THE DEVELOPMENT OF THE HUMAN IRIS*  

BY  

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ALTHOUGH the formation and growth of the iris has received a good deal of attention from embryologists and others, there are still some details of the subject which may be regarded as controversial. The following fairly complete series of stages of iris development in the human eye is described with the idea that such an account may be of value, even if only in confirmation of existing views on the subject. All the stages to be described were found in normal human embryos ranging in size from 4.5 mm. (3 weeks) to full term. It is not intended here to attempt to explain how congenital abnormalities of the iris might arise, though many of the stages are suggestive. This aspect of the subject has already been touched upon in a previous paper. The material utilized for the investigation falls into three groups according to the method of preparation. In the first group can be included all the embryos up to the fourth month. These were invariably embedded whole in paraffin and cut into serial sections of 10μ. In the second group are the foetuses of the fourth month and older which are too large to be sectioned whole, and in which the orbital contents have been removed, with or without previous injection of the carotid artery with Indian ink, and embedded and cut by themselves. The third group consists of specimens of the pupillary membrane in foetuses of five months and onwards. To obtain these the eye, after fixation in 10 per cent. formol saline and careful removal of the cornea with a keratome, was fixed by means of gelatine hardened in formalin, in a small glass cell having one plane side through which the pupillary membrane, iris and lens were examined with the Gullstrand slit-lamp and binocular microscope. In this way a much better idea of the gross arrangement of the vessels and also of the extreme delicacy of the membrane can be obtained than by means of paraffin sections.

The story of the development of the iris is essentially that of the forward growth of the margin of the optic cup and the differentiation of the anterior part of the mesoderm in which the whole cup is embedded. There is until after the third month no true iris, although of course the margin of the cup can be distinguished as soon as invagination of the primary optic vesicle has occurred. The complete iris (consisting of a mesodermal stroma backed by ectoderm derived from the optic cup) does not begin to appear till comparatively late, i.e., about the fourth month. A study of its

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development must, however, begin with a stage considerably younger than this, since certain of the mesodermal constituents of the definitive iris appear very early indeed, long before the margin of the optic cup shows any sign of forming the *pars iridica retinae*. The first portion of the iris to become recognizable is the mesodermal stroma with its blood-vessels and of these the so-called "annular vessel," which occupies the position of the future *circulus arteriosus iridis major* is the first to appear. The beginnings of this blood channel can be recognized as early as the 5 mm. stage (4th week), and it has formed an almost complete circle in the 10 mm. stage (5th week). After the appearance of the anterior chamber at 18 mm. (7th week) the rest of the mesodermal stroma and pupillary membrane can be recognized and later the ectodermal layers grow forward deep to this stroma. The muscles of the iris appear last, between the fourth and fifth months, and are developed from the ectoderm. We can, therefore, divide the development of the iris into stages, thus:

1. The stage before the appearance of any iris (mesodermal or ectodermal) but during which the annular vessel becomes distinguishable (4th to 7th week).
2. The stage of differentiation of the mesodermal portion of the iris with the formation of a definite anterior chamber (7th to 11th week).
3. The stage of commencing growth of the ectodermal portion of the iris (11th to 12th week).
4. The stage of differentiation of the ectodermal iris with the formation of the pupillary musculature (3rd to 8th month).

These stages will now be illustrated by a description of typical specimens, some of which are from embryos in the collections of Professor Frazer, of St. Mary's Hospital Medical School, and of Dr. Gladstone, of King's College, who have kindly allowed me to work on them.

The first stage is illustrated in Figs. 1 and 2. Fig. 1 represents a reconstruction model of the optic cup of a fourth-week human embryo. Invagination of the primary optic vesicle has commenced and the lens thickening (which is not shown in the model) is in contact with the invaginated portion of the cup, except below, in the region of the choroidal fissure, where mesoderm is beginning to grow in and separate the two. Otherwise the cup is surrounded by undifferentiated mesoderm. In this, below the cup and along the inferior surface of the optic stalk (the region of the choroidal fissure) primitive blood-vessels, consisting of endothelium-lined spaces containing nucleated red blood cells, can be seen forming. These form channels which anastomose freely, but which are aggregated in the main in three areas:
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1. Below, where there is a large vessel (V) a branch of which (H) is becoming included within the lips of the closing choroidal fissure, i.e., the primitive hyaloid vessel, and

2 and 3 on either side of the fissure along the margins of the optic cup, which are being vascularized by upward growing branches from 1 (CI). These upward growing branches are the earliest recognizable annular vessel, not yet of course anything like a complete circle.

Fig. 2 shows a front view of a model of the eye of a 10 mm. (5th week) human embryo. The lens is not shown. It will be seen that invagination of the cup has progressed and that the choroidal fissure is closed except for a small portion at the pupillary margin. The blood-vessels seen in Fig. 1 have grown upwards on either side of the cup and have at this stage formed a vascular circle complete except for a small region (A) at the upper part of the cup, where the two channels have not yet met. This vascular circle can now be considered as a definite circulus vasculosus occupying the site of the future circulus arteriosus iridis major and its vascular connections can be clearly recognized. These are arranged in two sets: (1) a series of channels (CH) connecting the circle with the general choroidal network which now entirely surrounds the optic vesicle—these channels possibly representing the anastomosis in the adult between the circulus and the anterior
ciliary arteries, and even at this stage more marked at the inner and outer sides of the pupil than elsewhere, although as yet none of the blood channels are sufficiently differentiated to be recognizable as distinct arteries or veins—and (2) a small number (in this specimen three) of fine channels (IH) connecting the circle with branches of the hyaloid vessel around the equator of the lens. These vessels I have called “irido-hyaloid.” They are the vessels which later form the lateral or capsulo-pupillary portion of the *tunica vasculosa lentis*. They run in a very fine connective tissue meshwork which connects the mesoderm which has now grown in between the lens and the surface with that which has passed into the interior of the optic cup with the hyaloid artery. This mesoderm surrounding the lens can be distinguished before the 10 mm. stage, but it does not at first contain blood-vessels (except behind the lens). The irido-hyaloid vessels begin to appear about 10 mm. At this stage then we have an eye without any iris or anterior chamber, but with a definite annular vessel anastomosing with anterior choroidal vessels. This stage ends with the earliest appearance of the anterior chamber at 18 mm. (six weeks).

The irido-hyaloid vessels increase rapidly in size and number after the 10 mm. stage, so that at the 26 mm. stage (8th week) they form a continuous series curling round between the margin of the optic cup and the equator of the lens (the lateral portion of the *tunica vasculosa lentis*). At its first appearance, as can be seen in Fig. 2, the annular vessel lies along the extreme periphery of the optic cup and indeed often just within it. Since in the

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**FIG. 2.**

Model of optic cup of 5th week human embryo. A = portion of margin of optic cup not yet vascularized. CH = branches of the circulus arteriosus iridis major anastomosing with choroidal vessels. IH = irido-hyaloid vessels.
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definitive condition the *circulus arteriosus iridis major* lies at the base of the iris, it is obvious that at least up to the eighth week there is no true iris, the anterior margin of the optic cup only reaching just beyond the equator of the lens, namely, as far as the situation of the future ciliary region. The pupillary end of the choroidal fissure closes before the eighth week and the irido-hyaloid vessels, curling over the margin of the cup, persist well into the tenth week, so that development of the ectodermal layers of the iris (those from the margin of the optic cup) does not really commence until the third month. The mesodermal parts are by this time well differentiated, as can be seen by considering the figures illustrating the second stage of iris development (Figs. 3 and 4) which begins with the formation of the anterior chamber.

After the separation of the lens vesicle from the surface ectoderm the mesoderm surrounding the optic cup grows in between the two so that at 15 mm. there is a homogeneous mass of mesoderm between the lens and the surface epithelium. At 18 mm. (six weeks) a sort of vacuolation takes place in the centre of this mesoderm, leading to a splitting of it into two parts, an anterior and a posterior. The anterior remains in contact with the surface ectoderm and forms the *substantia propria* of the cornea, and the posterior remains in contact with the anterior surface of the lens.

**FIG. 3.**

and the anterior margin of the optic cup, being of course continuous with the mesoderm of the irido-hyaloid vessels passing into the interior of the cup between the two. The space between these two portions of mesoderm is the anterior chamber, and it soon becomes lined by endothelium, which extends over the posterior surface of the anterior layer and the anterior surface of the posterior layer, so that at first the anterior chamber is a completely closed space bounded in front by the cornea and behind by the mesoderm in front of the lens (i.e., the pupillary membrane and the mesodermal iris).

![Diagram of anterior part of eye of 10th-11th week human embryo. C = fold in ciliary region.](image)

**Fig. 4.**

Section of anterior part of eye of 10th-11th week human embryo. C = fold in ciliary region.

The 26 mm. (7th to 8th week) embryo shown in Fig. 3 shows this condition. A represents the mesoderm of the cornea and B the anterior chamber. The posterior boundary of this must be described in more detail. The margin of the optic cup reaches to just in front of the equator of the lens. The mesoderm at the anterior margin of the cup can be arbitrarily divided into two portions, firstly, a portion carrying the irido-hyaloid vessels (H) and curving round the margin of the cup to blend with the mesoderm surrounding the hyaloid artery, and secondly, the portion passing across in front of the lens, forming the posterior boundary of the anterior chamber. This portion is much thinner in the middle (P) where it is in contact with the lens, than at the sides (I). The middle portion is that part of the anterior vascular capsule of the lens which forms the pupillary membrane and subsequently disappears; the lateral portions (I) thicken and persist as the meso-
dermal stroma of the iris. The backward prolongation of this
carrying the irido-hyaloid vessels (H) disappears in order to allow
of the forward growth of the ectoderm of the optic cup deep to (I) to
form the pars iridica retinac. In passing one may note that the
tunica vasculosa lentis is complete at this stage. It is formed
posteriorly by the branches of the hyaloid artery, laterally by the
anastomosis of these with the irido-hyaloid branches of the annular
vessel, and anteriorly by the mesoderm which will later form the
iris stroma and pupillary membrane. There is no tunica vasculosa
lentis apart from these structures, nor is there any iris anlage
separate from the antero-lateral portion of the tunica vasculosa
lentis (I).

At the eighth week, then, the mesodermal iris is well formed. Its
three portions (P, I, and H) can be seen in Fig. 3. Of these H
begins to retrogress before the eleventh week (48 mm.), and has
disappeared completely by the twelfth week (56 mm.); P remains
longer and disappears during the eighth month, while I persists.

The third stage is shown in Fig. 4. This shows a section
through the anterior part of the eye of a 48 mm. embryo. Just
before the complete disappearance of the irido-hyaloid vessels
increased growth of the margin of the cup occurs, and the first effect
of this is a slight puckering of the margin in the region of the
future ciliary processes (C). The irido-hyaloid vessels then rapidly
disappear and the margin of the cup grows forward deep to the
lateral portion of the mesodermal iris, so that in successive stages
after this the circulus arteriosus iridis major is seen to lie further
and further behind the margin of the cup as the ectodermal iris
forms in front of it. This is seen in the diagram, Fig. 5, which is
self-explanatory. Note the relative positions at the different stages
of the major circle and the edge of the optic cup. The stage of
retrogression of the irido-hyaloid vessels and growth of the
primitive ectodermal iris is almost complete by the fourth month.
Fig. 6 shows a three months’ eye. It will be seen that both the
mesodermal and ectodermal irides are present, the latter not
having reached its full size.

The differentiation of the circulus arteriosus iridis major as a
definitely recognizable artery appears to occur between the fourth
and fifth months. A certain amount of controversy has taken place
as to whether there occurs a direct transformation of the annular
vessel into an artery (Fuchs, Speciale-Cirincione and Seefelder)
or whether the definitive circulus arteriosus iridis major is a new
vessel arising as a secondary anastomosis between the terminal
branches of the long ciliaries and occupying the position of the
disappearing annular vessel (Versari). In either case it can be
granted that the site of the annular vessel corresponds with the
site of the definitive circulus arteriosus iridis major.
The fourth and last stage concerns the completion of the ectodermal iris with the formation of the sphincter and dilatator iridis from it, and the final differentiation and elaboration of the mesodermal iris into the various layers of vessels of the iris stroma.

To deal with the ectodermal iris first—this grows forwards deep to and in contact with the mesodermal iris until the fifth month. After that time the growing tip is not in contact with the mesoderm but a little behind it (see Figs. 9 and 10) so that although a little mesoderm is carried with it, the original mesodermal iris (now the fast vanishing pupillary membrane) appears to come off from the anterior surface of the iris and not from its free border. (This condition is of course very well seen in clinical cases of persistent pupillary membrane.) There is no sign of any splitting of the iris stroma into a superficial and a deep layer peripheral to the position of the lesser circle at this stage. Any such appearance seen in the adult appears to depend on the extent to which atrophy of the vessels concerned in nourishing the pupillary membrane spreads towards the periphery.
At the end of the third month differentiation of the ectodermal iris commences and this differentiation of the anterior and posterior layers continues pari passu with the forward growth of the whole ectodermal iris. The changes which occur in the posterior layer are the simplest and will be dealt with first. At the third month, as will be seen from Fig. 6, the posterior or internal layer of the cup at the growing edge is composed of columnar unpigmented cells arranged in a single row. At the extreme edge, just where the internal layer turns outwards to become the external layer the cells become cubical and a few granules of pigment appear at the edge. The marginal sinus, the space between the two layers of the optic cup, can be seen at the edge of the cup. This definite circular channel does not appear in the younger eyes, the two layers of the cup being everywhere separated by a space, which in some preparations appears wide and in others narrow. This space in Fig. 3 is seen all round the cup. In Fig. 4 it is wider and beginning to narrow towards the edge, while the first suggestion of a marginal sinus is seen in Fig. 6; in spite of the fact that in this specimen the inner layer was in places torn away from the outer, a definite marginal sinus is seen. It is at first very small, but increases in size as the iris grows, so that at five months—the period of most active growth and differentiation of the edge of the
**Fig. 7.**

Low power view of the iris of a 5 months' human foetus. MS = marginal sinus. M = developing iris musculature. S = pigment spur. CAIM = circulus arteriosus iridis major.

**Fig. 8.**

High power view of the iris of a 5 months' human foetus. Lettering as in preceding figure.
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cup—it is very large (Figs. 7 and 8). After this it gets smaller and has disappeared by the seventh month when growth is slowing down again. The persistence of this portion of the original cavity of the primary optic vesicle for so long appears to be correlated with the late differentiation of the iris and is probably the expression of the rapid change of shape, size, and position of the growing edge whereby cohesion between the layers is rendered more difficult than in the more firmly established retinal area. The pigment appears gradually to spread from the outer layer round the edge of the cup, so that by the fifth month the cells of the deep (inner) layer of the iris are pigmented more than halfway to the base of the ciliary processes. By the seventh month the pigmentation involves both layers of the whole of the iris. This arrangement of the pigment together with the wide open marginal sinus and the differentiation of the outer layer about to be described possibly suggests that growth is taking place almost entirely in the outer layer and that, as the iris comes into being, the redundant outer layer is turned over the edge and becomes the pigmented inner layer, rather than that the cells which were originally of the inner layer should develop pigment in themselves de novo.

The outer layer of the iris at the third month is composed of a single layer of epithelial cells containing pigment. In the earlier stages these cells are cubical and contain pigment granules which are, even in Fig. 3, seen to be more numerous in the deeper portions of the cells. At the third month it can be seen that the cells of the outer layer are rather more columnar near the margin of the cup than elsewhere and that the aggregation of pigment in the deeper parts is still more marked. Between the third and the fifth months a remarkable change occurs in the cells of the anterior layer at the growing tip. Their outer unpigmented portions elongate, divide and give rise to a small mass of non-pigmented sparsely nucleated protoplasmic elements (M in Figs. 7 and 8), which lie in front of the pigment layer and later form the unstriped muscle fibres of the sphincter pupillae. (With regard to the dilator fibres these probably come from the same mass. They are very difficult to recognize, but there is some evidence to show that they are part of the original muscle mass (M in Fig. 8), and that they grow peripherally outwards as a thin layer close to the anterior layer of the epithelium.)

The extent of the sphincter muscle mass peripherally is always shown by a spur-like projection of the pigment layer (S in Figs. 7, 8, 9, and 10). The area from which growth of the fibres is actually taking place is unpigmented and forms the anterior wall of the marginal sinus. At first (Fig. 8) the muscle rudiment is in close contact with the pigment layer and little projections and scattered
grains of pigment can be seen extending into it. It is solid and contains no blood-vessels or other mesodermal derivatives. Later it becomes broken up into definite bundles of unstriped muscle by the penetration of a mesodermal stroma into it and vascularized by

**Fig. 9.**
Low power view of iris region in a 7 months' human foetus. M = sphincter pupillae. S = pigment spur.

**Fig. 10.**
High power view of a portion of the iris of a 7 months' human foetus. V = large vessel in pupillary membrane. VV = branches of the vessels of the iris stroma vascularizing the pupillary muscles. M = the pupillary musculature. S = pigment spur.
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capillaries which grow out from the vessels in the mesodermal iris. Fig. 10 shows a portion of a seven months iris in which the blood-vessels have been injected with Indian ink. The vessels growing into the muscle mass are well shown (VV). The large vessel (V) is running in the pupillary membrane, which now appears to come off from the front surface of the iris as already described. To pass from this stage to the definitive condition only requires the disappearance of the pupillary membrane. The changes which occur in the mesodermal iris do not include the formation of a new layer, but consist in a richer vascularization of the thick peripheral portion, the central portion or pupillary membrane at the same time undergoing atrophy.

At five and a half months the anterior segment of the eye presents the appearance shown in Fig. 11. It will be seen that the relatively narrow ectodermal iris (in which can be distinguished a central paler, sphincteric region and a darker peripheral portion) is overlaid by a very vascular mesodermal membrane which extends over and almost occludes the pupil. At this stage the blood column can be easily seen in the vessels. In the drawing, only three of the four segments of the membrane are represented as the fourth was torn in making the preparation. The arrangement in broad-based loops which approach the anterior pole of the lens and turn back again is well known. The vessels at this stage are all almost on the same
level and there are not many anastomoses or deep branches. From this stage onwards there occur increasing anastomosis and branching of the peripheral portions of the vessels together with fresh ingrowth of vessels from the ciliary region, so that one can recognize in injected sections (of the seventh month and after) the condition seen in Fig. 10, already described by Versari, and classified into the following groups of vessels (see also Fig. 12 from Versari).

1. Superficial large vessels of pupillary membrane.
2. Vessels of middle stratum of iris.

3. Inter-sphincteric plexus of radial and antero-posterior vessels in substance of sphincter.
4. Sub-sphincteric plexus between sphincter and epithelium.

It will be noticed in Fig. 11 that the vessels of the pupillary membrane are large and extend in several tiers of arcades (usually three) towards the centre of the pupil which they do not quite reach. The lesser circle of the iris is not yet obvious, but its situation corresponds with the third or most peripheral of the anastomotic arcades, which at present, however, lies just beyond (central to) the edge of the ectodermal iris. The two central sets of arcades represent the parts of the vessels which will atrophy, the third tier will remain to form the lesser circle and the vessels peripheral to this as the large superficial vessels of the iris stroma. That this is happening is apparent in the front view of the iris of the seven months' foetus shown in Fig. 13. It will be seen that
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FIG. 13.
Surface view of iris of 7 months' human foetus (examined with Gullstrand Slit-lamp).

FIG. 14.
Surface view of iris of 8½ months' human foetus (examined with Gullstrand Slit-lamp).
the vessels peripheral to the third arcade are increasing rapidly in number and maintaining their large size while those of the first and second arcades, which in Fig. 11 formed loops practically covering the anterior surface of the lens, are shrinking, receding from the centre of the pupil and rapidly atrophying, though at this stage they still contain blood. The ectodermal iris has grown forward deep to the pupillary membrane to just beyond the third anastomotic arcade, so that this is now clearly recognizable as the circulus iridis minor. It is thus clear, as has so often been pointed out by anatomists, that the lesser circle is not an arterial circle, but an arterio-venous anastomosis.

By eight and a half months (Fig. 14) most of the central loops of the pupillary membrane have atrophied and the lesser circle is established as the sole channel of return of the blood reaching the central portion of the iris by way of the superficial vessels of the stroma. In places the remnants of the first and second arcades still contain blood. The vessels of the iris stroma have increased still further in number and complexity. Since the persistence of the third arcade as the lesser circle provides a free channel for the circulation of the blood in the peripheral portion of the pupillary membrane this peripheral portion does not usually undergo any atrophy, but the vessels of it continue to form throughout life the large thick-walled superficial vessels of the iris. The exact amount of atrophy of this superficial layer varies very considerably in the individual. In Fig. 15 is shown a portion of the iris of a full term foetus with the superficial layer of the iris complete up to the lesser circle, from which come fine strands (without any circulating blood) representing a few persisting remains of the central
loops of the membrane in Fig. 11. In Fig. 16 a portion of the iris of a man of 65 years of age is seen, in which the condition is similar, only without any strands coming from the lesser circle. This is the usual condition in the adult. In some cases the atrophy of the superficial layer may spread in places peripheral to the lesser circle giving rise to an appearance of pits in the iris, the so-called "Fuchs' clefts." The development of pigment in the stroma of the iris occurs after birth and to a very variable extent. In Fig. 16 are seen three small patches of pigment anterior to the vessels. In deeply pigmented eyes an extensive deposit takes place in the superficial layers; so that the details of structure may be entirely hidden. It must be realized that the so-called "sculpturing" of the iris seen in life in blue and grey eyes is due to the visibility of the vessel walls and occasionally, under magnification, of the blood column itself, the intervening stroma being quite transparent (though not "optically empty" to the narrow beam of the slit-lamp). In brown eyes the stroma is no longer transparent and the vessels cannot be seen, except those which may be in relief on the surface. In light blue eyes with good illumination and magnification of twenty-four it is often possible actually to make out two or sometimes three layers of vessels which may cross at acute angles, the deeper ones running to the pupillary margin, the superficial ones anastomosing at the lesser circle.

Summary

1. The development of the iris can be divided into four stages:

   (1) Fourth to seventh week, before formation of anterior chamber or ectodermal iris, during which stage the annular vessel is formed at the site of the future circulus arteriosus iridis major.
(2) Seventh to eleventh week, when, with the appearance of the anterior chamber, the mesodermal iris is formed.

(3) Eleventh to twelfth week, in which the ectodermal iris first makes its appearance.

(4) Third to eighth month, during which the pupillary musculature is formed from the ectodermal iris, and the central part of the mesodermal iris (up to the lesser circle) atrophies, leaving the pupil clear.

2. The definitive iris shows—

1. A peripheral portion consisting of the entire thickness of the original mesodermal iris plus the ectodermal iris and bounded internally by the *circulus iridis minor*.

2. A central portion consisting of a thinner layer of mesoderm carried forward secondarily by growth of the ectodermal iris and from the front of which the original central part of the mesodermal iris (pupillary membrane) has disappeared.

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INSTANTANEOUS STEREO-PHOTOGRAPHY OF THE ANTERIOR SECTION OF THE EYE WITH CONSIDERABLE MAGNIFICATION

BY

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On account of the constant movement, particularly of the diseased eye, and of the minuteness of the morbid changes, their photographic reproduction is attended by considerable difficulties. The ideal camera for the purpose is a stereo-camera giving considerable magnification, capable of rapid and easy adjustment and of working with an exposure of, at the utmost, no more than 1/25th second. One of the best instruments available is the mirror reflex camera