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A CONTRIBUTION TO THE STUDY OF ANOPHTHALMIA WITH DESCRIPTION OF A CASE*

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A STUDY of the literature reveals that not many examples of anophthalmia have been subjected to microscopical examination, and that only a few of these are of recent date. The investigation of a particular case—itsself of some special interest—suggests that the nature of anophthalmia and the interpretation of previous observations are worthy of further discussion in the light of modern views on histogenesis. In this paper, therefore, I intend to discuss some general problems which have not, perhaps, received sufficient attention in the past, reserving an account of changes in the visual pathways and centres for another publication.

The material on which this paper is based was obtained by Dr. R. F. Ogilvie, of the Pathology Department, University of Edinburgh, and given by him to Professor Brash, who placed it at my disposal; I am very much indebted to them both for the opportunity of research thus afforded to me.

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Material

A full-term male child was born September 7, 1940, with a left-sided hare-lip and apparent lack of the left eye. There was difficulty in sucking and swallowing, and the child was admitted to hospital when ten weeks old; but its condition rapidly worsened, and it died one week later, November 21, 1940. The body was emaciated, and the autopsy disclosed miliary tuberculosis of nearly all the organs.

Figs. 1 and 2 show the abnormalities present in the facial region. The left side of the mouth is enlarged and the hare-lip is evident as a small V-shaped cleft pointing to the left orbit and connected to it by a slight groove in the skin. Another groove extends from the right angle of the mouth to the right ear; the right two-thirds of the upper jaw, *i.e.*, the part to the right of the hare-lip, projects beyond the mandible, and the nose slants downwards to the right. The right orbit and eyeball appear normal, but there is no sign of the left eyeball. No malformations were found in any other region of the body.

The complete facial region, including the intact orbits, was available for investigation, and the brain, fixed in Kaiserling's fluid, was received complete.

Macroscopical observations.—The left palpebral fissure is narrower and shorter by 6.5 mm. than the right, as the eyelids fuse together near the lateral angle (Fig. 1). The medial angle is divided by a ridge of skin that begins in the shallow groove connecting the orbit with the hare-lip, and runs upwards and laterally into the conjunctival cavity. It ends by joining an irregular sub-conjunctival elevation which divides the cavity into upper and lower slightly deeper portions. At the lateral end of the ridge a black spot is visible through the conjunctival covering.

The general arrangement of the contents of both orbits was examined by dissection. The right orbit was entirely normal, and in the left the extrinsic muscles of the eyeball, the III, IV, V(1) and VI nerves, the ciliary ganglion, the lacrimal gland and the branches of the ophthalmic artery were found in approximately normal positions. But the left ophthalmic artery is about one-third narrower than the right, and the left optic nerve is completely absent. No trace even of a fibrous strand, such as has been described running to the optic foramen or beyond it, was found. The foramen itself, distinctly smaller than on the right side, was just wide enough to transmit the ophthalmic artery—the only structure that passed through it. The left orbit as a whole is distinctly smaller than the right; the difference in capacity, obtained after removal of contents by making casts and measuring

their displacements, is 3 c.cm. The left naso-lacrimal canal was closed by a thin membrane at its nasal end.

The right eyeball with its optic nerve and the contents of the front part of the left orbit (including the ridge which has been described, the conjunctival covering, lacrimal canaliculi, etc.) were embedded in celloidin, cut horizontally (40μ) and stained by Van Gieson's and Masson's methods; the complete serial sections of the left orbital contents were stained alternately by these methods.

Microscopical observations.—The right eyeball, in particular the retina proper and the pigmented layer, is structurally normal, and some of the contents of the left orbit are normal in appearance. The left lacrimal gland is well-developed with a palpebral process and numerous small accessory glands, mainly in the fornices and round the corneal border. The lacrimal puncta and canaliculi are present in both eyelids, but the inferior canaliculus bifurcates to form two parallel channels. These open, with the superior canaliculus, into a sac-like enlargement which, like the canaliculi, is lined with stratified epithelium. It has a narrow, blind upper end, and its lower part opens into the lacrimal sac, more spacious than the right, and made up of several pouch-like dilatations, incompletely separated by very thin walls, the whole lined with columnar epithelium.

The bottom of the conjunctival cavity is composed of dense fibrous tissue with many interlacing collagenous and elastic fibres, and is covered with stratified cuboidal epithelium with goblet cells. Into this fibrous tissue the orbital muscles are inserted in more or less normal relative positions. The elevation at the bottom of the conjunctival cavity appears in the horizontal sections as a projection composed of the same dense connective tissue (Fig. 3), with a short, narrow extension backwards into the orbit. The end of this extension receives the insertion of the inferior rectus muscle, and a small piece of cartilage lies medial to it. Over the elevation the stratified epithelium has fewer cell-layers than elsewhere and the most superficial consists of squamous cells.

The ridge that runs from the medial angle of the eye displays a skin-like structure with hair-follicles and sebaceous glands (Figs. 3 and 4); but the contents of the sub-conjunctival projection, with which the ridge fuses, are at first sight puzzling. Centrally there is an agglomerate mass—about 2 mm. in diameter—of plain muscle, nerve-fibres, capillary vessels, melanin clusters and structures like rods or ducts impregnated with melanin pigment. Around this mass numerous melanophores and scattered specks of melanin lie in the fibrous tissue (Fig. 3). Careful examination of the lower sections shows that a narrow prolongation of the mass of melanin pigment becomes superficial at the place where

the skin ridge joins the subconjunctival elevation. It seems to end in a small cleft-like space, lined also with pigment and filled with homogeneous coagulum (Fig. 4). This corresponds to the black spot already noted. No vestiges of retinal structure, of optic nerve, of lens or of hyaloid artery could be found in the left orbit.

Discussion

Our analysis of the contents of the left orbit shows that the mesodermal structures, situated external to the eyeball, are well developed, but that the eyeball itself is represented only by its anterior part, recognisable as vestiges of cornea and sclera, of muscle and vessels. Of the parts to which the surface ectoderm gives rise we find vestiges of everything but the lens. In the lacrimal apparatus, as already stated, only slight maldevelopments are evident, and the skin-like ridge may be regarded as nothing more than a malformed, enlarged lacrimal caruncle which covers the semilunar fold. The change in the epithelial covering, with the lack of goblet cells where the ridge fuses with the subconjunctival elevation, indicates that this is the region of the corneo-scleral junction.

Such a congenital ridge on the surface of the eyeball was observed by Fisher (1904). He considered it to be an embryonic skin-fold of the eyeball which, on account of its superficial position, had not been converted into conjunctiva. Also Ida Mann (1937), discussing palpebral coloboma, says: "Often bands or bridges of skin and conjunctiva arise from the region of the gaps and are joined to the eye (cornea or conjunctiva). . . . Sometimes, instead of a gap, the inner or the outer canthus may be absent, its place being taken by a smooth crescentic edge and a pterygium-like fold of thickened conjunctiva which stretches from this to the limbus" (p. 399); and further, "Sometimes a defective inner or outer canthus is occupied by a small dermoid growth which may have prevented the canthus from forming" (p. 402).

In our case this ridge is of special interest because, first, it is joined to the part of the conjunctival cavity which structurally appears to be a rudimentary corneo-scleral junction, and, secondly, it extends to the region of the agglomerate mass of melanin, capillary vessels, plain muscle and nerve-fibres which doubtless are the remnants of the ciliary body. But the appearance of the melanin pigment in clusters and rod-like or duct-like form makes it difficult to determine its origin (Fig. 5). The method of Alfieri—blanching the pigment and then staining with haematoxylin and erythrosin—shows, however, that the single "rods," or double "rods" that look like "ducts," are actually one or two layers of cuboidal epithelial cells with distinct nuclei (Fig. 6). This arrangement of cells is characteristic of the retinal pigment layer,

EXPLANATION OF PLATE

- FIG. 1.—Frontal view showing malformations of the face described in the text.
 FIG. 2.—Profile showing more distinctly the position of the ridge in the medial canthus of the left eye.
 FIG. 3.—Horizontal section through the subconjunctival (sclero-corneal) projection and the ridge showing the agglomerate mass of melanin pigment and other structures described in the text. $\times 12$.
 FIG. 4.—Horizontal section below the preceding. The pigment mass reaches the subconjunctival cleft, and the vestiges of ciliary body and pigment clusters are seen in the centre of the section. $\times 12$.
 FIG. 5.—Section showing the duct-like streaks of melanin pigment. $\times 82$.
 FIG. 6.—The next section after blanching by Alfieri's method and subsequent staining by haematoxylin and erythrosin. The epithelial arrangement of cells is clearly visible. $\times 82$.
 FIGS. 3, 4 and 5 are from sections stained by Masson's method (haemalum, eosin, saffron).

and we infer that the cells are melanoblasts derived from the pigment epithelium of the optic cup. In addition there are melanophores of mesodermal origin and clumps of free pigment in the tissue.

We have seen that this whole enigmatic mass extends to a space under the conjunctival covering by a narrow process that passes through the connective tissue at the corneo-scleral junction. It seems that there must have been a gap, as in the rare congenital coloboma sclerae ad limbum, with the formation of a subconjunctival cyst which is now seen as a little cleft filled with fluid.

Colobomata and cysts in this situation are very rare. One was cited by Fuchs (1924), who referred to a note of Harrington: "Coloboma of the sclera appearing as a fissure at the sclero-corneal junction with a tumour-like protrusion of the choroid has been described. The tumour was reduced and a gap covered with conjunctiva" (p. 618). In our case the relation of one end of the skin-ridge to a malformed and enlarged lacrimal caruncle and the lower eyelid, and of the other end to the sclero-corneal junction and the subconjunctival cyst suggests the possibility that we may be dealing with a kind of dermoid that divides the medial canthus in two.

Of cases in which, with or without a cyst, aggregations of pigmented tissue have been observed microscopically I can find only 14 in the relevant literature: 10 human—Haab (1881), Zimmermann (1893), van Duyse (1899), Bietti (1901), Hanke (1904), Cecchetto (1920), Triepel (1921), Gallemearts (1924), Recordon and Griffiths (1938), Whitnall and Norman (1940); and 4 in animals—de Bary (1887) and Albrecht (1895) in the calf, Collins and Parsons (1903) in the chick, and the Chases (1941) in mice. Some similar cases are cited by other authors also, but from clinical examination only. Of the authors mentioned, Bietti, Whitnall and Norman, Triepel and the Chases consider the pigment to be neuro-epithelial in origin; Gallemearts describes only the form of the cells as "polyedrique"; van Duyse, Collins and Parsons, Hanke, and Recordon and Griffiths, on the contrary, believe that the pigment is mesodermal. The others do not touch the problem of the origin of the pigment. Hanke alone blanched his sections, and his opinion was that "die nach Fick depigmentierten Präparate bewiesen dass die Zellen jedes epithelialen Charakters entbehren". Ida Mann (1937), describing primary anophthalmia, says, "The mass of fibrous tissue represents the sclerotic and having in its centre a cavity containing a small amount of pigmented vascular tissue representing the choroid with its mesodermal pigment" (p. 67); and further, discussing degenerative anophthalmia, she says with some reserve, "It is possible that those cases in which a fibrous nodule, containing pigmented tissue but no nervous

elements, is found with the extrinsic muscles attached to it, belong actually to this group, since it is difficult to be absolutely sure that the pigment in these cases is entirely mesodermal in origin " (p. 70).

In our case the location and the features of the pigmented masses give at first sight the impression that they are of mesodermal origin. But the appearance of the blanched sections confirms the view that they are neuroblastic derivatives. It may be that in all the cases so far described—in spite of some contrary opinions (van Duyse, Hanke)—the pigment cells, after good blanching and subsequent staining, could have been proved to be of neuroblastic origin. The melanophores only were evidently mesodermal.

The neuroblastic origin of melanoblasts finds confirmation in the researches of Wieting and Hamdi (1907) and of Masson (1926-1931). The former authors showed that melanin pigment develops either directly, or indirectly through nervous tissue, from the ectoderm. The investigations of Masson on melanin tumours proved the neurogenic character of their pigment cells. According to this author the melanin pigment in epithelium or in connective tissue is developed in close connection with the cells related to nerve-endings and then migrates into the epithelium or is dispersed by means of melanophores which function as phagocytes of the pigment.

It is well known that the conjunctiva, even in the white races, is capable of producing melanin pigment, particularly in the region of the corneo-scleral junction. According to Masson the nerve-endings in the conjunctiva participate in this process. It is possible, therefore, that in our case the optic cup did not develop at all, and that the melanin masses are of conjunctival nerve-ending origin. Or these masses might be a kind of melanin dermoid united to the remnants of the ciliary body by means of a malformed lacrimal caruncle. A third possibility is that the melanin masses developed in the nerve-endings of the ciliary body and afterwards collected on the walls of the colobomatous cleft and cyst. But the blanched sections which show the typical epithelial character of the cells, particularly in the deeper parts of the melanin aggregations, negate all these suggestions.

We can now distinctly characterise our case: The original abnormality must have occurred about the 5 mm. stage, *i.e.*, the stage at which the invagination of the primary optic vesicle should take place. But the only trace of the vesicle is the pigment epithelium, and there is no lens. The case might therefore be diagnosed as anophthalmia with vestiges of cyst (congenital cystic eye).

There are three main types of the malformations called anophthalmia or microphthalmia: (1) All parts of the eyeball are present, underdeveloped or malformed; (2) neither neuroblastic nor ectodermal structures (retina, pigment epithelium, lens) can be discovered, and only mesodermal parts of the eyeball, mostly malformed, are present; (3) neither retina proper nor lens nor vitreous body are to be found, but pigment epithelium is present and also the mesodermal parts, more or less developed. This third type suggests that the retina proper, vitreous body and lens are associated in some way in their development, but that the development of the pigmented layer is independent of the retina proper and related, in spite of its neurogenic origin, to the development of the mesodermal tissues that surround the optic vesicle. Consequently the following problems arise:—

1. Why in such cases does the pigment epithelium (*i.e.*, the outer layer of the optic cup, one part of the optic vesicle) remain, although sometimes malformed?

2. Why can no trace of the retina proper (*i.e.*, the inner layer of the cup, part of the same optic vesicle) be discovered in the vestiges of the eyeball?

The earlier writers on the subject do not touch on these problems, but make suggestions concerning only the cause of anophthalmia or microphthalmia as a whole. Among recent authors, Ida Mann (1937) defines degenerative or consecutive anophthalmia as including those cases in which "an optic outgrowth appears to have formed and subsequently to have degenerated" (p. 70). In the passage previously quoted she does not exclude the epithelial origin of pigment when it is found without nervous elements, but she does not try to explain how this may be possible. The Chases (1941) write, "A lens is absent and the optic cup may be absent or represented by a streak of pigment" (p. 286); and further, "If a lens does not form and the cup collapses but yet proceeds far enough to allow pigment to develop in the outer wall, a mass of pigment will usually result in the adult" (p. 287).

This interpretation might be of value if the normal development of the pigment actually depended on the cup itself, but that is not the case. This fact leads us to seek some other explanation in the normal development of the various parts of the eye, and particularly in the development of its blood-supply. We know that a local capillary network develops, about the 4-5 mm. stage, in the mesenchymal tissue that surrounds the optic vesicle and optic stalk, and that the arteries of the developing eye arise later from this local capillary network and not as new branches budding from a larger vessel. Thus two main vessels, each of which supplies one of two groups of the constituent parts of the eyeball, arise independently, but later join to form the common ophthalmic

artery. One of these is the hyaloid artery, the primordium of which sinks immediately into the fissure of the optic stalk and cup. The other vessel—the ophthalmic artery proper—ramifies on the mesodermal surface of the optic vesicle, or later the optic cup, and afterwards reaches the brim of the cup, where its capillary branches form the annular vessel that anastomoses with the distal ramifications of the hyaloid artery. The latter supplies only retina, vitreous body and lens, while the former supplies all the mesodermal covering and also the pigment epithelium. The further development of the pigment epithelium takes place, therefore, in the same conditions, as regards blood-supply, as the surrounding mesodermal tissue and in very intimate relation with it; at their contiguous surfaces the first choroidal capillaries develop, to form the chorio-capillaris layer; and it is in relation to the capillary blood-supply that the neuroblastic epithelial cells show the first appearance of melanin pigment.

This suggestion is confirmed by several writers on the development of the circulation in the eye. For example, Ida Mann (1928), in her monograph, "The Development of the Human Eye", which provides a minute study, with excellent drawings and reconstructions of the various stages of the circulation, does indeed take into account the intimate relation between pigment epithelium and the chorio-capillaris layer, saying: "The choroidal net seems to develop wherever mesoderm is in contact with pigmented epithelium. It appears *pari passu* with the pigment and appears to be in some way related to this, in that if for any reason pigment is absent over an area of the surface of the optic cup, the choroid is absent also. . . . Whether the presence of pigment is determined by the development of the choroid or *vice versa* is not definitely proven, as they seem to appear almost simultaneously" (p. 39).

Pedrals (1943) illustrates his recent paper on the development of the anterior chamber of the eye with photo-micrographs and drawings of sections of rabbit and mouse embryos which show exactly the independence of the two sources of blood-supply. This author is of opinion that the primary annular vessel is arterial and arises directly from the ophthalmic artery and not from the hyaloid artery. ("El primer vaso anular es de naturaleza arterial, por su derivación directa de la arteria oftálmica y no de la arteria hialoidea", p. 82). The fact that the pigmented, retinal layer of the iris gives rise to the sphincter pupillae muscle, the further development of which depends on blood-supply from branches of the ophthalmic artery, provides another example of the intimate relation between the pigment epithelium and that artery.

Although they do not touch our problem directly, some interesting observations on the lamina chorio-capillaris by Reichling and

Klemens (1937, 1940) may be cited. In the eyes of almost all people over 55 years they have found a new vascular connective tissue layer between the pigment epithelium and the basal lamina of the choroid; and they show that this new layer is developed from vessels of the chorio-capillaris that pierce the basal lamina.

The development of a normal circulation is most probably governed partly by inherited factors and partly by hydrodynamic conditions in the tissues. Minor deflections from the normal circulatory pattern do not necessarily disturb the normal development of an organ or part of the body, but greater deflections may do so. We do not know the reason for this; but there may possibly be a genetic inhibitory influence on the dynamics of cells in the mesodermal haematogenic tissue so that they are unable to create favourable conditions for the further development of "blood-islands", of capillary networks, or of vessels of sufficient calibre and length. Such disturbances must be detrimental to the progressive growth of established primordia of structures, through inadequate blood-supply. With particular reference to the problem under discussion, the noxious genetic factor would thus act not directly on the neuroblastic and ectodermal structures (future retina and lens), but indirectly through its effect on the mesoderm which normally gives rise to the hyaloid artery.

The features and course of the central artery of the retina in the adult support the view that the hyaloid artery develops independently. The central artery of the retina is essentially a branch of a cerebral artery, whereas the ophthalmic artery may have some other origin, *e.g.*, as a branch of the middle meningeal artery*.

The hyaloid artery supplies not only the inner layer of the optic cup, but also the optic stalk, which must be affected, too, by lack of this artery or its inadequate development. The stalk becomes the optic nerve as the various layers of neurones, including the ganglion cells, develop in the retina, and as the axones of these cells leave the retina to become fibres of the optic nerve, of part of the chiasma and of the optic tracts. It is evident that in anophthalmia the whole peripheral visual neurone, at least as far as the lateral geniculate body, must be undeveloped. Sometimes a strand of connective tissue may be seen as a vestige of an atrophied optic stalk.

The independence of the blood-supply of the two territories in

* I have found that there is a comparable arrangement in the dog and the pig: the so-called external ophthalmic artery takes origin from the internal maxillary artery and gives off the same extra-ocular branches as the ophthalmic artery in man. It anastomoses with the so-called internal ophthalmic artery, which arises from the internal carotid by a single small branch. See also Ellenberger's *Handbuch der Anatomie der Haustiere* (1926), and Bradley's *Topographical Anatomy of the Dog* (1943). The latter author says that the central artery of the retina arises from the anastomosis between the external ophthalmic artery and a twig of the internal carotid, the so-called internal ophthalmic artery.

the developing eye may serve to explain why teratological lesions may occur in one or the other separately; and a common blood-supply may explain likewise why retina and lens, although different in origin, should be simultaneously absent; while, in the same cases, the pigment epithelium and mesodermal structures, also different in origin, may both be present. In such cases the absence of the retina has probably led many authors to take for granted the mesodermal origin of the melanin pigment they have found, without an exact analysis of its epithelial character or even reference to its situation. But it should be remembered that most of these investigations were made without our present knowledge of melanin pigment.

There has been a failure, too, to distinguish between anophthalmia and microphthalmia. Cases with similar microscopical findings or examined only clinically have been published indifferently as anophthalmia or microphthalmia. In recent years two classifications of these lesions have appeared. Ida Mann (1937) distinguishes in the first place between primary and secondary anophthalmia, due respectively to failure of the optic outgrowth itself and to "suppression or abnormality of the whole of the fore-brain"; and she recognises a third type, consecutive or degenerative anophthalmia—a condition in which an optic vesicle had formed and had subsequently degenerated and completely disappeared—"which links up with the extreme degrees of microphthalmia but microscopically can be distinguished from them" (p. 65). Duke-Elder (1938) designates as anophthalmos "those cases where there is complete failure in the outgrowth of the primary optic vesicle", as microphthalmos those cases "where the essential nervous structures are present", and as degenerative or consecutive anophthalmos "those cases which show signs of inflammation at birth, for in these it is possible that inflammatory shrinkage of the globe may have occurred subsequent to its development" (p. 1241).

On the basis of either classification it is likely that there may be at times some difficulty in assigning a particular case to its proper group. For example, how are we to decide whether a case in which we find no neurogenic structures is a "primary" anophthalmia, from failure of the optic outgrowth, or "degenerative", with disappearance of an optic vesicle which had been formed? Nor is the designation "secondary" very satisfactory for an anophthalmia due to complete suppression of the whole fore-brain, since the genetic inhibition of neuroblastic tissue is primary whether it affects the whole of the fore-brain or only part of it.

We should perhaps base our definitions rather on the structures which are found in each case—distinguishing essential from non-essential parts of the eyeball—and on the interpretation of their

presence from the embryological point of view. It seems to me that the distinction between the two groups of the constituent parts of the developing eye which receive their blood-supply from two separate sources, and the corresponding distinction between two main types of malformation microscopically determined, suggests a different kind of definition less subject to possible misapprehension.

All cases in which the essential parts of the eye, *i.e.*, retina proper and lens, are lacking, whether the mesodermal constituents and the pigment epithelium are present or not, should be called "anophthalmia". The term "microphthalmia" should be reserved for those cases in which all the eye constituents, including retina proper (or optic nerve) and lens, are present either underdeveloped or malformed or only vestigial.

Anophthalmia, thus defined, may be divided into two groups: (1) "Complete anophthalmia", in which no vestiges of the optic outgrowth can be found; in such cases we cannot determine whether the optic vesicle had been formed and suffered complete atrophy or had never been formed at all; (2) "Consecutive anophthalmia", in which an optic vesicle or cup has been certainly formed but has atrophied in the very early stages, leaving, as its vestige, more or less malformed pigment epithelium. Each group may be bilateral or unilateral, and both are almost certainly genetic in origin, the fault being either in the neuroblast itself or in other tissues, *e.g.*, in the haematogenic mesoderm with disturbance of the blood-supply.

Our case belongs to the second type of anophthalmia so defined, and not to the third type of Ida Mann, as according to her definition it would do. It may be added that no case can be diagnosed as anophthalmia on clinical examination alone.

From the purely embryological point of view I would rather exclude a "degenerative" type of anophthalmia, as it presupposes some pathological lesion due to an adverse external influence. No matter whether it occurs during pregnancy or later, degenerative microphthalmia or anophthalmia is the sequel of a pathological process and not a teratological lesion *sensu strictiori*; it may be congenital but not genetic in origin.

Summary

1. A rare case of unilateral anophthalmia is described with details of its microscopical examination.

2. The problem of the apparent independent development, in such cases, of the retina proper and the pigment epithelium—which have a common origin in the optic outgrowth—is discussed,

and the suggestion is made that it is due to a difference in their blood-supply.

3. Definitions of anophthalmia, with two groups, and of microphthalmia are suggested.

I have purposely concentrated the discussion upon anophthalmia. The malformations of the face are less rare and more frequently discussed, and in my opinion they are not directly related to the lesions of the eye itself. The groove that passes from the hare-lip upwards to the left lower eyelid recalls a similar case recorded by Schwalbe (1913, Fig. 123), and the groove across the right cheek from the right angle of the mouth to the right ear is very like one depicted by Keith (1940, Fig. 85).

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