anangiotic type or else may be considered as intermediate between both types.

Angiotic Type: The retinal vessels emanate from numerous trunks at or near the disc periphery from which they spread over the greater portion of the retina. This is the case in most of the carnivora e.g. felidae, and in some of the rodents e.g. muridae, sciuridae, leporidae, the vessels are restricted to the transverse expansion of the medullated fibres of the optic nerve (fig.18). Some of the carnivora, on the other hand, e.g. nasua, approach the euangiotic type.

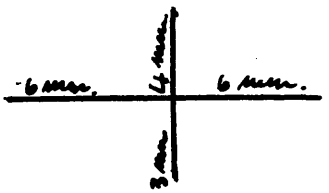
Euangiotic Type: In these animals the vessels form a system generalised over the retina (fig.19). This type is found in some marsupials, for example didelphys and dasyurus; in some carnivora, for example viuerridae; canidae; and in all the primates.

A brief description will be made of the retinal vascular systems of the horse, rabbit, cat, rat and man, which are representative of the vascular types already detailed. These animals were chosen because all were easily available for ophthalmoscopic examination and because in all of them, except the horse, there was opportunity to inject the retinal vessels and to examine the retina in bulk and in microscopic sections.

THE HORSE.

Material & Methods: Most of the details regarding the retina of this animal were obtained from the works of Langenbacher (1880) and Bach (1909) as there was no opportunity to make injected preparations.

Adult Conditions: Coming from the disc are about 30 fine arteries and an equal number of veins, the arteries being about 25 μ and the veins 35 μ in diameter fig. 20. These are the branches of the central artery and vein which divide always before reaching the disc. Langenbacher and Bach are of the opinion that the vessels supplying the retina from the disc are mostly ciliary in origin, which opinion Nettleship (1905) would appear to confirm by his work on various ungulates. In addition the disc is covered by a thick net of vessel loops which are twigs from the larger vessels before they reach the disc or just after they have entered the retina. The vessels do not pass far into the retina, the following diagram indicating their extent:-



The vessels divide 0.3 to 1.0 mm from the disc and continue to do so dichotomously until

until each vessel has formed 10-16 branches. At the periphery the arteries do not pass into a capillary net but communicate directly with veins, the arterioles and venules there being about 12 μ wide. Beyond the first dichotomous division there are fine T shaped vessels between the main ones (fig.20). Leaving the arteries at a right angle these vessels pass for about 25 μ before bending again to run a course of about 15 μ parallel with the parent vessel. They then turn on their tracks until the level of exit from the parent vessel is reached. There they turn once more and enter the adjacent vein.

Sections show that the larger vessels lie deep in the nerve fibre layer or in the ganglion cell layer. The smaller vessels lie in the nerve fibre layer.

THE RABBIT.

Material & Methods: Fifteen rabbits were successfully injected - four adults and eleven young rabbits taken from three different litters. Embryos were not used as the retinal vessels at birth are extremely few and extend for only a short distance beyond the optic disc.

All the injections were made into the heart; in adults 50-60 Mls of Indian ink at 100 mm. mercury pressure, and in the young animals 10-35 Mls. Indian ink at about 50 mm mercury pressure.

Adult Conditions: The retinal vessels of the rabbit are confined to two wing-shaped areas of medullated nerve fibres spreading horizontally on either side of the optic disc (fig.21). The vascularised area anterior to the disc is somewhat more extensive than that posterior to it. In an adult rabbit the measurements of these extents from the edge of the disc were found to be 8.71 and 7.47 mm respectively. The vascular system can therefore be considered to be rather intermediate between the angiotic and pseudo-angiotic types.

The central vessels in the adult rabbit pass into the optic nerve a short distance behind the disc, close to which artery and vein divide into two main stems. A large vein and artery pass into the medullated nerve fibres on either side of the disc, the artery being about 35 μ and the vein about 45 μ in diameter. They cross, artery or vein being superficial, and divide dichotomously until in the periphery of the retina the artery passes into the vein by means of very delicate loops fig. 21. These peripheral loops are more irregular and wider than those found in the retina of the horse. A further difference is that while in the horse each peripheral loop is regularly composed of a single artery and vein, in the rabbit the returning vein of a peripheral loop may drain two looping arterial vessels (fig.22). Peripheral loops are also present all round the upper and lower limits of the medullated fibre bundle (fig.23). To reach these latter limits branches leave the main vessels at right angles, run to the edge of the vessel area, continue in the direction of the parent vessel and then after looping return as a vein along the same direction. In addition to the peripheral loops there exists a capillary system between the main branches of the artery and the vein. According to His (1880) these capillaries are arranged in two layers, the

external being chiefly venous and the internal arterial in character. This could not be confirmed from the specimens examined. The capillaries do not form a reticular net but are arranged in irregular loops which overlap one-another (fig.24).

In the view of many authors (Langenbacher 1880, Schultze 1892, Fuchs 1905,) all the vessels lie within the retina; although the contrary opinion has had much support (His 1880, Bruns 1882). In our own findings the appearance of the vessels in the adult retina shows that the larger vessels lie on the surface of the retina (fig.25). The appearance in this figure of a vessel-crossing and of a smaller vessel arching away from the retina supports this clearly.

Development
Foetal Stage: Lenhossek (1903) and Fuchs (1905) have made a detailed study of the development of the intra-ocular vessels of the foetus of the rabbit. By the 11th day the optic cup possesses on its surface a fairly dense capillary meshwork limited anteriorly by a regular and complete annular vessel. On the second half of the 11th day a hyaloid artery can be seen arising from the annular vessel on the caudal side, its termination within the cup forming a large bulbous swelling on the 12th day. The first anlage of the hyaloid artery in the rabbit thus is not the immediate continuation of the

internal ophthalmic artery but comes from the capillary system on the outer aspect of the optic cup by means of the annular vessel. Fuchs (1905) therefore described it as the primary hyaloid artery. The definitive hyaloid artery, which is the terminal branch of the internal ophthalmic artery, appears on the 13th day and forms an anastomosis with the primary hyaloid artery somewhere between its bulb and stem. The definitive hyaloid artery enters the optic cup in the region of the medial end of the optic fissure. In later embryos it can be observed to run a direct course from the internal ophthalmic artery to the optic nerve. The blood circulation in the vitreous drains anteriorly to the choroidal vessels and vortex veins.

On the 13th day there is yet no trace of retinal vessels. On the 14th day buds of cells from the vessel channels in the optic nerve head can be seen pushing laterally and externally to the internal limiting membrane of the retina. On the 15th day these buds have formed a network of cell-columns, which later become canalised and contain blood from the vessels on the disc.

While most of the retinal vessels thus develop from the central vessels in the optic nerve several of them appear to communicate at the

disc with the ciliary vascular system. There are no buds into the retina from the vitreous vessels.

1 day old rabbit: A few vessels can be seen passing from the disc into the retina for a very short distance. Their appearance, however, is obscured by vessels of the hyaloid system which form a rather densely packed series of loops lying on the retina (fig.26).

3 day old rabbit: The hyaloid system has disappeared to a great extent permitting a clearer view of the retinal vessels. In the specimen examined these extended 0.96 mm and 0.82 mm on either side of the optic disc. Larger vessels and smaller ones which form loops can be differentiated.

4 day rabbit: There is but little remnant of the hyaloid system lying on the retina fig.27. The retinal vessels in the specimen examined extended 0.99 mm and 0.83 mm on either side of the optic disc.

8 day rabbit: The extent of vascularisation on only one side of the optic disc could be measured. It was found to be 2.16 mm.

11 day rabbit: The extent of vascularisation could be measured on only one side of the optic disc. It was found to be 2.91 mm.

The findings in rabbits 15,16 and 18 day old were confined to measurements of the

vascularised area on either side of the disc. These are tabulated below together with the measurements already noted in 3, 4, 8 and 11 day old rabbits:-

Age of Rabbit.	Extent of vascularised areas measured from disc's edge.		
1 day	x		x
3 days.	0.96 mm	and	0.82 mm.
4 days.	0.99 mm	and	0.83 mm.
8 days.	2.16 mm	and	x
11 days.	2.91 mm	and	x
15 days.	4.15 mm	and	3.48 mm.
16 days.	5.04 mm	and	4.08 mm.
18 days.	5.12 mm	and	4.64 mm.

x Could not be accurately measured.

The difference in extent of the vascularised areas on either side of the disc is illustrated in fig.28 which is from an 18 day old rabbit.

In order to indicate in some way the growth rate of the vascularised area a graph has been constructed from these measurements fig. 29. In this group the mean between both measurements of the extent, if available, is used. The growth rate is apparently about 0.27 mm per day or about 11 μ per hour, although it should be noted that the measurements were necessarily taken from different individuals, each of whom, even if of the same litter, may have had a separate growth rate. The rabbits

1, 4, 11 and 18 days old were of the same litter.

The difference found between the measurements of the vascularised area on either side of the optic disc might be indicative of different rates of vessel growth anteriorly and posteriorly from the disc or of a difference in starting times of the anterior and posterior vessels. Such a finding would have been of interest in view of the normally greater extent in the definitive rabbit eye of the vascularised area anterior to the disc. Unfortunately it was not possible to arrange the injected and mounted retinae so as to be certain that the orientation of the vessels as in life could be traced in each specimen. This could be done only by carefully noting in each rabbit during life with the ophthalmoscope, such vascular peculiarities as would suffice for the proper orientation in the mounted specimen.

THE CAT.

Material & Methods: Numerous foetuses of different ages, as well as several litters of kittens and three adult cats were used. The ages of the foetuses were 35, 45, 51, 53 and 56 days. Of the kittens, four members of a litter were examined between the 1st and 22nd day; four members of a litter between the 4th and 8th week; two members of a litter in the 2nd and 3rd weeks; and four members of a litter within the first 10 days.

The cats and kittens were killed with chloroform. In the foetuses and in most of the kittens injections of a commercial Indian ink preparation (Reeves) diluted 50% with water were made through the left ventricle; in the others the injections were made into the common carotid artery. The ink was usually injected under a pressure of slightly more than 100 mm mercury. The quantity used varied with the size of the animal. For a good injection of a 45 day old foetus, 5 - 10 Mls were necessary. The requirements for kittens from new born to 22 days old varied from 10-25 Mls, while in the adult cat about 30 Mls were injected into the common carotid artery.

Adult Conditions: The major retinal vessels in the cat consist of three pairs of arteries and veins which run from the optic disc to the periphery, one pair nasally, one

pair upwards and temporally and one pair downwards and temporally. Fig.30 illustrates the appearance of an injected retina mounted in glycerine. Between the temporal pair are several smaller vessels running to the macular region. These vessels curve round the edge of the disc and are in communication for the most part with the choroidal circulation rather than with the central vessels of the optic disc (Schultze 1895). Otherwise, there is a great similarity between the definitive retinal circulation of cat and man. The vessels run at a superficial level in the nerve fibre layer, successive divisions of the vessels remaining at this level until the pre-capillaries are reached. A striking feature of the vessel crossings is that the vein appears to be always superficial to the artery, an observation which was made on 170 crossings. The capillaries, as in man, fall into two groups; a superficial capillary net lying in the layer of nerve fibres and a deep capillary net lying in the outer and inner aspects of the inner nuclear layer (fig.31). The arterial precapillary vessels arising from the small arterioles, the arteriae afferentes, pass directly into the superficial capillary net and from the latter anastomotic vessels pass into the deep capillary net. As many venous pre-capillaries drain directly from the deep net, it may be considered to be

more venous in character than the superficial one. It is unusual to find an arterial precapillary passing into the deep net. In this respect the capillary circulation of cat differs from that of man (Michaelson and Campbell 1940) but resembles that of the rat (Hesse 1880). The deep capillary net is in general more dense than the superficial one. In representative parts of the fields the average area of a capillary mesh was found to be about 2000 sq μ in deep net and about 7000 sq μ in in the superficial net with however, great variations within both nets. Figures 32 and 33 illustrate this difference in mesh size. Bruns (1882) found the capillary mesh diameter to vary from 40-90 μ. A striking feature of the capillary distribution is the absence on either side of the arterioles of capillaries from the superficial net in a zone which has an average width of 100 μ - 200 μ. Only a few capillaries of the deep net traverse this zone and these do not communicate with the arterioles (figs. 34 and 35). The capillaries do not avoid the neighbourhood of the veins in a similar manner. In the macular region there is an almost completely avascular zone having an average diameter of 300 μ. The peripheral margin of the retinal vascular system is formed by wide capillary arches joining the terminal branches of the arteries and the veins.

Between these and the ora serrata there is a narrow avascular zone about 500 μ in width.

Development: To illustrate the mode of development of the retinal circulation in the cat a description is given of the vascular appearances in the embryo at 35, 45, 51 and 56 days, and in the kitten at successive periods after birth until the 22nd day.

35 day embryo; The optic disc and posterior portion of the hyaloid artery are illustrated in fig.36. It can be seen that no retinal vessels are present at this stage.

45 day embryo: Several vessels can be seen proceeding from the edge of the disc into the retina, where they pass for a distance of 0.12 - 0.24 mm (fig. 37). With higher magnification it can be seen that in many vessels there is a solid column of cells extending for a short distance beyond the end of the Indian ink column. These probably represent the as yet uncanalised portion of the developing vessels.

51 day embryo: The vessels have progressed further towards the periphery (fig. 38) and are now 0.36 - 0.72 mm, from the optic disc. At places branches can be seen connecting the straight vessels and constituting the early vessel loops, or vessel complexes. It must at this stage be only a conjecture that one limb of this loop represents the future artery and the other the vein, as

no difference in the walls of these limbs can be detected.

56 day embryo: The vessel complexes which are three in number have developed in several ways (fig. 39). They have grown further to the periphery, being 5.6 mm, 4.80 mm, and 4.56 mm respectively from the optic disc and their more complicated arrangement is apparently the result of vessel growth from the limbs of the original loop described in the 51 day embryo. The limbs of the original loop can now be recognised as artery and vein in the light of the definitive stage appearances and the intermediate stages still to be described. At an average distance of 0.6 mm from the optic disc, where the main vessels begin to diverge from one another, a capillary system can be seen developing, although much of the retina remains still unvascularised. The developing capillary system shows several striking characteristics:

(a). By far the greater part of the developing capillary system is growing from the veins and forms around them a triangular shaped bed whose base is directed peripherally (figs. 40, 41, 42 and 43).

(b). The capillary growth from the vein is by a process of budding. These buds which are placed at fairly regular intervals have pointed growing tips. (fig. 44).

(c). If neighbouring artery and

vein are close to each other the capillary growth is confined initially to the side of the vein remote from the artery. Fig.45 made at a higher magnification than the previous ones illustrates this feature quite clearly. As artery and vein diverge, capillary growth now takes place from the side of the vein towards the artery as well as from the distal side. If a vein is situated midway between two arteries the capillary growth occurs equally on either side of the vein.

(d). The embryonic capillary net formed at this stage differs from the definitive net in the greater diameter of the lumen and the smaller size of the mesh. The net is entirely in the layer of nerve fibres (fig. 46a). The large size of lumen is illustrated in fig. 46b.

(e). The embryonic capillary net grows towards the neighbouring artery but stops short of it so that a capillary free area is left around the artery (fig. 45). This zone is traversed by occasional single vessels which grow from the artery and judging from their position, probably represent the future arteriae afferentes of the system. These vessels are the products of the arteries and not of the surrounding capillaries as evidenced by the occasional protrusion from the arteries of vascular buds which have not yet reached the neighbouring capillary bed (fig. 45). At the periphery of the

vascularised area the terminal venules and arterioles are linked up with each other by capillary arcades. Around these arcades there is also a dense capillary development. There is nowhere any evidence of capillary formation that is not a budding from pre-existing vessels.

1 day old kitten: The development described in the 56 day embryo has now progressed to that illustrated in fig. 47. The three vessel complexes have grown farther towards the periphery being 5.04, 5.04 and 6.00 mm from the disc, and the non-vascularised areas between them are now much more limited than they were in the 56 day embryo. The capillary bed clustered around each vein retains its triangular shape noted in the 56 day embryo, the base being at the periphery of the vascularised portion of the retina and the apex still at the same distance from the optic disc. While the capillaries on the periphery of this triangular area retain their embryonic appearance, those nearer to the disc assume that of the definitive reticulum with narrower lumen and broader mesh. The capillary free space around the arteries is even more pronounced than in the 56 day embryo as the capillaries have grown more completely towards the arteries.

8 day old kitten: The periphery of the vascularised area is now on the average 6.2 mm from the disc and practically all of the retina is vascularised.

The capillaries near to the periphery are still of the primitive type.

15 day old kitten: The periphery of the vascularised area is now on the average 6.7 mm from the optic disc. In some places a deeper capillary network can be seen developing from the superficial net. The peri-arterial capillary free zone is fairly well demarcated (fig. 48).

22 day old kitten: The vascularisation of the retina which now extends about 7.20 mm from the optic disc is very similar to that of the definitive stage with the exception of two features. There are still capillaries of the primitive type in the peripheral areas and the deep capillary network has not yet formed completely. The capillary free zone around the arteries is well demarcated, almost better than in the adult cat, (fig. 49). This zone may even be found around the arteriae afferentes (fig. 50).

The growth rate of the vascularised area of the retina in the cat is indicated graphically in fig. 51. It can be seen that from the 56th day of foetal life until the 22nd day of post-natal life the rate of growth is about 0.10 mm per day or about 4 μ per hour. This must of course remain an approximation as the measurements were taken from five different

individuals. All, however, excepting of course the 56 day foetus, were from the same litter.

The pattern of capillary development outlined above was found to be reproduced in all the embryos and the different litters of kittens examined, with however some notable differences in the rate of development. For example of three 53 day embryos two showed development similar to that described above for a 51 day embryo while one was similar to the 56 day embryo described; and a 28 day old kitten belonging to a poorly nourished litter continued to show a large number of capillaries of the embryonic type (fig. 52).

Discussion: The present conception of development of the vascular system is that its primordium consists of a general capillary net preceding the formation of individual vessels (Krause 1876, Evans 1909, Sabin 1920 and 1922, Hughes 1934 and 1935, Hamilton,Boyd and Mossman 1946). The endothelium of such a net is considered to arise from a syncytium of cells differentiated from the local mesenchyme (Finley 1922 and Sabin 1920 and 1922). The mesenchymal origin of vascular endothelium in the rabbits choroid has been described by Fuchs (1905). Out of the capillary net so formed the circulation develops certain

broader and more defined lines of traffic in accordance with haemo-dynamic forces first postulated by Thoma (1893). The line of development according to these conceptions may be summarised thus; mesenchymal cell, angioblast, vascular endothelium, capillary, and finally artery and vein. This method of vascular development is not present everywhere since the heart itself is formed from chains of angioblasts rather than from a complicated plexus, and in the opinion of Federow (1910) supported later by Squier (1915) the pulmonary vein of the chick is produced at a very early stage of embryonic life as a proliferation of endothelium from the dorsal sinus wall which projects into the mesocardium. Into this proliferation the sinus cavity tunnels thus producing a short vessel which is the anlage of the vein. The vein ultimately branches into capillaries which anastomose with capillary outgrowths from the lung arteries. Further, Buell (1922) found angioblasts coming directly from the wall of the sinus venosus of the chick and failed to find clumps of angioblasts unconnected with the mass and therefore originating in mesenchyme.

From the description given it appears evident that the vessels of the retina in the cat do not develop from a syncytium of cells differentiated locally but from vessels growing from the optic nerve head. The

former possibility would appear to be precluded by the absence of mesenchymal tissue in the developing retina. The initial buds from the optic nerve head join to form loops between the limbs of which a reticular capillary system appears. The capillaries develop predominantly from the venous limb of the loop, and to begin with from the side of the vein remote from the artery, if the artery and vein are close to each other. These capillaries progressively spread in the nerve fibre layer between vein and neighbouring arteries to a well defined distance beyond which they do not go leaving the definitive appearance of capillary free zone around the arteries in the nerve fibre layer. This zone is traversed by arteriae afferentes while deep to the arteries a few vessels from the deep capillary net pass in the inner nuclear layer and therefore about 45 μ from the artery. The capillary free zone lateral to the artery averages about 150 μ in breadth.

The development of capillaries from veins, the initial growth of the capillaries from the side of the vein remote from the neighbouring artery, and the presence of a capillary free space around the arteries of the definitive retina are facts which appear to be closely associated with each other and to be inherent to the process of capillary formation in the retina of the

cat. On these facts, considered as a group, the manner of capillary morphogenesis becomes explicable by the assumption of a factor or factors present in the retina and capable of affecting the budding of new vessels from the endothelium of veins.

The fact that the budding to begin with occurs predominantly, if not entirely, on one side of the vein suggests that the growth affecting factor is not in the circulating blood plasma as it is difficult to conceive of a factor within the plasma stimulating the endothelium on one side of the vessel only.

The fact that the capillary budding from the side of the vein nearer to the artery takes place later than that from the side remote from the artery suggests that the factor under consideration is present in a gradient of concentration such that it differs in arterial and venous neighbourhoods. This assumption seems to be supported also by the presence of a capillary free space around the arteries. A factor present in the retina in a concentration gradient which is affected by the relative proximity of artery and vein is possibly of a biochemical nature.

The mode of spread from the veins laterally towards the arteries and the maintenance of a capillary free space suggest that the factor determining

the initiation of growth of the capillaries probably determines the distance to which it shall extend in a given time, initiation and cessation depending on variations in concentration of the suggested factor.

No more can at present be said regarding the nature of this vessel growth promoting factor in the retina. The findings of embryologists working in their several directions may however, prove significant or applicable to the present problem. These include the discovery by Byerly (1926) that chick embryo which was "suffocated" by the removal of the shell covering the air space and then immersed in water glass solution so that the respiratory change was quite stopped and finally allowed to incubate for 96 hours, developed among other defects extraordinary blood vessels and anomalous sinuses; and the investigations of Robbins and Child (1920) and Child and Hyman (1926) and others into the association of morphological gradients of oxidative metabolism or metabolic rate.

Summary and Conclusions. (1) Vessel growth in the retina of the cat is by a process of budding from pre-existing vessels. No evidence could be found of vascular differentiation from local cells.

(2) The formation of retinal capillaries is pre-eminently a function of the retinal veins. Only the arteriae afferentes appear to originate from arteries.

(3) If vein and artery are close to each other, growth takes place predominantly from the side of the vein remote to the neighbouring artery.

(4) The spread of capillary growth towards an artery extends for only a certain distance leaving, finally, in the definitive cat eye a well marked capillary-free space around the arteries similar to that present in other mammalian retinae such as those of man, dog, rat and pig.

(5) These anatomical facts are clearly associated with each other. Considered as a group they suggest the presence of a factor which affects the growth of retinal blood vessels and which has the following characters:-

(a). The factor is present in the extra-vascular tissue of the retina.

(b). It is present in a gradient of concentration such that it differs in arterial and venous neighbourhoods. The factor possibly is therefore of a biochemical nature.

(c). Its action is on the retinal veins predominantly.

(d). The factor initiating capillary growth from vein probably determines the distance to which the capillary growth will extend, initiation and cessation

depending on variations in concentration of the factor.

(6) The present study of ontogeny shows that the bulk of the capillary system in the retina of the cat can be considered as part of the venous system. The arterial system is shown to be supra-capillary.

[illegible] of development in the day old rat it was not necessary to examine the foetal retina. By the [illegible] the main elements of the general vascular [illegible] were found to be present.

[illegible]tions: The blood vessels in the [illegible] the developed rat have been adequately described [illegible]50) and Bruno (Loc. [illegible]. The central artery [illegible] divides into six branches which radiate towards [illegible]ry in a very symmetrical fashion. The arteries [illegible] narrower than the veins. The arteries divide [illegible] at acute angles until [illegible] the smallest [illegible] The arterial afferents turn off at right [illegible] from the superficial capillary net which [illegible] placed in the layer of nerve fibres.

THE RAT.

Material & Methods: Three adult rats were successfully injected, 10-12 mls of Indian ink being injected into the ventricle at a pressure of 70 mm Mercury. Eleven young rats varying in age from 1-11 days were also injected, about 3 mls of ink being passed into the ventricle at a pressure of about 50 mm Mercury. The rats 1,2,3 and 8 days old were of the same litter. As the intra-retinal vascular system was found to be at a very early stage of development in the day old rat it was not considered necessary to examine the foetal retina. By the eighth day the main elements of the general vascular morphology were found to be present.

Adult Conditions: The blood vessels in the retina of the developed rat have been adequately described by Hesse (1880) and Bruns (1882). The central artery and vein each divides into six branches which radiate towards the periphery in a very symmetrical fashion. The arteries are usually narrower than the veins. The arteries divide dichotomously at acute angles until from the smallest arterioles the arteriae afferentes come off at right angles to pass into the superficial capillary net which like the arteries is placed in the layer of nerve fibres. From this superficial net vessels pass perpendicularly or by obliquely directed loops into a deep capillary

net which lies on either side of the inner nuclear layer. The arteriae afferentes do not pass directly into the deep capillary net. On the other hand venae efferentes are formed in the deep net and these slope slowly to the level of the nerve fibre layer where they enter the veins. At many places capillaries from the superficial capillary net pass directly into the veins or else into the venae efferentes shortly before their juncture with the veins. The general distribution of the capillaries is illustrated in fig. 53. The close association of the deep capillary net with the veins in indicated in figs. 54 - 56, which illustrate the appearances in the neighbourhood of a vein as seen at three different levels. At the most superficial level two venae efferentes can be seen draining into a large vein; at the intermediate level the venae efferentes are passing deeply into the retina; and at the deepest focus (fig. 56) they are in communication with the deep capillary net. These appearances are typical of the entire fundus. The independence of the deep capillary net from the arteries is illustrated in figs. 57 and 58, which are taken at different levels of the same portion of the fundus. At the superficial level an artery can be seen without any associated capillaries. At the deep level the disposition of the capillaries of the deep net is

unaffected by the proximity of the overlying artery. It is clear that the deep capillary net is morphologically at least much more closely associated with the veins than with the arteries of the system.

The meshes of the superficial capillary net are much more open than those of the deep net. Variations of mesh size in the superficial net are very great but the average diameter of mesh estimated by numerous readings was found to be about 130 μ. In the deep net, on the other hand, the meshes are much more regular in size and were found to have an average of only about 80 μ.

A prominent feature of the capillary arrangement is that there is a zone around each artery, arteriole and, in places, arteria afferens, which is free from capillaries of the superficial net (fig. 53). This capillary free zone which is of rather variable size has an average diameter of 100-200 μ.

Development. 1 day old rat : Lying on the retina there is a system of vessel loops which extends for about 1.3 mm from the disc (fig. 59). These are embryonic vitreous vessels and they gradually disappear until at the end of the first week of life but few remain. Deep to these vessels there is a net of very fine vessels arranged around the optic disc and extending about 0.3 mm from it (fig. 59). These represent the beginning of development

of the intra-retinal vessels. Both systems of vessels are shown in section in fig. 60.

2 day old rat: The embryonic vitreous vessels are much fewer in number, while the intra-retinal vessels now extend to about 0.5 mm from the optic disc.

3 day old rat: The intra-retinal vessels now extend to about 1.0 mm from the optic disc. It is possible to differentiate the large retinal vessels.

4 day old rat: The intra-retinal vessels extend to about 1.4 mm from the optic disc. Arteries and veins can be distinguished from each other. The formation of capillaries is apparently taking place predominantly from the veins and there is a broad area around each artery which is free from capillaries (fig. 61). The capillaries in the periphery of the vascularised area are of the primitive type, that is the calibre is broader and the mesh size smaller than in the developed eye.

6 day old rat: The vessels of the retina have extended to about 2.4 mm from the disc. The capillaries are disposed superficially in the retina between arteries and veins but around each artery there is a zone free of capillaries (fig. 62). This zone is about 100-200 μ in breadth. In the periphery of the vascularised area the capillaries are still of the embryonic type. There are no signs of a deep capillary net. Remnants of the embryonic

vitreous vessels can be seen in places.

8 day old rat: The vascularised area extends to about 2.6 mm from the optic disc. The primitive type of capillary can still be seen in places. The deep capillary net is now forming in numerous areas of the fundus.

11 day old rat: The development of the deep capillary net is more advanced. The vascularised area extends to about 2.9 mm from the optic disc.

The varying extents of the vascularised area in rats 1-11 days old are shown graphically in fig. 63. From the data obtained with these animals it would appear that the growth rate of the vascularised area in the rats retina is about 0.24 mm per day or about 10 μ per hour between the first and the eleventh days from birth.

Discussion: The vessels of the rat show features very similar to those already described in the cat. They are formed by a process of budding from vessels in the optic disc and they are not formed by the differentiation of local cells. The formation of capillaries is chiefly a function of the veins, and the spread of their growth towards an artery extends for only a certain distance leaving in the fully developed retina a well marked capillary free zone around the artery.

These anatomical facts are similar to those observed in the cat and support the suggestion that there is in the retinal tissues a factor, which promotes the growth of capillaries especially from the veins. It was not possible to be certain in the specimens examined that budding occurs initially more from one side of the vein than from the other. The greater number of main vessels in the retina of the rat than is present in the cat and their confinement to a much smaller area might be considered to preclude that possibility, each vein being relatively close to the arteries on either side.

M A N.

Material & Methods: The normal architecture was studied on preparations made by peeling the retina off the choroid and spreading it out flat. The vessels were demonstrated by the benzidine stain evolved by Pickworth (1934) for showing the cerebral capillaries; in this technique the red blood cells within the vessels are selectively stained by applying the benzidine-peroxidase reaction to the material, so that those vessels which contain blood are sharply shown against a colourless background. For the purpose of our study the method has the disadvantage that many capillaries are either incompletely filled with blood at death, or become emptied of blood in the course of the handling unavoidable in dissection at autopsy. We overcame this difficulty, however, by reinforcing the natural blood content of the vessels as follows:. The sedimented red cells of citrated human blood are mixed (in the proportions of 2:1) with a 15 per cent gelatin solution; and at the autopsy (preferably in a case of congestive heart failure, where the capillaries are already fairly well filled) this gelatin-blood mixture is injected warm into the ophthalmic artery. Within a few minutes the injection fluid has set within the vessels, and the posterior part of the eyeball is removed and fixed in 10 per cent

formalin. The retinal vessels remain well filled. The skin of the face around the injected eye appears, of course, considerably congested; but the disfigurement is trivial as compared with the frightening result of injecting such a substance as Indian ink.

After a few days' fixation in formalin the retina is peeled away from the eyeball, and the benzidine stain is applied to it. It is then dehydrated, cleared in xylol and mounted on a slide in balsam. In successful preparations the entire vascular system may be completely demonstrated.

Results are rather variable. This may, perhaps, be due to agglutination reactions between the injected blood and that already in the vessels. It would be desirable to use blood known to be of the same group as that of the cadaver. However, by using blood of Moss Group IV one has a reasonable chance of securing compatibility without too many failures.

In the nine foetuses which were used, injections were made with Indian ink. Their sizes varied from 70-240 mm. With the smaller foetuses the injections were made into the ventricle and with the larger into the carotid artery, the pressures of the fluid varying from 50-90 mm of Mercury, according to the age. The pressure factor appeared to be more important for the

human foetus than for most of the other species investigated as leakage of ink or of blood was produced very easily and most disturbingly. The best results were obtained with the carotid route when in the course of the injection the jugular veins were clamped.

Much of the information regarding the earliest stages of the vascular development was derived from the contributions of Schultze (1892), Voll (1892), Versari (1903), Bach and Seefelder (1914), and Mann (1928).

Adult Conditions: As is well known, the general plan of vascularisation of the retina is as follows: The major branches of retinal artery and vein run peripherally from the papilla at a superficial level, in the nerve-fibre layer. Successive divisions of the vessels remain at this level until the immediate pre-capillaries are reached; these fall into two groups; one the superficial group, gives rise to a capillary net which remains at the same level - the superficial capillary net; the other or deep runs usually at a steep angle to a deeper level where it gives rise to the deep capillary net, lying in the boundary plane between inner nuclear layer and outer plexiform layer. The two capillary nets are not however independent; anastomotic capillaries run from one to the other. The markedly lamellar structure of the retina causes these capillary nets to be largely two-dimensional, in contrast to the

three-dimensional net found in most other organs, including the brain.

This basic two-layered pattern of the vascular architecture is modified in certain parts of the retina - by the addition of other layers, and by the reduction to a single layer.

Small arterioles and venules - the arteriae afferentes and venae efferentes of His - run from or to the larger arteries and veins. The larger arteries and veins do not, of course, run together; and in the spaces between them their arterioles and venules run towards each other in a rather regular interdigitating pattern (figs. 64a and b). From these interdigitating arteriae afferentes the venae efferentes pre-capillaries arise which feed and drain the superficial and deep capillary nets. His, in his classical paper described the superficial net as arterial and the deep net as venous; but we cannot support this. Both arterial and venous precapillaries run to both superficial and deep nets, and there is no arterial or venous predominance in one or the other. Venous precapillaries are of course, more noticeable and striking than arterial precapillaries, since, in view of the much slower blood flow in them, they are of larger calibre, and hence a fallacious impression may be given that the only

pre-cappilaries in the deep net are venous.

The deep capillary net is in general a denser and more complex one than the superficial net. In the equatorial zone of the retina, where the two-layered pattern is most distinct, the difference can be most easily demonstrated (figs. 65 and 66). We have found, for example, in representative fields of this zone that at 9 to 10 mm lateral to the nerve head the average width of the capillary mesh was 54 μ in the deep net and 65 μ in the superficial; for fields 9 to 10 mm medial to the nerve head the corresponding figures were 63 μ and 74 μ. In general, one may say that the capillary pathway between arterial and venous pre-capillaries is a more direct and simple one in the superficial than in the deep net.

In all parts of the retina the capillary nets show regularly varying density in the following way. Firstly, as His pointed out, around the arteries of all calibres down to the arterial pre-capillaries there is a zone which is quite free from capillaries. This zone extends on either side of the artery for an average of 50 μ (at the extreme periphery it becomes much wider - about 120 μ). The capillaries do not avoid the neighbourhood of the veins in this way. Secondly, within both superficial and deep capillary

nets, the nearer one approaches to the venous pre-capillaries and their draining venae efferentes, the denser the capillary net becomes; so that the capillary net shows a regular alteration of dense areas centred around the venae efferentes and open area (or areas completely devoid of capillaries) around arteriae afferentes (see Fig. 67). This is only to be expected, since the poorer oxygenation of the blood in the venous ends of the capillaries must be compensated for by a denser distribution of capillaries in this region if the tissue is to be uniformly supplied with oxygen.

Modifications of the Basic Two-layered Pattern; In the posterior, thicker part of the retina, the pattern is considerably modified. The deep layer is unaltered, remaining as a remarkably flat, two dimensional net. The superficial layer, however, becomes increasingly three-dimensional, fewer capillaries run from arteriole to venule entirely in the nerve-fibre layer; and many capillary loops come to run at the superficial (internal) boundary of the inner nuclear layer. A three-layered pattern therefore appears, of which, however, the two superficial layers are much less perfectly two-dimensional than the deep layer. This three-layered pattern is particularly well

developed in the macular region (see fig. 68).

Furthermore, in and around the papilla, where the nerve-fibre layer is thick, yet another, most superficial capillary net appears, lying in this layer. Precapillaries and capillaries from the superficial layer proper turn superficial to the plane of this layer and break up into an extremely dense net of close-set, radially arranged capillaries (see fig.69). This network is the densest of all those present in the retina. In this central zone therefore there are four capillary nets at four different levels; the peri-papillary radial net in the superficial part of the nerve fibre layer (fig.70), the superficial net proper in the deeper part of the nerve fibre layer (fig. 71), the reduplication of the superficial net at the inner boundary of the inner nuclear layer, and the deep net at the outer (deep) boundary of the inner nuclear layer (fig. 72). The extent of the peripapillary radial net is symmetrical; it extends on the medial side for 4 mm from the nerve head and on the lateral side for 7 mm; it avoids the macula, however, so that its lateral margin is deeply indented, and in the horizontal plane it only extends 2 mm lateral to the nerve head (see fig. 73).

In the macular region, the fovea, as is well known, shows a completely avascular area see (fig. 74) varying in the few retinae in which we have measured it from 0.4 to 0.5 mm in diameter, (figures which agree with the generally accepted view - Leber 1903). Towards the periphery of the retina the mesh of the capillary nets becomes wider and the peri-arterial space increasingly prominent. Eventually the two-layered pattern becomes intermittent, the deep net being present only around the venae efferentes (see figs. 75 and 76). Still further towards the periphery the deep net disappears entirely, and there is only a single net of wide mesh and wide calibre capillaries. The peripheral margin of the retinal vascular systems is formed by wide calibre capillary arches joining the terminations of the arteries and the veins. There are no anastomoses with the vessels of the ciliary body.

The double net extends peripherally for a distance from the nerve head varying from 11.5 mm to 14.5 mm., its greatest extent being in the lateral horizontal axis, and its least in the inferomedial quadrant. The extreme margin of the retinal vascular system lies about 1 mm being the ciliary body, leaving a narrow peripheral zone of the retina entirely without blood vessels (see fig. 73).

Measurements of the width of the Capillary Mesh: We found it possible to make such measurements only in those parts of the capillary nets which are strictly laminar (two-dimensional). This applies to the deep net throughout its whole extent, to the superficial net in the equatorial zone (c in fig.73) and to the peripheral single-netted zone (d in fig.73). We made measurements of the width of the mesh therefore in those areas. For each area considered, from 3 to 5 microscopic fields were projected at a magnification of 375 X, the capillaries were traced on paper, and numerous measurements were made of the width of the mesh at various points. As the mesh is of very irregular width and as the selection of points for measurement was necessarily arbitrary, the results must be taken only as approximate. Fields were selected which lay as far as possible midway between arteriae afferentes and venae efferentes, in order to obtain the most accurate average figures; it will be remembered that the capillary mesh is of greatest density around the venae efferentes, while the capillary-free zone around the arteries results in wide gaps in the mesh around the arteriae afferentes. Had fields centred on these two types of vessel been included the range between maximum and minimum mesh widths would have been increased.

The results of our measurements were as follows (all areas examined were in or near the horizontal axis, the distance given being distance from the centre of the papilla):

Area examined.	Range of width.	Average width.
2-3 mm lateral (i.e. in medial part of macula): deep layer	20-110 μ	45 μ
5-6 mm lateral (i.e. in lateral part of macula): deep layer	16-120 μ	29 μ
9-10 mm lateral:		
Superficial layer	16-150 μ	65 μ
Deep layer	16-120 μ	54 μ
14-15 mm lateral (i.e. in single layered zone.)	55-195 μ	100 μ
2-3 mm medial : deep layer	20-130 μ	51 μ
5-6 mm medial : deep layer	16-110 μ	52 μ
9-10 mm medial :		
Superficial layer	30-145 μ	74 μ
Deep layer	23-110 μ	63 μ

Minor variations in different areas in the range of width are obviously not significant. All over the posterior part of the retina the mesh width of the deep net is approximately constant - a range of about 15 to 130 μ, with an average of about 50 μ. In the single-layered peripheral zone the mesh was much wider than that of either superficial or deep net in the double-net area.

These figures are of the same order as those given by Leber (1903) who states that the width of the retinal capillary mesh varies from 20 to 75 μ. He does not give figures for different areas of the retina. Our figures also correspond reasonably well with those obtained entoptically by Fortin (quoted by Damel, 1936) who gives the range of width in the macular region as 25 μ to 75 μ. If a good correspondence could be established between the size of mesh as observed entoptically and that demonstrated anatomically by an injection under pressure such as we use, it would support the view that (under the conditions of entoptical observation) there are no closed reserve capillaries in the macula. Fortin, however, does not give the average width of the mesh in his observations, and in our opinion this is the information essential in order to compare the results of the two methods.

Development: Already at the 4.5 mm embryo stage the hyaloid artery can be seen entering the foetal fissure. In doing so it communicates with a set of vessels which, growing up on either side of the fissure, finally form a vessel along the margins of the cup - the annular vessel. Branches from this vessel and the anterior branches of the hyaloid artery anatomose with

each other. It is not possible to state whether the blood entering the cup by the hyaloid artery leaves it via the annular vessel or whether it enters the cup through the annular vessel. In the opinion of Mann (1928) the direction of circulation probably varies from time to time. In the vitreous the hyaloid artery breaks up into branches and forms the foetal intra-ocular blood system. One set of vessels forms a net-work on the posterior surface of the lens and communicates forward with the annular vessel while another set ramifies within the vitreous. The latter are the vasa hyaloidea propria and they continue to function until to the 60 mm stage, when they shrink in calibre and finally lose their connection with the main vessels. During this period of development the retina and optic nerve are completely avascular, excepting for the presence of the hyaloid artery in the optic nerve to which, however, it gives no branches.

About the 70 mm stage a number of fine vessels can be seen alongside the hyaloid artery in the optic nerve. Soon these fine accompanying vessels join to form two stronger vessels one on either side of the artery with communicating branches between them. Later these two vessels join each other at a certain distance from the disc to form a common stem corresponding to

the central vein, their places of juncture approaching the disc with the growth of the foetus. Finally in the 220-240 mm foetus the position of the juncture is fixed at a distance which varies with each individual.

About the 100 mm stage a small bulbous swelling appears on the trunk of the hyaloid artery where it passes through the disc. From this swelling buds of cells grow into the nerve fibre layer. The buds do not leave the hyaloid artery at the same level so that one may begin deep in the optic cup while the other does so more peripherally or even in the vitreous. In the last case the branch must needs take a backward bend to reach the retina. Initially these buds are solid but later they become canalised and at the 125 mm stage there is a blood circulation in them for a considerable stretch. Simultaneously there are further vessel buds which form a vascularised area around the disc. Versari was the first to show that these new built vessels take the shortest way and do not pass into the retina via a membrana vasculosa retinae. From these beginnings vessels pass further towards the periphery of the retina. In the 8th month the vessels reach the ora serrata when the vascularisation can be considered to be complete.

The process of capillary formation: This is very similar to that already noted in the cat and the rat. As in these animals, growth is by a process of budding from pre-existing vessels there being no evidence of vascular differentiation from local cells. The formation of capillaries is a function of the veins, only the arteriae afferentes appearing to originate from the arteries (fig. 77). As already noted in the cat, capillary growth takes place initially from the side of the vein remote from the artery where vein and artery are close to each other (figs. 78 and 79). The venae efferentes, when they cross an artery, do not divide into capillaries until they have passed the artery by a definite distance (figs. 80 and 81). The capillaries formed in this way lie in the same plane as the arteries and veins, that is in the layer of the nerve fibres. The early formation of the deep capillary net from this superficial layer is illustrated in fig. 82 from a 230 mm foetus. The depth of the deep capillaries from the superficial vessels at the place illustrated is 30 μ. Similar capillary extensions from the superficial net are present in a patchy distribution all over the fundus of this foetus.

At the periphery the terminal branches of the arteries and veins join to form arches with which a capillary formation is associated (figs.83 and 84).

Rate of vessel growth; The following table shows the lengths of the major vessels in foetuses of 110-240 mm:-

Extents of retinal vascularisation in the foetus.

RIGHT EYES.

Length of foetus .	Up. Temp.	Low Temp.	Up.Nasal.	Low Nasal.
110 mm.	2.28.	1.92.	1.39.	1.39.
140 mm.	3.20.	N.K.	2.22.	N.K.
190 mm.	8.4.	7.9.	5.5.	6.0.
190 mm.	8.4.	7.8.	6.0.	6.0.
225 mm.	9.1.	8.3.	6.6.	6.2.
230 mm.	9.6.	9.6.	7.7.	7.9.
240 mm.	12.4.	12.2.	9.6.	9.6.

LEFT EYES.

110 mm.	2.04.	2.16.	1.56.	N.K.
140 mm.	3.2.	N.K.	2.24.	2.40.
190 mm.	8.4.	7.9.	6.5.	5.3.
190 mm.	8.6.	8.2.	6.5.	6.5.
225 mm.	8.7.	8.3.	7.4.	6.6.
230 mm.	9.6.	9.3.	8.1.	N.K.
240 mm.	12.2.	12.2.	N.K.	N.K.

All measurements are in mm.

N.K. Injection insufficiently complete to permit of exact measurement.

It can be seen that the upper temporal vessels are nearly always longer than the lower, and that in the same fundus both temporal vessels are always longer than the nasal vessels (figs. 85 and 85a). Measurements were taken from the edge of the optic disc.

For the statistical analysis of these figures I am indebted to the kind help of Dr.R.A. Robb (see appendix). The analysis shows a significant difference between the extents of the temporal and nasal vascularised areas in the foetuses examined.

The consistent presence of this difference between the lengths of the temporal and nasal vessels can be due either to a difference in growth rates of the temporal and nasal vessels or else to a difference in starting times of these vessels in their growth from the disc or to both circumstances. The statistical analysis of the figures, however, shows there is no significant difference in the growth rates of the vessels in the temporal and nasal portions of the retina. It would then seem that there is a difference in starting times, the temporal vessels budding earlier than the nasal ones. It would appear that during a certain period of embryonic life the retina possesses temporal but no nasal vessels.

On the basis of the figures

tabulated it is estimated that the growth rate of the retinal vessels in the human embryo is about 0.1 mm per day or about 5 μ per hour during the 110-240 mm period. These figures are very approximate for any one stage because of the great growth rate variation shown during the period under review.

The ciliary vessels; The ciliary vessel system has no part in the development of the retinal vessels. Although at the 140 mm stage Versari has shown fine anastomoses between the posterior ciliary vessels and those in the optic nerve in the position of the later vessels of Zinn, there is no development of a cilio-retinal vascular system. The presence of a cilio-retinal vessel in the developed eye is therefore an aberration and not an abnormal persistence of a normal embryonic state.

Discussion: It is evident that the general development of vessels in the human retina is similar to that described in the cat.

The capillaries bud predominantly from venous channels which like the arteries have grown from vessels in the optic disc. The budding takes place initially from the side of the vein remote from the artery if the artery and vein are close to each other. The capillary growth stops at a well defined distance from the arteries leaving in the fully developed retina a capillary free zone around

them. This zone is traversed by occasional arteriae afferentes while deep to the arteries a few vessels from the deep capillary net pass in the inner nuclear layer and therefore about 80 μ from the arteries. The capillary free zone lateral to the artery extends to as much as 120 μ in breadth.

The similarity of morphological findings suggest that in man as in the cat there is present in the developing retina a factor which affects the budding of new vessels especially from the veins, and which has similar attributes. It is present in the extra-vascular portions of the retina; it is present in a gradient of concentration such that it differs in arterial and venous neighbourhoods; and its action is chiefly on the veins.

The difference in the starting times of the temporal and nasal vessels is probably further evidence of such a factor. The portion of the retina temporal to a line drawn vertically through the optic disc is different from that nasal to the disc in two important respects. It contains a much greater number of ganglion cells and it is more extensive, its area being about fifty per cent more than the area nasal to the disc. If these are the features which influence the growth of the temporal vessels so that for one period they are present when there are as yet no nasal vessels in the retina, it would appear that they can do so only on the hypothesis that new-vessel

formation is a function of retinal activity or in other words that there is in the extra-vascular portions of the retina a factor or factors affecting the budding of new vessels. This would appear a more acceptable hypothesis than the alternative assumption which would imply a morphological specificity resident in the artery in the optic disc and capable of ordering a temporal before a nasal budding.

Review of Adult Conditions of inner ocular vessels in the mammalian eye.

Apart from the differences in extent of retinal vascularisation according to which mammalian retinae are separated into the four types, anangiotic, pseudo-angiotic, angiotic, and euangiotic, there are certain features which permit of generalisation and classification.

Division of vessels at the optic disc: The number of vessels which pass from the disc varies from species to species but it has two fairly constant features - there is usually an equal number of arteries and veins and in each animal there is a fair constancy in the number of vessels at the disc. The number of main arterial branches crossing the disc margin in several of the commoner mammals are as follows:-

Horse	about	30.
Rat		6.
Man		3-4.
Dog		3-4.
Ox		3-4.
Pig		3-4.
Cow		3-4.
Cat	usually	3.
Rabbit		2.

Length of vessel branches: In man the vessels enter the globe a little to the nasal side of the posterior pole with the consequence that the temporal vessels are longer than the nasal. On the other hand

in the ruminants the optic nerve enters the globe below and external to the centre of the posterior surface of the globe with the result that the vessels running inwards are longer and wider than the temporal ones. In the carnivora, pig and rat the nerve enters the globe a little below the centre so that the vessels going upwards are somewhat longer than those passing downwards.

Nature of the division of the vessels: The retinal vessels divide dichotomously. This applies to veins as well as to arteries.

Relationship of vessels at crossings: Although in some animals as in man there is no constant relationship between the artery and vein at the crossings, in others the relationship is almost constant. For example in the sheep and the pig the vein is always external to the artery while in the cat the artery is always external to the vein. The constancy with which in certain animals the crossings are either arterio-venous or veno-arterial is so notable as to suggest a significance for the mode of vascular development. No tenable hypothesis can however, be advanced for it. It is of interest that this constancy may be present in animals other than mammals. For example in the frog where the vessels lie on the surface of the vitreous body the vein is always external to the artery at the crossing (Virchow 1881).

An artery crossing an artery or a vein crossing a vein has not once been reported or been personally observed.

The architecture of the capillary bed: The capillary bed in the mammalian retina may be either reticular or composed of independent loops. In many animals however, the arrangement is intermediate in type both loops and network being present. In all mammals where there are intra-retinal vessels loops are present at the periphery of the vascularised zone.

Capillary loops: In the guinea pig a few loops are present around the optic disc. In the horse the retinal capillaries are more extensive but they too form loops exclusively. In the rabbit the bulk of the distribution is in the form of loops which by their overlapping give the appearance of a network in places.

Capillary nets: In many mammals including the cat, dog, ox, pig, rat, sheep and man there is a highly developed reticular capillary system. This system generally consists of two main networks, an external one situated usually in the outer portion of the inner nuclear layer, and an internal one lying in the layer of the nerve fibres. Capillaries communicate between both networks.

The meshes of the deeper networks are usually smaller than those of the superficial

one (Hesse 1880, Bruns 1882, His 1880, Michaelson and Campbell 1940). In man the average size of a mesh of the deep layer is 50 μ with a range of about 15 to 130 μ, while the size of a mesh of the superficial layer is about 80 μ with a range extending to 195 μ. In the cat the mesh of the deep capillary net in representative parts of the field was found to vary from 30-70 μ, while that of the superficial net had an average diameter of about 100 μ. In the superficial net in this animal, the variations in diameter of mesh were very extreme and extended to as much as 400 μ.

The ranges noted by Bruns (1882) in several animals were as follows:-

Pig.	22 - 33 μ.
Sheep.	120 - 53 μ.
Calf.	83 - 22 μ.
Cat.	40 - 90 μ.

The vessels joining the capillary nets may be perpendicular or oblique. In the latter case they may as in the calf take the form of loops. Relation of capillary nets to the larger vessels: Although there is a general similarity in the architecture of the capillary nets, in many mammals interesting differences do exist in respect of the relationship of the capillary nets to the neighbouring vessels.

Hesse (1880) demonstrated that the superficial capillary plexus in the rat is formed by the

branching of the ultimate arterioles. The deep plexus on the other hand in that animal has no such arteriolar association and drains into the venules. This was confirmed by our personal findings which are represented diagrammatically in fig. 86. In the rat, the draining venae efferentes lie at their commencement in the ganglion cell layer.

A similar association between the deep capillary net and the veins has been observed by us in the cat.

Such an association has been observed by Bruns (1882) in the calf, sheep, pig, and dog, and by His (1880) in man.

Neither Hesse (1880) nor Michaelson and Campbell (1940) could, however, support in this respect the findings of His in the human retina. Their findings demonstrate that there is no great arterial or venous preponderance in either capillary network. They concluded that the deep capillary plexus is a kind of appendage to the superficial one as shown diagrammatically in fig. 87. There is, however, at many places of the human retina a condensation of the deep capillary net the nearer approach is made to the draining venae efferentes. This is indicated in fig. 67. In some parts of the human retina the deep net is absent in the neighbourhood of the arteries (fig. 75).

It may be generally said of the mammalian retina that the deep capillary net in many places is closer in position to the veins than to the arteries.

Capillary free zone around the arteries: The presence of an area relatively or absolutely free from capillaries around the arteries is a notable feature of mammals which possess a reticular capillary system in the retina. It has been described by His (1880) and Michaelson and Campbell (1940) in the retina of man; by Hesse (1880) in the retina of the rat; and by Schultze (1892) in the retina of the pig. It was found to be present in all the mammals personally examined which possess a well developed reticular capillary system (Man, dog, cat, rat and pig).

The vessels of the deep capillary net lie at some distance from the arteries, about 70-80 μ, so that the capillary free zone exists as a space radially around the arteries.

Review of the development of inner ocular vessels in the mammalian eye.

In the mammalian embryo the developing retinal vessels grow from vessels in the optic disc and at no time develop from the vitreous or hyaloid system of vessels. Prior to this stage of development there is in each embryo a period during which the retina is completely avascular.

Membrana vasculosa retinae: In certain mammals the earliest vascular development of the retina is a vascularised membrane which lies between the retina and vitreous in the neighbourhood of the disc as first described in the pig embryo by Schultze (1892). It is internal to the internal limiting membrane of the retina and the appearance of vessels in it is preceded by the presence of a cellular net in which the cells are arranged in columns. As the membrana vasculosa retinae grows out towards the periphery of the retina it gradually becomes incorporated into its structure until finally all the vessels, arteries, veins and capillaries, lie external to the internal limiting membrane. In some animals, for example the rabbit, the larger vessels do not sink into the retina but remain on its surface.

The vessels destined for the retina do not necessarily form a membrana vasculosa.

In man, the initial vascular buds grow directly from the hyaloid artery into the nerve fibre layer of the retina. Nor apparently is there a membrana vasculosa in the cat or rat.

Degree of vascular growth: The degree of the vascularisation varies in direction and in extent. It may, as in the rabbit, spread only into the portion of the retina where the nerve fibres are medullated. In some animals it may reach to within a short distance of the ora serrata while in others it may cease very close to the disc. According to these variations the mammalion retinae have been classified into the four types, anangiotic, pseudoangiotic, angiotic, and euangiotic.

Capillary development: The retinal capillaries develop by a process of budding from vessels which have preceded from the optic disc and there is no evidence of local capillary formation independent of pre-existing vessels. In retinae examined for this purpose, those of man, the cat, and the rat, the following features of capillary development were observed:-

(1). The formation of retinal capillaries is pre-eminently a function of the retinal veins. Only the arteriae afferentes appear to originate from arteries.

(2). If vein and artery are close to each other, growth takes place initially from the side of the vein remote from

the neighbouring artery.

(3). The spread of growth towards an artery is limited leaving, finally, in the definitive eye a well marked capillary-free space around the arteries.

Although this process of capillary development has been observed only in man, the cat and the rat, it is probable that the process is similar in other mammals possessing a reticular capillary system within the retina. The development of such a capillary system was investigated only in the species mentioned. The rabbit is not included as the retinal capillaries in it do not form a reticulum but an overlapping system of loops.

The adult conditions of the retinal vessels were examined in the pig and the dog in both of which the capillaries are arranged in reticular fashion. In both species the arteries were found to have around them a zone free from capillaries (fig. 88). As it is probable that such a zone is conditioned by the mode of capillary development described, it may be reasonably assumed that the capillary development in the pig and the dog is similar to that in man, the cat and the rat.

In its early stages the capillary net frequently has a syncytial appearance produced by the calibre of the vessel channels being as

great or greater than the mesh diameter. With development this proportion is changed until the capillary diameter and the wide mesh typical of the definitive system is produced.

Initially the capillaries are confined to the layer of nerve fibres. From them, a second system, the deep capillary net is formed. This lies finally in most mammals about the level of the outer surface of the inner nuclear layer although in some a portion of the net is disposed on the inner surface of that layer.

However well developed the reticular capillary system may be the capillaries at the periphery of the extending vascular bed are always in the form of loops,an arrangement maintained in the definitive eye at the ora serrata.

Relationship of retinal capillary growth to arteries and veins: A study of ontogeny in the cat, rat and man shows that the bulk of the capillary system in the retina can be considered as part of the venous system. The arterial system is shown to be supra-capillary.

Period of growth: The growth of the retinal vascular system begins fairly early in embryonic life and in most species is completed before birth. The following indicates the periods of vascularisation as given by Schultze (1892):-

Pig.	8 - 20 cms. foetus.
Sheep.	6 - 16 cms. foetus.
Ox.	9 - 28 cms. foetus.
Man.	7 - 27 cms. foetus.

In others it is not completed until after birth. In the cat, rat and rabbit vascularisation is not completed until several weeks after birth.

Rate of growth: The rate of growth of the vascularised area of the retina has been studied in the rabbit, cat, rat and man, and graphs have been given indicating the results (figs. 29,51,63 and 85a). In the rabbit, cat and rat measurements were made from about the first day of life and over fairly comparable periods. The results in these animals have therefore been brought together in fig. 89.

In man the growth rate was necessarily taken from foetal retinae over a longer period. The approximate growth rates in these species over the periods measured were found to be as follows:-

Man.	5 μ per hour.
Rabbit.	11 μ per hour.
Cat.	4 μ per hour.
Rat.	10 μ per hour.

It should be emphasised that these figures must be approximate as each was necessarily

taken from a different individual. Moreover the rate may within each individual vary according to the period of development.

Early growth of temporal vessels in man: In man there is evidence to show that the temporal vessels bud from the disc earlier than do the nasal vessels.

Relation to the ciliary system of vessels: In many if not most mammals there is evidence that the vessels supplying the retina originate from the ciliary vascular system at the edge of the optic disc (Schultze 1892). In many of these mammals communication with the central vessels of the optic nerve takes place only later and then incompletely; while in the others the vascularisation of the retina remains cilio-retinal throughout life. In man there is no cilio-retinal system of vessels at any stage of development and the occasional appearance of a cilio-retinal artery in the developed eye is no evidence of a more extensive embryonic pattern.

A factor affecting the growth of retinal vessels: The mode of development of the retinal vessels in mammals indicates the probable presence of a factor or factors in the retina which affect the growth of the vessels. This factor has the following characters:-

(a). It is present in the extra-vascular tissue of the retina.

(b). It is present in a gradient of concentration such that it differs in arterial and venous neighbourhoods.

(c). Its action is on the retinal veins predominantly.

(d). The factor initiating the capillary growth from a vein probably determines the distance to which that growth will extend, initiation and cessation depending on variations in concentration of the factor.

Review of the Vessels of the inner eye of vertebrates.

When the known facts of the vitreous vessels of vertebrates are considered it can be seen that these vessels fall into two groups.

(1). The vitreous vessels which appear in the mammalian embryo.

(2). the superficial vitreous vessels found in certain fishes, the anuren amphibians and the snakes.

The vitreous vessels of the mammalian embryo: The vitreous vessels of the mammalian embryo develop according to a regular pattern - an arterial bud growing through the foetal cleft and passing across the vitreous to the tunica vasculosa lentis from which there is an association through the annular vessel to the venae vorticosae of the developing choroid. V.Koelliker first showed that the vessels of the mammalian foetal vitreous are always arterial. This can be noted easily in the foetus of an animal, such as the ox, in which the hyaloid vessel divides after leaving the disc, but in the embryo of the pig where the vessel divides before reaching the vitreous the determination of the arterial nature of the hyaloid vessel demanded an examination of several sections of the optic nerve (Schultze 1891). The hyaloid vessels divide several times, the divisions joining

each other so that finally a complete arterial net is formed. In those animals in which the disc is low for example ox, pig and sheep, the upper part of the vitreous is more strongly vascularised than the lower (Schultze 1892). In all mammals this temporary vitreous vascular system atrophies and disappears in the course of development excepting for occasional embryonic remnants which persist in the developed eye.

The superficial vitreous vessels of certain fishes, anuren amphibians, and snakes. These superficial vitreous vessels form a system totally different from the embryonic vitreous vessels of the mammal.

(a). In this system the circulation is venous as well as arterial.

(b). The vessels do not extend anteriorly beyond the ora serrata.

(c). The vessels do not form a tunica vasculosa lentis.

(d). There is a close association with the retina. The superficial vitreous vessels cling to the retina if an effort is made to remove the vitreous. In the eel numerous fine vessels connect the superficial vitreous and the intra-retinal vascular system.

In the superficial vitreous system arteries and veins alternate with intervening

capillaries. The veins usually drain into an annular vessel which is placed peripherally and leaves the inside of the globe through the ciliary body.

Relation between the vitreous vessels of the mammalian embryo; the superficial vitreous vessels of certain fishes, anuren amphibians and snakes; and the mammalian retinal vessels:

It is generally accepted that all these three vascular systems are not homologous with each other. Confirmation of this is given by the few studies that have been made of the embryos of animals containing a superficial vitreous system. Virchow (1883) has shown that in smooth snakes (Coronella laevis) there grows from the surface of the disc into the vitreous a system of vessels similar to that of the mammalian embryo; and that only later do vessels appear which spread over the surface of the vitreous in the posterior part of the globe to form the definitive superficial vitreous vessels. Likewise v. Kittlitz (1907) has demonstrated in the trout a temporary vascular system distinct from the definitive system lying on the surface of the vitreous.

The bulk of the evidence is in favour of considering the superficial vitreous vessels of the cold blooded animals as being homologous or even identical with the mammalian retinal vessels in their definitive stage or when in the course of their development they have formed a membrana vasculosa retinae (Wiedersheim 1896). The

definitive circulation of the inner eye of the rabbit with its larger vessels lying between retina and vitreous, and the definitive circulation of the inner eye of the eel with superficial vitreous and intra-retinal vessels may be considered to be intermediate in type between the superficial vitreous vessels of the cold blooded animals and the retinal vessels of the mammals in general.

It would appear then that the changing circumstances as observed in the ontogeny of the mammal - a primary or temporary hyaloid system and a secondary or permanent retinal one - is found in a considerable number of other vertebrates (the teleostii; anuren amphibians; and snakes), but with this difference that the secondary retinal circulation remains pre-retinal or located in the superficial vitreous. In these cold blooded animals as in the mammals evidence in the fully developed stage of the temporary hyaloid system is minimal. For example neither the carp nor the frog possess a processus falciformis or arteria pectenis.

In some vertebrates however, this double line of development does not occur. In them there is no attempt at the development of a retinal or superficial vitreous vascular system and there remains in the definitive stage the single line of embryonic development, as represented by the processus falciformis of certain fishes

and the pectens of birds and certain reptiles.

Considered from a broad phylogenetic view-point the hyaloid vessels, of which those found in the mammalian embryo can be taken as an example, have reached their height in development, while the retinal vascular supply has been progressively more and more important. Yet within the classes pisces, amphibia and reptilia, now the retinal or pre-retinal, now the hyaloid vascular supply, has become of greater significance for the nourishment of the inner eye so that the variations found within this small portion of the general vascular tree cannot be considered to parallel exactly the general evolution of the vertebrates. That this parallelism may be extremely slight is indicated by the high degree of vascular development found in the retina of the eel and the very slight development in that of the guinea-pig.

Summary of the sources of nutrition for the retinae of vertebrates: The diversity of types of vascularisation present in the inner eye of the vertebrates is indicated diagrammatically in fig. 1. The nutrition of the retina is probably at least in part served by all these types of vascularisation. Lindsay Johnson (1901) has adequately summarised the possible vascular supplies which may effect the nutrition of the retina by dividing them into indirect and direct sources of supply. The following table

has been taken from his description somewhat modified:-

Indirect Supply.	(a).	The choroid.
	(b).	Pectens of tailed amphibians, certain reptiles and birds. Superficial vitreous vessels of teleostii, untailed amphibians and snakes.
	(c).	Hyaloid vessels of the mammalian embryo.
Direct Supply.	(a).	Intra-retinal vessels of the mammals.
	(b).	The eel.

Evidence of the presence in the vertebrate retina of a factor or factors affecting vessel growth.

Mammalia: As already indicated there is presumptive evidence in some mammals at least, that there exists in the developing retinal tissue a factor or factors which affect the growth of retinal blood vessels especially from the endothelium of veins, and which determine the ultimate extent as well as the initiation of the capillary growth.

Pisces and Amphibia: It has also been suggested that the mode of capillary growth dependent on this factor conditions in the retina a capillary-free zone around each artery. The presence of a capillary-free zone around the superficial vitreous arteries of the teleosts (Virchow 1882, Schultze 1892 and personal observation) and of the untailed amphibians (Iwanoff 1868 and personal observation) indicates the possibility that the development of vessels within the inner eye of vertebrates generally is by a process similar to that described for mammals and like it dependent on the accumulation within the retina of a factor or factors capable of affecting growth from neighbouring vessels.

Human Pathology: As a general support for the existence of a factor capable of affecting vessel growth in the retina, consideration may now be given to the new vessel formation in the inner eye occuring during the course of

certain pathological conditions observed in man. These new vessels may be intra-retinal (fig. 90), pre-retinal (fig. 91 and 92), intra-vitreous (fig. 93), or on the optic disc (fig. 91); and are found in the course of venous occlusion, vasculitis retinae of young adults (Eales' disease), and diabetic or hypertensive retinopathy (Ballantyne and Michaelson 1947).

These pathological conditions have this in common that they are chronic processes with profound and prolonged changes in retinal and possibly vitreous metabolism. It is reasonable to suppose that the new vessels which they produce are a response to disturbed metabolism; the accession of vessels being directed towards insufficiently or non-vascularised situations, intra-retinal, pre-retinal or intra-vitreous (Michaelson 1948).

Thus there is in retinal pathology evidence of capillary formation being a function of its surroundings; and more particularly a response to a factor or factors situated within the retina and associated with metabolic changes. It is of significance that the new capillaries so formed have been found to bud almost always from veins (Ballantyne and Michaelson 1947).

It has been shown that, in ontogeny, the inner ocular vessels of the mammal retrace the steps of vertebrate phylogeny. It is of interest that

the adult human retina reacts to certain diseases by the formation of types of vessel-pattern which have already served not only its own development but also the general requirements of its vertebrate ancestry. The pre-retinal, intra-vitreous and disc vessel patterns occurring in retinal pathology may be considered to be analogous to the superficial vitreous, hyaloid, and pecten vascular systems occurring normally in the vertebrate eye.

In the consideration of new-vessel formation in the inner eye there would appear to be but little need to think in terms of a morphological specifity resident in the blood vessels. The evidence would rather indicate that new-vessel formation, physiological and pathological is a function of changes occurring in the extra-vascular portion of the retina.

The Role of the Choroid in the Nutrition of the Retina.

In so far as the choroidal vessels supply the nutritional needs of all or part of the retina of different animals or of the same animal at different stages of its development the choroid may be considered to play a role in determining the type of vessel pattern in the inner eye.

Nutrition from the chorio-capillaris for the retina must pass through the membrane of Bruch which presumably acts as a semi-permeable membrane.

Although permeable to nutrient matter, this membrane acts as a barrier to capillary growth. Evidence for this statement is based on two circumstances. Firstly; there is no reported case in which there has been a vascular communication passing through Bruch's membrane between the choroid and retina in the healthy eye in any vertebrate. Secondly; in disease conditions where such a communication exists there is a pathological interruption of Bruch's membrane. Such interruption may be the result of trauma as reported by Michaelson and Krause (1943) and illustrated in figures 94 and 95; or it may be associated with the profuse haemorrhage of macular disciform degeneration (Ballantyne 1946). In these pathological conditions capillaries may pass from the chorio-capillaris

into the retina.

The membrane of Bruch is everywhere interposed between choroid and retina except at the edge of the optic disc. The disc is the only portal in the normal developing or definitive eye through which vessels can bud from the choroid into the retina and constitute the cilio-retinal system which plays a role in the vascularisation of the retina of some mammals. This sytem is, of course, present only in mammals.

Excluding the cilio-retinal vascular system which is slight in many mammals and absent in others including man, the nutritional supply of the retina from the choroid may be summarised as follows:-

(1). Before the formation of the hyaloid system:

The retinal tissue is probably completely dependent on the choroid for nutrition.

(2). During the period of the hyaloid system:

The retinal tissue is at least greatly dependent on the choroid for nutrition.

(3). In the fully developed eye:

(a). Vertebrates without inner ocular vessels e.g. Selachii: In these animals the retina is completely dependent on the choroid for nutrition.

(b). Vertebrates with only a pecten: In these animals the retina is at least greatly dependent

on the choroid for nutrition. In the birds the choroid is well developed (fig. 13).

(c). Vertebrates with only a superficial vitreous system of vessels: In these animals the retina is partially dependent on the choroid for nutrition.

(d). Mammals of the anangiotic type: In these animals the retina is entirely dependent on the choroid for nutrition.

(e). Mammals of the eu-angiotic type: In these animals the portion of the retina including the rods and cones, outer nuclear and probably outer molecular layers is dependent on the choroid for nutrition, as are likewise the entire thickness of the retina at the fovea, and at the periphery close to the ora serrata. The retina in these three regions supplied entirely from the choroidal vessels are in man, 130 μ, 120 μ, and 140 μ in thickness respectively.

(f). The eel: In this animal there is a complete absence of choroid. In the absence of nutrition from the choroid there is developed a retinal vascular system more extensive than is found in any other vertebrate.

It can be seen that early in phylogeny as in ontogeny the choroidal vessels assume complete responsibility for the nutrition of the retina; but from then it becomes, generally speaking, progressively

less important for much of the retina's nutrition until in the euangiotic mammal such as man its nutritional activity is confined to a zone of the retina within about 140 μ from the membrane of Bruch.

The variations in sufficiency of the choroid for retinal nutrition are probably dependent on two circumstances:

(1). The nutritional requirements of the retina and

(2). The degree of choroidal development.

It follows that the degree of retinal vascularisation will vary inversely with the degree of the sufficiency of the choroid to meet the retina's nutritional needs. The less this sufficiency, the more elaborate must be the retinal vascularisation.

An interpretation of some features of the vascular pattern of the inner eye of vertebrates in terms of the choroid's capacity to nourish the retina and of the activity in the retinal tissue of a factor which affects vessel growth.

It has been shown that the vascularisation of the inner eye may be affected by two influences: the choroid's capacity to nourish the retina and the activity in the retinal tissue of a factor which affects vessel growth. The former influence presumably is the primary, prepotent one; while the latter is secondary and mediating as the accumulation of the growth-affecting factor in the retina is dependent on that tissue's metabolism which in turn is dependent on the sufficiency of nutrition received from the choroid.

To make this clearer the conditions in the human retina may be taken as an example. Before the third month of foetal life the choroid is capable of nourishing the retina. After that period the nutritional needs of the developing retina cannot be fully met by the choroid; vessels grow into the retina from the optic disc, and capillaries appear first in the portion of the retina furthest from the choroid, that is in the nerve fibre layer, and only later in the inner nuclear layer. This retinal vascularisation is mediated by the accumulation in the retina of a factor or factors associated with a retinal metabolism whose requirements are not fully met

after the third month by the choroid's nutritional supply. In certain regions, however, the nutritional needs of the retina continue to be fully met by the choroid even in the adult state. These regions are the fovea, the periphery of the retina and the external portion of the retina comprising the rod and cone, outer nuclear and probably outer molecular layers. These regions include all the retina which is within 140 μ of the chorio-capillaris. This feature will be further discussed shortly.

The general diversity of vessel pattern: The vessel patterns of the inner eye of vertebrates differ from each other essentially by the degree with which the finest vessels are brought into contact with the cellular elements of the retina. These patterns vary from those in which the vessels are localised to the optic disc region (pecten of the tailed amphibians, certain reptiles and birds; and the hyaloid system of the mammalian embryo;) to those in which, as in adult mammals, the capillaries reach the outer surface of the inner nuclear layer; and to that in the eel where the retinal capillaries are in contact with the outer limiting membrane. As intermediate patterns of vessel proximity there are the membrana vasculosa retinae of certain mammalian embryos and its homologue, the superficial vitreous vessels of the teleosts, untailed amphibians, and certain reptiles.

All these vessel patterns are dependent on the choroid's insufficiency to meet the retina's needs and the type of vessel pattern is a function of the degree of that insufficiency. Wherever in the retina that insufficiency occurs, there accumulates a local intra-retinal factor which effects the local development of capillaries.

Capillary-free zones: Capillaries may be absent in four situations within the mammalian retina; the outer portion of the retina, the fovea, the extreme periphery at the ora serrata, and around the arteries. It is of importance that the thickness of avascular tissue is approximately the same in each of these four situations. In man the measurements are as follows:-

Thickness of outer portion of the retina consisting of rods and cones, outer nuclear and outer molecular layers. (Salzmann.1912).	130 μ.
Maximum thickness of the retina at the fovea (Salzmann.1912).	120 μ.
Thickness of the retina at the periphery. (Salzmann.1912).	140 μ.
Maximum thickness of capillary free zone around the arteries. (Michaelson and Campbell 1940).	120 μ.

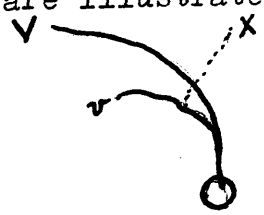
It would appear that in health in man retinal tissue about 140 μ in thickness can be adequately served by neighbouring capillaries. Expressed in another way it may be said that the chorio-capillaris

is capable of supplying nutrition into the retina for a distance of about 140 μ and that where the retina is not thicker than this amount there is no need for an intra-retinal supply. The result is the absence of retinal capillaries at the fovea and at the periphery as well as in the outer portion of the retina. As already stated the choroidal vessels are developed before vascularisation of the embryonic retina commences. In the developing retina within the areas destined to be vessel-free the physiological circumstances differ from those present elsewhere in the retina. Elsewhere, that is more than 140 μ from the choroidal nutrient depot, metabolism becomes such that capillary buds are necessarily attracted into the retina from neighbouring vessels. Variations in different portions of the retina of the factor affecting vessel growth will determine whether or not these portions will remain free from capillaries.

The existence of a peri-arterial zone free from capillaries has already been explained in terms of the activity of the vessel growth factor. The great similarity in thickness of all the avascular portions of the retina dependent on the choroidal vessels for nutrition and their similarity in that respect with the peri-arterial avascular zone may to some extent be considered as confirmatory evidence for

the postulated mechanism of vascular development.

Vessel Crossings: Among the inner vessels of the eye, arteries do not cross arteries, nor do veins cross veins. This is a necessary consequence of the suggested mechanism of vessel development. According to species each quadrant, sectant, or octant of the retinal area arranged around the optic disc accumulates in development sufficient of the factor affecting vessel growth to attract to itself a separate vessel complex, that is accompanying artery and vein. Further vascular requirement within the sector is satisfied by budding from the parent vessel, a process in the definitive eye recognised later as dichotomous division. If it can be assumed that the vessel growth factor affects maximally the nearest vessel it follows that no area, which can be supplied by budding from a vessel local to it, will be trespassed upon by a branch from a vessel further away. Such a trespass is presumed in the possibility of an artery crossing an artery or a vein crossing a vein. The circumstances are illustrated in the following diagram:-



If X be the area of the retina in need of new vessels the factor affecting vessel growth will act on vein V rather than on its branch v. If it

acted on vessel v the new vessel (indicated by a dotted line) would necessarily result in a vein crossing a vein.

range of ages is roughly

The eyes can be distinguished

classifications:-

A ——— Age, given by length

L ——— Left or Right Eye.

T ——— Temporal or Nasal

eye.

U ——— Upper or Lower

data we note for

measures plotted

then a result

rate of

Appendix: Analysis of data regarding extents of retinal vascularisation in the human foetus.

A group of twelve eyes from six individuals has been examined. These six individuals may be considered to be a random sample from the population of eyes whose range of ages is roughly that shown by the sample. The eyes can be distinguished according to the following classifications:-

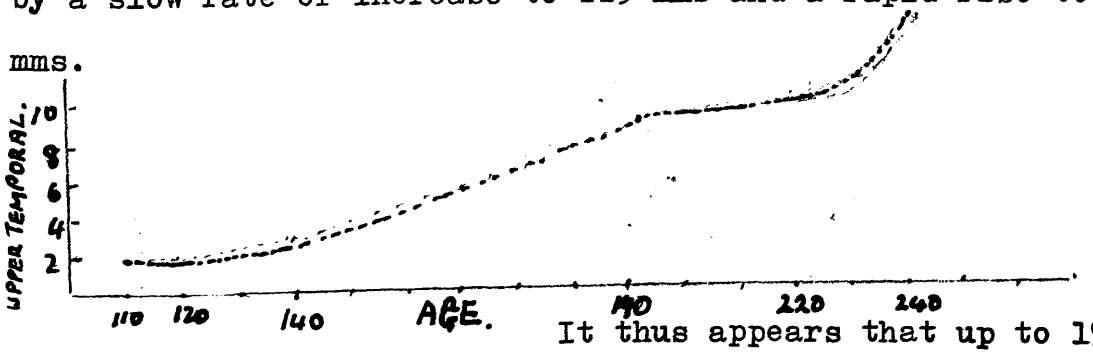
A ----- Age, given by length of foetus.

L ----- Left or Right Eye.

T ----- Temporal or Nasal measurements in any one eye.

U ----- Upper or Lower measurements in any one eye.

From a graphical representation of the given data we note for instance that the Upper Temporal measures plotted against Age show a slow rate at the start, then a rapid increase from 140 to 190 mms, followed by a slow rate of increase to 225 mms and a rapid rise to 240 mms.



It thus appears that up to 190 mm at any rate a curve of the form:-

$$y = ab^x$$

where y = Upper Temporal measures.

x = Age in mms.

would be most suitable and accordingly logarithms of the measures to the bases e have been used rather than the actual measures themselves. There does seem to be a change in the rate of growth from 190 mm to 230 mm but an analysis is required to establish this possible variation.

TABLE. 1.

Right eye. Logarithms of lengths to base e.

Foetus.	U.T.	L.T.	U.N.	L.N.
110 mm.	0.8241	0.6523	0.3293	0.3293
190 mm.	2.1283	2.0668	1.7048	1.7919
190 mm.	2.1283	2.0541	1.7919	1.7919
225 mm.	2.2082	2.1633	1.8870	1.8246
230 mm.	2.2618	2.2618	2.0413	2.0668
240 mm.	2.5177	2.5015	2.2618	2.2618

Left eye.

Foetus.	U.T.	L.T.	U.N.	L.N.
110 mm.	0.7129	0.7704	0.4446	(0.4446)
190 mm.	2.1283	2.0668	1.8718	1.8718
190 mm.	2.1518	2.1041	1.8718	1.8870
225 mm.	2.1163	2.1163	2.0014	1.8870
230 mm.	2.2618	2.2301	2.0919	(2.1631)
240 mm.	2.5015	2.5015	(2.2618	(2.2618)

Table 1 gives the logarithms to the base e of all measurements. Measures in brackets indicate estimated values. The analysis of Table 1 requires the following two-way tables.

TABLE. 2.

Right and Left-Eyes and Age.

Age \ L	Right	Left	Totals.
110 mm.	2.1350	2.3725	4.5075.
190 mm.	7.6918	7.9387	15.6305.
190 mm.	7.7662	8.0147	15.7809.
220 mm.	8.0361	8.1680	16.2041.
225 mm.	8.6317	8.7469	17.3786.
230 mm.	9.5428	9.5266	19.0694.
Totals	43.8036	44.7674	88.5710

It will be noticed that the sum of the logarithms for the Right Eye is slightly less than that for the Left Eye. It is a matter of analysis to find whether such a difference is significant. (The figures in the above table are obtained by summing from Table 1.) Thus the figure 2.1350 in the first row is given by $0.8241 + 0.6523 + 0.3293 + 0.3293 = 2.1350$.

TABLE. 3.

Temporal or Nasal and Age.

Age	Temporal	Nasal	Totals
110 mm.	2.9597	1.5478	4.5075
190 mm.	8.3902	7.2403	15.6305
190 mm.	8.4383	7.3426	15.7809
220 mm.	8.6041	7.6000	16.2041
225 mm.	9.0155	8.3631	17.3786
230 mm.	10.0222	9.0472	19.0694
Totals	47.4300	41.1410	88.5710

TABLE. 4.

Upper and Lower and Age.

U / Age.	Upper	Lower	Totals.
110 mm.	2.3109	2.1966	4.5075
190 mm.	7.8332	7.7973	15.6305
190 mm.	7.9438	7.8371	15.7809
220 mm.	8.2599	7.9442	16.2041
225 mm.	8.6568	8.7218	17.3786
230 mm.	9.5428	9.5266	19.0694
Totals.	44.5474	44.0236	88.5710

TABLE. 5.

Temporal and Nasal and Upper or Lower

T / U.	Temporal	Nasal	Totals.
Upper	23.9880	20.5594	44.5474
Lower	23.4420	20.5816	44.0236
Totals.	47.4300	41.1410	88.5710

TABLE. 6.

Left or Right Eye and Upper or Lower

L / U.	Right	Left	Totals.
Upper	22.0845	22.4629	44.5474
Lower	21.7191	22.3045	44.0236
Totals.	43.8036	44.7674	88.5710

TABLE. 7.

Left or Right Eye and Temporal or Nasal.

T \ L	Right	Left	Totals
Temporal	23.7212	23.7088	47.4300
Nasal	20.0824	21.0586	41.1410
Totals	43.8036	44.7674	88.5710

TABLE. 8.

The analysis of Variance is as follows:-

Source of Variation.	Degree of freedom.	Sum of squares.	Mean square.
Main Effects			
1. A	5	16.8034	3.3607 Significant.
2. T	1	0.8240	0.8240 Significant.
3. U	1	0.0057	0.0057
4. L	1	0.0193	0.0193 Significant.
First Order Interactions			
5. A T	5	0.0386	0.0077
6. A U	5	0.0105	0.0021
7. A L	5	0.0069	0.0014
8. TU	1	0.0067	0.0067
9. LT	1	0.0204	0.0204 Significant.
10. UL	1	0.0010	0.0010
11. Error	* 17	0.0264	0.0016
Totals.	47	17.7629	

* The number should, if all measures had been obtained, be 21 but one degree of freedom is removed for each of the estimated measures. We find that there is a significant difference between the logarithms of the measure

for Age. This significance was found by comparing the Mean Square in row 1 with that in row 7. Similarly there is a significant difference between Temporal and Nasal measures. A significant difference is shown between the Right and Left Eye, but none between Upper and Lower measures.

In addition the first order interaction between Left and Right eyes and Temporal and Nasal is significant, in the sense that the Temporal growth on the Right Eye is larger than that for the left, whereas the Nasal growth is larger in the Left Eye than that for the Right.

The error mean square obtained with 17 degrees of freedom has been taken as the sampling error variance of a single value of Table 1. In particular the difference between Temporal and Nasal growth is to be investigated.

Considering the Right Eye we find

Right Eye.

Age	Temporal		Nasal	
	Mean Value	Standard error	Mean Value	Standard error
110 mm.	0.7382	0.028	0.3293	0.028.
190 mm.	2.0945	0.020	1.7702	0.020.
Differences.	1.3563	0.035	1.4409	0.035

The difference between the growth on the Temporal and Nasal sides against 1.3563 1.4409 of the

eye is not significant. Thus between the ages represented by 110 mm and 190 mm the relative rates of growth on the Temporal and Nasal sides are not significantly different from each other. Similar analyses can be performed for the remaining ages giving the following table:-

Right eye. TABLE. 9.

Age	Temporal		Nasal	
	Mean Value	Difference from previous value	Mean Value	Difference from previous value.
110 mm.	0.7382		0.3292	
		1.3563		1.4409
190 mm.	2.0945		1.7702	
		.0678		.0856
225 mm.	2.1623		1.855.	
		.0995		.1983
230 mm.	2.2618		2.0541	
		.2478		.2077
240 mm.	2.5096		2.2618	

The comparison of the difference columns for Temporal and Nasal shows that there are no significant differences between the Temporal and Nasal rate of growth, but we note that between the ages represented by 225 and 230 mm the difference (.1983-0.0995) = .0988 is bordering on the significance level.

The data are not so complete for the Left Eye since measures for the Upper Nasal at 240 mm)
Lower Nasal at 110 mm)
" " 230 mm)
" " 240 mm)
were not possible.

However with the remaining material we find -

Left Eye. TABLE. 10.

Age	Temporal		Nasal	
	Mean Value	Difference from previous value	Mean Value	Difference from previous value
110 mm.	0.7417		0.4446	
		1.3718		1.3762
190 mm.	2.1129		1.8208	
		0.0269		0.1234
225 mm.	2.1398		1.9442	
		0.1062		0.1477
230 mm.	2.2460		2.0919	
		0.2555		-
240 mm.	2.5015		nk.	

The comparison of the difference columns for Temporal and Nasal reveal no significant differences.

Thus over the different ages we find that the relative growth rates between any two successive ages are the same on the Temporal and Nasal sides of the eye, apart of course from random fluctuations.

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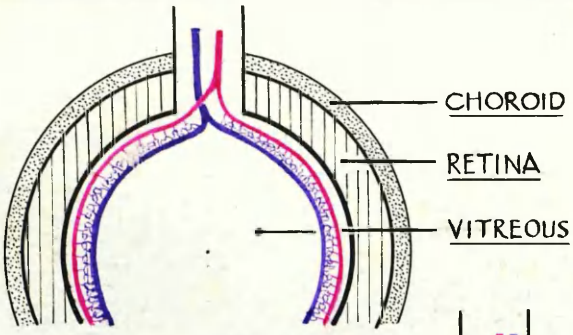
The nutrition of the retina and the inner eye.

(Illustrations and Graphs).

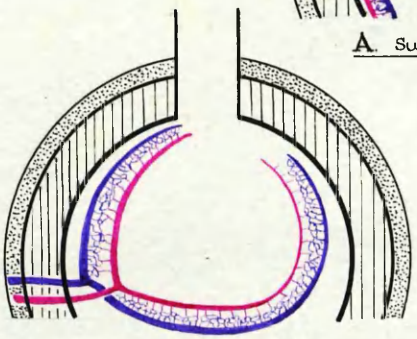
I.C.MICHAELSON.

Fig. 1.

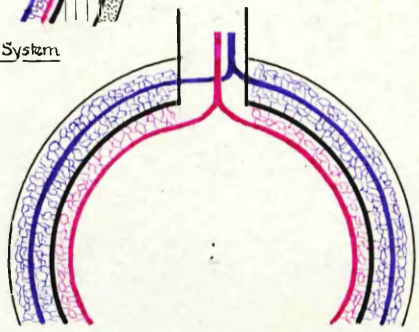
DIAGRAMMATIC REPRESENTATION OF THE INNER OCULAR VESSELS OF VERTEBRATES.



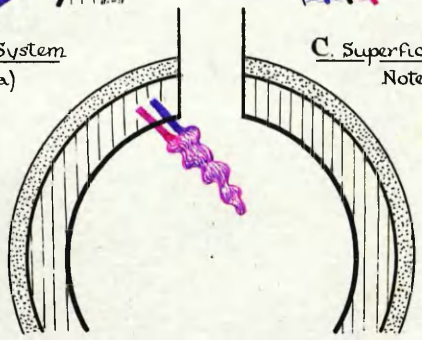
A. Superficial Vitreous System
eg Teleostii



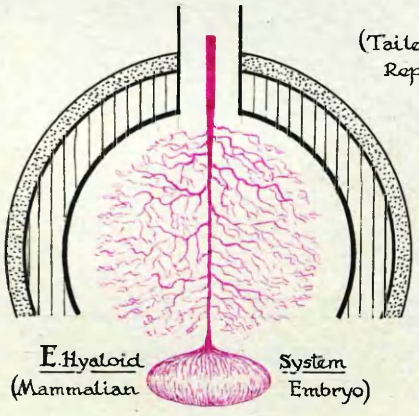
B. Superficial Vitreous System
(Untailed Amphibia)
e.g. Frog



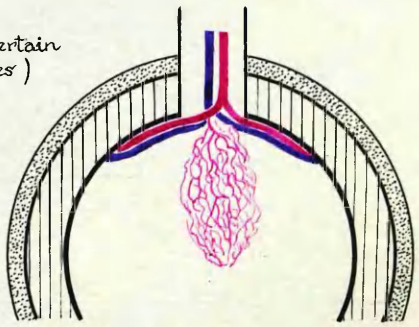
C. Superficial Vitreous & Retinal System
Note absence of Choroid
Eel



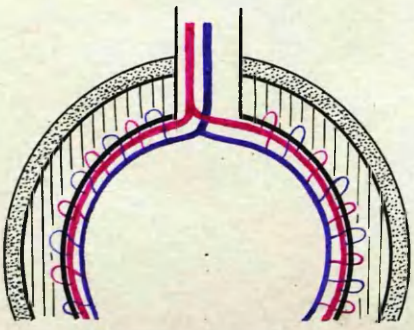
D. Pecten
(Tailed Amphibia, certain Reptilia and Aves)



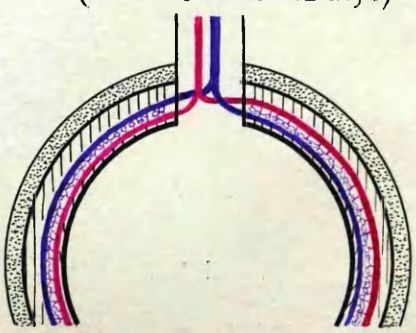
E. Hyaloid System
(Mammalian Embryo)



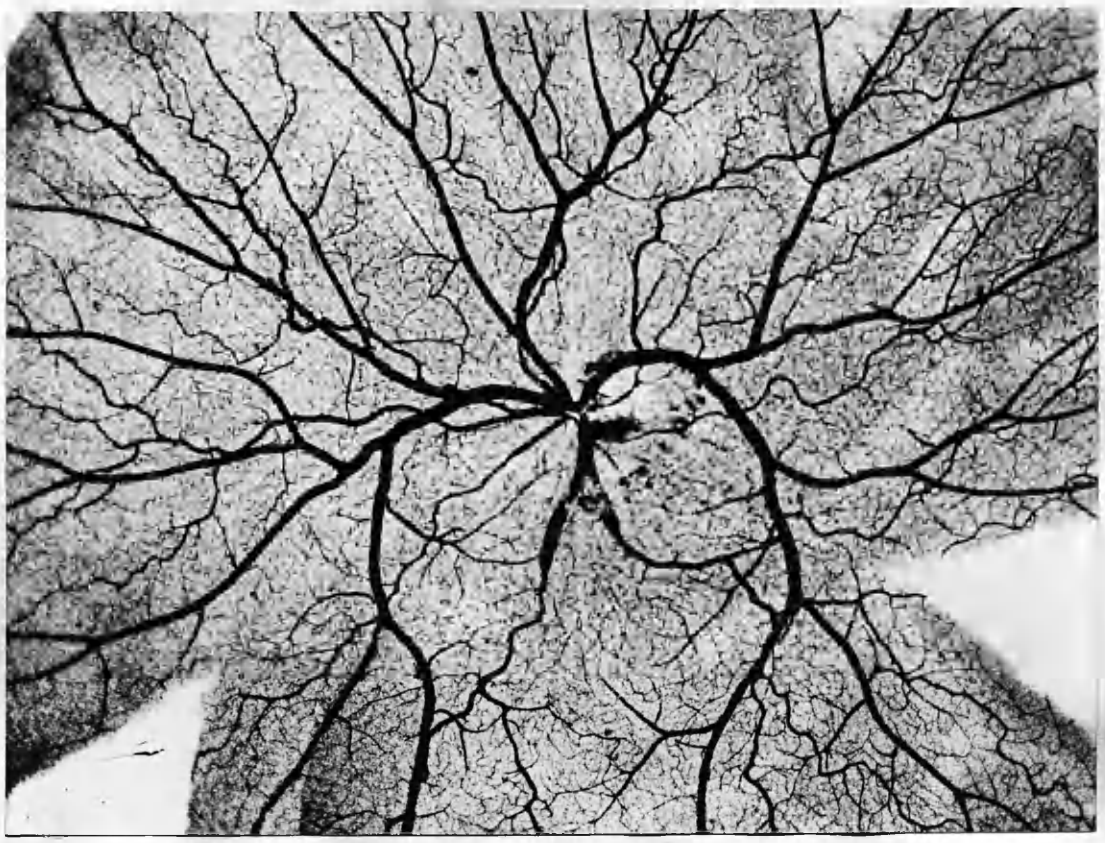
F. Membrana Vasculosa Retinae
Note absorbing Hyaloid System
(Certain Mammalian Embryos)



G. Retinal System
Certain Adult Mammalia eg Rabbit



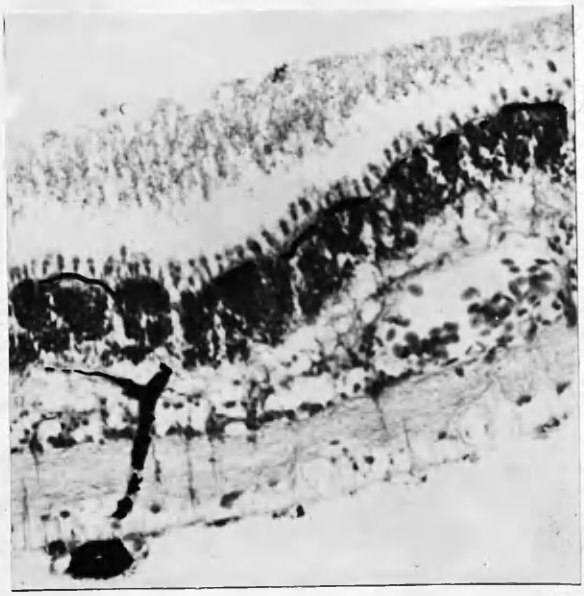
H. Retinal System
Certain Adult Mammalia eg Man



Injected retina of the eel mounted in glycerine. The superficial vitreous and intra-retinal vessels can be seen. (x 25)

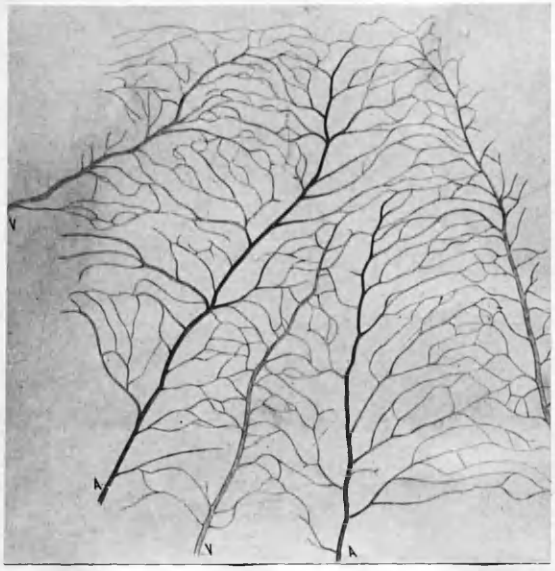
Injected retina of the eel mounted in glycerine. The superficial vitreous vessels are in focus. These are arterial. (x50)

Injected retina of the eel mounted in glycerine. The intra-retinal vessels are in focus. These are venous. (x 50)



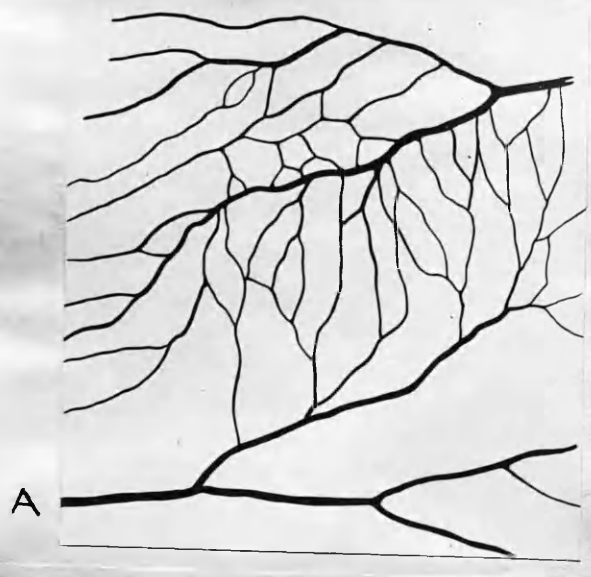
Section of injected retina of the eel. A superficial vitreous vessel, communicating vessel, and capillaries of both retinal nets can be seen. (x600)

Section of injected globe of the eel. The superficial vitreous and both retinal capillary nets can be seen filled with indian ink. The cells of the retinal epithelium form a broad layer. There is no choroid present, the epithelial layer lying directly on the sclera. (x225)

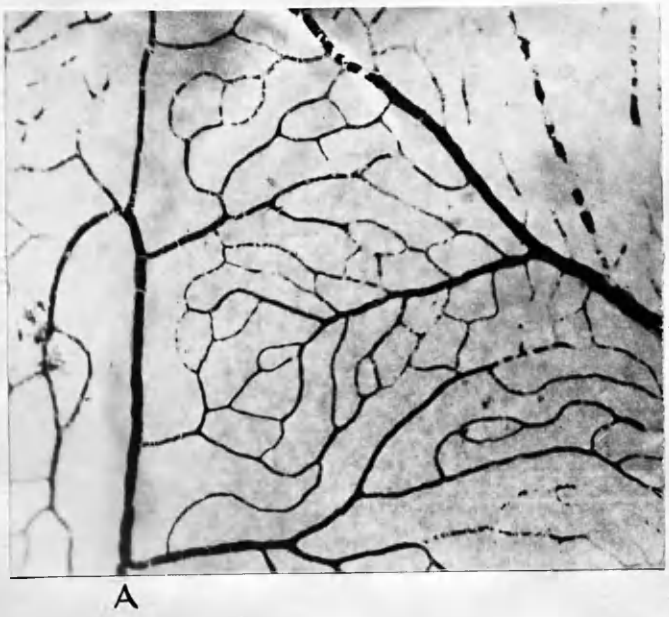


Superficial vitreous vessels of the conger vulgaris. (H.Virchow).

7a

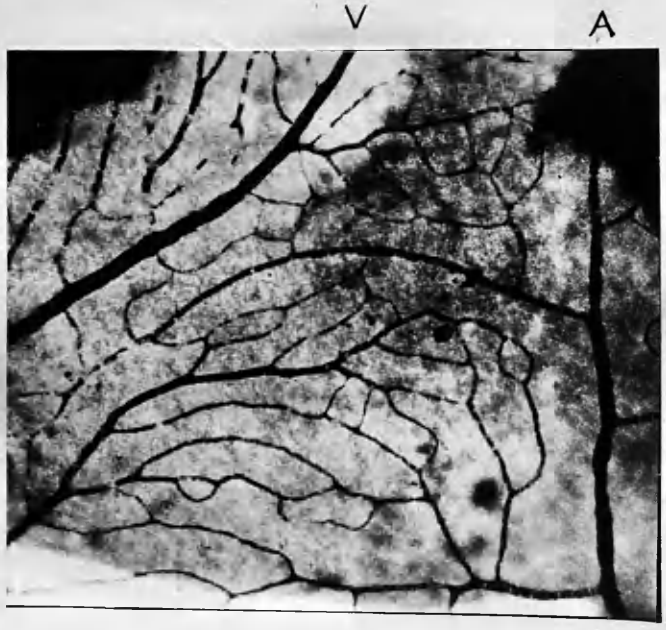


Sketch of injected retina of a roach showing the concentration of capillaries around the vein while the peri-arterial zone is relatively free from capillaries. (x 30)

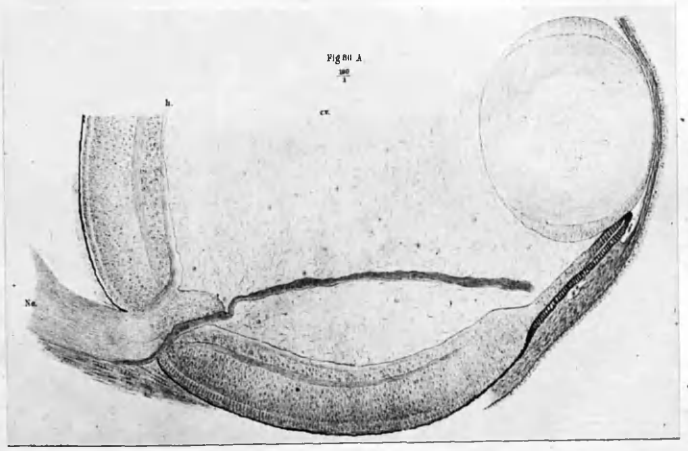


Injected superficial vitreous vessels of an adult frog. There is a capillary free zone around the artery. (A).
(x 215)

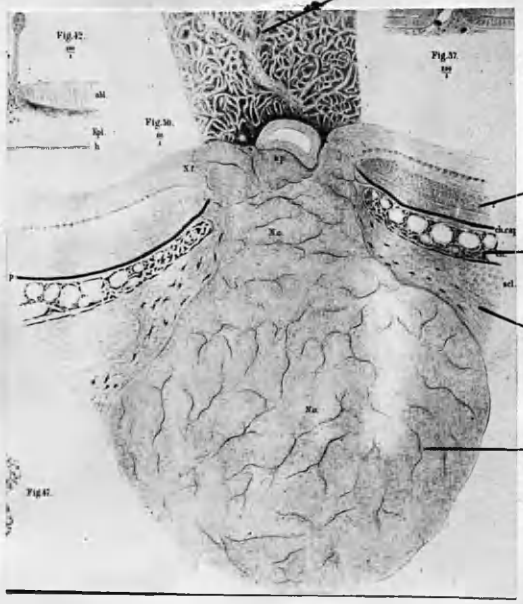
9



Injected superficial vitreous vessels of an adult frog. There is a capillary free zone around the artery. (A).
(x 450)

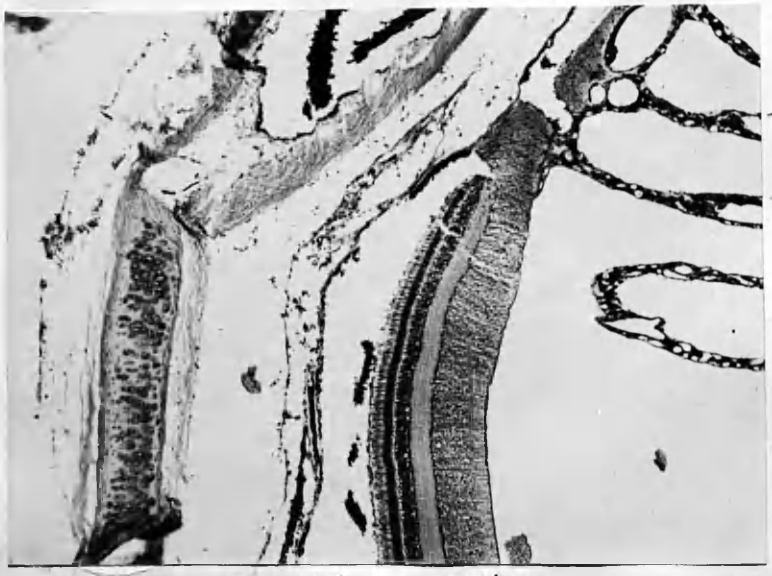


Section through eye of lacerta embryo showing the hyaloid vessel. The intra-vitreous portion of this vessel atrophies later. The pecten has not yet formed.(L.Kessler.)

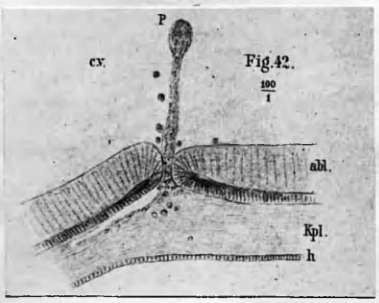


Section of pecten of adult hen (L.Kessler).

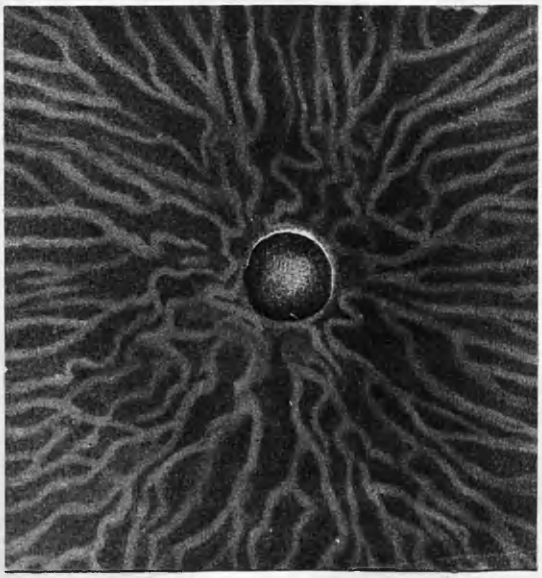
Section o f injected eye of the pigeon showing the pecten and its vascular communications at the optic disc.
(X17)



Section of injected retina of the pigeon. There are no intra-retinal vessels. The choroid is particularly well developed. (Paraffin embedding).
(× 75)

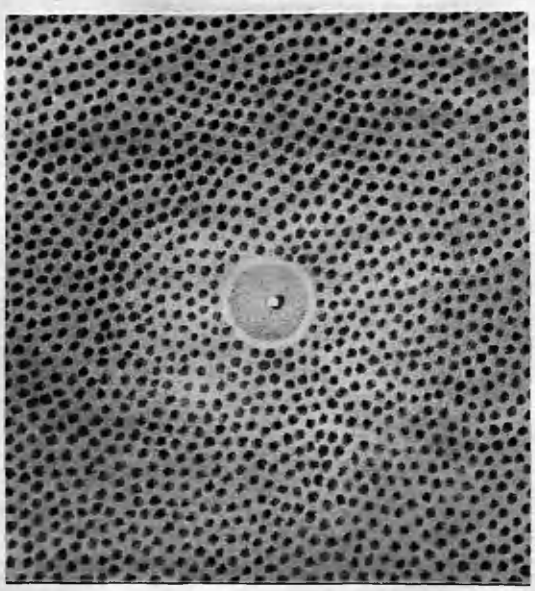


Section through eye of 5 day hen embryo, showing the passage of vascularised tissue through the foetal fissure.
abl= optic vesicle. (L.Kessler).

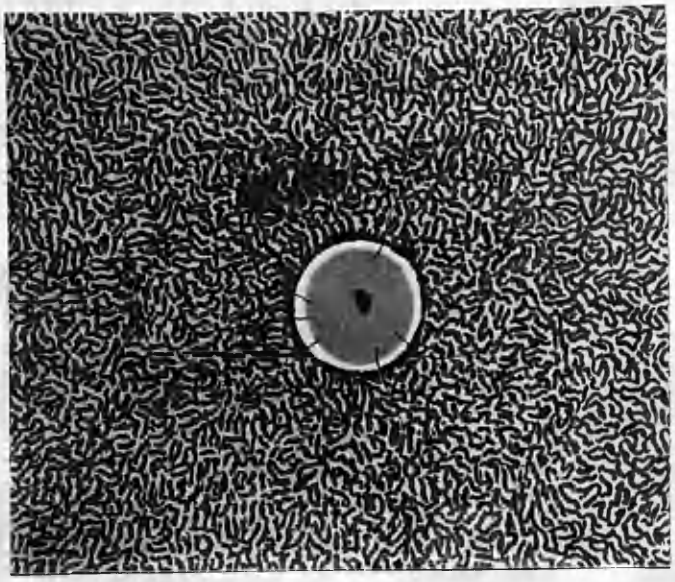


Fundus of Brazilian porcupine (hystricidae) (L.Johnson).

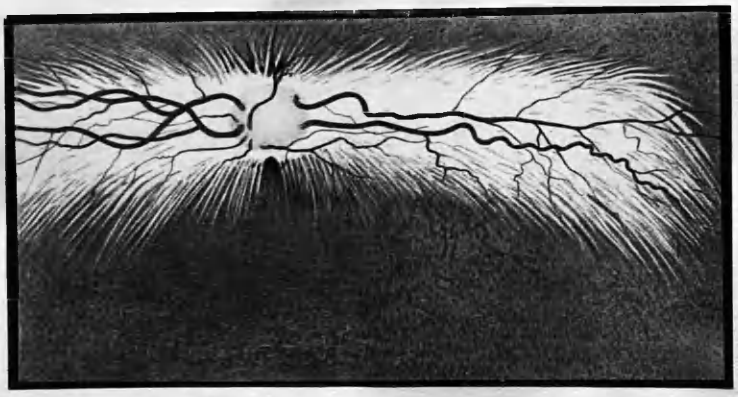
16



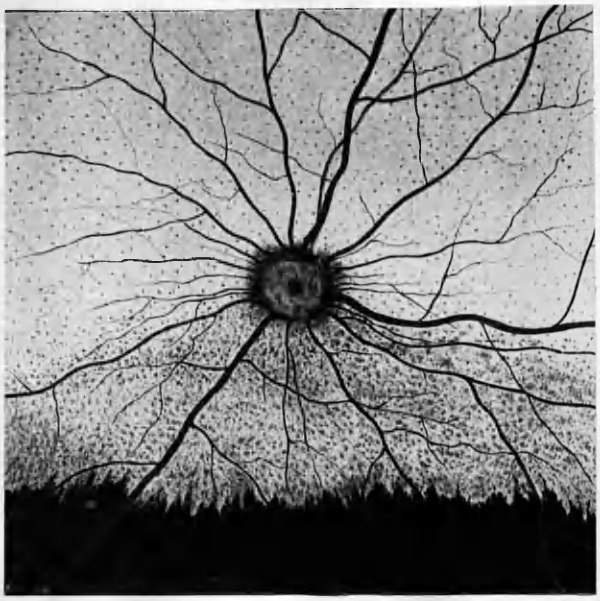
Fundus of Australian fruit-bat (Pteropus) (L.Johnson).



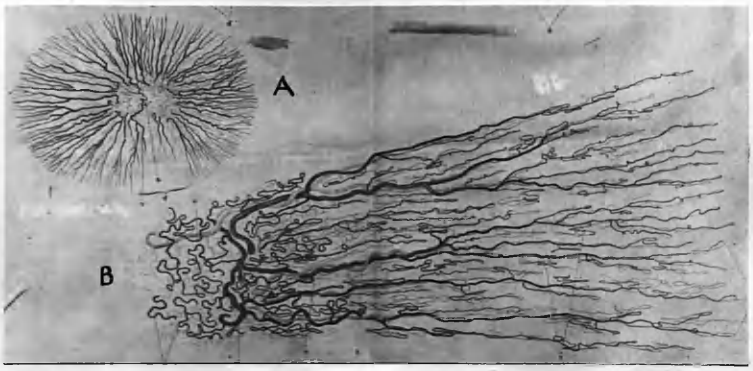
Fundus of African elephant. (L.Johnson).



Fundus of common rabbit (Leporidae). (L. Johnson).

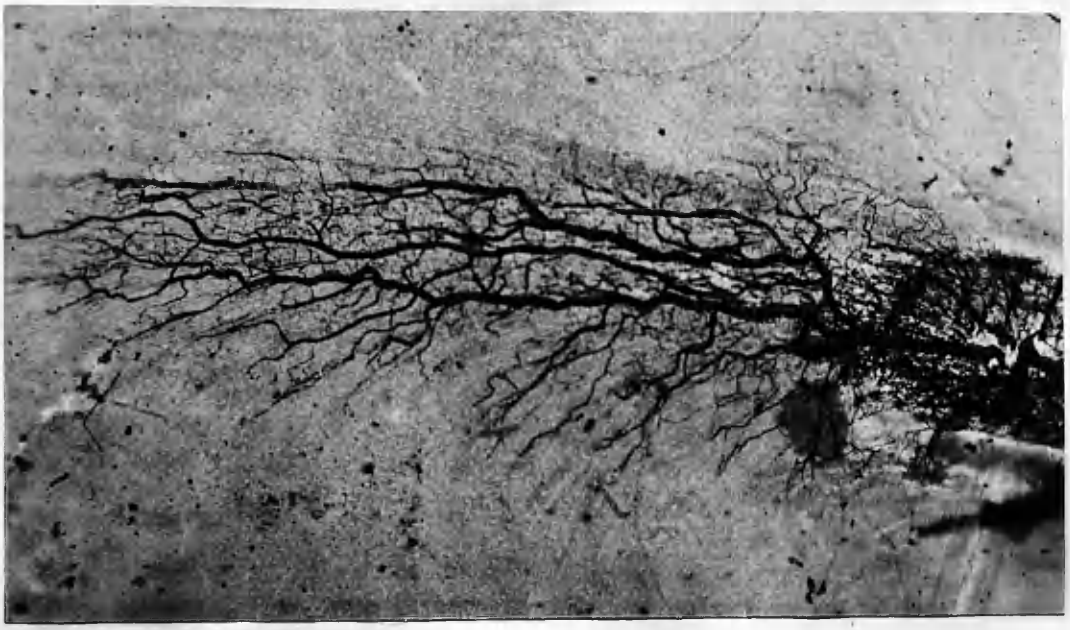


Fundus of civet cat (viverridae). (L. Johnson).



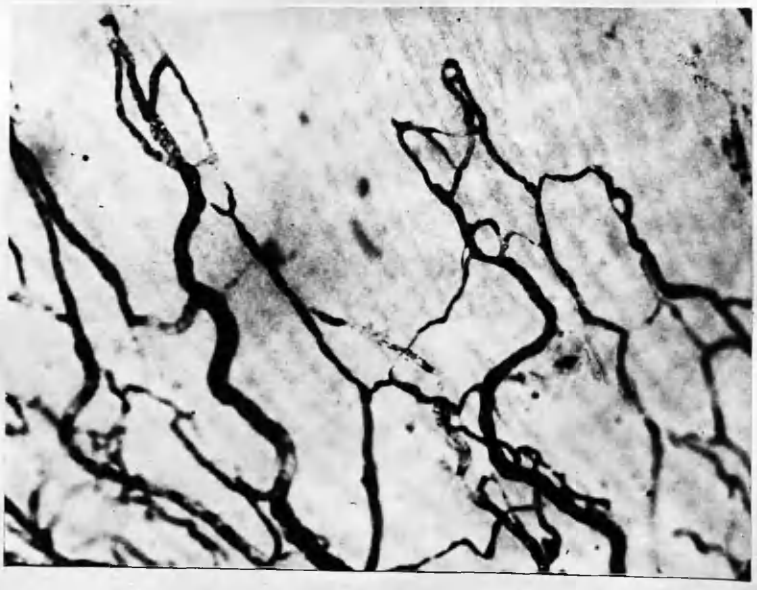
A. Arrangement of retinal vessels in the horse.
B. A portion of the vascularised retina of the horse showing the peripheral loops, the T shaped loops between the branches of the main vessels. There are many fine vessels in the optic nerve head. (L. Bruns.)

21



Injected retina of young rabbit mounted in glycerine.
(x 24)

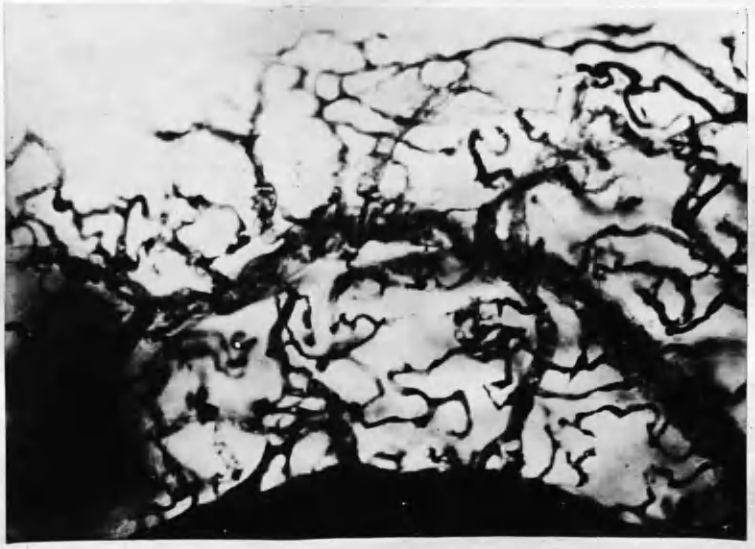
22



Injected retina of rabbit mounted in glycerine, showing the arrangement of the peripheral loops.

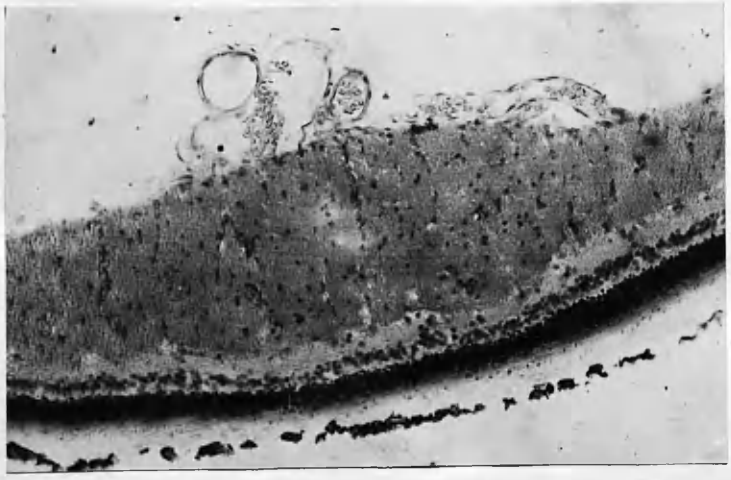
(x 230)

Injected retina of rabbit mounted in glycerine. The vessel loops at the upper and lower margins of the vascularised area can be seen. (x50)



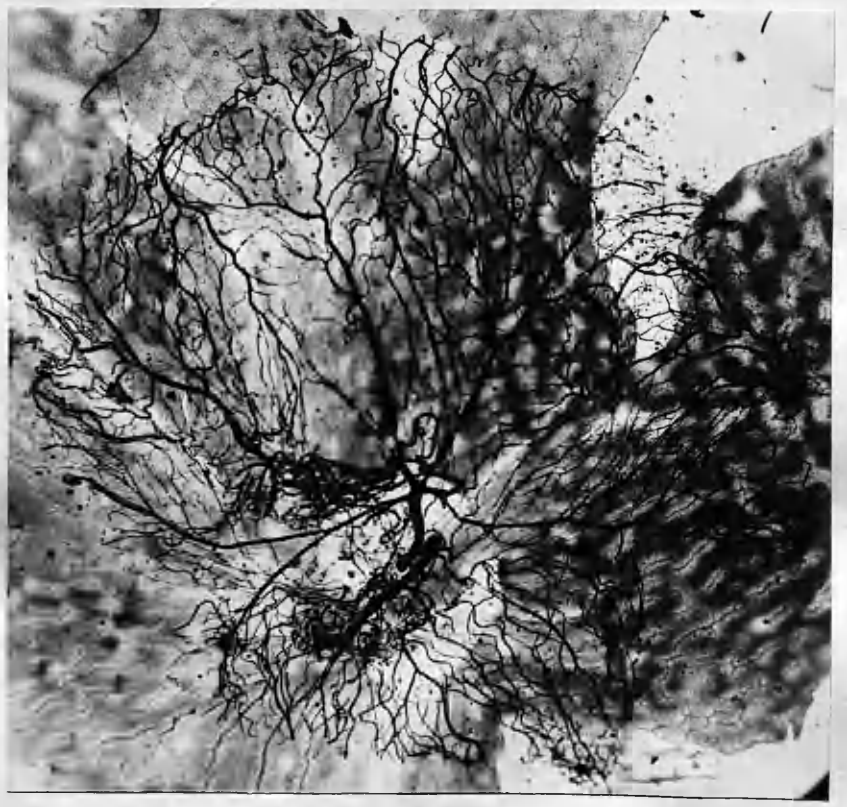
Injected retina of rabbit mounted in glycerine. The area is close to the disc and shows the over-lapping of the capillary loops.
(x 233)

25

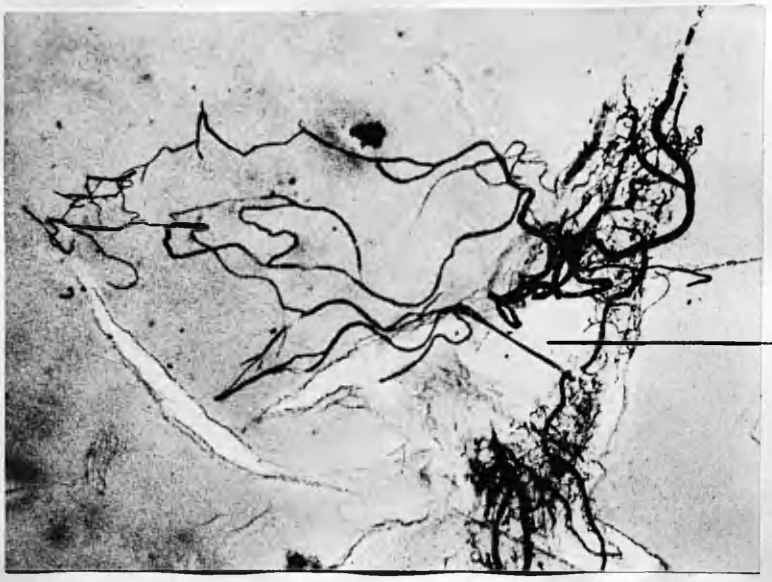


Section of rabbit's retina including the medullated nerve fibres. The large vessels are clearly pre-retinal.
(X 133)

26



Injected retina of 1 day old rabbit. The main mass of vessels belongs to the hyaloid system. These vessels disappear within a few days.
(X17)



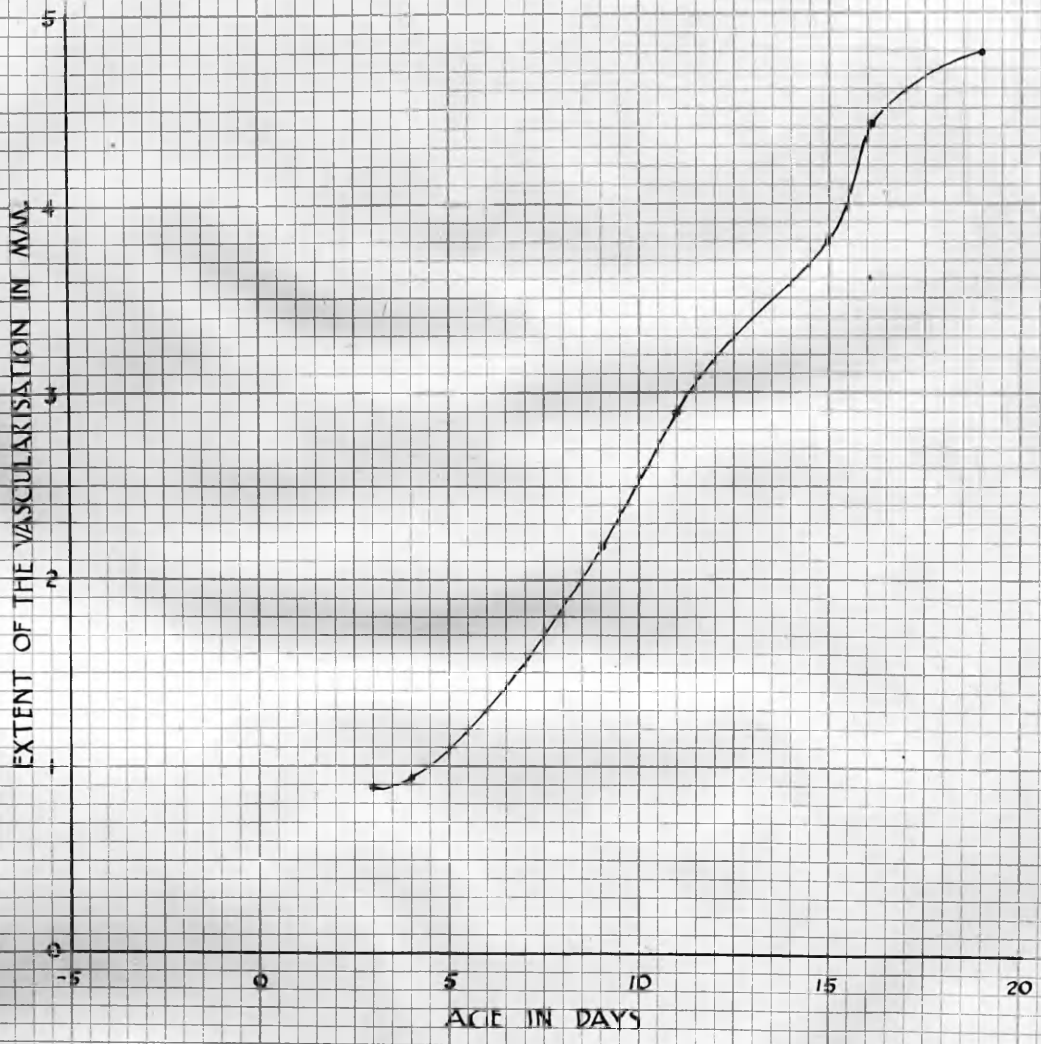
Injected retina of 4 day old rabbit. Few hyaloid vessels remain. Vessels are growing into the retina from the optic disc. (x 27)

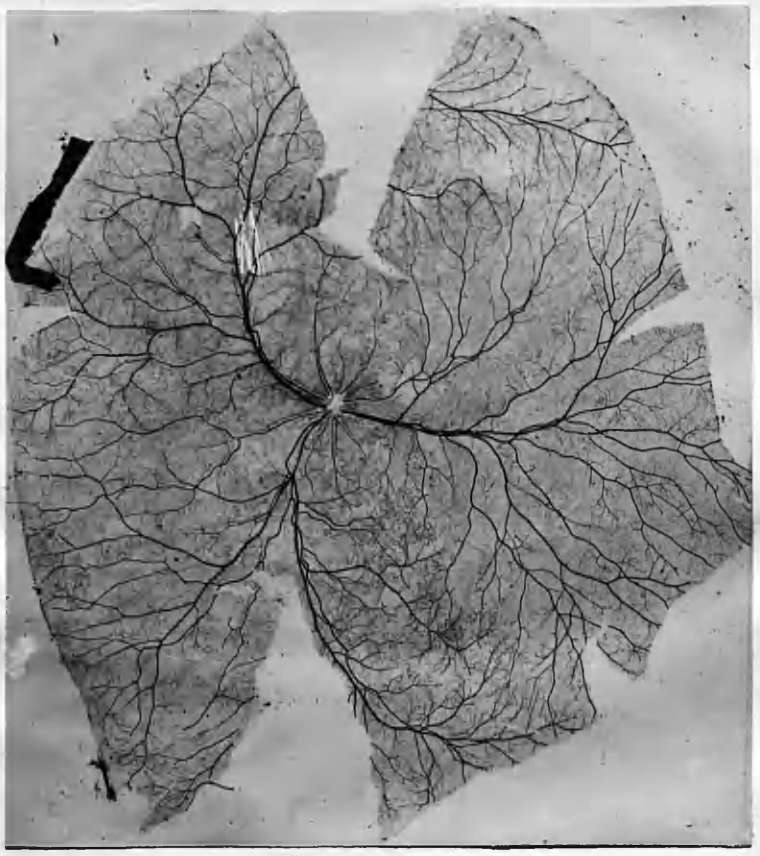
Injected retina of 18 day old rabbit. The difference in extent between the anterior and posterior vascularised areas can be seen. (x 10)

Fig 29

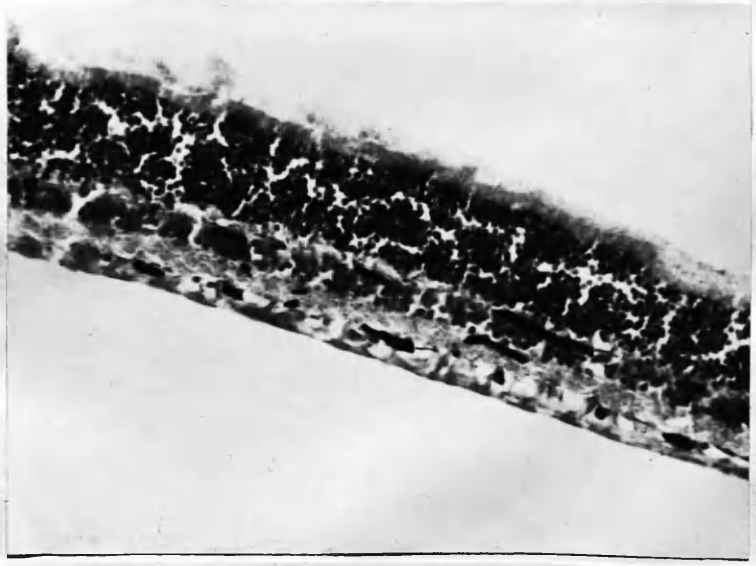
THE RABBIT

GROWTH RATE OF THE RETINAL VASCULARISATION



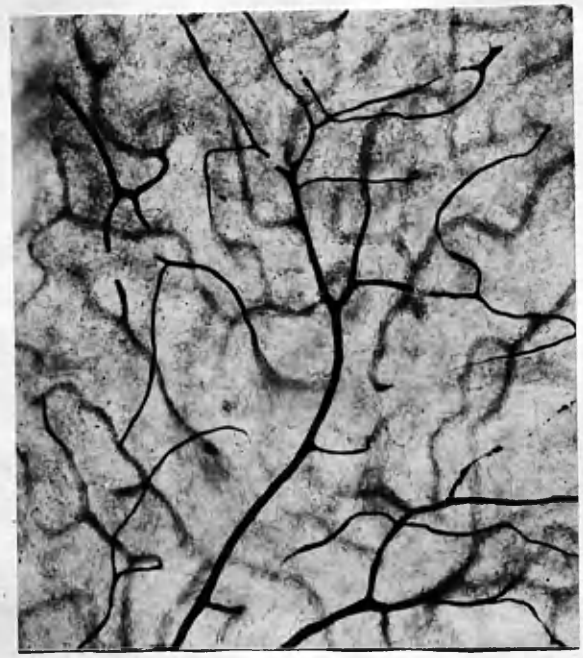


Appearance of injected retina of the adult cat.
(x 3·3)



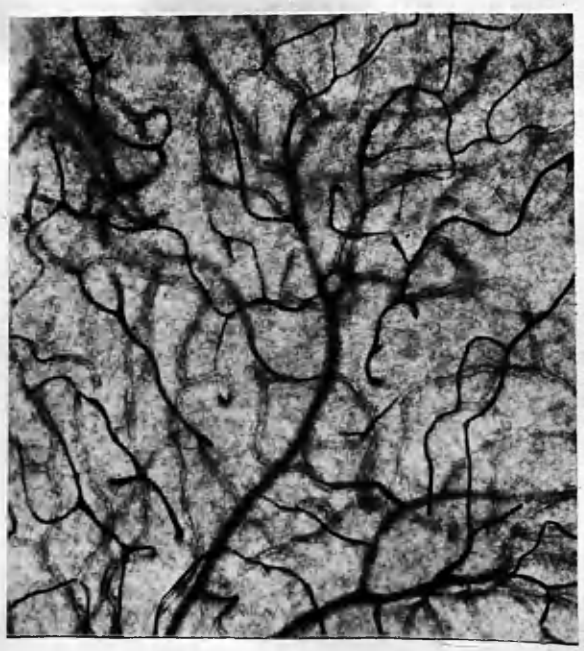
Section of injected retina of adult cat showing superficial capillary net in the nerve fibre layer and a deep capillary net lying on the inner and outer aspects of the inner nuclear layer.
(x 130)

32



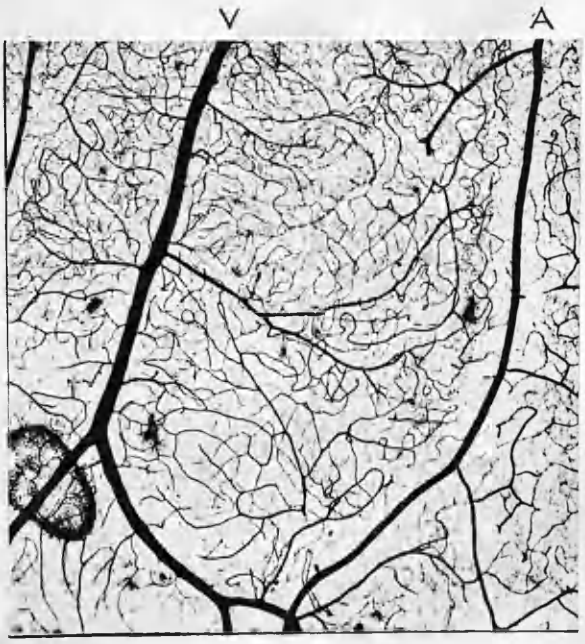
Injected retina of adult cat showing the superficial capillary net.
(x100)

33



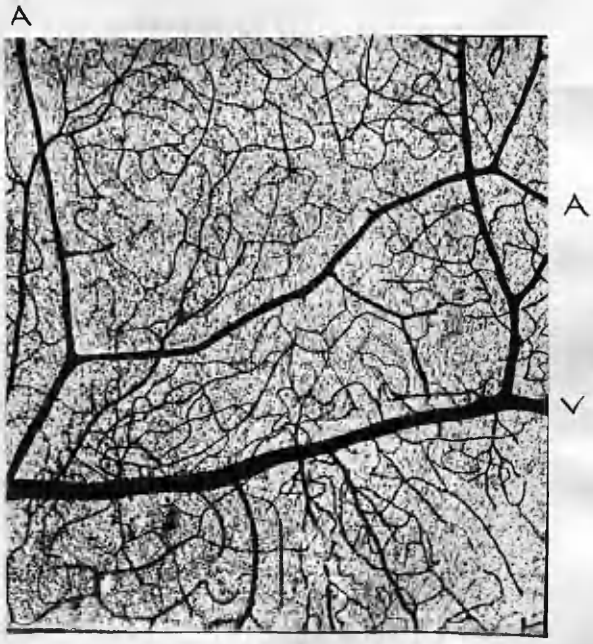
Injected retina or adult cat showing the same area as illustrated in fig:32 but with the deep capillary net now in focus.
(x 100)

34



Injected retina of adult cat showing the area on either side of the artery free of capillaries from the superficial net. Behind the artery, however, can be seen a few capillaries belonging to the deep capillary net. There is no capillary free zone around the vein. (x 35)

35



Injected retina of adult cat showing the area on either side of the artery free of capillaries from the superficial net. Behind the artery, however, can be seen a few capillaries belonging to the deep cap illary net. There is no capillary free zone around the vein. (x 35)

Fig. 36.

Injected retina of 35 day cat foetus. There are no vessels at the disc excepting the Hyaloid artery.

(x 3)

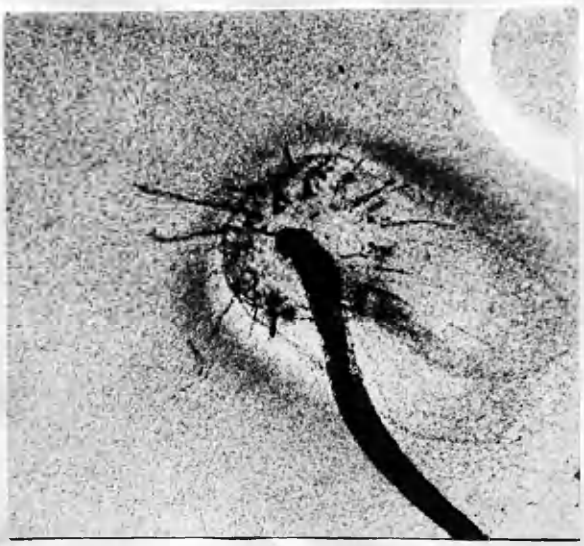


Fig. 37.

Injected retina of 45 day cat embryo. Several vessels can be seen proceeding from the disc for a distance of 0.12 - 0.24 mm.

(x 4·3)

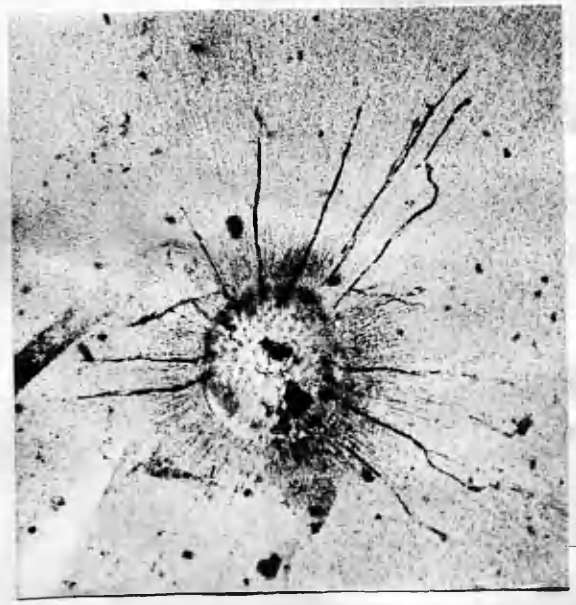
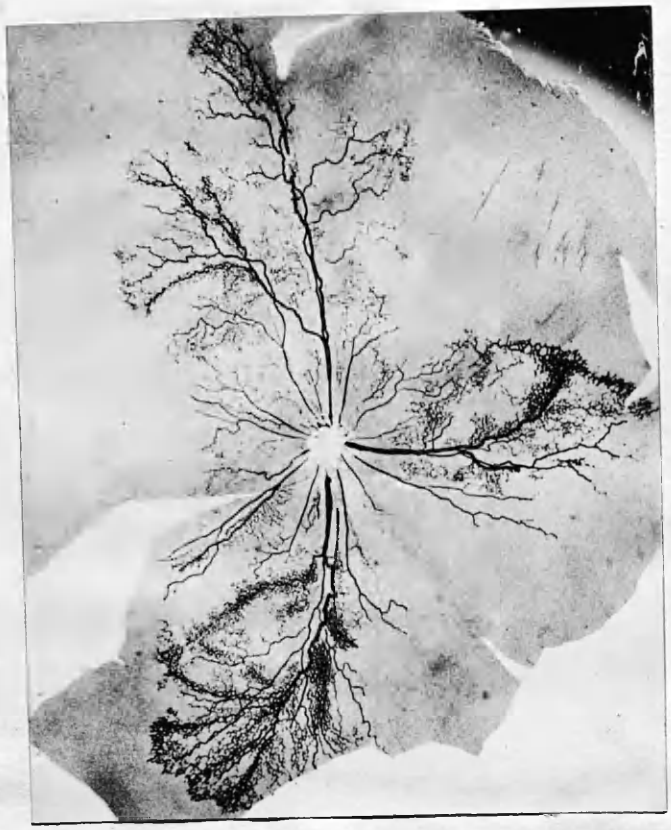


Fig. 38.

Injected retina of 51 day cat embryo. The vessels have proceeded from the disc for a distance of 0.26 - 0.75 mm. The early formation of loops, although clearly seen with the microscope, are not reproduced in the photograph.

(x 4·3)



Injected retina of right eye of 56 day cat embryo. Capillary growth is taking place predominantly from veins and in many places from the side of the vein distal to the neighbouring artery. (× 10·5)

Fig. 40.

The Nasal vessel complex of the retina illustrated in fig. 39. It shows that the growth of the capillaries takes place chiefly from veins and in places from the side of the vein distal to the neighbouring artery.
(x 22)

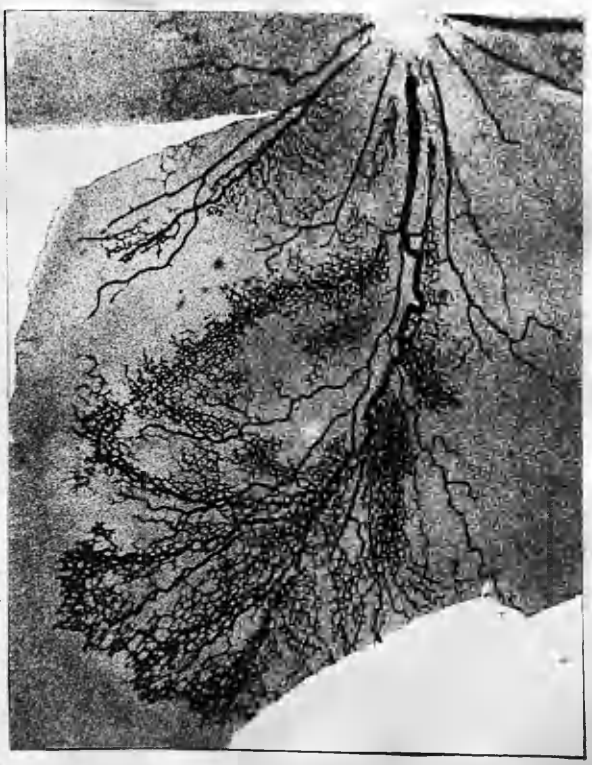


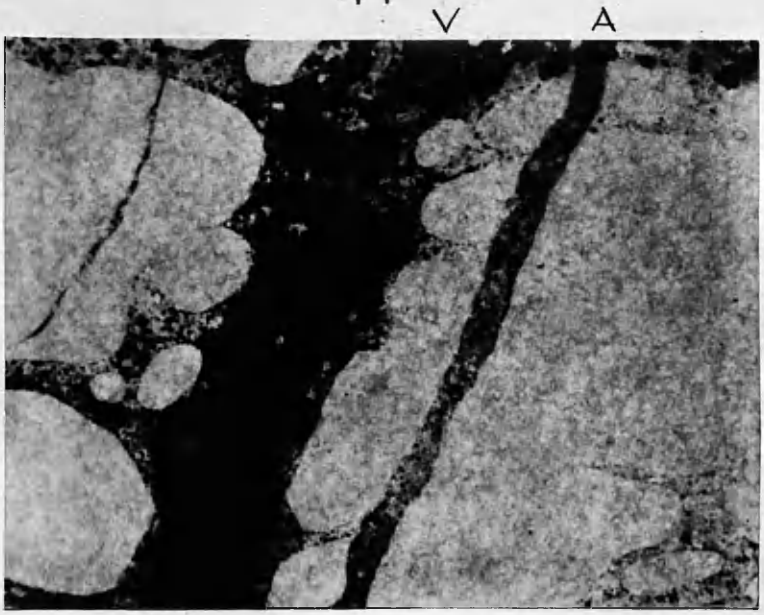
Fig. 41.

The lower temporal vessel complex of the retina illustrated in fig. 39. It shows that the growth of capillaries takes place chiefly from veins and in places from the side of the vein distal to the nrighbouring artery.
(x 22)

The lower temporal vessel complex of the retina illustrated in fig 39. It shows the growth of the capillaries takes place chiefly from the veins and in places from the side of the vein distal to the neighbouring artery.
(x 27)

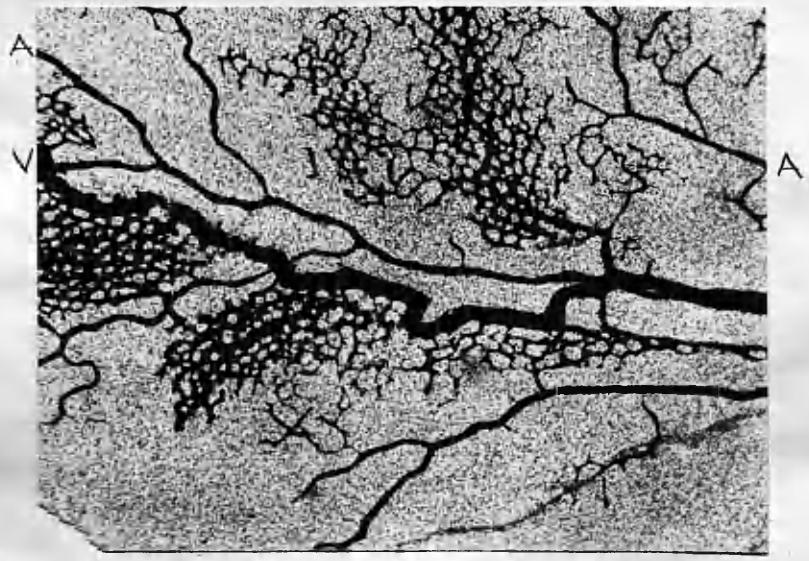
Injected retina from 56 day cat foetus other than that illustrated in fig 39. It shows that the growth of capillaries takes place chiefly from veins and from the side of the vein distal to the neighbouring artery. (X26)

44



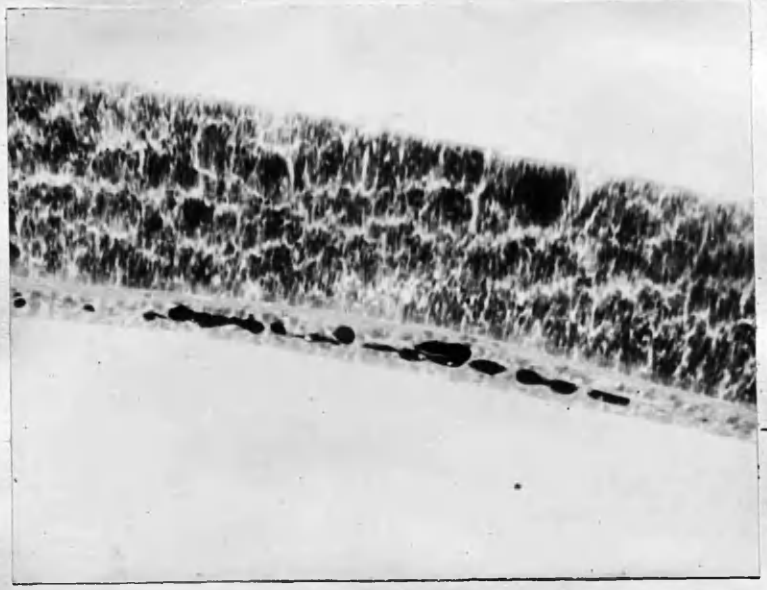
Vein and artery in injected retina of cat foetus. The capillary growth is from the vein by a process of budding. (x 200)

45



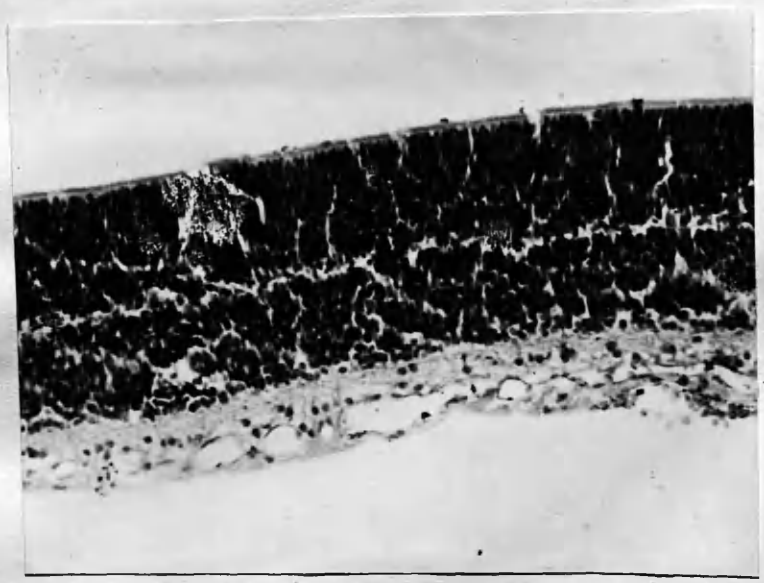
From injected retina of 56 day cat embryo showing capillary growth from veins and its confinement to the side of the vein away from the artery. The capillary growth can be seen taking place fairly equally in either side of a small venous branch which is situated nearly midway between two arterial branches. The early formation of a peri-arterial capillary free zone can be seen, as well as the arterial precapillaries which traverse this zone. These precapillary vessels are budding from the arteries. (x60)

46a

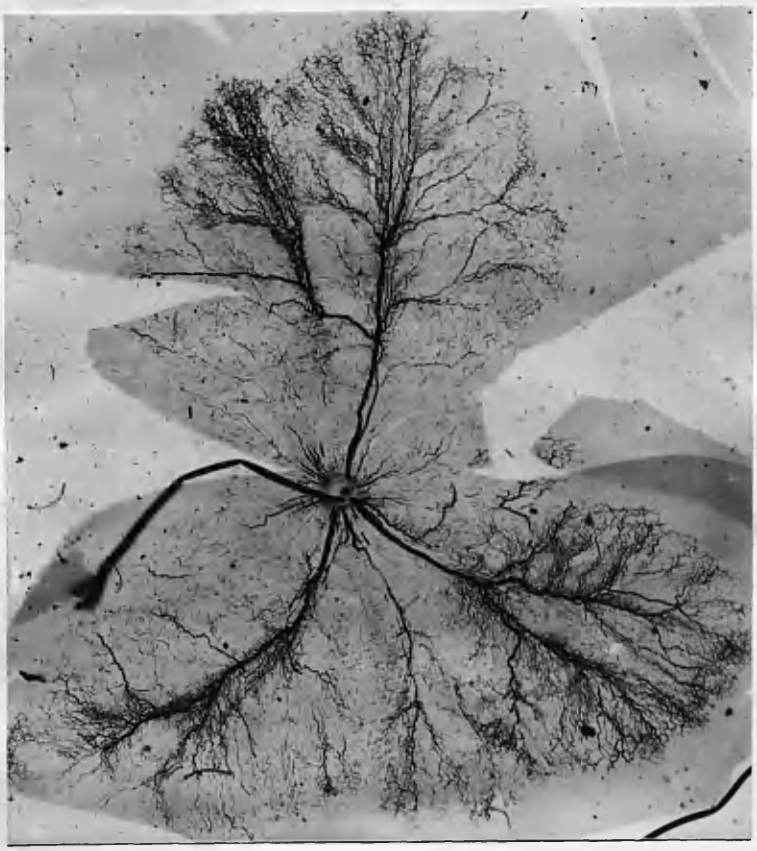


Section of injected retina of cat foetus showing the capillary net placed entirely within the nerve fibre layer. (x 170)

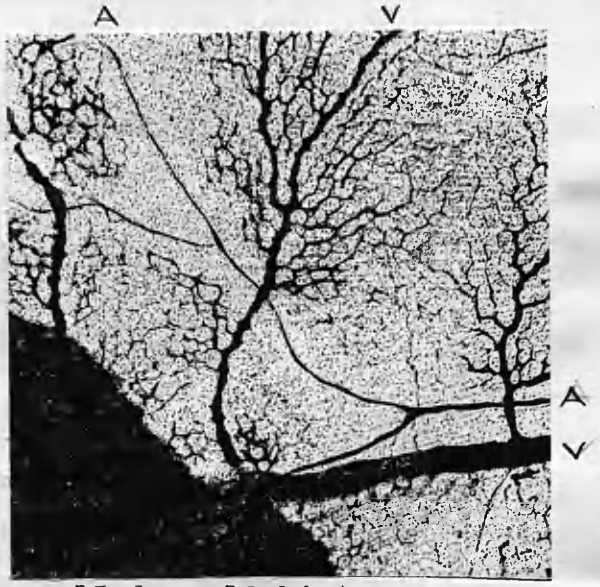
46b



Section of retina of cat foetus showing the appearance of embryonic capillary vessels. (x 200)

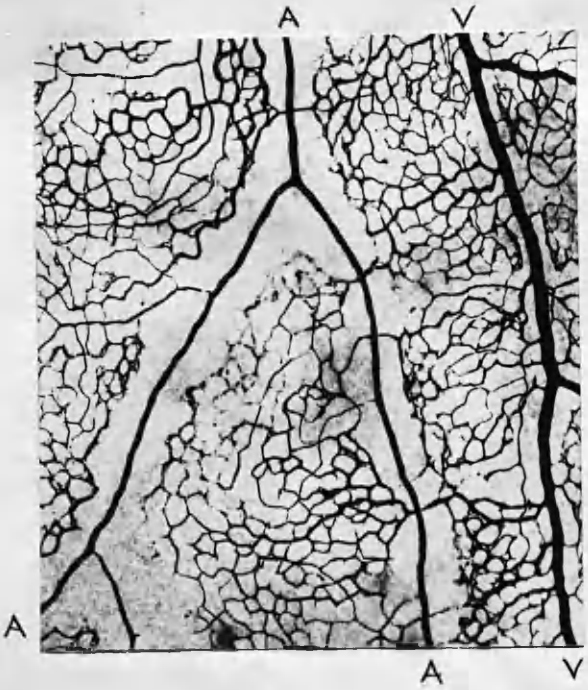


Injected retina of one day old kitten.
(x 10)



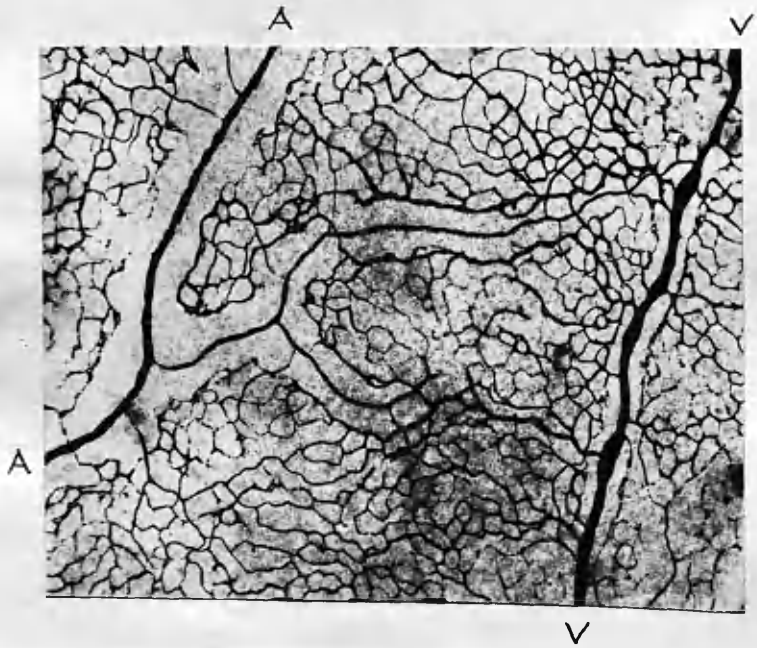
Injected retina of 15 day old kitten showing the peri-arterial capillary free zone. The capillaries are concentrated around the veins and at places a deep capillary net can be seen forming. (x 55)

49



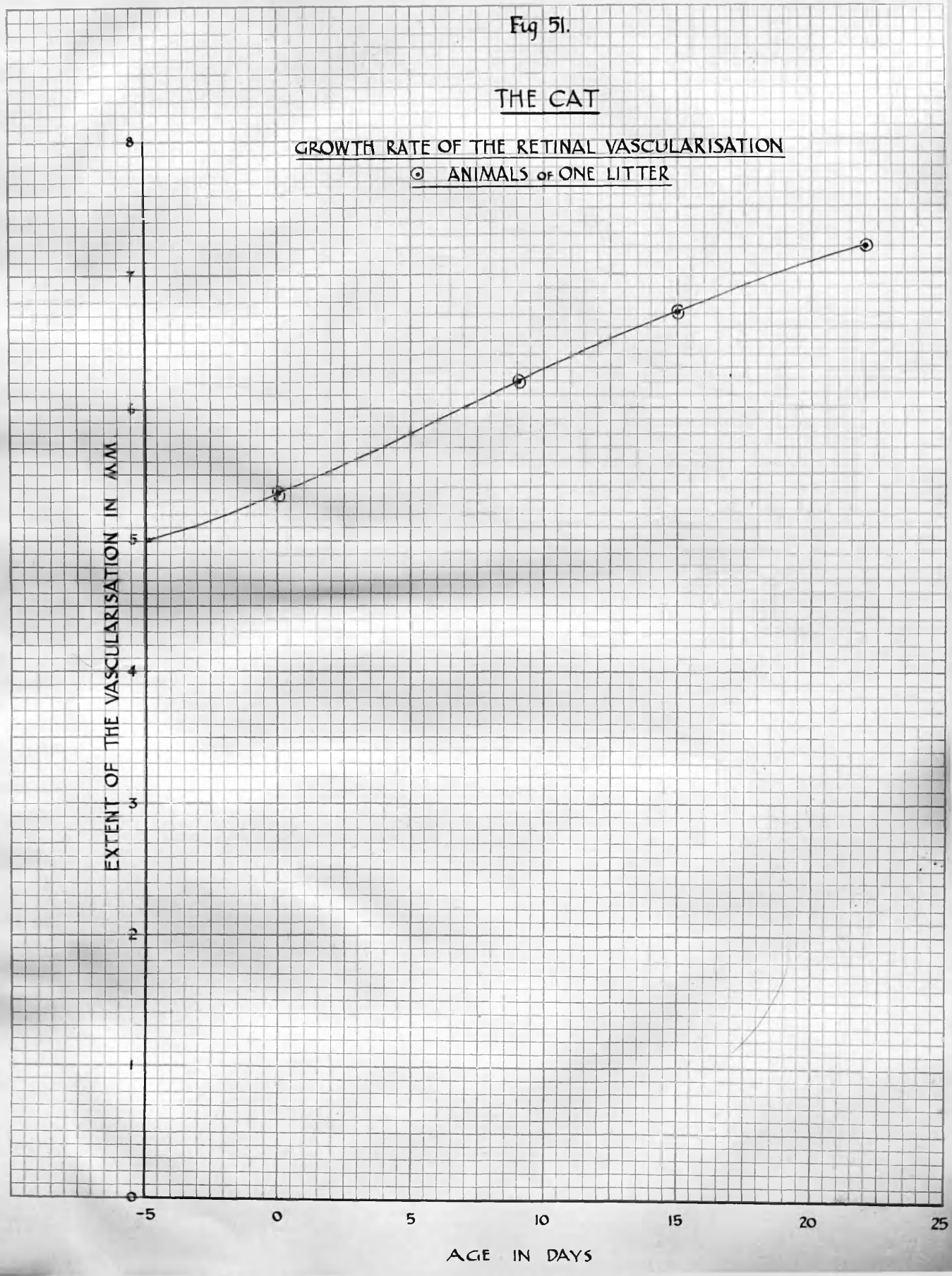
Injected retina of 22 day old kitten showing a well formed peri arterial capillary free zone. (x60)

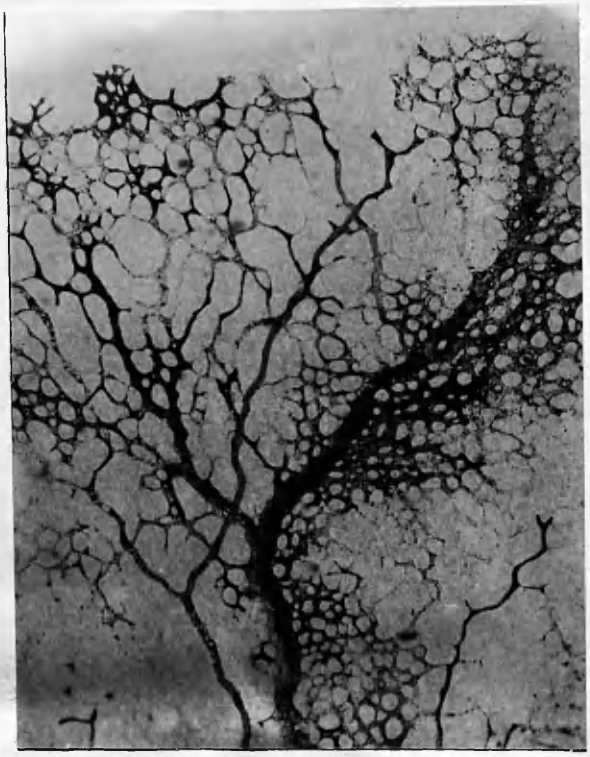
50



Injected retina of 20 day old kitten showing the per-arterial capillary free zone even around the arterial pre-capillaries. (x60)

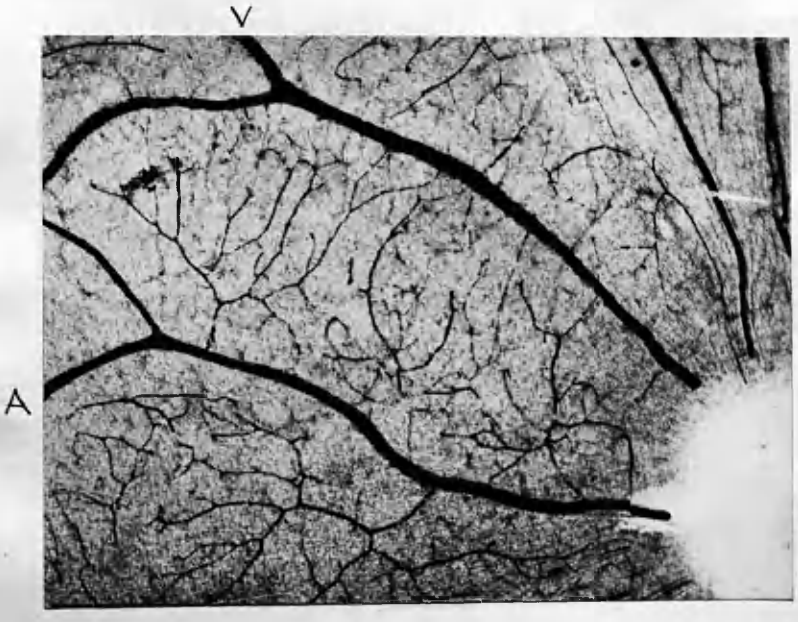
Fig 51.


THE CAT
GROWTH RATE OF THE RETINAL VASCULARISATION
⊙ ANIMALS OF ONE LITTER
EXTENT OF THE VASCULARISATION IN MM
0
1
2
3
4
5
6
7
8
-5
0
5
10
15
20
25
AGE IN DAYS



A V

Injected retina from a 20 day old kitten which was badly nourished. Many of the capillaries were of the embronic type as illustrated. Note the capillary free zone around the arteries. (x 60)



Injected retina of an adult rat. The peri-arterial capillary-free zone can be seen. (x 75)

54

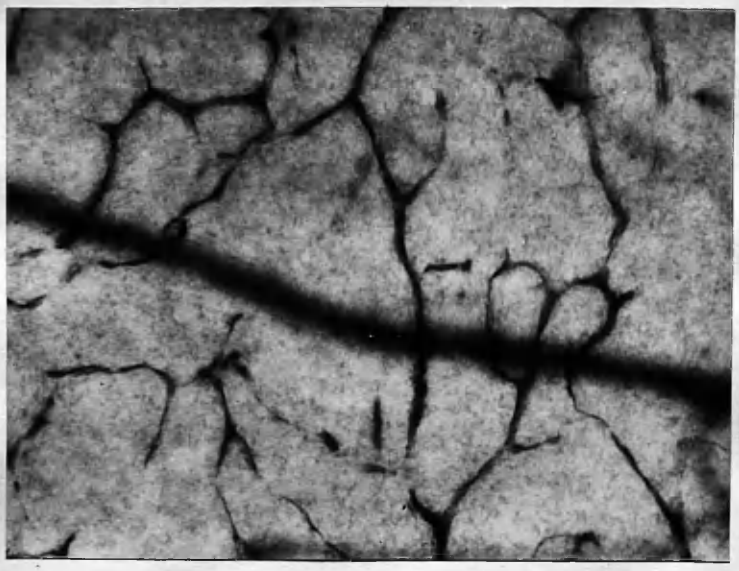
55

56

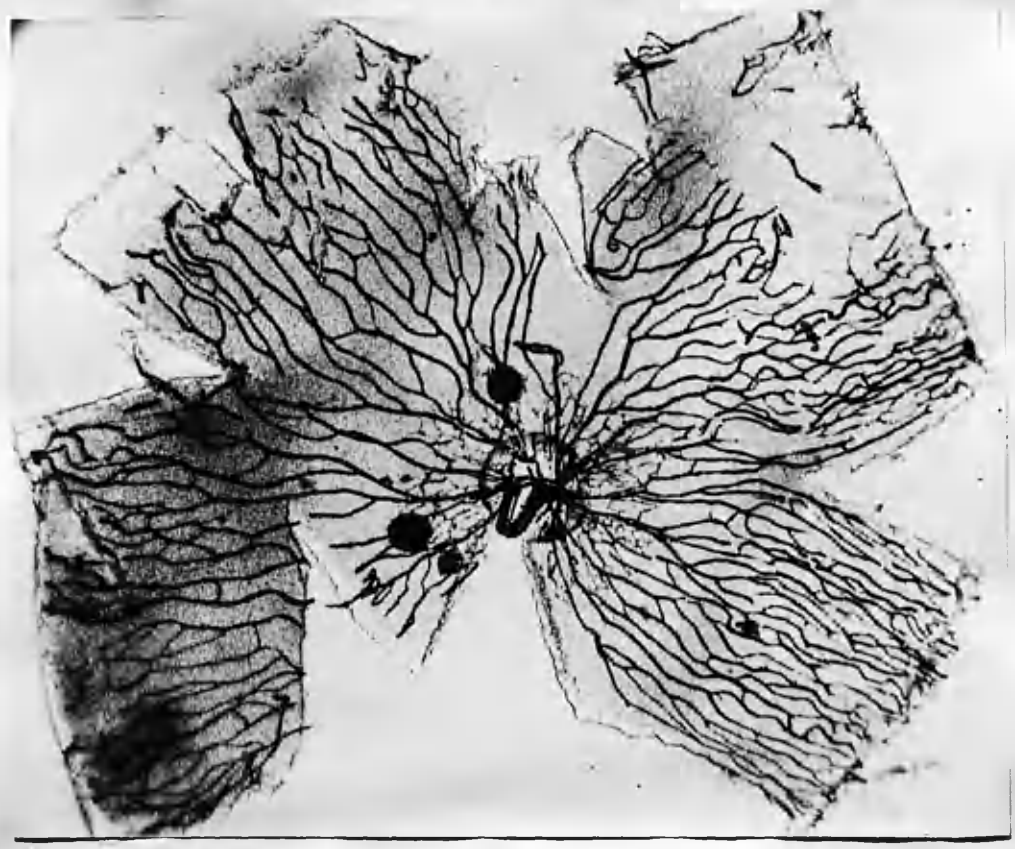
Injected retina of a rat. Two venae efferentes have been successively photographed at superficial, intermediate and deep levels. In the last the vessels of the deep net can be seen.

(x 550)

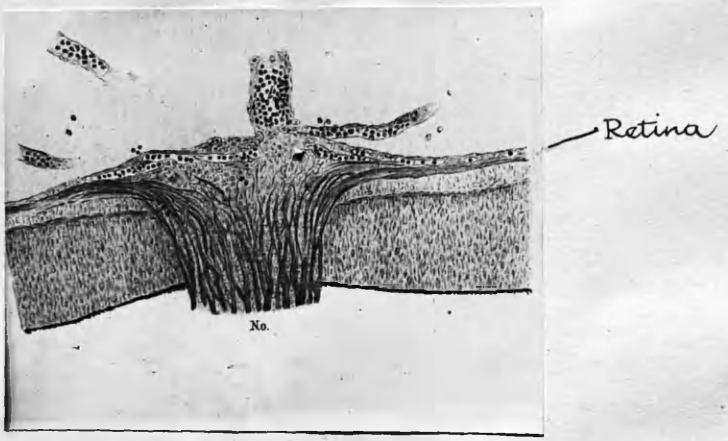
58



Injected retina of a rat showing the neighbourhood of an artery focussed at the levels of the superficial and deep capillary nets. The deep net is not associated with the overlying artery. (x 500)



Injected retina of 1 day old rat. The bulk of the vessels belong to the temporary hyaloid system but around the disc the early intra-retinal vessels can be seen.
(x 35)

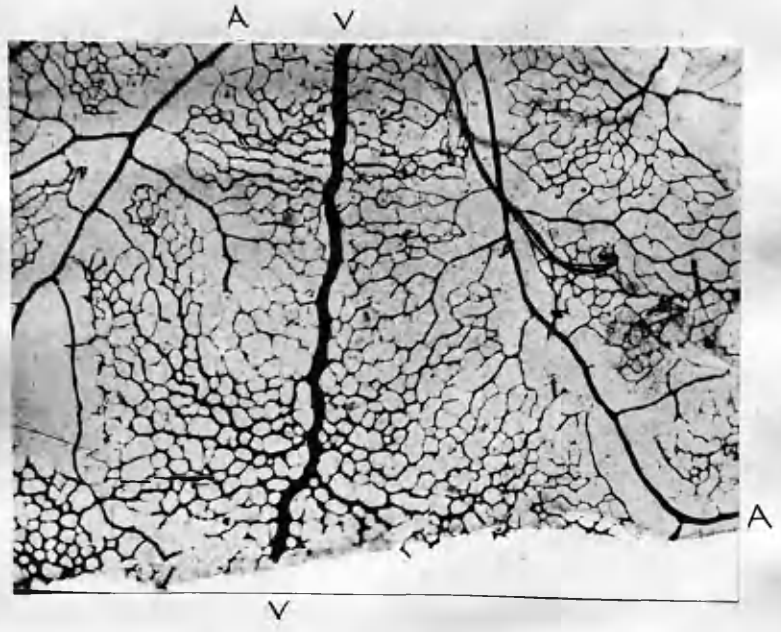


Section of retina from the developing rat showing the intra-retinal vessels budding from the disc. Vessels of the temporary hyaloid system can be seen in the vitreous.
(L.Kessler).

61

Injected retina from 4 day old rat showing the predominant capillary budding from the veins (v), the more extensive budding from the side of the vein remote from the local artery and the peri-arterial zone free from capillaries. (x 44)

62



Injected retina of 6 day old rat shows the peri-arterial capillary free zone. The capillaries are of the embryonic type in places.

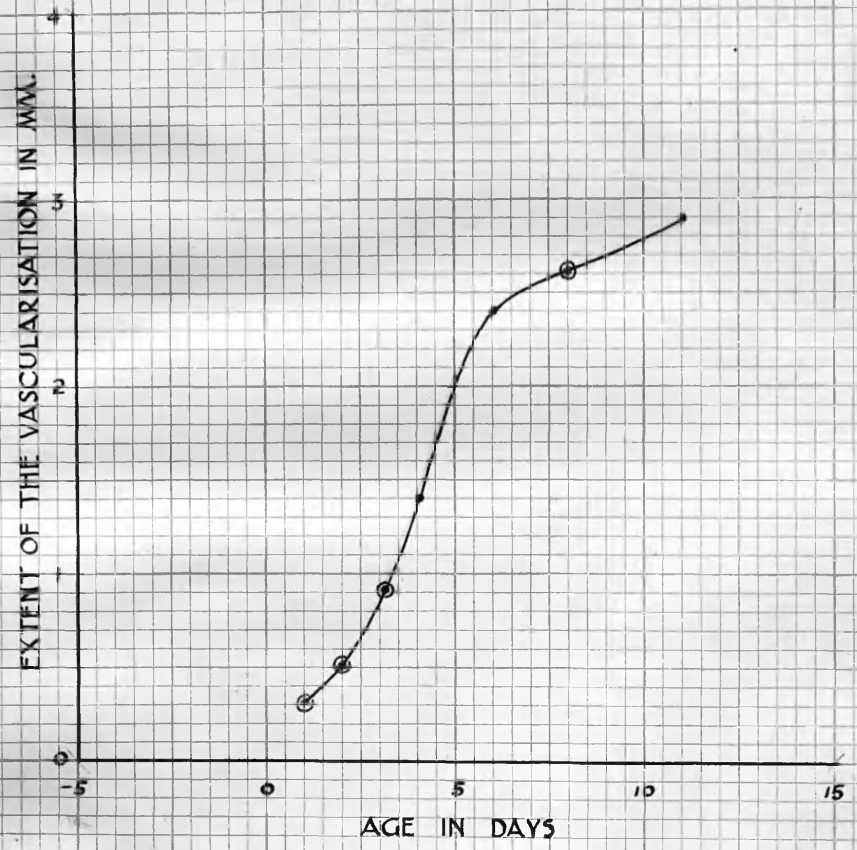
(x44)

Fig 63

THE RAT

GROWTH RATE OF THE RETINAL VASCULARISATION

⊙ ANIMALS OF ONE LITTER

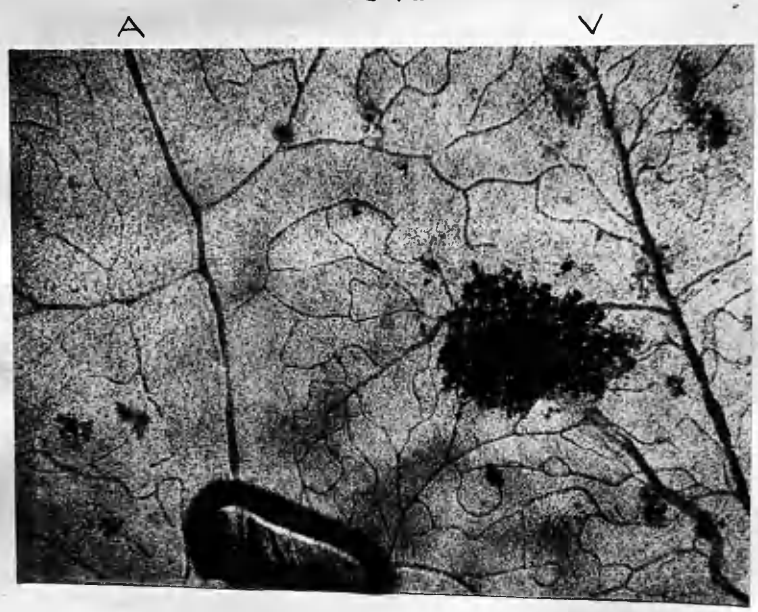


64a

Field from equatorial zone of retina, showing a vein on the left and an artery on the right. Note the interdigitation of the venae efferentes (v) with the arteriae afferentes (A). Note also the capillary free zone around the artery

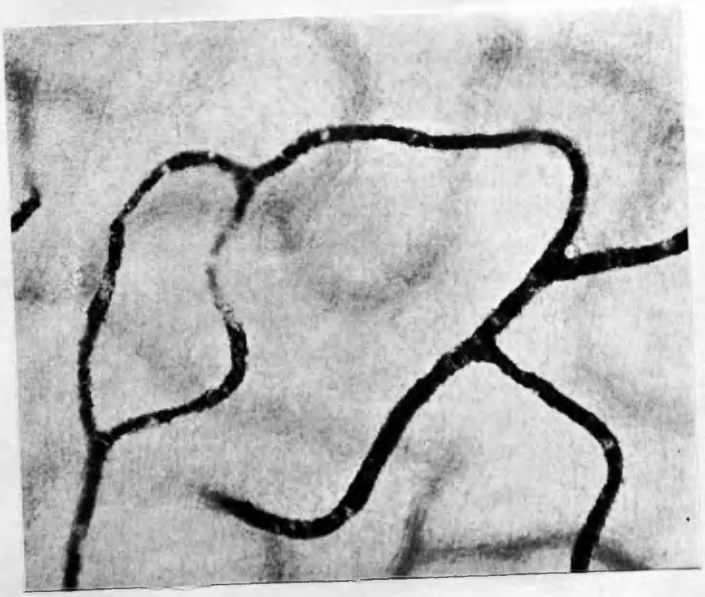
(× 30)

64b

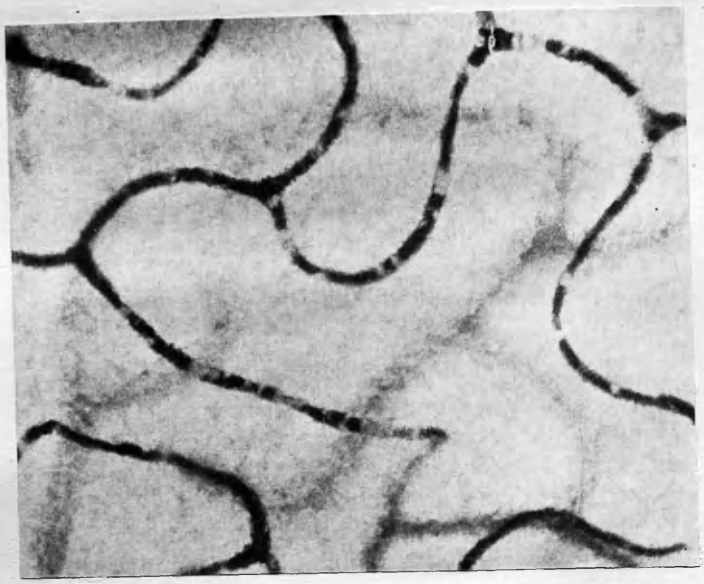


Uninjected retina from case of venous occlusion showing a natural filling of the capillaries. The zone around the artery (a) is free from capillaries.

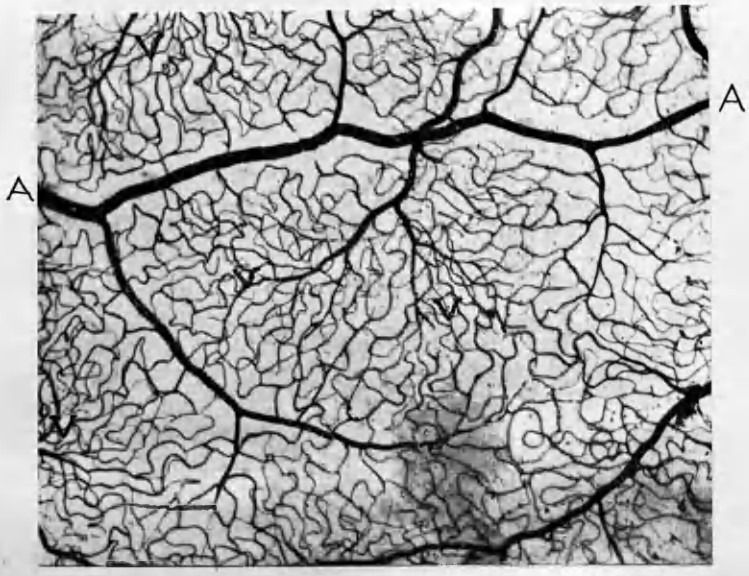
(x 55)



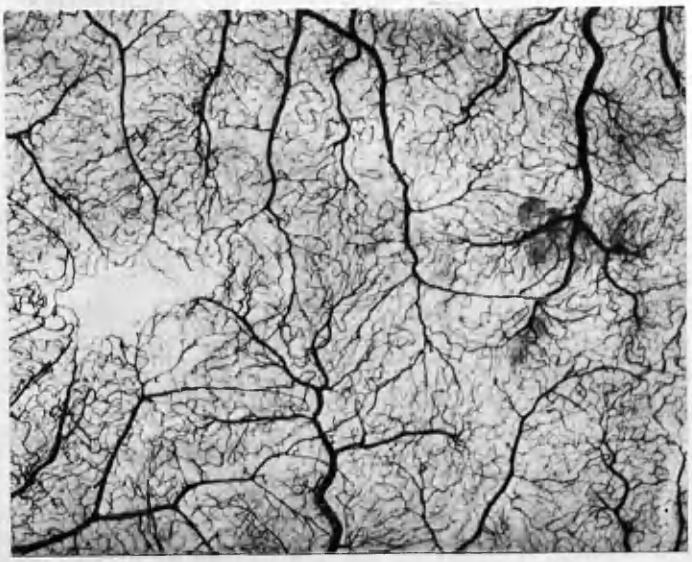
66



Field from equatorial zone of retina focused in (65) to show the superficial capillary net, and in (66) to show the deep net. X 350



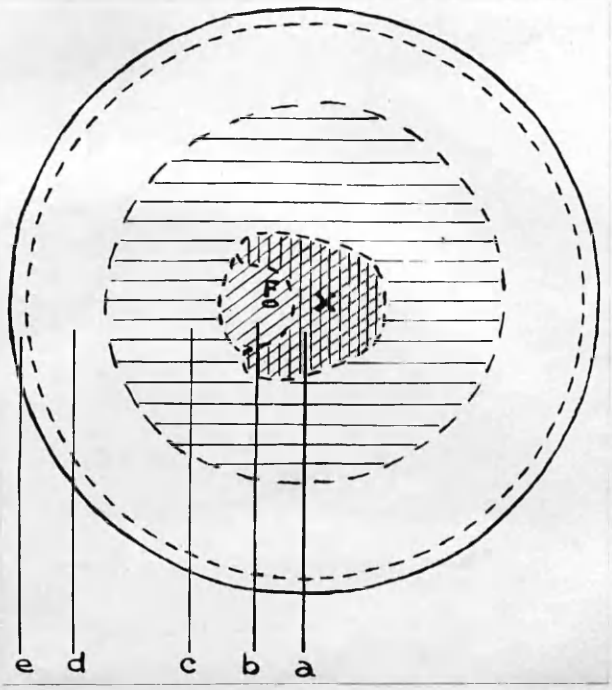
Field from equatorial zone of retina. Note the varying density of the capillary mesh, the denser areas being in the neighbourhood of the venae efferentes. (v). X 45



Lateral part of macula. Note its greater vascularity as compared with the field in Fig 64a due to a narrower capillary mesh and to the appearance of a third capillary layer. X30.

Supero-lateral peripapillary area. Note the very dense radial peri-papillary capillary net. X 30.

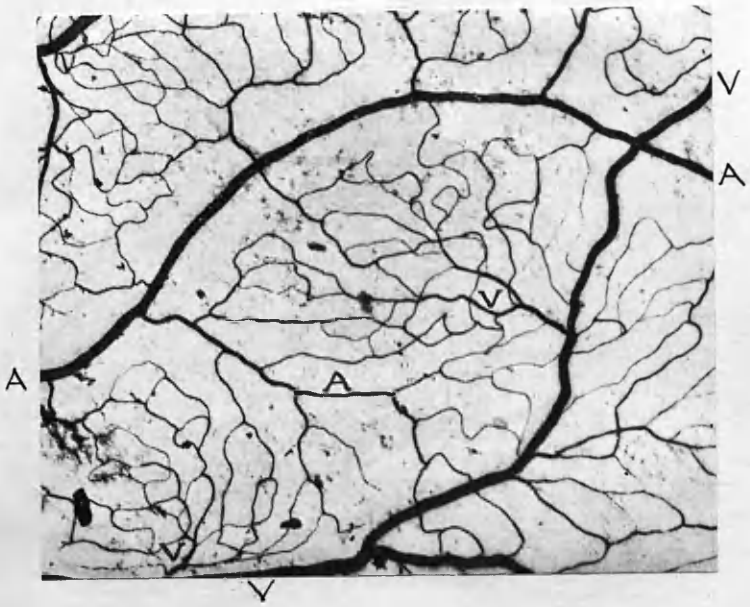
Field from peripapillary area, successively focused to show (70) the most superficial peripapillary radial capillary layer, (71) the superficial layer proper and (72) the deep layer x 350. (The deep reduplication of the superficial layer is not shown);



A flat projection of the right retina X 2, X,nerve head; F, fovea; a, extent of radial peripapillary capillary net; b,extent of triple capillary net; c, extent of double capillary net; d, extent of single capillary net; e, peripheral avascular zone.

The fovea, showing its capillary-free area. X 45.

75



Field fron transitional zone between the two-layered area and the peripheral single-layered area. A double capillary net is present in the neighbourhood of the venae efferentes (v), but becomes single in the neighbourhood of the arteriae afferentes (A) X 45.

76

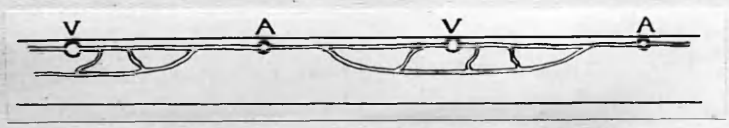
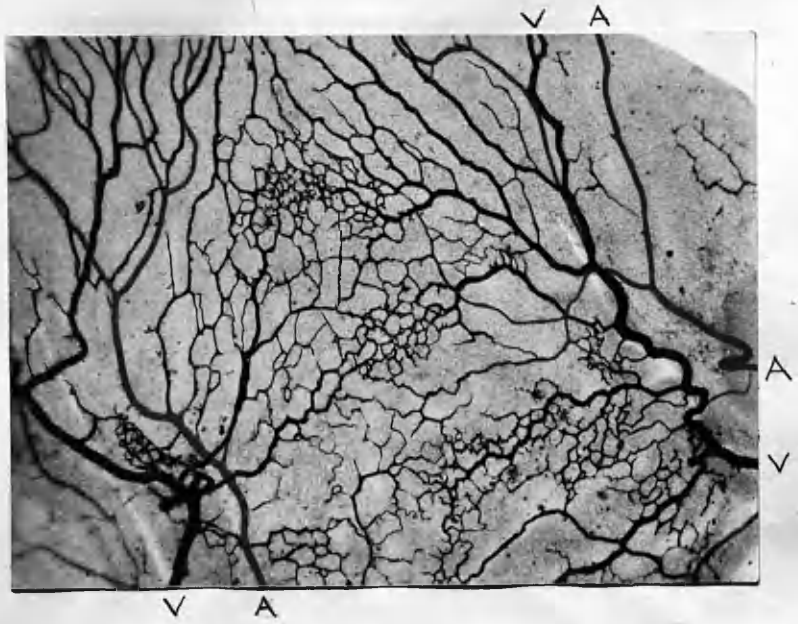


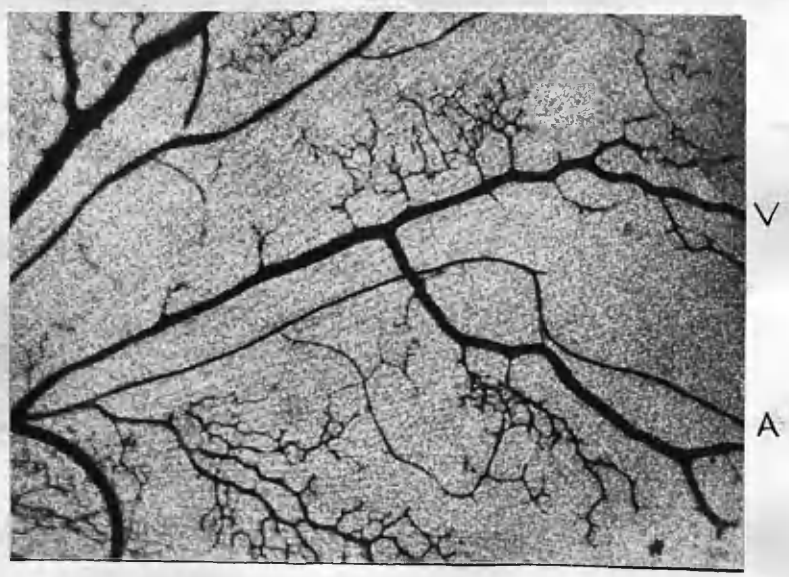
Diagram of vertical section of retina at the transition zone shown in Fig 75.

77

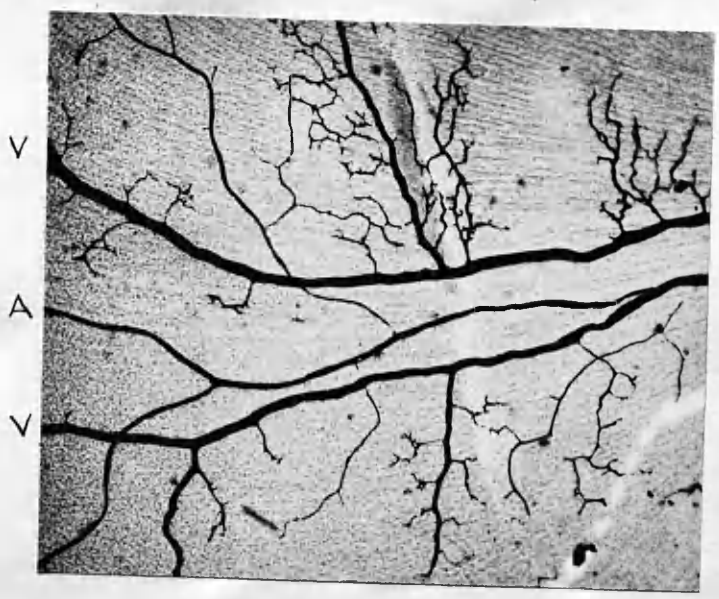


Injected retina of a human foetus showing capillary formation taking place almost entirely from veins. The arteries have been indicated in pale grey. (×26)

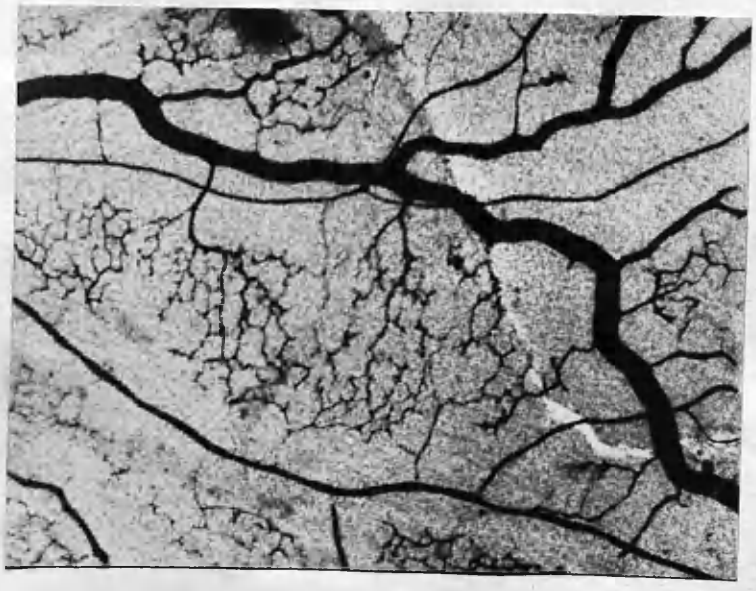
78



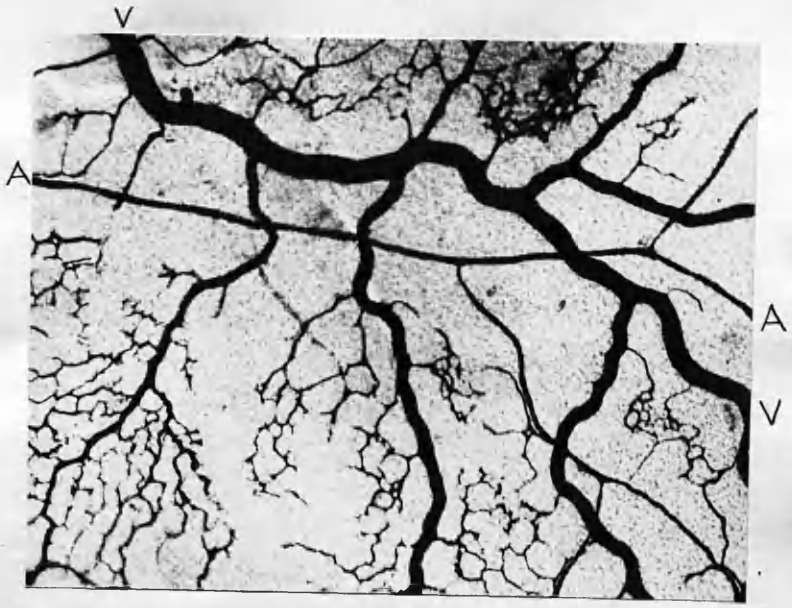
Injected retina of 18.5 cm human foetus showing capillary budding from the side of the vein remote from nearest artery. (× 42)



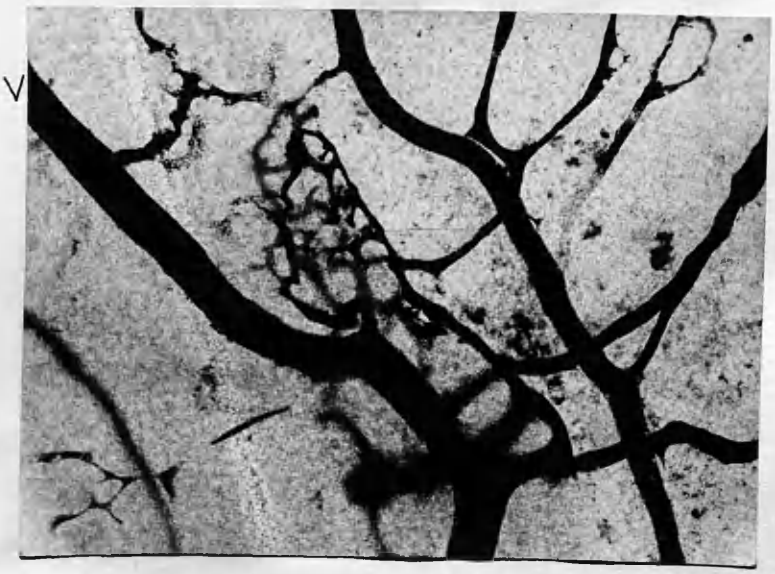
Injected retina of 19 cm human foetus showing capillary budding from the sides of two veins remote from the intervening artery (A).
(X 30)



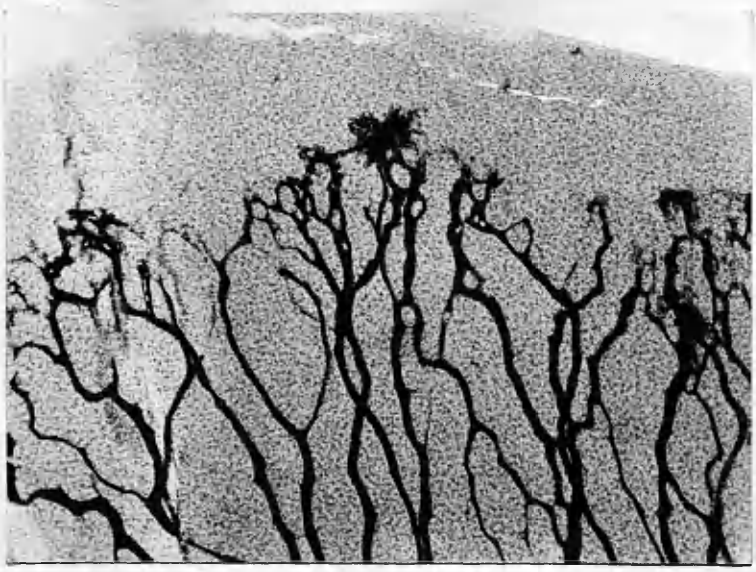
Injected retina of 18.5 cm human foetus showing capillary growth from the veins and the formation of a capillary-free space around the arteries. (X50)



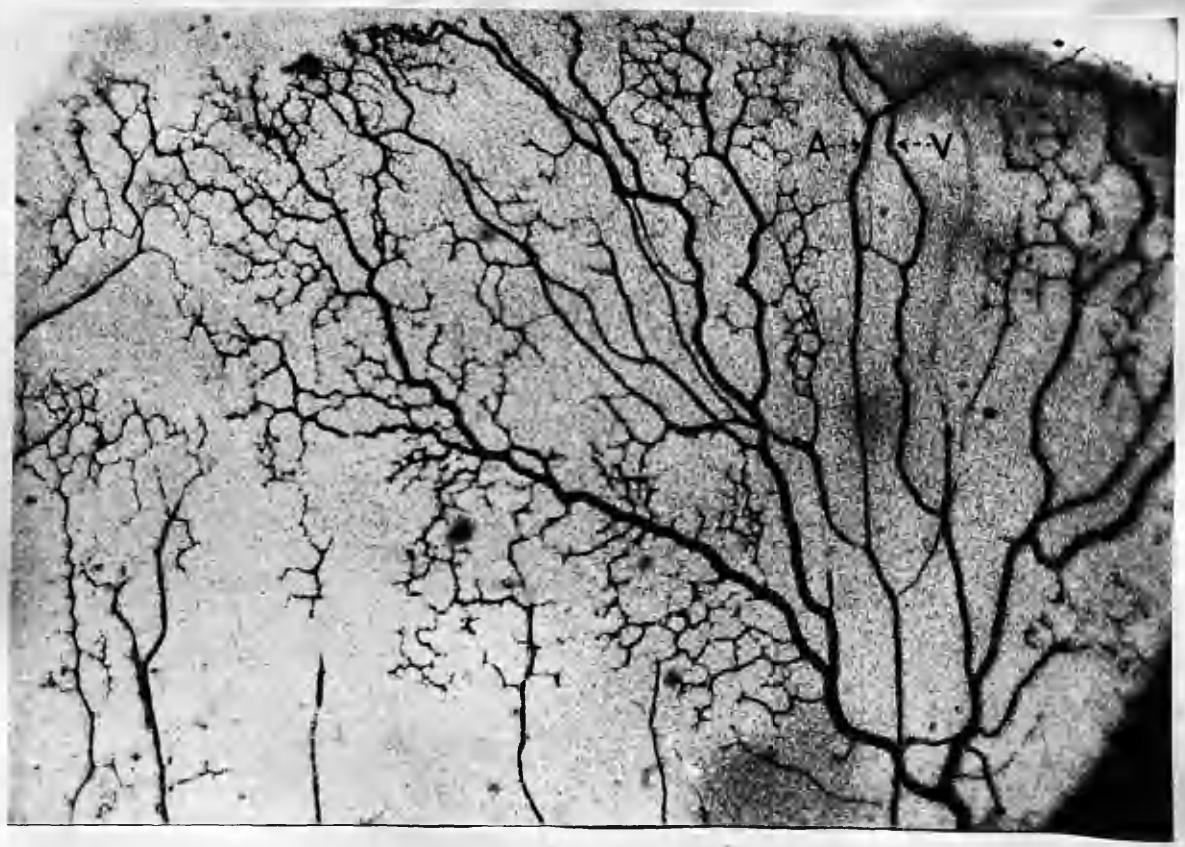
Injected retina of 18.5 cm. human foetus showing capillary growth from the veins and the formation of a capillary-free space around the arteries. The venules which cross the artery do not branch into capillaries until they have passed the artery by a certain distance. (x 62)



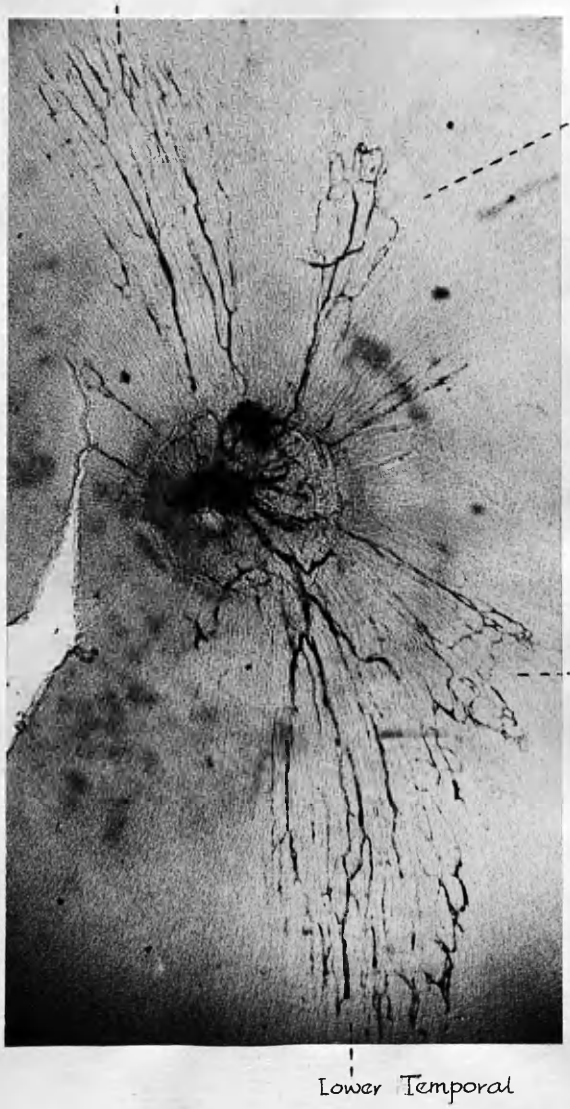
Injected retina of 23 cm human foetus showing early formation of the deep capillary net from the superficial net. The superficial net is in focus. (x 75)



Injected retina of 23 cm human foetus showing the formation of capillary loops in the periphery of the vascularised area. (×35)



Injected retina of human embryo showing the formation of peripheral loops. Arteriole A and venule B join at the periphery.



Injected retina of 110 mm. human foetus. The four vessel complexes can be distinguished, upper temporal, lower temporal, upper nasal, and lower nasal. These measure in extent 2.28 mm, 1.92 mm, 1.39 mm, and 1.39mm respectively. (X 25)

Fig 85a

GROWTH RATE OF THE UPPER TEMPORAL, LOWER TEMPORAL AND NASAL VESSELS IN THE RETINA OF THE HUMAN FOETUS (RIGHT EYES)

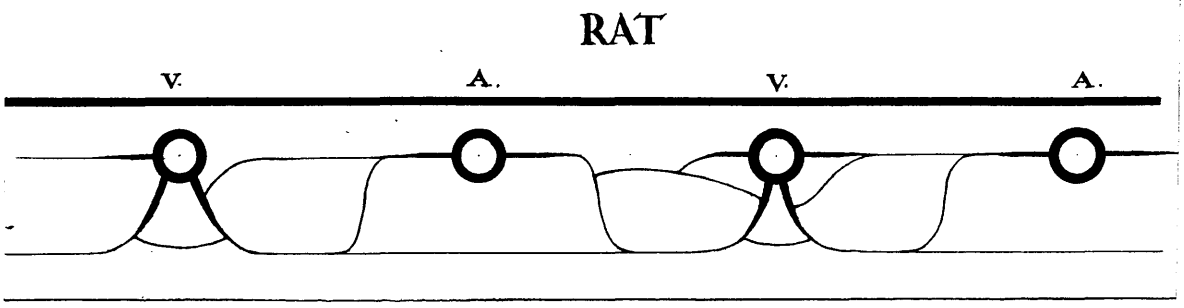


Diagram showing the capillary a rrangement in the retina of the rat.

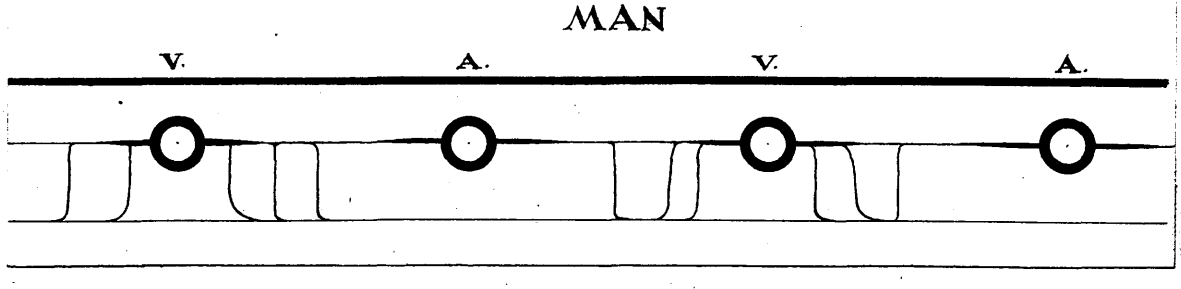
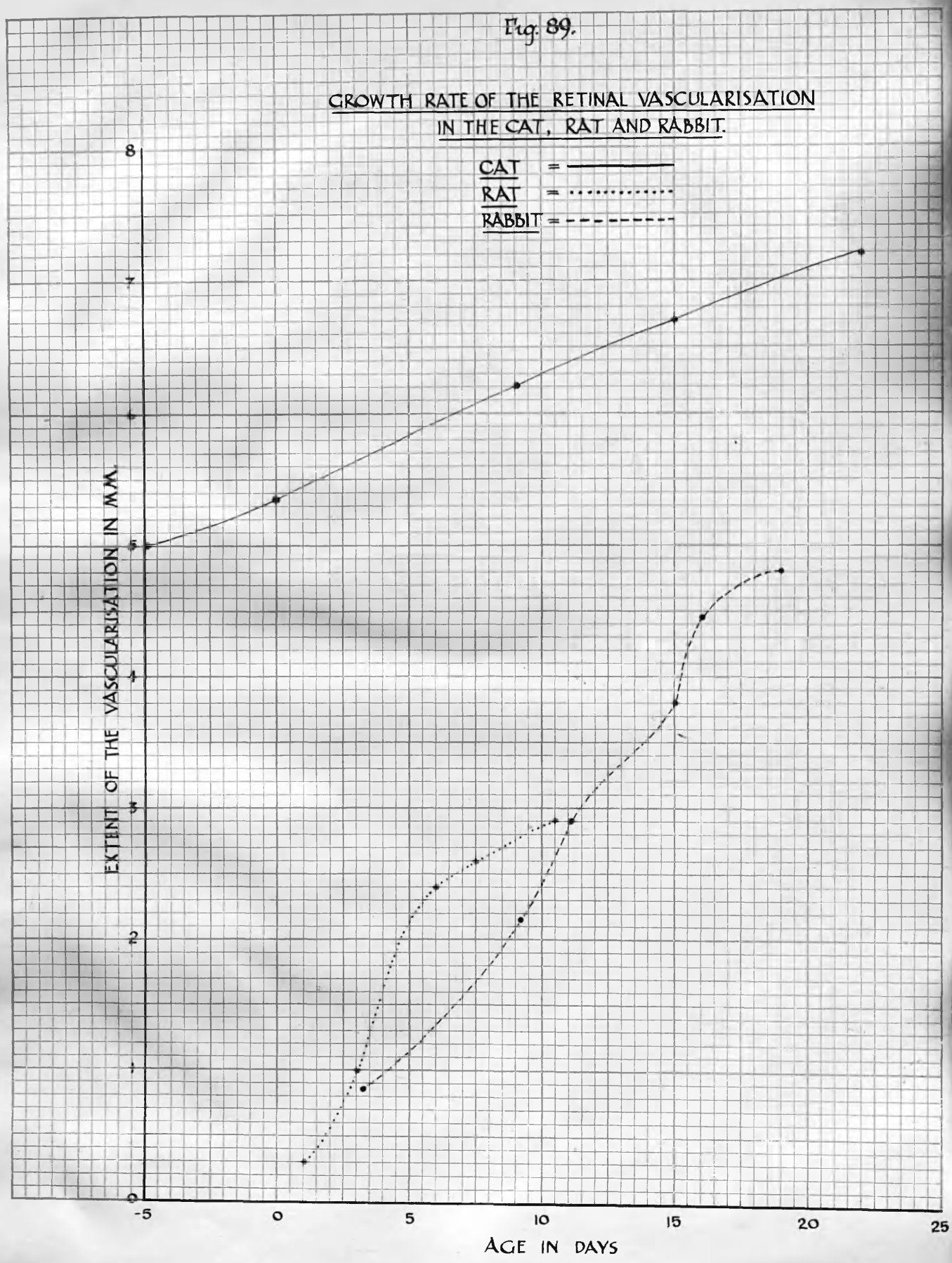
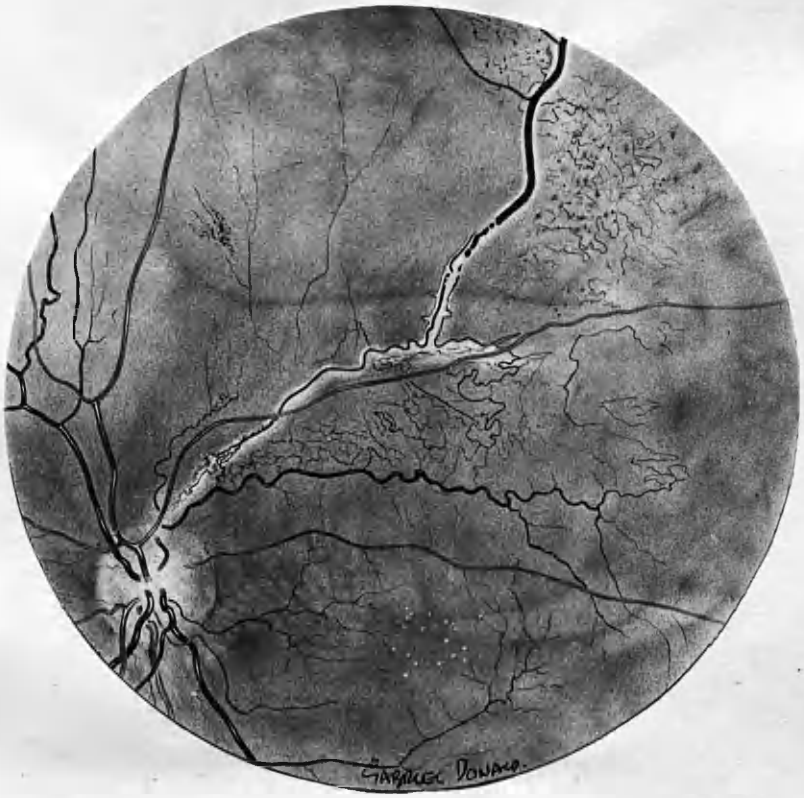


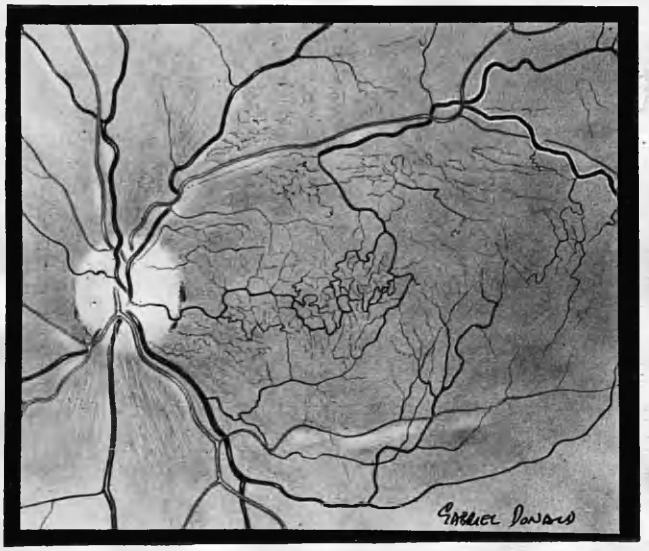
Diagram showing the capillary arrangement in the retina of man.

Injected retina of a young dog. The zone around the artery (A) is free from capillaries. (× 85)

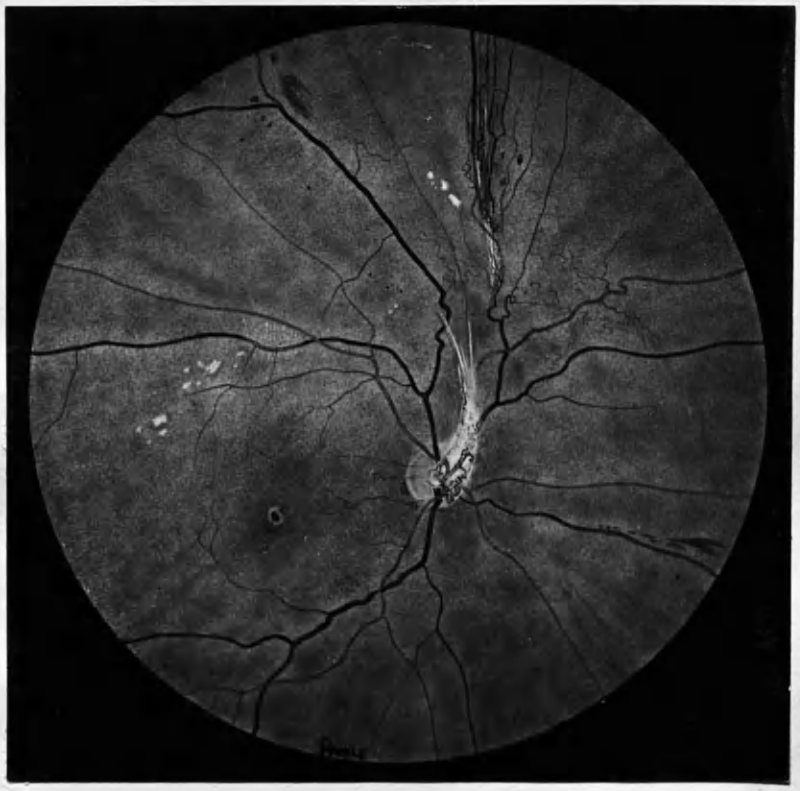
Fig. 89.


GROWTH RATE OF THE RETINAL VASCULARISATION IN THE CAT, RAT AND RABBIT.
CAT =
RAT =
RABBIT =
EXTENT OF THE VASCULARISATION IN MM.
0
1
2
3
4
5
6
7
8
-5
0
5
10
15
20
25
AGE IN DAYS





Fundi of cases of obstruction of a retinal vein showing the formation of intra-retinal vessels.



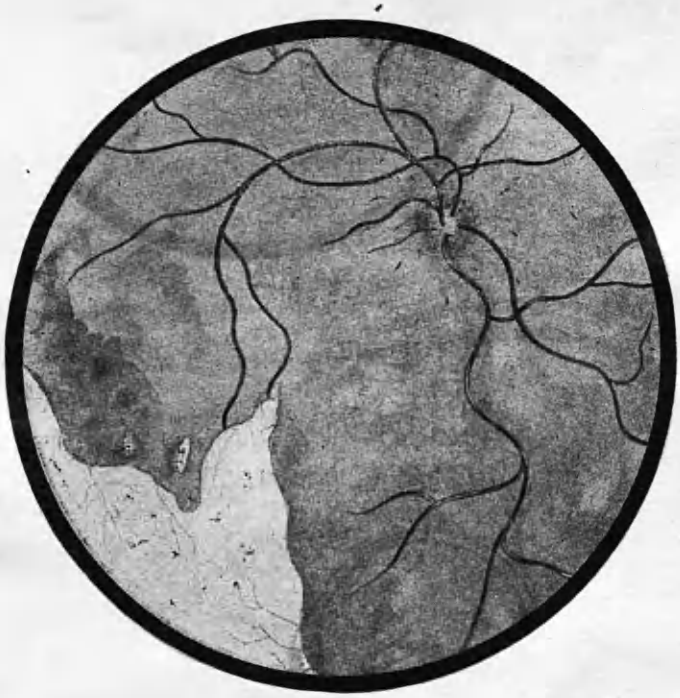
Fundus from a case of diabetes showing a pre-retinal plexus of veins and new vessels at the optic disc.

92

Section of the retina of a case of a diabetic retinopathy showing a plexus of new capillaries on the inner surface of the retina. These new vessels communicate with large intra-retinal veins.

Fundus of case of Eales' disease showing a frond of intra-vitreous new vessels growing from an area of retinitis proliferans.

94



Fundus of case of perforating injury of the globe showing a triangular mass of proliferative choroiditis. In this mass there can be seen fine vessels which have no relationship with the normal retinal vessels.

95

Section from a case of perforating injury of the globe similar to that illustrated in fig 94. The retinal gap is filled with proliferated tissue from the choroid. In it new vessels can be distinguished. The edges of the torn retina are turned towards the choroid.