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SYNOPHTHALMIA AND CYCLOPIA: A HISTOPATHOLOGIC, RADIOGRAPHIC, AND ORGANOGENETIC ANALYSIS*

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ABSTRACT

This paper presents the results of a detailed gross and histologic examination of the eyes and brain in a case of synophthalmia as well as radiographic studies of the skull. Data on 34 other cases of synophthalmia-cyclopia on file in the Registry of Ophthalmic Pathology, Armed Forces Institute of Pathology (AFIP), are also summarized. In synophthalmia-cyclopia, the median ocular structure is symmetrical and displays two gradients of ocular organization: (1) The anterior segments are usually paired and comparatively well differentiated, whereas, posteriorly, a single, more disorganized compartment is present; (2) the lateral components show more advanced differentiation than the medial. There is invariably a single optic nerve and no chiasm. The brain, the nose, and the bones and soft tissues of the upper facial region, while malformed, are symmetrical and show a similar gradient of organization in that the lateral parts are better developed than the medial. The constant occurrence of a profound cerebral malformation along with the ocular deformity suggests a widespread abnormality of the anterior neural plate from which both the eyes and brain emerge. The data indicate that the defect occurs at or before the time of closure of the neural folds when the neural plate is still labile. The probability of fusion of two ocular anlagen in synophthalmia-cyclopia seems less likely than the emergence of incomplete bicentricity in the ocular fields of the neural plate during the period when the eye primordia are initially induced by the mesoderm. Embryologic studies in experimental animals provide insight into possible mechanisms by which inperfect eye and brain primordia are established. Nonetheless, once established, the eye and brain primordia in synophthalmia-cyclopia are capable of and do complete each step of

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the usual sequence of ocular and cerebral organogenesis in an orderly manner. The resulting eyes and brain are organogenetically incomplete but histogenetically mature. Ancillary facial and osseous defects result from the faulty migration of neural crests and development of embryonic facial processes secondary to the abnormal ocular and cerebral rudiments.

INTRODUCTION

Synophthalmia and cyclopia represent a continuum of anomalies in which the organogenetic development of two separate eyes is variably suppressed. In synophthalmia, which is more frequently recorded in human fetuses (Duke-Elder, 1964; Nishimura et al., 1968), the ocular rudiment is composed of mirror-image portions of two incomplete eyes overlapping medially; in true cyclopia, which is less common, only a single median eye is formed. Invariably the maldevelopment extends beyond the eyes and includes the brain, upper face, and bones of the skull.

Synophthalmia-cyclopia has been ascribed to an embryologic error leading to early fusion of the developing ocular anlagen (Adelmann, 1936; Duke-Elder & Cook, 1963; Duke-Elder, 1964; Mann, 1957; Warkany, 1971). The term synophthalmia reflects this bias, since it connotes a union or fusion. An alternative explanation invokes a failure of division of a single primordial eye center or field in the anterior neural plate during early embryogenesis.

Previous reviews have highlighted the gross aspects of the facial and ocular deformities and have not focused on the detailed histopathologic features of synophthalmia-cyclopia as they relate to the theories of fusion and nondivision (Mann, 1957; Duke-Elder & Cook, 1963; Duke-Elder, 1964). The fundamental importance of this group of anomalies to our understanding of ocular development prompted us to undertake the present study, which consists of a detailed gross, histopathologic, and radiographic examination of a case of synophthalmia and a review of 34 additional cases of synophthalmia-cyclopia on file in the Registry of Ophthalmic Pathology, AFIP.

On the basis of this extensive histopathologic study and of our survey of the relevant embryologic literature, we believe that the essential problem in synophthalmia-cyclopia is the lack of sufficient forebrain anlage for the emergence of eye and brain (telencephalon) bicentricity. The associated facial defects result from interference (by the ocular rudiment) of migration of neural crest cells and development of the embryonic facial processes.

Our objective in this paper is to synthesize our pathologic findings with the results of embryologic studies that have probed the interplay of neural plate, mesoderm, and neural crest in the course of ocular development.

A 1,710-gm female infant was the firstborn of a 21-year-old woman. At birth the upper facial region of the baby showed the typical appearance of cyclopia (Fig. 1). The remainder of the face and the body of the child were unremarkable. The baby lived for 40 minutes.

Polyhydramnios had been noted during pregnancy. No other information about the pregnancy or the health of the mother was available. Chromosomal studies were not performed.

Two specimens were received – the head of the child, with the synophthalmic structure in place, and the brain, which was submitted separately and consisted of an intact brain stem and multiple fragments of the cerebral cortex.

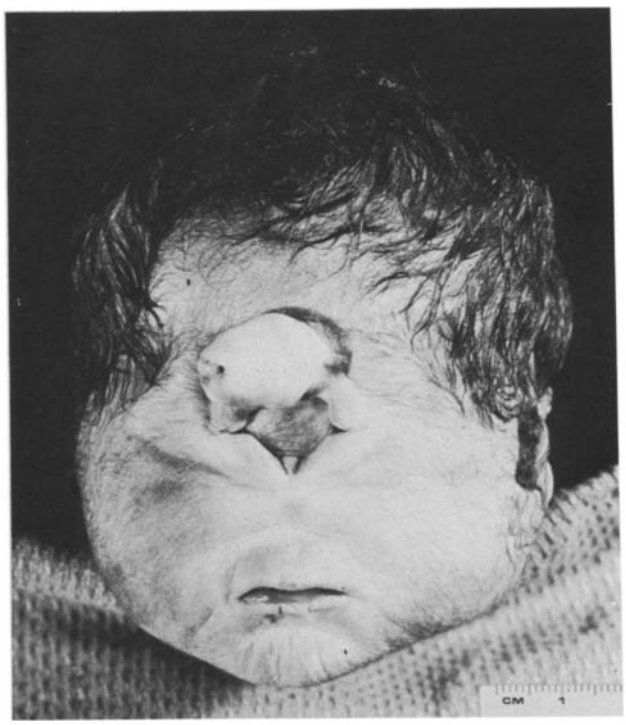

Fig. 1. Face of synophthalmic fetus (35 weeks' gestation) dominated by a proboscis situated above a single diamond-shaped palpebral fissure outlined by lids that are well developed laterally and hypoplastic medially. The inferior midline caruncle is visible, while the superior caruncle is obscured by the overriding proboscis (case 18, Table 7).

Gross and microscopic description

Head and face

The external features of the face (Fig. 1) included a single median ocular structure (Fig. 2), a tubular proboscis with a single nasal pit (naris) arising from the forehead above the eye and measuring 16 x 12.5 x 9.5 mm. (Figs. 3 & 4); a single diamondshaped palpebral fissure; and a mouth with thin, flat lips. The nose and philtrum were absent.

Eyelids: Transversely, the palpebral fissure measured 25 mm from outer canthus to outer canthus and 12 mm vertically. Only the lateral aspect of the lids contained well-formed cilia, tarsal plates, and meibomian glands.

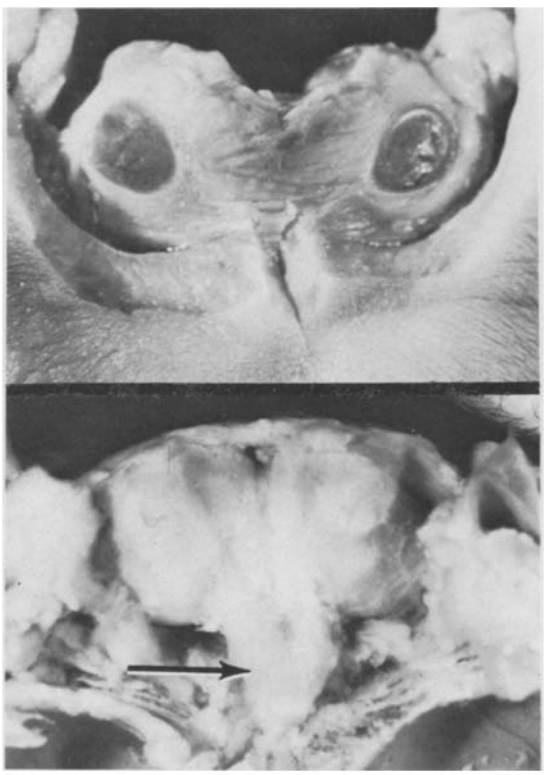

Fig. 2. (Top) The lids and caruncles have been removed and the orbit unroofed. Conjunctival tissue bridges the anterior synophthalmic structures. (Bottom) View from above. Arrow points to cystlike site of egress of single, hollow optic nerve.

Medially, the palpebral fissure was wider since the lids were hypoplastic, and cilia and glands were small and sparse. In the midline, rudimentary lids were joined, forming angles superiorly and inferiorly; two 2- to 3-mm caruncles were also situated centrally (Fig. 5). A canaliculus was found in one lid (Fig. 6). The inside of the lids was lined with conjunctiva.

Proboscis

A probe was passed through the external opening of the proboscis, and it slid easily through the entire length, entering the frontal bone for 1 mm, at which point the cavity ended blindly. On longitudinal sectioning, the proboscis, which widened in its midportion (Fig. 3), had an irregularly shaped cavity. Sections of the proboscis disclosed a keratinized squamous epithelium covering the cutaneous surface and continuing for a short distance into the cavity, where it merged with ciliated pseudostratified epithelium. Subsurface skin appendages were numerous. The wall of the proboscis contained a layer of striated muscle, cartilage, adipose tissue, vessels, and nerves. Between a plaque of hyaline cartilage and the pseudostratified epithelium there was an intermediate layer composed of many heterotopic salivary glands intermingled with bundles of collagen (Fig. 4).

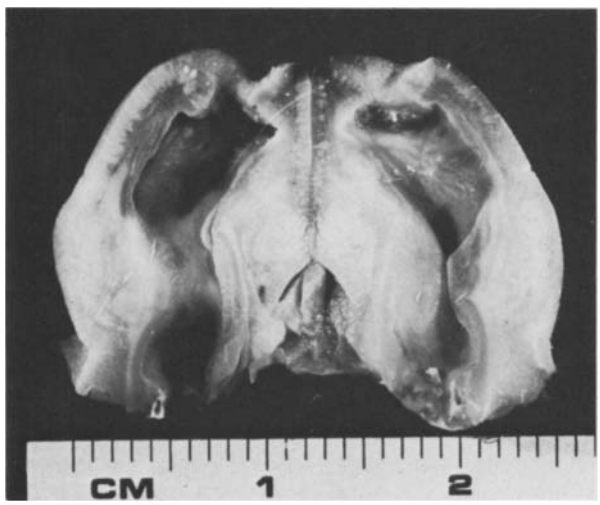

Fig. 3. Proboscis sectioned sagittally with single naris above.

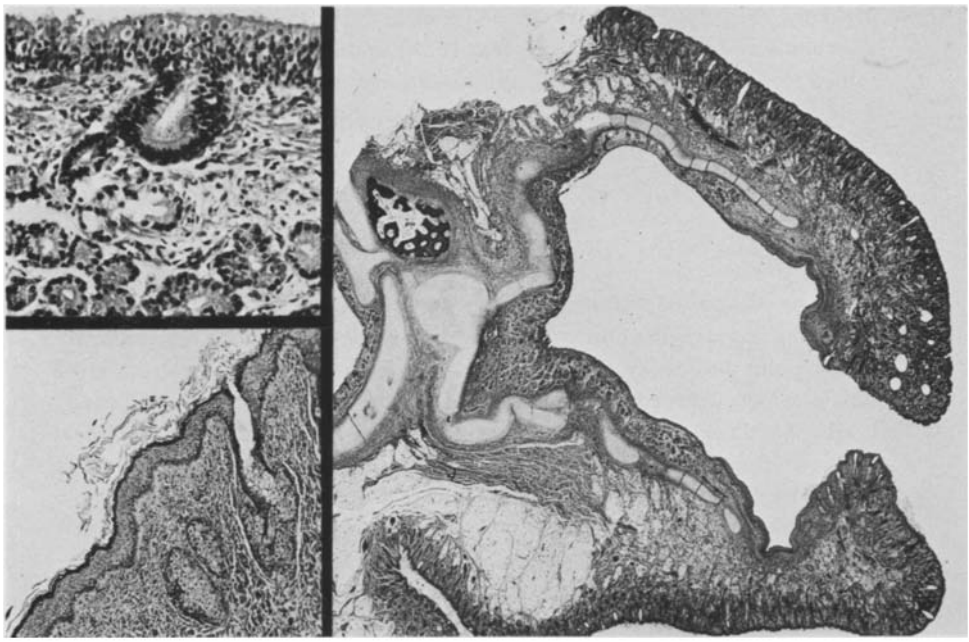

Fig. 4. The central cavity of the proboscis (right) is lined by respiratory epithelium (inset, upper left) with minor salivary glands. No olfactory ganglion cells were found. The external opening is covered by keratinizing epithelium (inset, lower left). Bone is seen posteriorly, and cartilage is present in the walls. (Hematoxylin-eosin; upper left, x150; lower left, x50; right, x5).

Orbit

When the orbit was unroofed, muscle bundles were found attached to each globe superiorly, laterally, and inferiorly. Inferomedially a single muscle occurred in the midline. Orbital tissues and muscles were removed to reveal the external shape of the ocular structure (Fig. 2). Histologically the extraocular muscles were unremarkable.

Synophthalmic structure

Grossly the synophthalmic structure was triangular with the base formed by the two corneas directed anteriorly, while the apex was formed by a single optic nerve directed toward the brain (Fig. 7). The corneas were directed somewhat laterally. Anteriorly, two anterior segments were observed, while

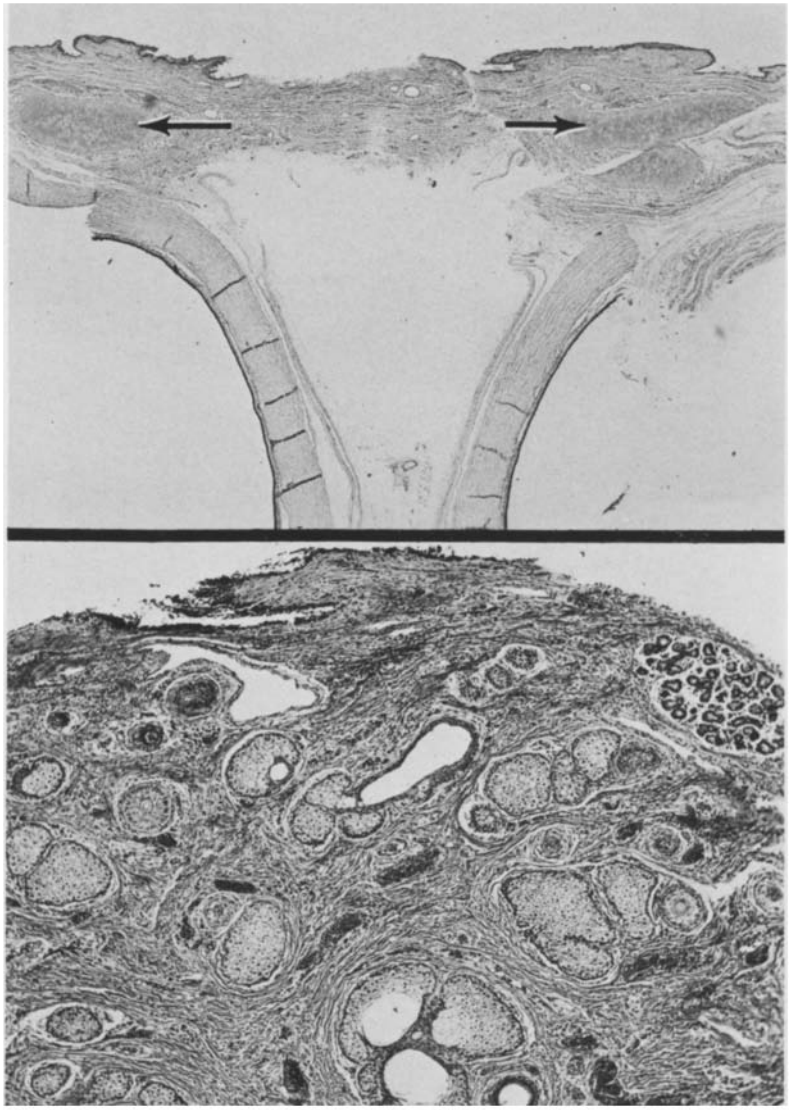

Fig. 5. (Top) Trochlear cartilages (arrows) are located anterosuperiorly in a wedge-shaped area anterior to the medial scleral hemiseptum. (Alcian blues, x13). (Bottom) Caruncle contains lobule of lacrimal gland tissue in upper right corner as well as many sebaceous glands and hair shafts. (Hematoxylin-eosin, x50).

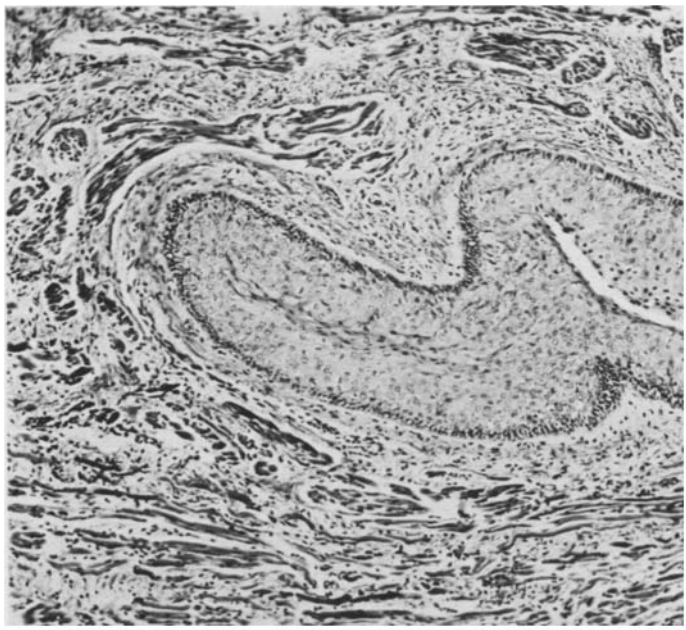

Fig. 6. Canaliculus surrounded by striated muscle fibers. (Hematoxylin-eosin, x85).

posteriorly the paired ocular elements blended into a single common fundus or chamber. The tripartite structure was covered by a continuous outer scleral shell. From midpoint of the common fundic region a single tubular and partially hollow optic nerve stalk projected toward the brain (Figs. 2 & 7). The nerve, covered by a single nerve sheath, entered a single median optic foramen at the apex of the orbit.

Each globe measured 13 x 13 x 12.5 mm. The individual corneas measured 6 x 5 mm. The pupils were slightly oval, and the longest diameter of each was directed inferonasally. On transillumination, the synophthalmic structure and the hollow nerve transmitted light evenly and regularly. The ocular structure was opened horizontally just above the junction of the hollow optic stalk and the sclera. The anterior chambers were shallow. Small spherical lenses were present in each anterior segment. Thin vessels and white fibrous strands surrounded the lenses and extended posteriorly into the vitreous cavities near the single nerve head, where they were lost in a tangle of fibers and debris that filled the hollow center of the optic nerve stalk. The vitreous body was partially liquid. The retina was artifactually detached.

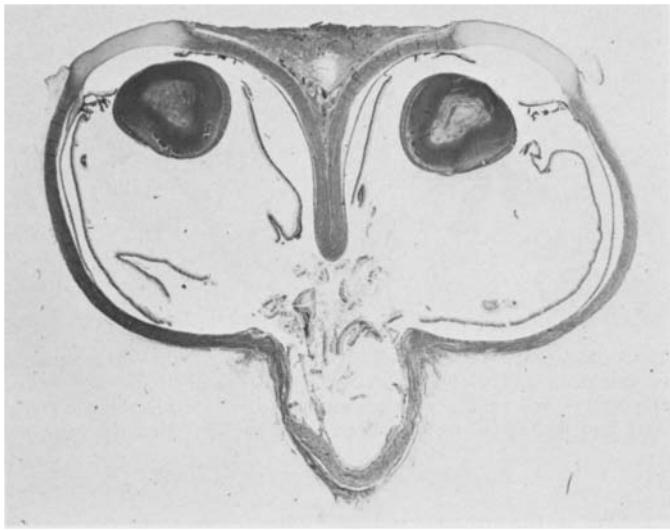

Fig. 7. Synophthalmic eye displaying high degree of anterior symmetry and median scleral hemiseptum. The hollow optic nerve head contains fragments of dysplastic retinal tissue and vitreous; walls of the nerve stalk are lined with pial columns. (Hematoxylin-eosin, x7).

No optic discs, other than the hollow tubular stalk, and no maculae were seen.

Microscopically a conjunctival-type epithelium covered the central wedge-shaped area between the anterior segments of the globes (Fig. 7). Loose connective tissue, bundles of smooth muscle, nerves, vessels, and adipose tissue filled the deeper zone of the triangular space. Superiorly, small islands

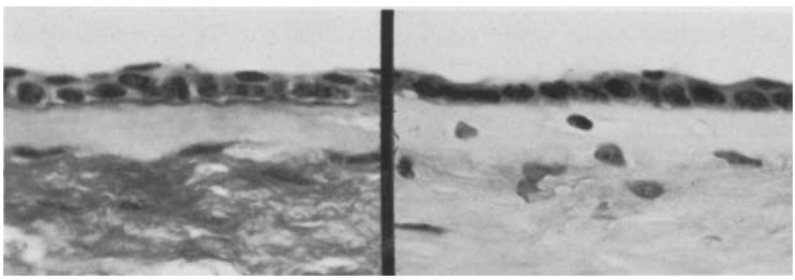

Fig. 8. (Left) Temporal aspect of Bowman's membrane and basement membrane of corneal epithelium are well developed. (Periodic acid-Schiff, x575). (Right) Nasal Bowman's membrane with entrapped stromal cells. (Hematoxylin-eosin, x575).

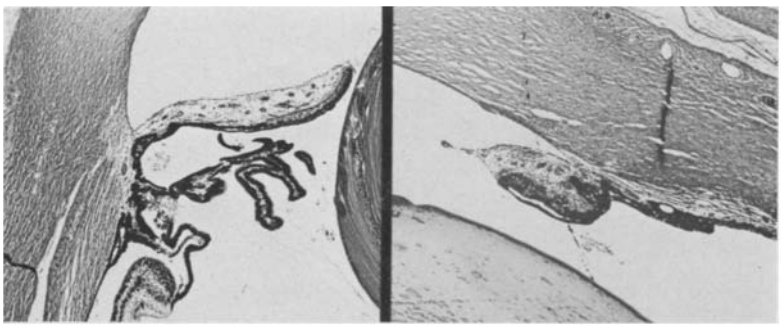

Fig. 9. (Left) Chamber angle temporally is deeply cleaved; the ciliary muscle and iris leaflet are well formed. The ciliary processes are elongate. (Hematoxylin-eosin, x25). (Right) Hypoplastic iris nasally with a strand of pupillary membrane. The chamber angle, ciliary muscle, and ciliary processes are rudimentary. Hematoxylin-eosin, x40).

of cartilage lay in the subconjunctival tissues adjacent to the medial scleral wall of each anterior segment (Fig. 5, top).

The corneal stromas were hypercellular, and an occasional cell nucleus was noted at the level of Bowman's membrane (Fig. 8). The anterior chamber angles were structurally immature; cleavage of the angle was more advanced temporally than nasally in each globe (Fig. 9). Schwalbe's line was prominent nasally (Fig. 10, top). Nasally, the pigment epithelium of the iris puckered inward into the iris stroma (Fig. 10, middle). Temporally, the irides contained a sphincter muscle and occasional fibers of a dilator muscle (Fig. 10, bottom). Nasally, they were short and blunted, the sphincter muscle was poorly formed, and no dilator muscle was found.

The cortical layers of the spherical lenses were vacuolated and fragmented. The lenses were surrounded by a thin fibrovascular membrane (Fig. 11), which continued posteriorly to blend with the contents of the hollow nerve stalk (persistent tunica vasculsa and the hyaloid system) The ciliary bodies were thin and flat nasally. The anteromedial sclerae between the two hemiglobes (Fig. 7) blended posteriorly to form a medial but incomplete septum covered by pigment epithelium and choroid (Fig. 12). Posterior to the hemiseptum the vitreal cavities formed a single, common chamber.

At the posterior pole, there was an opening in the retina, choroid, and sclera constituting a single, hollow optic nervehead and hollow distal optic nerve (Fig. 7). To either side of this midline cavity the retina was attached temporally in both globes except immediately adjacent to the single median optic nerve stalk where it was artifactually detached. The retina covered the scleral hemiseptum but was fragmented near its tip; pieces of retina were

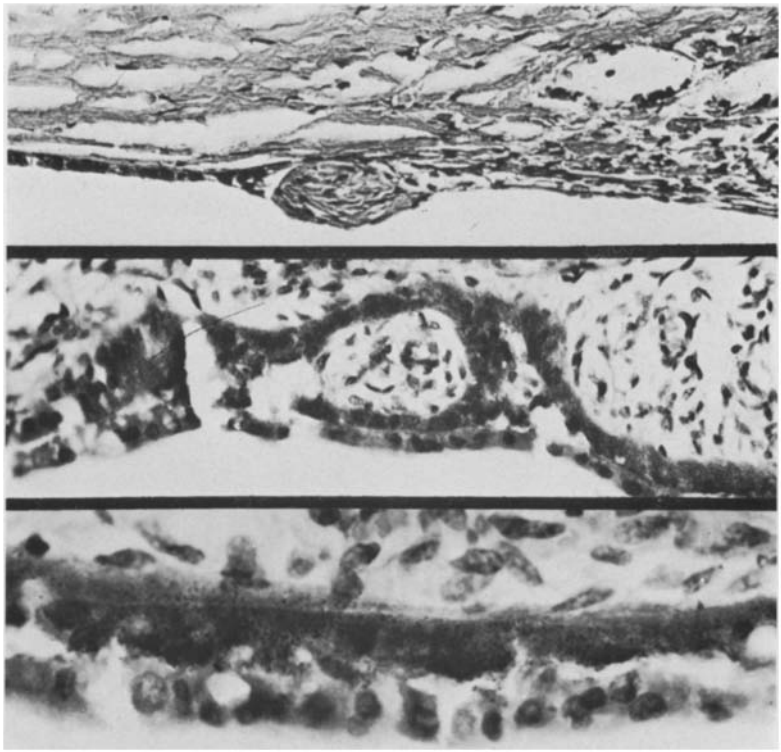

Fig. 10. (Top) Nasal portion of Schwalbe's line is prominent and is bordered on left by corneal endothelium and on right by poorly developed chamber angle trabeculae. (Masson trichrome, x245). (Middle) In disorganized nasal iris, reduplicated pigment epithelium encircles iris stroma. (Bleached hematoxylin-eosin, x395). (Bottom) Focal dilator muscle differentiation, temporal iris. (Bleached hematoxylin-cosin, x660).

scattered in the vitreous body (Fig. 7). The cytoarchitecture of the retina was generally preserved, but degenerative changes were present in the photoreceptors (Fig. 13, top). Nerve fibers, although few in number, were demonstrated in the retina with the Bodian stain for axons (Fig. 13, bottom). A few ganglion cell nuclei were present. There were occasional areas of mild retinal dysplasia characterized by immature neural cells in rosette formation (Fig. 14, top, middle). Minimal capillary proliferation occurred temporally adjacent to the optic nerve stalk (Fig. 14, bottom) and over the scleral hemiseptum. One remnant of neurosensory retina lay within the sclera adjacent to the optic nerve stalk (Fig. 15, top). Several strands of rudimentary retina extended from the scleral hemiseptum and were attached

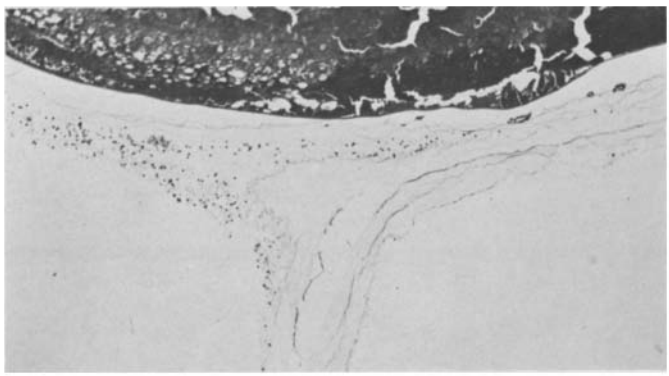

Fig. 11. The lenticular cortex contains vacuoles and fragmented fibers. Note hyaloid artery and tunica vasculosa lentis. (Hematoxylin-eosin, x50).

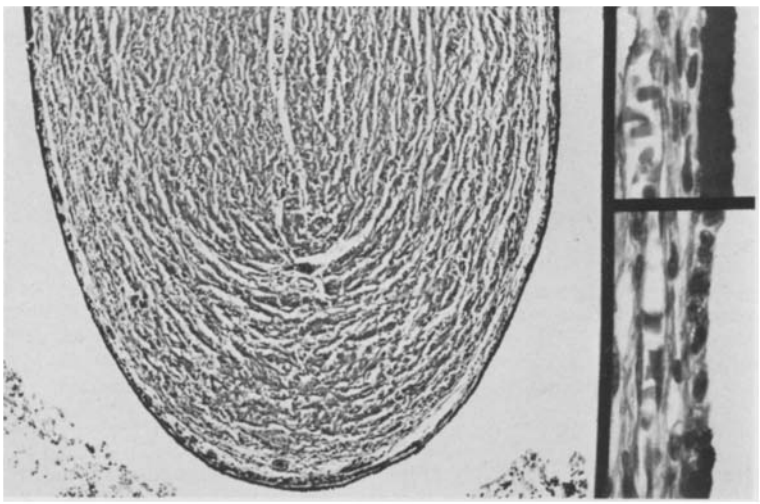

Fig. 12. Median scleral hemiseptum covered anteriorly by highly melaninized cuboidal pigment epithelium (inset, upper right) and by flatter, more lightly melaninized pigment epithelium posteriorly (inset, lower right). The fully differentiated choriocapillaris lies beneath the pigment epithelium throughout. (Hematoxylin-eosin, x50; insets, x485).

to the walls of the optic nerve stalk (Fig. 15, bottom). Deeper sections, taken near the base of the scleral hemiseptum, revealed a transitional zone in which the retinal pigment epithelium was continuous with rudimentary and poorly differentiated primitive retinal cells (Fig. 16). Here the choroidal coat was also defective. The retinal pigment epithelium and choroid formed

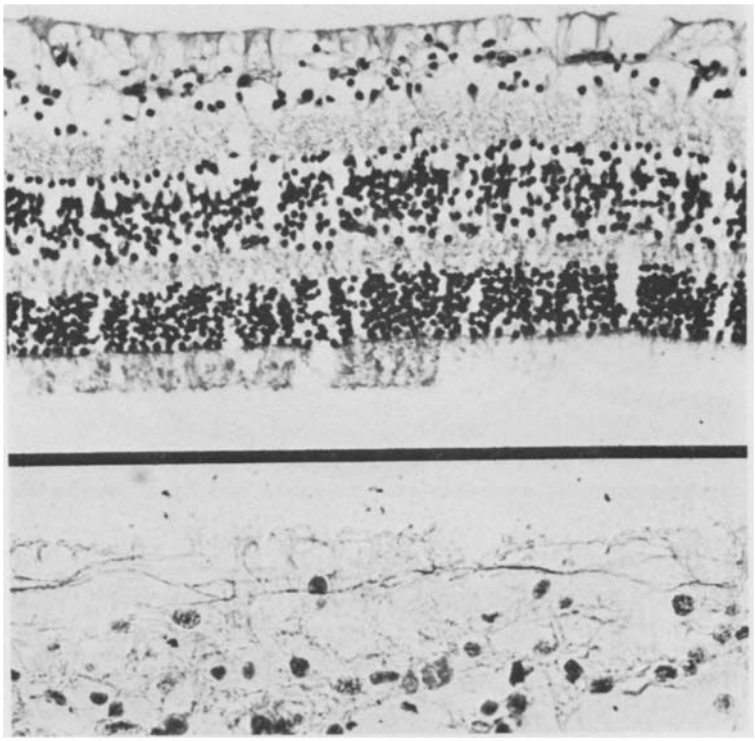

Fig. 13. (Top) Relatively normal retinal cytoarchitecture including ganglion cells and photoreceptors. (Hematoxylin-eosin, x225). (Bottom) Inner retina displays severe depletion of nerve fibers. (Bodian stain, x440).

a continuous covering over the scleral hemiseptum except where the septum blended into the two globes posteriorly; here pigment epithelium and choroid were focally absent and replaced by a nonpigmented layer of dysplastic neuroepithelium.

Dysplastic retinal rosettes and undifferentiated retinal cells were intermixed with the fibrous septa of the optic nerve stalk (Fig. 17). The arachnoid covered most of the nerve but was discontinuous over short segments. The intraorbital dural sheath was intact. Within the walls of the hollow nerve stalk neuroglial columns containing axons were found beneath the primitive and aberrant retinal cells (Fig. 17).

The single median optic nerve left the orbit through a single median foramen. Intracranially, the pia and internal neuroglial septa were clearly present and resembled the orbital portion of the optic nerve. Nerve fibers,

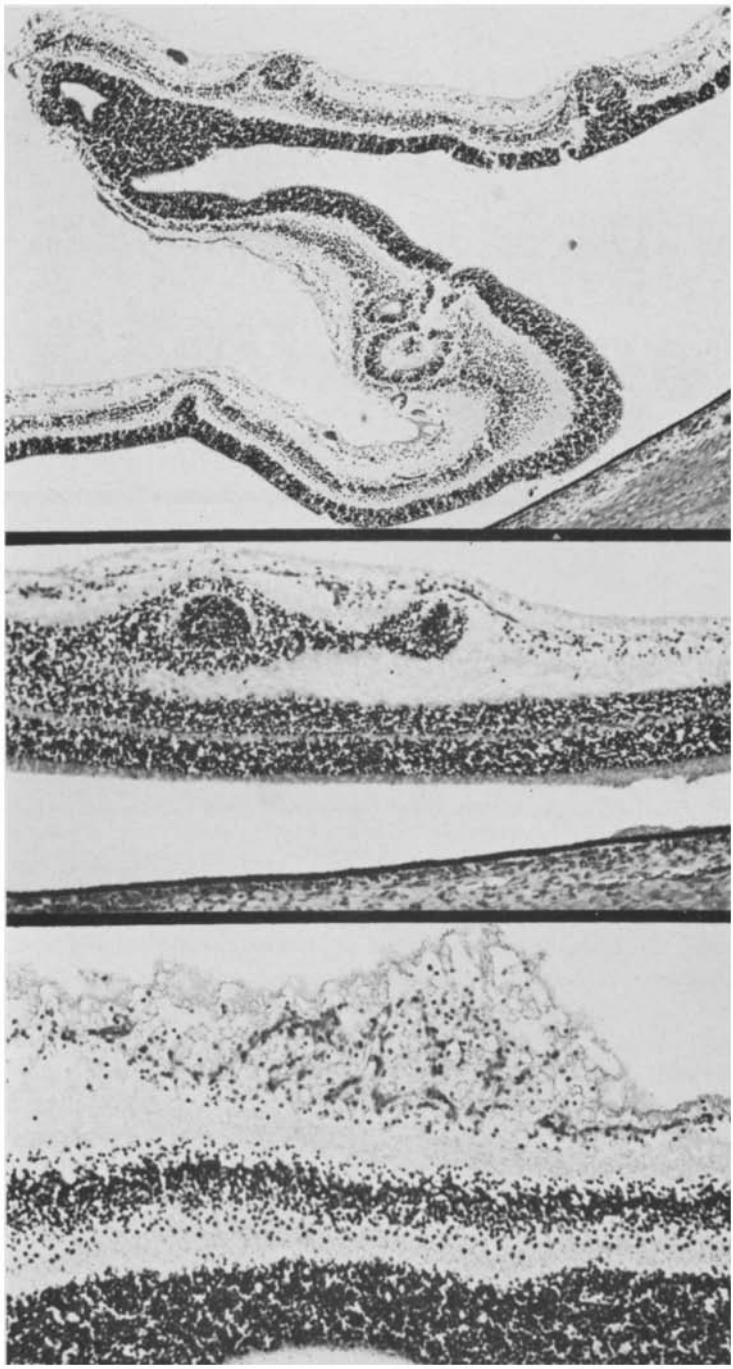

Fig. 14. (Top) Region of posterior pole shows dysplastic retina with rosettes. (Hematoxylin-eosin, x50). (Middle) Area of abnormal posterior retinal lamination. (Hematoxylin-eosin, x70). (Bottom) Capillary proliferation in inner retina. (Hematoxylin-eosin, x90).

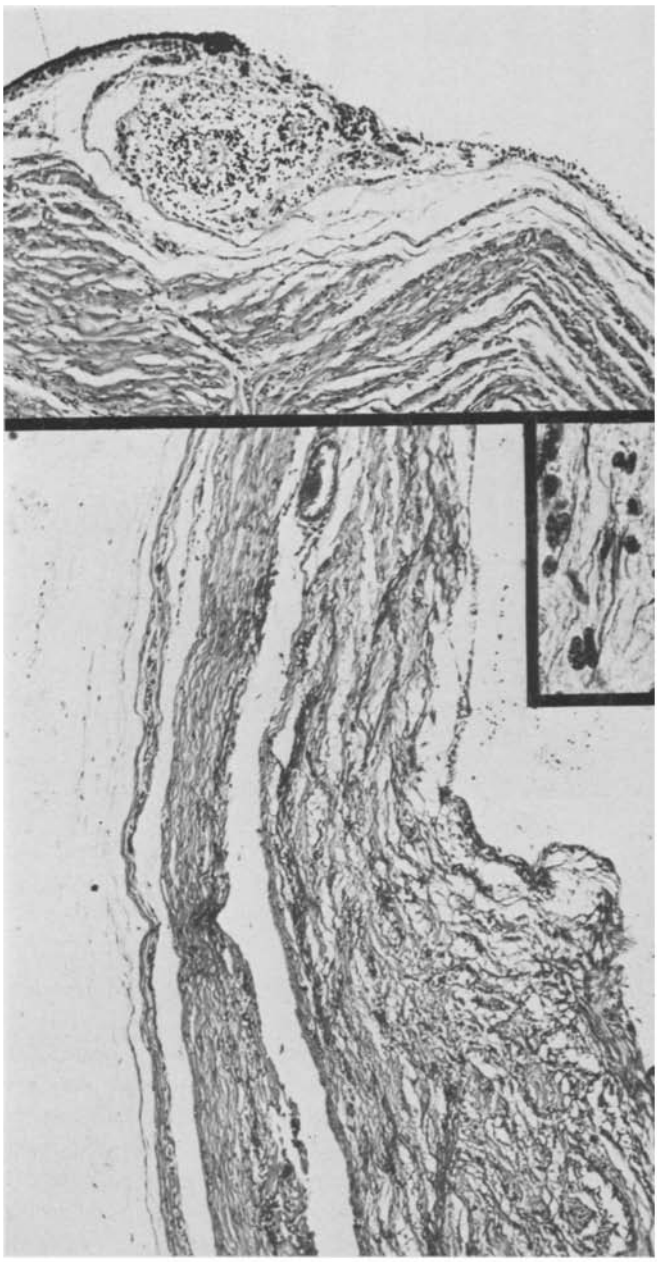

Fig. 15. (Top) Dysplastic rosettes at edge of optic nerve. (Hematoxylin-eosin, x75). (Bottom) Wall of the hollow optic nerve stalk containing glial and neural tissues and occasional axons, shown in inset. The leptomeninges are poorly developed. (Hematoxylin-eosin, x90; inset, Bodian stain, x440).

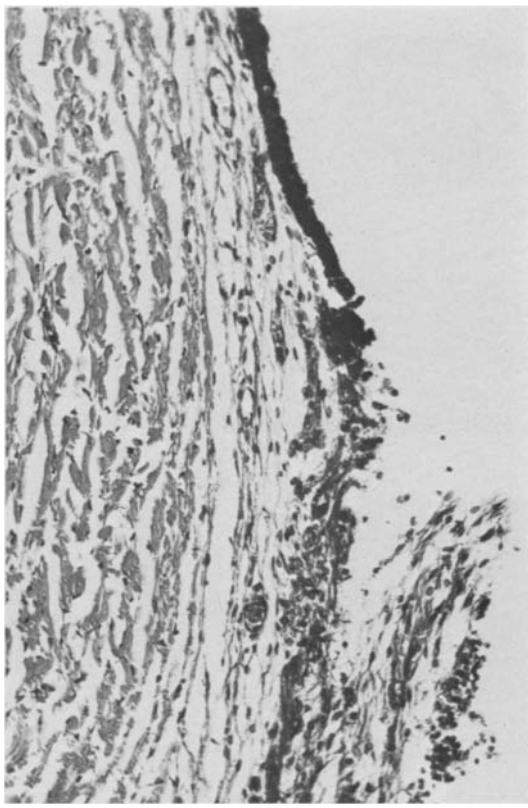

Fig. 16. Retinal pigment epithelium (above) blends into dysplastic cells below. Section taken in the region where scleral hemiseptum joins the globes. (Hematoxylin-eosin, x165).

though few in number, were demonstrated with the Bodian stain in the intracranial portion of the optic nerve (Fig. 18).

The histopathologic findings of the ocular structure are summarized in Table 1. The structure of the single median eye consisted of symmetrically paired anterior parts of two eyeballs blending medially and posteriorly into a single nonpaired globe (oculus impar). Histologically, the ocular tissues were differentiated, as shown by the presence of ganglion cells in the retina and of axons in the orbital and intracranial portions of the optic nerve. Differentiation and organ development were more advanced in the lateral (temporal) parts of the globe than nasally (Table 2).

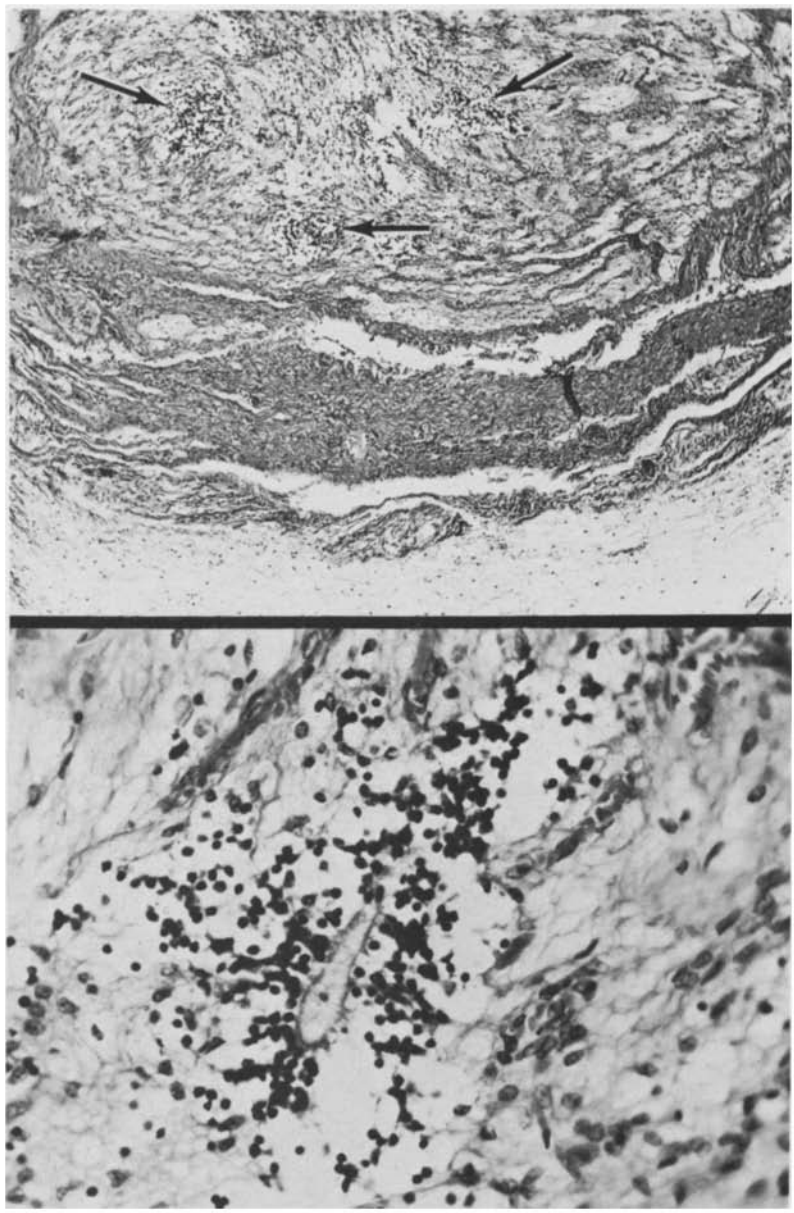

Fig. 17. (Top) Optic nerve near globe containing dysplastic retinal elements (arrows); the nerve is surrounded by thickened meninges. (Hematoxylin-eosin, x50). (Bottom) Dysplastic retinal rosette within disorganized optic nerve. (Hematoxylin-eosin, x75).

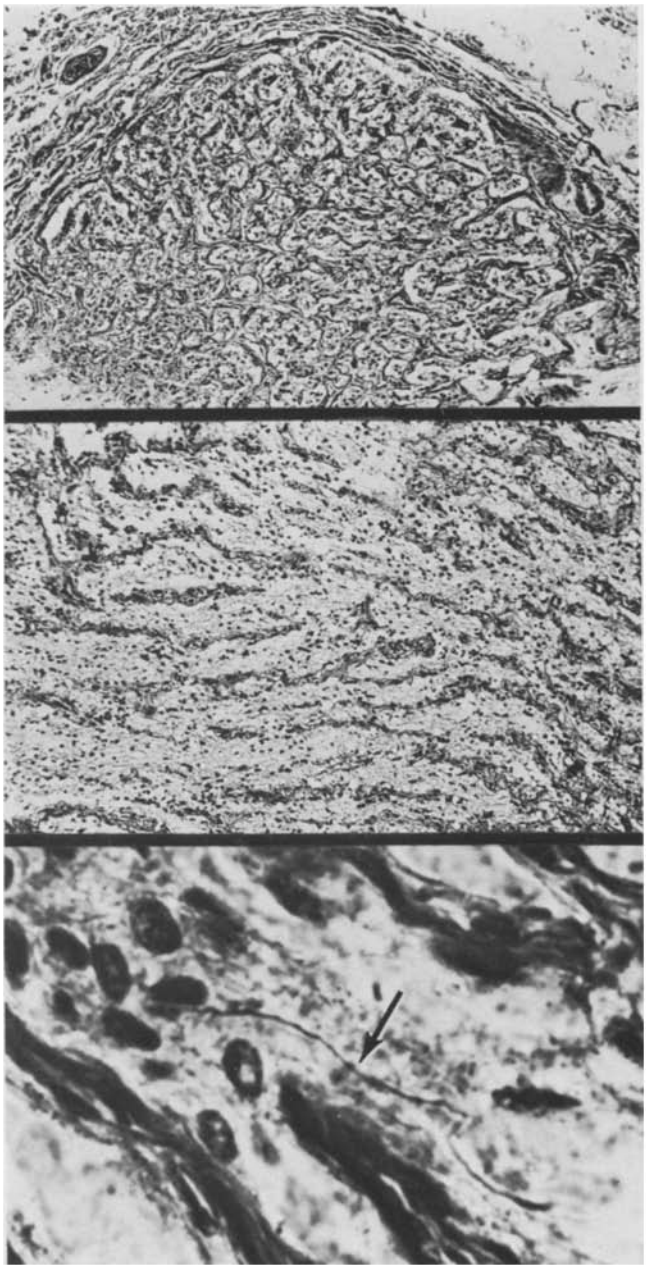

Fig. 18. (Top) Cross section of intracranial portion of single optic nerve (no chiasm present) displaying fibrous septa and atrophic meninges. (Hematoxylin-eosin, x40). (Middle) Longitudinal section of intracranial optic nerve. The septa are somewhat misaligned, but there is apparent internal organization. (Hematoxylin-eosin, x80). (Bottom) A solitary surviving intracranial axon (arrow) between the connective tissue septa. (Bodian stain, x1,100).

Table 1. Summary of the ocular histologic findings in the present case of synophthalmia

Two complete, well-formed anterior segments
Immature cleavage of the chamber angle, bilaterally
Hypertrophy of Schwalbe's line, nasally
Absence of dilator muscle of iris, nasally
Persistence of tunica vasculosa lentis and hyaloid arteries, anteriorly and bilaterally
Spherical, cataractous lenses, bilaterally
Mild retinal dysplasia, posteriorly
Midline hemiseptum of sclera, choroid, and retina
Common vitreous chamber, posteriorly
Single median hollow tubular optic nerve lined with scant axons and glial columns; islands of primitive retinal cells in nerves as well as entrapped in walls of optic nerve
Absence of the maculas

Table 2. Comparison of the maturation of the lateral and medial structures in present case of synophthalmia

	Lateral	Medial
Incomplete development of chamber angle	++	+
Iris	++	+
Stroma	++	+
Dilator muscle	+	0
Sphincter muscle	++	+
Ciliary body	++	+
Retinal differentiation	++	+
Retinal pigment epithelium	++	+
Choroid	++	+
Sclera	++	+
Optic nerve, pial columns	++	0

++ = Greater maturation of structures.
+ = Lesser maturation of structures.
0 = Absent.

Ocular findings consistent with the immaturity of the fetus (1,710 gm) and not necessarily denoting malformation included (1) the small size of the globes, (2) increased cellularity in the corneal stroma, (3) immature chamber angles, (4) persistent tunica vasculosa lentis, and (5) persistent hyaloid arteries.

Skull and brain

Grossly the anterior cranial fossa was foreshortened. The bones of the middle and posterior cranial fossa were unremarkable posterior to the petrous portion of the temporal bones and posterior clinoids (Fig. 19, left). Within the

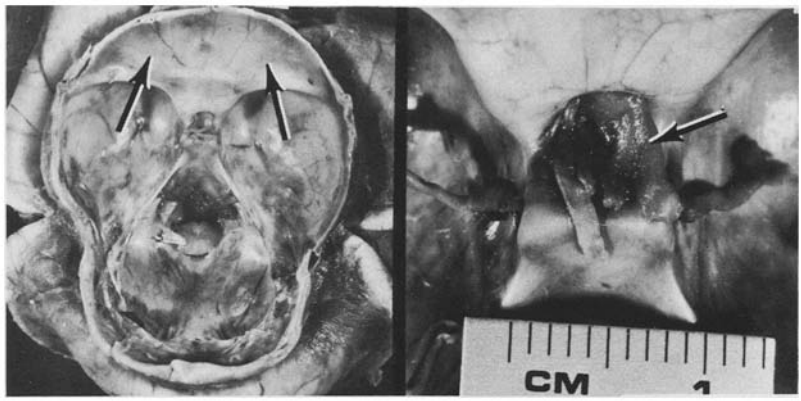

Fig. 19. (Left) Dorsal view of base of skull. The anterior fossa is markedly foreshortened (arrows). (Right) The single optic nerve (arrow) enters the cranial cavity via a single optic canal.

cranial cavity, remnants of the two internal carotid arteries lay adjacent to the pituitary fossa. The single midline optic nerve stalk entered the anterior wall of the pituitary fossa from the orbit through a single, central optic

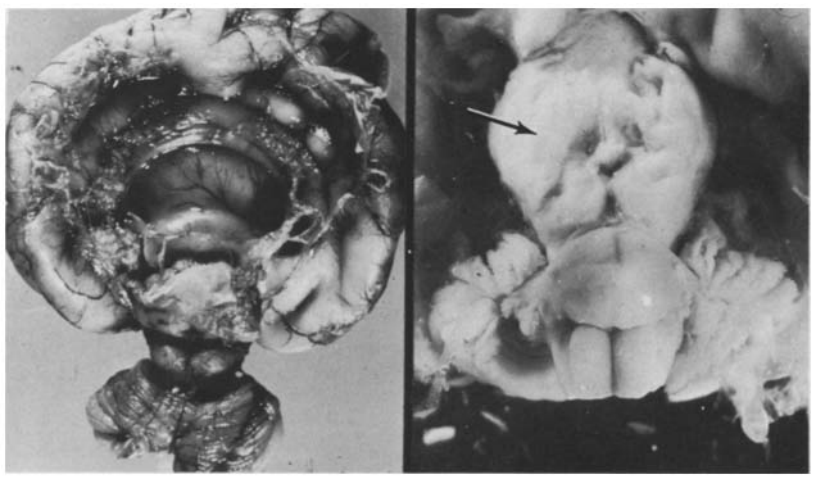

Fig. 20. (Left) Dorsal view of holoprosencephalic brain taken by the contributor prior to shipment to the AFIP. The roof of the dorsal cyst has been removed to reveal a large single ventricular cavity, banked by brain tissue; prominent superior colliculi and cerebellum are present. (Right) Ventral view of dysplastic diencephalon (arrow). The pons and olives below are bare as a result of the absence of the corticospinal tracts.

foramen (Fig. 19, right). Remnants of the 3rd, 4th, 5th, 6th, 7th, and 8th cranial nerves were present bilaterally at the base of the skull.

The brain consisted of multiple pieces of cerebral cortex, some of which were attached to the brain stem (Fig. 20, left). The corpus callosum, falx cerebri, and olfactory apparatus were absent. Remnants of the cortex covered a single enormous ventricular cavity. The gyri were wide and anomalously distributed. Fibrovascular remnants of the *tela choridea* were attached to the rim of the cortex. A single midline mass was noted at the level of the hypothalamus and diencephalon (Fig. 20, right). A small stalk, possibly the pituitary stalk, protruded from the mass ventrally. The cerebellum and remainder of the brain stem were unremarkable except that the pons was small ventrally and the inferior olives were prominent. The pituitary gland was not found.

For microscopic examination the brain stem was sectioned at 5-mm intervals. The longitudinal fibers of the corticospinal and corticobulbar tracts were virtually absent at all levels. The nuclei of the 12th cranial nerve was present in the floor of the 4th ventricle. The outer molecular layer (Obersteiner's) of the cerebellum was thick. The aqueduct was distended. The ependymal cells lining the ventricle were thrown into redundant folds. Clusters of large motor neurons aggregated into nuclei were found in the pons. Ventrally, the cerebral peduncles were absent or hypoplastic, and the interpeduncular fossa was shallow. The nucleus of the 3rd nerve and its fiber tracts were relatively large. The superior colliculi were present dorsally. The choroid plexus was not found in the roof of the large midline ventricle. A mass of glial tissue bridged the ventricle medially. The optic tracts, *substantia nigra,* and pyramidal tracts could not be identified. Sections of the presumptive midthalamic region disclosed an undivided median mass of ganglion cells, glial cells, and capillaries (Fig. 21, top and bottom). The basal ganglia and the optic chiasm were not identified.

Random sections of cerebral cortex were taken. The cortex was dysplastic, but in many sections the neurons appeared glomeruloid, suggestive of the temporal lobe; other neuronal organizations were reminiscent of uncal cortex. In many sections small groups of nuclei of undifferentiated neuroblastic cells of the germinal mantle cuffed the blood vessels. The neural structures were richly vascularized. The diagnosis of the totality of the cerebral findings was holoprosencephaly.

Radiographic studies

Radiographs of the decerebrated head of the infant were taken using fine-grain industrial film having exposure factors of 300 MAS and 55 KEV. The

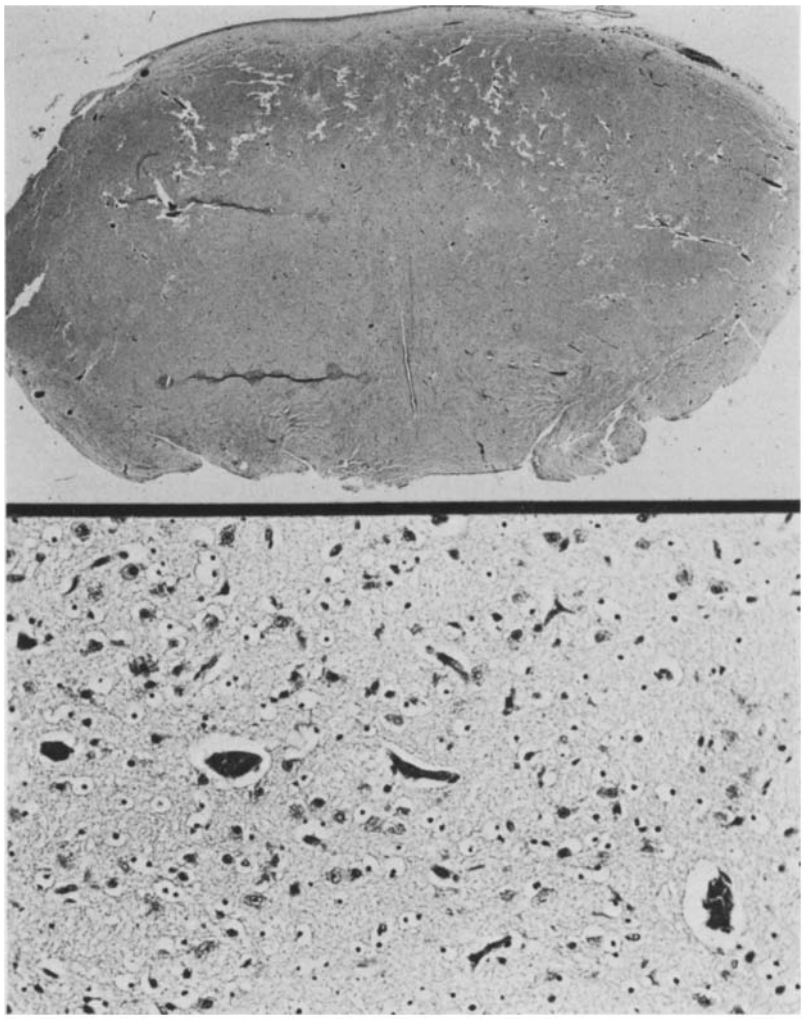

Fig. 21. (Top) Featureless diencephalon fails to show any internal organization (cross section at level of arrow in Fig. 20, right). (Bottom) Neurons and glia are randomly arranged in a neuropil that is heavily vascularized (dark structures are capillaries). (Hematoxylin-eosin, x165).

basic views included the Water's view (Fig. 22, upper left); the submental vertex (Fig. 22, upper right); the posterior-anterior view (Fig. 22, lower left); and the lateral view (Fig. 22, lower right). Tomographs taken in the

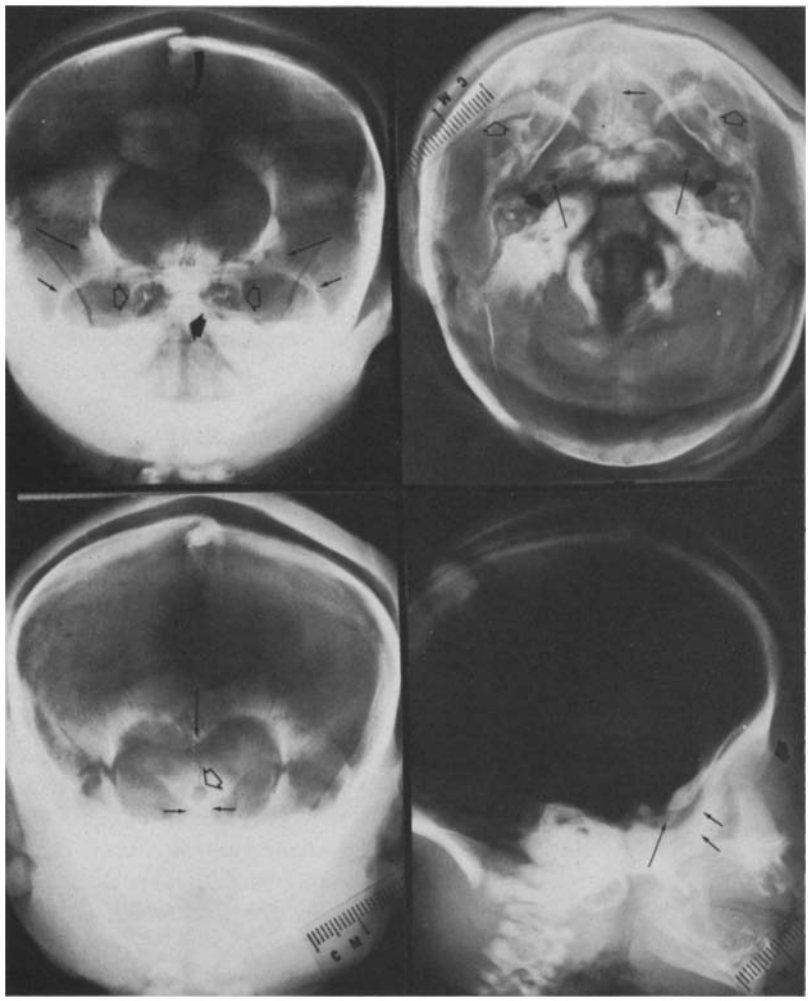

Fig. 22. (Upper left) Water's view of the skull demonstrates the proboscis (curved arrow), midline single orbit, hypoplastic maxillary bony structure with developing teeth (between open arrows), zygomatic temporal arch (short arrows), zygomatic bone (long arrows), and hypoplastic nasal septum (thick arrows). This view stresses the hypoplasia of the median facial bone. (Upper right) Submental vertex radiograph of the skull shows the striking anterior hypoplasia of median facial bones, intact greater wing of the sphenoid (open arrows), foramina ovale (long arrows), foramina spinosum (thick arrows), hypoplastic nasal septum (short arrow), and normal mandible. (Lower left) Posterior-anterior view of the skull illustrates the classic single midline orbit with a superior median ridge (long arrow), single optic canal (open arrow), and the narrow sphenoid bone (short arrows). The soft tissue density of the proboscis is seen above the orbit. (Lower right) Lateral view demonstrates shallow orbits, small anterior cranial fossa, intact greater wing of the sphenoidal bone (short arrows), abbreviated projection of the superior orbital margin (thick arrow), single optic canal (long arrow), absent nasal bone, and flat face.

Water's posterior-anterior, and lateral positions corroborated the bony findings demonstrated on the conventional films.

The anteromedial facial structures were absent or hypoplastic (Fig. 22, upper left). The submental vertex view showed that the small anterior median facial area was hypoplastic, in sharp contrast to the normally developed posterior structures. The posterior aspects of the calvarium, including the temporal bone with its petrous portion and basilar foramina, were normally developed (Fig. 22, upper right).

The submental vertex view (Fig. 22, upper right) and Water's view (Fig. 22, upper left) showed that the superior, lateral, and inferior orbital walls were present bilaterally; however, the medial orbital walls were absent, resulting in a single median orbit. The zygoma (Fig. 22, upper left) was displaced inferolaterally with respect to the midline orbit, and the zygomatic temporal arch (Fig. 22, upper left) curved medially in a superior direction. The lateral walls of the orbit were drawn medially because of the abnormal development of the frontal and maxillary bones. A midline ridge partially divided the orbital cavity superiorly (Fig. 22, lower left). The ethmoid bones were severely hypoplastic; the nasal, vomer, and lacrimal bones were absent.

The orbit was shallow (Fig. 22, lower right) as a result of the hypoplasia of the frontal bone and its high arch. There was a less-than-normal projection of the superior orbital margin (Fig. 22, lower right). These findings resulted in a shallow anterior cranial fossa and a flat face, best seen on the lateral view (Fig. 22, lower right). A single optic nerve canal was present in the middle portion of the sphenoid bone, as seen on the posteroanterior view (Fig. 22, lower left) and lateral projections (Fig. 22, lower right). The greater wing of the sphenoid was displaced medially but was intact (Fig. 22, upper right, open arrows). Both foramina ovale (Fig. 22, upper right, long arrows) and foramina spinosum (Fig. 22, upper right, thick arrows) were present bilaterally.

The maxilla was hypoplastic, medially located, and contained teeth that appeared to be normal for this age of gestation (Fig. 22, upper left, open arrows). The nasal cavity, and nasal bones were absent, but a small hypoplastic nasal septum was present (Fig. 22, upper right, and Fig. 22, upper left). The proboscis with a lucent cavity (Fig. 22, upper left) was present above the midline orbit. The radiographic findings are summarized in Table 3.

REVIEW OF 34 CASES

Forty-eight cases coded as synophthalmia or cyclopia in the Registry of Ophthalmic Pathology at the Armed Forces Institute of Pathology were

Table 3. Summary of radiographic findings in the present case of synophthalmia

Shallow single median orbit
Hypoplasia of ethmoidal, sphenoidal, and maxillary bones
Absence of nasal, vomerine, lacrimal, and premaxillary bones
Narrow spenoidal bone with single midline optic canal
Hypoplasia and medial displacement of the zygoma and zygomaticotemporal arch
Well-formed cranial bones posterior to the pituitary fossa, including petrous portions of the temporal bones
Absence of central incisors

reviewed. Cases were included in this study if the gross description or a picture of the upper facial region of the fetus confirmed the presence of a single midline orbit and usually a proboscis above the eye region. In instances in which no proboscis was present, the case was included if there was no evidence of a normally situated nose. In cases in which only slides or the microscopic description was available, the case was accepted if the ocular structure contained parts of two eyes; there were no cases eliminated because only parts of one eye were found. The diagnosis was made on data obtained from the gross or microscopic description of the specimen, the histologic sections of the eyes, and/or clinical pictures of the face. Thirty-four cases conformed to the criteria and were included in this study. Fourteen cases were eliminated for the following reasons:

1. Neither the slides nor the clinical description were adequate to confirm the diagnosis in seven cases;
2. The autopsy report or histopathologic report of the eyes described two separate eyes or unspecified primitive ocular tissues in two cases;
3. Two specimens were examples of severe diposopus tetrophthalmus with partial twinning of the head and face, each with a set of two eyes, and fusion of the orbits laterally. One specimen on gross examination had two optic chiasms;
4. In two specimens the eye and brain tissues were grossly so rudimentary and abnormal that the diagnosis could not be confirmed and tissue sections were not available;
5. One case of cebocephaly was also coded as cyclopia, but there were two distinct orbits, only one of which contained an eye grossly, a case better described as unilateral anophthalmos.

Clinical data

A summary of the findings in the 34 cases included in this study follows. Sixteen were females, nine were males, and the sex was not stated in nine.

One was stillborn; 17 lived less than 2 hours; and one lived 10 hours, one 8 days, and another, 28 days. The condition at birth was not stated in 13. The gestational age of the fetuses varied. The youngest specimen was a 5-cm fetus (case 3). Four fetuses were less than 24 weeks of gestational age. The age in ten was estimated at 24 to 38 weeks and at 40 weeks in three; it was not stated in sixteen. The two largest infants weighed 8 lbs 13 ozs (case 15) and 9 lbs (case 25). Most of the fetuses weighed from 1,500 to 2,500 gm.

The pregnancy was listed as unremarkable in only one case. No information about the pregnancy or the family was available in 26 cases. One mother had received parenteral medroxyprogesterone once every 3 months for 3 years but had not received this hormone for 4 months prior to the conception of the child (Batts et al., 1972). One mother suffered from mild preeclampsia that was treated with cholorothiazide during the third trimester (Fujimoto et al., 1973). In one case the mother was treated for syphilis before the 18th week of pregnancy and had polyhydramnios (case 12). Vaginal bleeding was present in two mothers. In another instance, the pregnancy resulted in twins, one infant being normal and the other a cyclops. The final specimen was one of 14 siblings. Of the others, three were normal, four had cleft palate, and six had one of the following disorders – cerebral palsy, bifid uvula, strabismus, seizures, and facial peculiarities. The remaining two pregnancies of this mother resulted in miscarriages (case 26).

Chromosome studies were available in only three cases, and two were examples of trisomy 13. The karyotypes were 47, XY, D+ in case 16 (Batts et al., 1972) and 46, XX, −14, +t (13q14q) in case 17 (Fujimoto et al., 1973). The third karyotype was 46, XX. In an additional case, the father of one child with synophthalmia had by another wife a second child similarly affected.

A central midline proboscis above a single orbit was present in 18, absent in 6, and not described in 10. Only one of the proboscises was listed as imperforate (case 16).

The cerebral malformations are tabulated in Table 4. The available descriptions of the brains varied from a single diagnosis of 'arhinencephaly' to a detailed autopsy report. In fourteen patients the cerebral descriptions essentially conformed to a diagnosis of arhinencephaly (holoprosencephaly), i.e., nondivision of the cerebral hemispheres, single ventricular cavity, telencephalic cyst, and absence of the corpus callosum, olfactory apparatus, and septum pellucidum. These were listed under holoprosencephaly. Detailed descriptions of the brain were available in seven cases. In these cases the neural structures caudal to the mesencephalon were unremarkable except

Table 4. Cerebral anomalies in 35* cases of synophthalmia-cyclopia

Holoprosencephaly+	14
Holoprosencephaly with frontal meningoencephalocele	1
Holoprosencephaly with hydrocephalus, calcification of meninges	1
Malformation of brain, frontal meningoencephalocele	1
Craniorachischisis	1
Agenesis or hypoplasia of cerebral hemispheres	5
Hydrocephalus	1
Agenesis of right cerebral hemisphere	1
Not described	10
Total	35

* Includes the present case and 34 additional cases on file in the Registry of Ophthalmic Pathology.
+ Includes cases diagnosed as holoprosencephaly or arhinencephaly and cases with a description compatible with this diagnosis.

for the absence of the corticospinal or bulbospinal tracts. Other cerebral abnormalities are listed separately in Table 4. In most cases, no comment was made about the presence or absence of the pituitary gland, and therefore this feature could not be tabulated.

Somatic defects were found in 13 out of 34 cases and are listed in Table 5. Cases in which multiple somatic defects were found are summarized in Table 6. Two cases with multiple somatic defects are proven cases of trisomy 13 (cases 16 and 17). In one previously unreported case with multiple somatic defects, intraocular cartilage was found in both eyes (case 19). This case occurred before techniques of chromosomal analysis were available. In case 26, 10 of 14 siblings had deformities of the face. The eyes here were severely disorganized, suggesting that either inherited or environmental factors were involved. In case 27, the jaw was absent, but a rudimentary mouth was present suggesting cyclopia associated with otocephaly. Calcification of the meninges and myocardium and hydrocephalus in case 6 may indicate an intrauterine infection, but no chorioretinal scars were described.

Genitourinary and cardiac anomalies were noted most frequently.

Ocular findings

The 34 cases included in this study were divided into two groups. The first group consists of 24 cases in which a picture, a description, or a microscopic slide of the ocular structure was available. In each of the cases in group 1, some information was available on both the anterior and posterior parts of the ocular structure. There were two cases of true cyclopia; the remaining

Table 5. Summary of somatic findings in 13 cases of synophthalmia-cyclopia

Cardiovascular anomales		9
Two leaflets of tricuspid valve, right ventricular hypertrophy	1	
Truncus arteriosus, patent foramen ovale, ventricular septal defect	1	
Tetraology of Fallot	1	
Interventricular septal defect, overriding aorta	1	
Calcification of myocardium, cor biloculare	1	
Atrial septal defect, dislocation of right ventricle, mitral valve aplasia	1	
Patent foramen ovale	1	
Interventricular septal defect	1	
Transposition of the great vessels	1	
Genitourinary anomalies		12
Bicornuate uterus	2	
Bicornuate uterus, hyperlobulation of kidneys	1	
Bicornuate uterus with hyperplasia of kidneys	1	
Bicornuate uterus, imperforate vagina	1	
Cryptorchidism	1	
Cryptorchidism, hyperplasia of kidneys, hypoplasia of penis and testis	1	
Bilateral renal dysgenesis	1	
Polycystic kidney	1	
Polycystic right kidney, aplastic left kidney urogenital cloaca	1	
Hydronephrosis, hydroureter	1	
Horseshoe kidney	1	
Gastrointestinal anomalies		6
Omphalomesenteric duct	1	
Meckel's diverticulum	1	
Malrotation of intestines	1	
Splenic cyst	1	
Accessory spleen	1	
Dilatation of colon	1	
Skeletal anomalies		11
Supernumerary digits	5	
Talipes equinovarus, congenital hip lesion, genu valgus	1	
Talipes equinovarus, aplasia of fifth finger, webbed toes	1	
Supernumerary finger, anomalous cervical vertebra, hypoplasa of ethmoidal, nasal, and sphenoidal bones	1	
Absence of nose and nasopharynx and ethmoidal and sphenoidal bones	1	
Atresia of nasal cavity	1	
Simian creases in hands	1	
Pulmonary findings		3
Trilobed lung	1	
Atelectasis	1	
Hypoplasia of right lung	1	
Other findings		5
Pyramidal lobe of thyroid	1	
Hypoplasia of adrenal and thyroids	2	
Hyperemia of viscera	1	
Lymph nodes, cervical	1	
Physical appearance, other than cyclopia, was unremarkable		5
Physical appearance, other than cyclopia, was not described		16
Number with somatic defects		13
Total		34

Table 6. Ten cases with multiple somatic anomalies (M.C.A.)*

Case No.+	Anomalies
1	Supernumerary digits of hands and feet; low-set ears; bicornuate urterus, hyperplastic kidneys; tetrology of Fallot; absence of right umbilical and inferior hypogastric arteries; accessory spleen; cervical lymph nodes
4	Hydronephrosis, hydroureter, patent foramen ovale, hyperemia of viscera
6	Calcification of meninges and myocardium, cor biloculare, splenic cyst
8	Interventricular septal defect with overriding aorta, malrotation of intestines, polydactylism, uterus didelphys. (Twin was normal.)
16	Omphalomesenteric duct, cryptorchidism, microcephaly, supernumerary fingers, hyperplasia of kidneys, hypoplasia of penis and testes, pyramidal lobe of thyroid, karyotype 47, XY, D+ (Fig. 28) (Batts et al., 1972)
17	Supernumerary digit on left hand, bicornuate uterus, two leaflets on tricuspid valve, Meckel's diverticulum, hyperlobulation of both kidneys, hypoplasia of right lung, right ventricular hypertrophy, mother with preeclampsia, karyotype 46, XX, −14, ++ (13q14q); (Figs. 25 & 26) (Fujimoto et al., 1973)
19	Interventricular septal defect, talipes equinovarus, absence of fifth digit on right hand, hypoplasia of fifth digit of left hand, incomplete separation of toes, trilobed lung, possible trisomy 13 (Fig. 21)
23	Polycystic right kidney, aplasia of left kidney, urogenital cloaca, clubbed feet, congenital hip, gena valga
30	See Table 8.
33	See Table 8.

* See Table 7 or 8 for data on eye, brain, proboscis.
+ Case number as listed in Table 7 or 8.

twenty-two showed some degree of partial pairing, that is, synophthalmia. In Table 7 the eye structures in each of these cases and in our case report (total of 25) are tabulated in order of degree of increasing doubleness of ocular rudiments, called bicentricity. The two cases of true cyclopia with single median eyes and no evidence of bicentricity are listed first (Figs. 23 & 24). In case 2, the cyclopian eye contained two choroidal colobomas; all other parts were single. Each ocular structure about which data were available is listed separately, so that cornea, anterior chamber, etc. were given a numerical value to indicate the degree of singleness or doubleness of each part of the eye. When two structures were clearly present, as two separate corneas, a value of 2 was given. When a structure was partially double but blended into a single structure, a value of 1+ was given, e.g., the scleral hemiseptum in our case report (case 18). In cases 3 to 25 some degree of bicentricity was observed; bicentricity was described only in the cornea in case 4, whereas in case 25 the globes were almost completely separate and only the optic nerve was single. In all cases, the bicentricity was more fully developed anteriorly, and singular structures occurred wit-

Table 7. Summary of anterior-posterior organization of the ocular structures in 25 cases of synophthalmia-cyclopia (Proboscis & Brain included)

Case Number	Cornea	Anterior Cham.	Pupil	Irides	Coloboma	Angle	Lens	Ciliary Body	Coloboma	Vitreous	Med. septum retina	Med. septum ret. ch. scl.	Post. seg.	Op. N. head	Coloboma	Op. nerve	Proboscis	Brain	Other
1.	1	1	1	1	–	1	–	1	CC	D						+	P	H	Multiple congenital anomalies.
2.	1		1	1	–	1	1	1	2	–	–	–	1	0	–	0	ND	ND	Meyer, S., Verhoeff Soc. 1969.
3.	1+	–	–	–	–	–	–	–	–	–	–	–	–	–		–	R	ND	5 cm fetus with hemosiderosis.
4.	2	*			–	–	–	–	–	–	–		–	–	–	1	R	A	
5.	1+	–	2	2	–	–	–	–	–	–	–	1+	–	–	–	1	O	M	Frontal bone defect.
6.	–	–	2	1+	–	*	–	–	–	–	–	–	–	–	–	–	P	H+	Calcifications of meninges & myocardium, cor. biloculare.
7.	2	*	–	–	–	–	–	–	–	–	–	–	–	–	–	–	P	C	
8.	2	*	–	–		–	–	–	–	–	–	–	–	–		–	P	H	Twin with normal sibling.
9.	2	*	–	–	–	–	–	–	–	–	–	–	–	–	–	0	P	A	Body grossly normal, Optic nerve absent (contributor).
10.	2	2	2	2	*			–	–	–	–	–	–	–	–	0	P	H	Body grossly normal.
11.	2	1	1+	1	1	1	2	2	CC	1+	1+	–	1	1	1	1	O	As	Facial, cerebral, ocular asymmetry specimen; poorly differentiated ant. seg. of small globe.
12.	2	2	2	2	–	2	2	1+	–	1	1+	–	1	0	–	0	P	H	Mother with syphilis; op. n. aplasia; R. Levine; AFIP Oph. Path. Alumni; June, 1975.
13.	2	–	2	2	2	*	2	1	–	1+	1+	–	1+	1+	+	1	P	H	
14.	2	2	2	*	–	–	–	–	–	–	–			–	–	1	ND	ND	Davies, W., Ophthal. Path. Club, 1953.
15.	2	2	2	1+	+	2	2	0	–	2	1+	–	2	1	1	1	R	A	Pupillary blink, EOM's present; lived 8 days (Melian, 1964)
16.	2	2	2	2	–	2	2	–	–	–	D	1+	1+	–		1D	P	H	Trisomy 13, Common post. seg. filled with undifferentiated neural and mesodermal tissues (Batts et. al., 1972)
17.	2	2	2	2	2	2	2	2	–	–	–	1+	D	1+	–	1	P	H	Trisomy 13. Spencer, Wm., Teaching Slide Exchange Program; Estelle Doheny Foundation (Fujimoto et. al., 1973)
18.	2	2	2	2	–	2	2	2	–	1+	–	1+	1+	1+	1+	1	P	H	Present case
19.	2	2	2	2	2	2	2	2	CC	1+	–	1+D	1+	1		1	P	H	Poss. Trisomy 13; M.C.A. cartilage present bilaterally in colobomas.
20.	2	2	2	2	–	2	2	2	–	2	–	1+	–	1+	–	1	ND	ND	Lund, O.E., European Ophthal. Path. Soc. 1963.
21.	2	2	2	2	2	2	2	2	2	1+	1+	–	1+	1+	1+	1	P	H	Ferry, A., Eastern Ophthal. Path. Club; Miami; 1970
22.	2	2	2	2	–	2	2	2	–	–	–	1+		–	–	1+	ND	ND	Christenson, L., Verhoeff Society, 1966.
23.	2	2	2	2	–	2	2	2		2	–	1+	–	–	–	1	P	H	Multiple congenital anomalies
24.	2	2	2	2	–	2	2	2	–	2	–	1+	2	1+	+	1	P	H	Uniocular atypical coloboma (Lowe, 1967)
25.	2	2	2	2	–	2	2	2	–	–	2	2	1+	1+	–	1+	P	H	9-lb. infant; lived 28 days; normal body and limb movements. Twitching of eye with seizure.

Legend:

2 = Fully developed structure present in each eye.
1+ = Partially paired structures blending into single structure.
1 = Single structure.
+ = Less than a complete structure.
* = Synophthalmic structure; doubling of anterior parts; single optic nerve; area of blending not specified.
0 = Structure absent.
ND = Not described.
A = Cerebral agenesis or hypoplasia.
C = Craniorachischisis.
CC = Coloboma with cartilage.
D = Dysplasia.
M = Meningoencephalocele.
H = Holoprosencephaly.
H+ = Holoprosencephaly with hydrocephalous.
M = Meningoencephalocele.
P = Proboscis present.
R = Rudimentary proboscis.

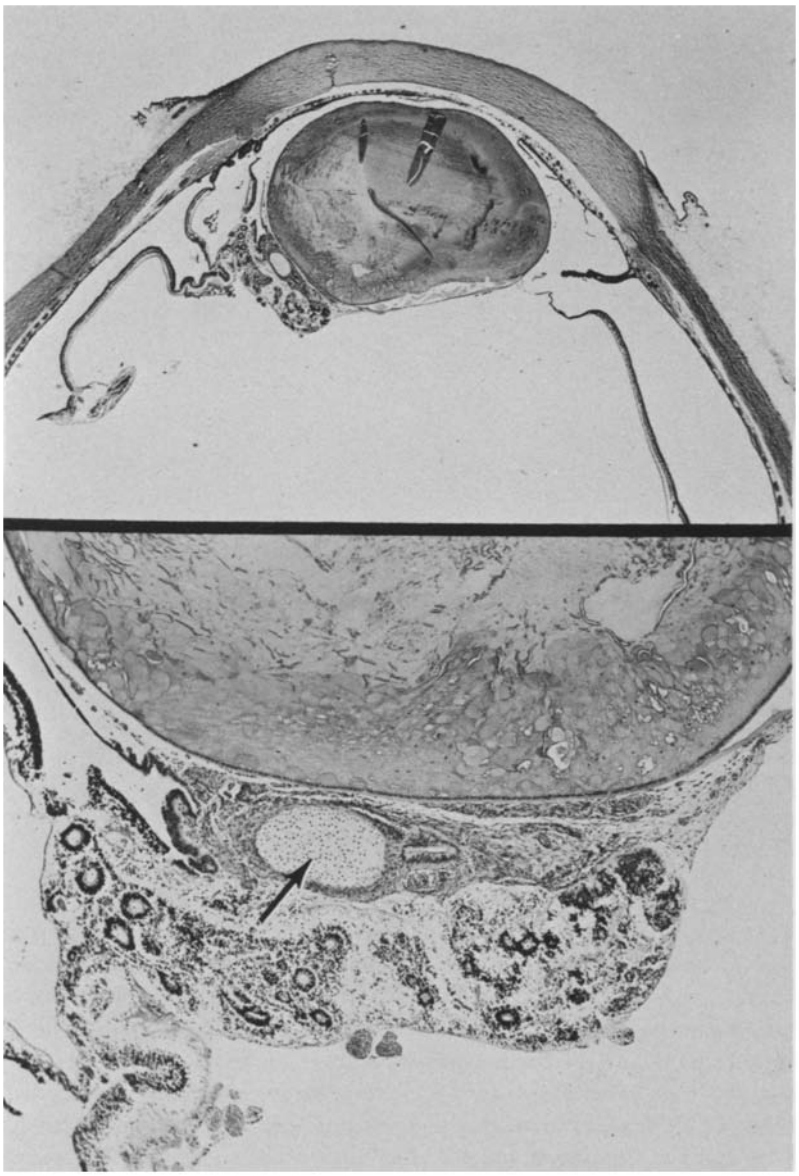

Fig. 23. (Top) True cyclopia. Rare midline ocular structure shows no evidence of bicentricity in anterior segment (case 1, Table 7). (Hematoxylin-eosin, x1-1/2). (Bottom) Arrow indicates cartilage in midline coloboma. (Hematoxylin-eosin, x50).

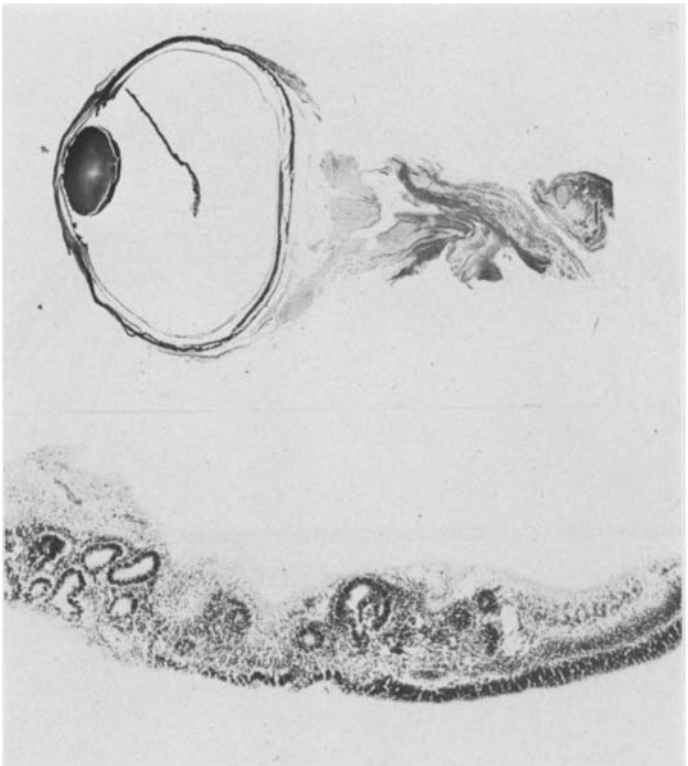

Fig. 24. (Top) Cyclopia. Retrobulbar tissue does not contain axons or dural sheaths (case 2, Table 7). (Hematoxylin-eosin, x4-1/2). (Bottom) Retinal dysplasia in posterior portion of retina. (Hematoxylin-eosin, x55).

hout exception posteriorly and medially (Fig. 25). In no case was the anterior segment singular and the optic nerves or other posterior structures clearly double. In most cases there was evidence of mild dysplasia or poor differentiation of the tissues in the zones that extended between the double anterior parts and the single posterior parts. This was not listed separately, but in all instances dysplasia was more apparent posteriorly and medially (Figs. 7; 25, top and middle). In all but one specimen the two partial eyes were equal in size, shape, and degree of differentiation. In case 11 one globe was larger than the other (Fig. 26). The smaller globe did not contain an anterior chamber, but the ciliary body and a small lens were present. In the smaller globe the ciliary body was colobomatous and contained cartilage. The retina was dysplastic in the common posterior chamber, more severely

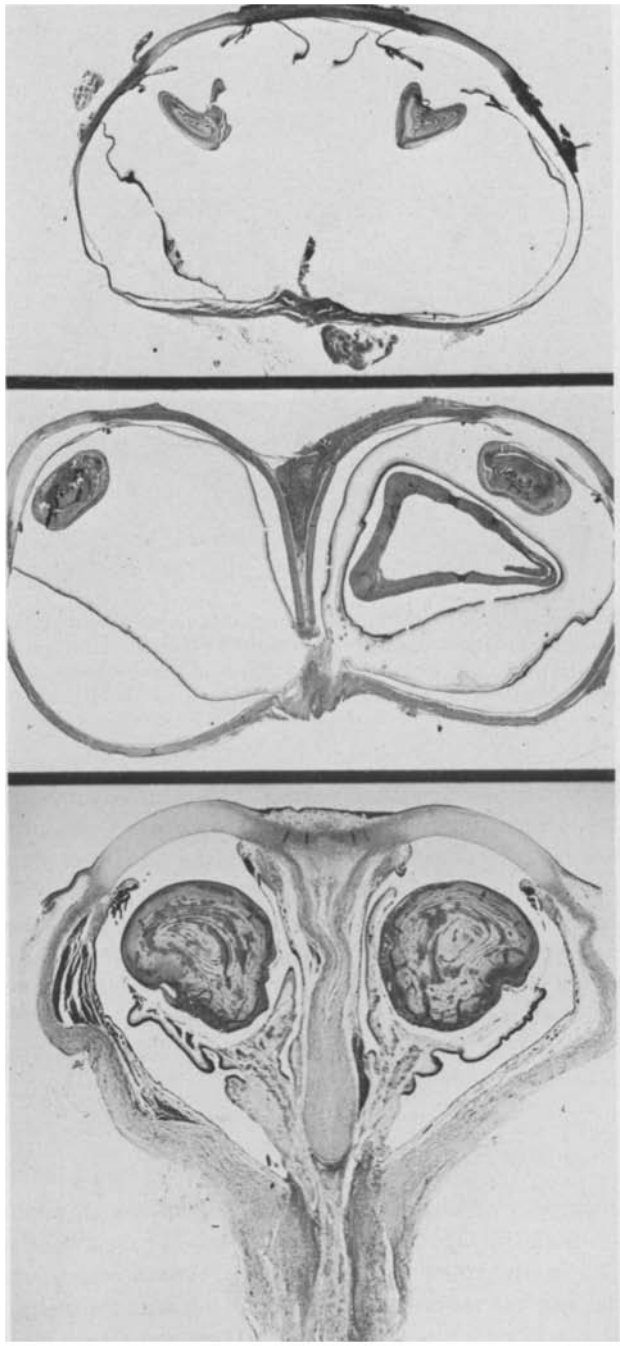

Fig. 25. (Top) Synophthalmic globe with minimal bicentricity and complete absence of median scleral septum (case 15, Table 7). (Hematoxylin-eosin, x3). (Middle) Synopthalmic globe with marked bicentricity and almost complete medial scleral septum. A single optic nerve exits from the globe (case 24, Table 7). (Hematoxylin-eosin, x4). (Bottom) Synophthalmic globe in case with multiple congenital anomalies indicating an underlying chromosomal disorder. Despite advanced bicentricity there is marked retinal dysplasia extending axially down the single optic nerve (case 17, Table 7). (Hematoxylin-eosin, x4).

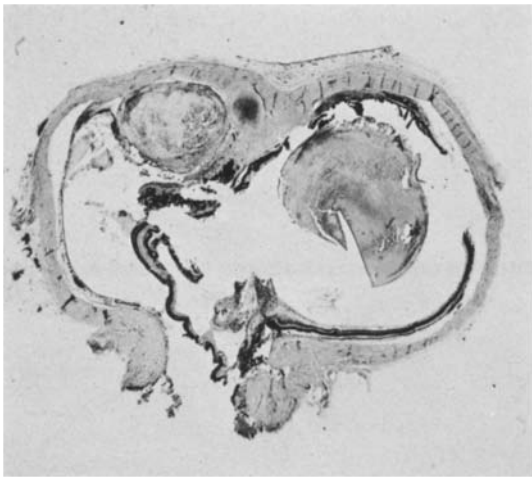

Fig. 26. Asymmetric ocular structure with smaller incomplete globe on left exhibiting poorly differentiated anterior segment filled with the lens, a choroidal coloboma with cartilage, and retinal dysplasia. Incomplete globe on right displays well-developed anterior chamber (case 11, Table 7). (Hematoxylin-cosin, x5).

toward the side of the smaller globe. In the three cases with chromosomal defects, the degree and distribution of the dysplasia posteriorly was still symmetrical, and the development of the lateral structures was more advanced than that of the medial (Figs. 25, bottom; 27).

The second group, consisting of 10 cases not included in the above tabulation, is summarized in Table 8. The ocular structures were not described in these cases, or they were otherwise too dysplastic to be included in Table 7. In three cases (cases 30, 32, & 34) only rudimentary neural tissues were found. In case 35, a dysplastic optic nerve tissue was found intracranially, but no ocular tissues were found in the orbit.

Comment on interesting cases

Case 15, reported by Melian (1964), was an 8-lb 13-oz male infant who was fed through a gastric tube and lived for 8 days. The facial appearance was typical. The pupils constricted, and the lids blinked when tested with a light beam. The extraocular muscles moved the synophthalmic structure. The pupils dilated poorly with mydriatics. There was a pink fundus reflex. Microscopically, the eyes were separated medially by a septum of mildly dysplastic retina (Fig. 26, top). No tunica vasculosa was present. The optic

Table 8. Summary* of 10 cases not included in Table 7+

Case No.	Summary
26	Male; 36 weeks; lived 1 hour; 10 of 14 siblings with facial anomalies; lids fused to cornea, uveal pigment lined the cornea, no Bowman's membrane, no anterior chamber or angle structures, lens with several layers of epithelium, poorly differentiated retina, globe incomplete posteriorly, no optic nerve; proboscis; ND; polycystic kidney; Douglas L. Johnson, Univ. Minn., Midwest Ophthal. Path. Club, 1968; cryptophthalmus with cyclopia.
27	Female; 7 months; ND; two eyes in midline; proboscis; ND; lower jaw absent, mouth appeared as a slit beneath the projecting upper lip; transposition of great vessels.
28	Female; full term; ND; ND; two eyes in midline orbit, rudimentary proboscis; ND; cardiac defects.
29	Female; 2,150 gm.; lived 1 hour; ND; eyes not described; single midline orbit, lids with lashes laterally, no eye sockets or nose; round pedicle at glabella; holoprosencephaly; ND.
30	Female; 2,350 gm.; ND; optic nerves were in continuity with eye structure, which was a single amorphous red mass in center of face; proboscis; hydrocephalus; hypogenesis of ethmoidal, nasal, parietal, sphenoidal bones; imperforate vagina, bicornuate uterus, supernumerary digits, anomalous cervical vertebrae.
31	Male; 902 gm.; lived minutes; ND; quadrangular midline orbital opening; eyes not described; no proboscis; defect in frontal bone with meningoencephalocele; brain without convolutions or fissures, single ventricle; mouth well formed.
32	Female; 580 gm.; lived 2 hours; maternal bleeding; no definite eyes but some 'gray' tissue in midline orbit; no proboscis; no telencephalon or anterior end of the neural tube, but there was a single cavity enclosed by a thin membrane; well-formed superior colliculi and cerebellum; no other anomalies; total failure of anterior neural plate.
33	Male; 1,500 gm.; lived 10 hours; ND; gross description lists single median eye; proboscis; ND; truncus arteriosus; patent foramen ovale, ventricular septal defect.
34	ND; ND; ND; disorganized tissue resembling pigmented and nonpigmented epithelium and dark-staining glial cells (retina) in median orbit; ND; T. Makley, Verhoeff Society, 1967; severe microphthalmia with cyclopian orbit.
35	Female; 2,200 gm.; ND; 4-mm. knot of optic nerve containing primitive retinal cells in anterior cranial fossa ended at calvarium anteriorly; section of tissues from midline orbit showed epithelial and sebaceous glands but no derivatives of neural plate; proboscis; holoprosencephaly; microcephaly; polydactyly, bicornuate uterus, secondary degeneration of cyclopian eye.

* Sequence of data: sex; gestational age or weight; condition at birth; maternal or hereditary factors; description of eye or orbital tissues; proboscis; brain; other anomalies; previous report; secondary diagnosis.

+ Description of eye tissue was not adequate to include in Table 7 or was of special interest.

ND = not described.

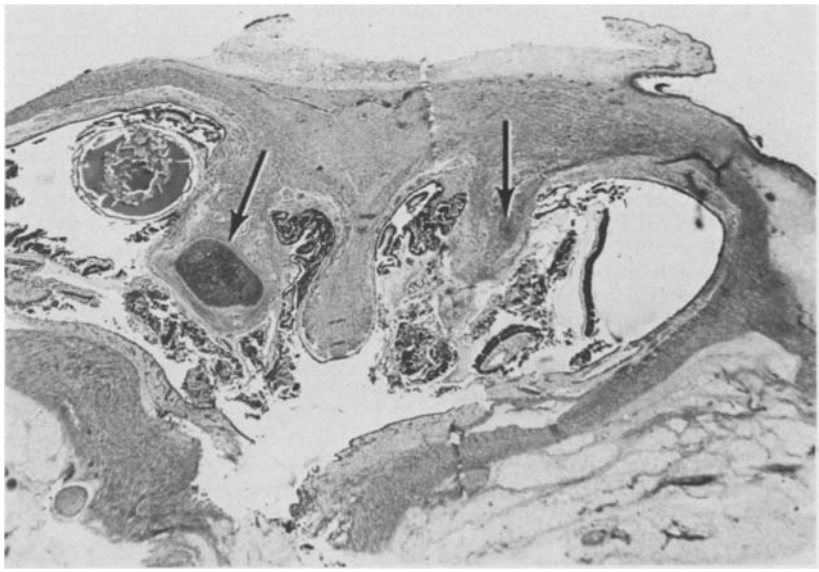

Fig. 27. Synophthalmic globe in patient with multiple congenital anomalies. Bilateral colobomas containing cartilage (arrows) disrupt internal organization of globe (case 19, Table 7). (Hematoxylin-eosin, x11).

nerve appeared atrophic histologically. Autopsy also revealed hypoplasia of the cerebrum, undescended testicles, pneumonia, atelectasis, suppurative bronchitis, and congestion of the viscera.

There were multiple congenital anomalies in case 16 (Batts et al., 1972) and case 17 (Fujimoto et al., 1973), and these cases on karyotyping demonstrated trisomy 13 (Figs. 25, bottom; 28). The posterior segments of these globes were more markedly undifferentiated and dysplastic in contrast to most of the other specimens.

In case 25, the infant weighed 9 pounds at birth and lived for 28 days. He breathed through his mouth and ate from a dropper. The face was cyclopic, and the body was unremarkable. Movements of the trunk and extremities were described as normal. Ocular reflexes were not recorded. The brain was holoprosencephalic, and the autopsy report described the brain stem as lacking the pyramidal tracts. The nuclei of the 3rd through the 12th cranial nerves and the median longitudinal fasciculi were present and paired. The optic nerves emerged from the globes and fused posteriorly in the orbit. The thalami and geniculate bodies were poorly formed.

In case 26, the lids and dysplastic eye tissues were fused, a case of cyclopia with cryptophthalmus.

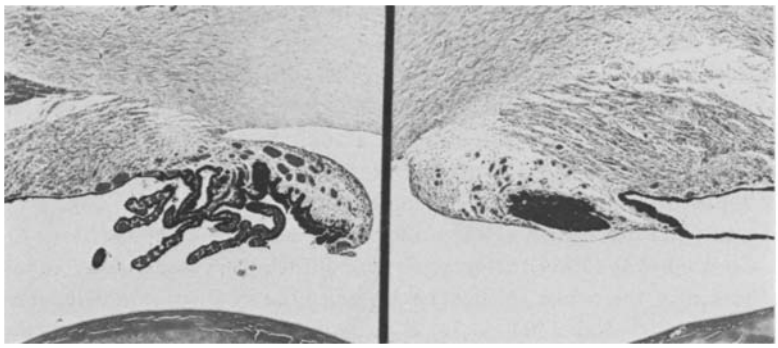

Fig. 28. Anterior segment structures of case illustrated in Fig. 25, bottom, showing typical gradient of more advanced differentiation of iris and ciliary body, temporally (left), than their counterparts, nasally (right). Both portions, however, are highly dysplastic in this case (case 17, Table 7). (Hematoxylin-eosin, left, x50; right, x50).

DISCUSSION

The foregoing data indicate that the defect in synophthalmia-cyclopia is not limited to the eyes but it also includes all rostral structures – upper facial region, the brain, the skull, and the soft tissues. Most of the tissues of the upper head region originate from some form of modulated ectoderm: Neuroectoderm provides brain and eyes, surface ectoderm, and epithelial structures; and from neural crest cells (originally ectodermal) develop the mesenchymal structures (ectomesenchyme or mesectoderm). In the orbit and globe only vascular endothelia and the striated extraocular muscles arise from the mesoderm (Gilbert, 1957; Jakobiec & Tannebaum, 1975). At the root of synophthalmia-cyclopia there must consequently be some widespread disturbance in the growth of these diverse ectodermal primordia.

While this paper is on the subject of synophthalmia-cyclopia, it is also intended as a reassessment of our knowledge of the early development of the eye and its supporting structures, as well as an integration of the often overlooked parallel events that transpire in facial and cerebral morphogenesis. This complex problem will be subdivided into four main lines of analysis: (1) the synophthalmic-cyclopic structure, (2) the cerebral anomaly, (3) the facial and osseous anomalies, and (4) the associated defects.

Synophthalmic-cyclopic structures

To our knowledge this is the largest series of human cases of synophthalmia-cyclopia that have been examined and analyzed systematically and in which

the ocular findings were tabulated in a quantitative manner. The organization of the data available enabled us to identify and isolate the usual or uncomplicated example of synophthalmia-cyclopia from those few cases which have special or atypical features. Our data, obtained from relatively mature human fetuses, also provide a solid basis by which observations derived from the study of animal embryos or from experimentally induced cyclopia can be judged to be relevant and instructive.

In an extensive review of the present subject, Duke-Elder and Duke-Elder & Cook (1963) (1964) categorized synophthalmia-cyclopia as an anomaly of fusion of the ocular anlagen; he described the findings of individual cases and summarized the microsurgical experiments in which synophthalmia-cyclopia had been produced, as well as the teratogenic agents that have been incriminated in its occurrence. Many reports have described synophthalmia-cyclopia associated with teratogenic agents (Binns et al., 1960; Binns et al., 1963; Binns et al., 1959; Bryden et al., 1971; Ingalls & Philbrook, 1958; Rogers, 1964A; Rogers, 1964B; Stockard, 1909); chromosomal anomalies (Batts et al., 1972; Cohen, 1966; Fujimoto et al., 1973; Howard et al., 1974; Pfitzer, 1967). Other reports have focused on concomitant defects (Cohen et al., 1971; Landauer, 1956). Cases with unusual histopathologic features (Leroy et al., 1972; Lowe, 1967) or associates somatic anomalies (Bates et al., 1972; Warkany, 1971) have also been published. All of this previous work provides no clear model of ocular organogenesis, whereby one can understand the embryologic sequence of events underlying this malformation, or of the roles and interactions of the various tissues known to be influential in ocular development.

Yakovlev (1959) describes malformations as simplified models of the ultimate form and structure of normal organs, i.e., curtailments of developmental programs. He divides malformations into two groups. In the first, disorders in cellular differentiation and maturation create disturbances at the level of the tissues, but the organ itself appears grossly to be relatively well formed. These are *histogenetic* malformations. In the second category, cells and tissues differentiate and mature rather well, but the organ itself is disorganized and misshapen. These are *organogenetic* malformations. The phakomatoses are histogenetic malformations; anencephaly, spina bifida, and the Arnold-Chiari malformations are organogenetic. There may be some overlapping of the two groups. The data gleaned from our 35 cases, summarized in Tables 1, 2, 7, and 8, illustrate the histogenetic orderliness of synophthalmia-cyclopia, whereas the hideous cyclopian appearance of these children grossly expresses the organogenetic nature of most cases. This conclusion is reinforced by the functional capacity of the synophthalmic eye, the holoprosencephalic brain, and the orbital structures manifested and

recorded in our cases: pupillary response, blink, and extraocular movements in case 15 (Melian, 1964) and the normal body and limb movements described in case 25. In these instances, many neural cells had differentiated fully and were able to form synapses and transmit neural impulses; the complex reflex neural arcs for pupillary response and limb movements were at least partially intact.

One important exception to the concept of orderly histogenesis in synophthalmia-cyclopia is found in cases where there is an underlying chromosomal anomaly (see Fig. 28 and Table 7, cases 16, 17, and 19). Since a defective genome is carried by each cell in the body, the ocular tissues in cases of synophthalmia-cyclopia with abnormal karyotypes show a high degree of dysplasia in addition to the organogenetic malformation. Compare the marked retinal dysplasia and disorganization of the posterior segments of the globes in Fig. 27 with that depicted in Fig. 13. Additionally, uveal colobomas, not a conspicuous feature in most of our cases, were found in cases 16, 17, and 19, in which a chromosomal defect occurred. The only other case in our series that had a coloboma with cartilage was case 1, the true cyclops, and this case also had multiple somatic malformations, suggesting an underlying genetic defect.

In cytogenetic studies of cases of synophthalmia-cyclopia, the most frequently encountered karyotypes are those with an extra chromosome in the 13 group or rarely an unbalanced DqDq translocation (Batts et al., 1972; Fujimoto et al., 1973). Other abnormal karyotypes have included a deletion of the short arm of chromosome 18, 18 ring formation, mosaicisms, and trisomy B (Batts et al., 1972; Cohen, 1966. Cohen et al., 1971; Howard et al., 1974; Warkany, 1971) (see Table 9). Although the association between

Table 9. Chromosomes in synophthalmia-cyclopia

Chromosomal Analysis	Author
Normal 46XX, 18p− 46XY, 145XY, G− 46XY, 147XY, mar.+ 46, XX, D−, +(u.c. Dq)+mat. 47, XX, D+	Batts et al., 1972 (summary)
18 ring	Cohen, 1966
47, XX, +13 46, XX, −14, +t(13q14q)	Fujimo et al., 1973
B trisomy	Howard et al., 1974

trisomy 13 and synophthalmia-cyclopia is well documented most infants with trisomy 13 do not have synophthalmia-cyclopia, and many infants with synophthalmia-cyclopia have normal karyotypes or a variety of other chromosomal defects (Cohen et al., 1971; Warkany, 1971). This fact underscores the distinctness of the organogenetic disturbance, which probably can occur in the absence of a chromosomal alteration. Although the presence of multiple somatic anomalies in a case of synophthalmia raises the possibility of an underlying chromosomal defect, cases of synophthalmia-cyclopia, cebocephaly, and trigonocephaly with multiple somatic defects have been shown to display normal karyotypes by the conventional techniques used in cytogenetics (Karseras & Laurence, 1975; Duke-Elder & Cook, 1963; Warkany, 1971). The defect may reside in the alteration of a single gene rather than in additional chromosomal material or faulty location of chromosomal fragments. The multiple somatic defects of the synophthalmic fetus in case 8 are listed in Table 6. The twin of this case was described as normal. Chromosomal studies were not undertaken in these twins.

Apart from those cases in which a chromosomal abnormality was associated with the ocular and somatic anomalies (Batts et al., 1972; Fujimoto et al., 1973), the overall orderliness of the midline ocular structure in these anomalies is striking. We found two gradients of differentiation: proximal-distal (or anteroposterior, if the reference is the eye) and lateral-medial. Even in the cases with chromosomal defects, these organogenetic gradients were noted, although the tissues participating in organ formation were more disorganized than in the cases of isolated cyclopia.

Table 7 lists all cases in which data were available on the appearance of the anterior and posterior segments of the ocular structure in order of increasing degree of bicentricity. The first two cases were the only examples of true cyclopia in the series. Each had a single cornea and displayed singleness of all ocular structures posteriorly. The final specimen tabulated showed the greatest degree of bicentricity, in that all of the ocular structures were paired, but two nerve trunks subsequently blended to form a single optic trunk without chiasm (case 25). In general, the portions of the synophthalmic structure most distal from the brain showed the highest degree of bicentricity. Comparatively well-formed anterior segments were usually present, whereas more proximal to the brain there was often a single vitreous chamber, mild retinal dysplasia, a large hollow opening at the optic nerve head, and a single optic nerve. The axons present in the optic nerve indicate that retinal development and ganglion cell differentiation had reached an advanced stage of sytogenesis.

The second gradient of differentiation, the lateral-medial, evidenced itself

in relatively normal architecture along the lateral aspects of the synophthalmic structure. Temporally, corneal differentiation, cleavage of the angle, iris, and ciliary body architecture, and retinal lamination were more advanced when compared to their nasal counterparts.

A brief review of the early embryologic events that normally occur in ocular development will help to put the remainder of the discussion in perspective (Adelmann, 1936; Duke-Elder & Cook, 1963; Duke-Elder, 1964; Hamilton & Mossman, 1972; Johnston, 1974; Johnston et al. [in press], Mann, 1957; Saxén & Rapola, 1969). In the human, paired optic primordia appear in the neural plate before the 2.6-mm stage (third week of gestation). The induction of the ocular anlagen occurs during the second and third week after the mesoderm has migrated to lie subjacent to most of the ectodermal layer. Evagination of the optic vesicles begins as the cranial end of the neural tube closes. The ocular anlagen are present bilaterally well before the telencephalic vesicles begin to evaginate.

A primary fusion of the two ocular anlagen during early organogenesis, when the cells are still labile and not fully committed as eye-forming tissue, might conceivably result in the mirror-image symmetry demonstrated in these cases. If one postulates a later fusion of established eye vesicles, however, then it must also be postulated that selective, symmetrical degeneration of midline cerebral and mesenchymal tissues occurred, allowing the eyes to come near enough to each other to fuse. If this hypothesis were the usual mechanism for the development of synophthalmia-cyclopia, then other types of midline structures, such as a single anterior segment and doubled posterior segments with two optic nerves, should also have occurred. Since anomalies with various configurations, such as doubling of the posterior segment combined with a single anterior segment, did not occur, one can assume that from the beginning there was an error in organogenetic programming in the neural plate.

Additionally, degeneration of midline structures and fusion should have produced more asymmetry and disorganization of the ocular, cerebral, and osseous structures than was usually found in our specimens. Of the 25 cases listed in Table 7, only one (case 11) showed ocular asymmetry, whereas the remaining 24 cases were symmetrical. Unilateral cerebral agenesis and asymmetry of the face were also noted only in this one case. It may be speculated that in this case a second embryologic disaster (e.g., unilateral ischemia) occurred after the synophthalmic structure was established and resulted in asymmetry and more profound disorganization of tissues on the affected side. Nonetheless, ocular bicentricity in an anterior-posterior gradient was present in case 11.

In view of the advanced stage of histogenesis of the synophthalmic-cyclopic

structures, adverse events resulting in synophthalmia-cyclopia must occur at an extremely early stage of embryogenesis. The ocular anlage in synophthalmia-cyclopia induced from the neural substrate was capable of completing an elaborate program of ocular histogenesis. The usual sequence of secondary induction in ocular development had occurred with a high degree of fidelity; e.g.: the optic vesicles induced the lens placodes from surface ectoderm, the invagination of the optic cups and lenses occurred, and axons from the retinal ganglion cells secondarily induced the organization of the glial septa as they grew through the orbit toward the diencephalon. Without exception in this series, the posterior aspects of the globes were not separated, only a single optic stalk was formed, and the chiasm was constantly absent.

In an attempt to provide information related to the primary and secondary developmental alterations leading to cyclopia, some fundamental embryologic studies will be reviewed. Included in this summary are studies in which operative interference led to cyclopia, or else environmental alterations or genetic defects were shown to be the responsible agents.

Adelmann, building on the antecedent work of Stockard (1909, 1913), Spemann (1931), and Mangold (1931) [as well as many others listed in his review (1936)], provided a cogent experimental model for cyclopia, based on micromanipulations of the embryos of *Amblyostoma* and *Triturus* (Adelmann, 1934A, 1929A, B; 1930). His work had two objectives: to establish the extent of the eye-forming territories of the anterior neural plate (Adelmann, 1929a, B) and to determine the tissue that was primarily defective when cyclopia was produced. Spemann (1931) had suggested from his own early experiments that the prospective eye-forming neural plate material was constituted by a fixed mosaic of parts, each of which was strictly predetermined in a tight topographic arrangement to develop into a particular structure of one eye. In his first experiments, Adelmann (1929A,B) excised portions of the presumptive ocular neural plate and showed that, within certain limits of excision, two eyes would almost always form. The missing neural plate was reconstituted by proliferation of the remaining cells; he thus refuted the concept of a fixed mosaic in the neural plate.

From Adelmann's experiments with amphibians (1929), it was determined that the prospective material for the two eyes occupied between one-fourth to one-third of the width of the anterior end of the neural plate. When the middle one-third of this area was excised, two eyes and two optic nerves still grew out of the reconstituted neural plate. If the lateral third of the neural plate was excised on one side, two eyes would still develop from the residual median neural plate, but the eye on the excised side might be microphthalmic. If the excision was carried close to the midline, anoph-

thalmia on the side of the excision was usually produced; the remaining lateral neural plate did not proliferate to produce part of an eye, as occurred with the median tissues. Cyclopia was never observed in any of these experiments, regardless of the extent or location of the excisions of neuroectoderm (Fig. 29, top). Adelmann concluded that the presumptive ocular medullary epithelium is a diffusely organized, labile field, which in its incipient stages is equipotential with respect to the development of all parts of the eye that originate from the neural plate. The chiasmatic-optic nerve region was not confined to the midline material, which is plastic and relatively indifferent with respect to its final fate until the later stage of bicentricity appears.

Next Adelmann transplanted presumptive ocular neural plate to the abdominal wall of the embryo (1929B). Transplants of midline neural plate, usually with only remnants of underlying mesoderm, grew out as abortive ocular structures but only in a minority of instances. Chiasmatic tissue never developed from the transplanted midline material.

In a related series of experiments in which the underlying mesoderm was also intentionally transplanted in larger amounts with the neural plate, a much higher yield of ocular differentiation was obtained (Adelmann, 1930). The median neural plate in company with the underlying mesoderm was even able to develop occasionally into two eyes but always without optic nerves and chiasm.

In his third group of experiments, Adelmann (1934A, B) folded back the neural plate and excised some of the subjacent mesoderm; with this maneuver he was frequently able to produce cyclopia (Fig. 29, bottom). This experiment confirmed the critical role of the mesoderm in bringing out the full eye-forming potencies of the anterior medullary epithelium in amphibians.

In agreement with other embryologists, Adelmann (1936) summarized the experimental data on cyclopia produced in various fish and amphibian embryos: 1) A fusion of established eye vesicles did not usually occur; 2) the potential eye-forming tissues are located in the anterior end of the neural plate; 3) the localization of eye-forming potencies in the neural plate proceeds largely under the inductive and/or otherwise supportive influence of the underlying mesoderm.

Since the neural plate would already have been induced by the underlying mesoderm before the developmental stage at which Adelmann conducted his experiments (Saxén & Toivonen, 1962), it seems probable that subsequent decreased neural plate development leading to coalescence of the optic fields would be related to the lack of growth support by the mesoderm (Källen, 1956). Raising amphibian embryos in media containing increased salt concentration leads to incomplete migration (gastrulation) of

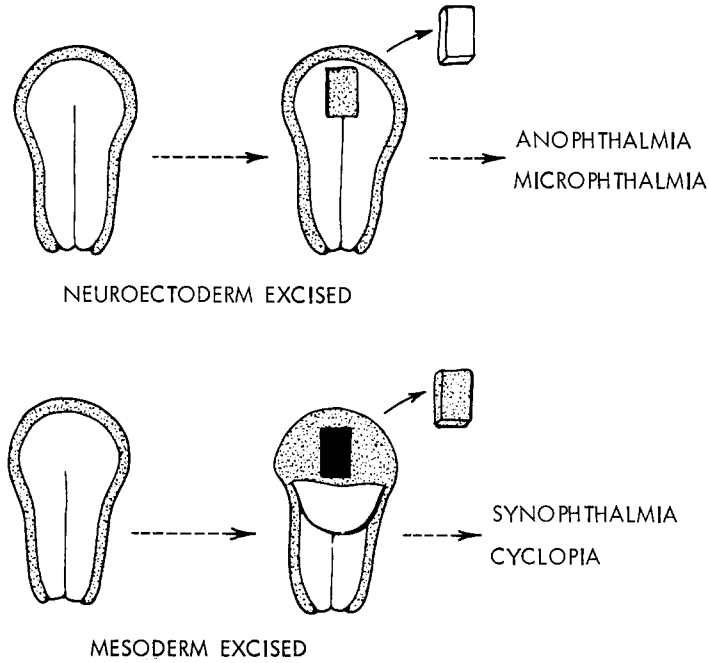

Fig. 29. Experiment of Mangold and Adelmann in amphibians. Excision of a portion of the midline neural plate (neuroectoderm) failed to produce synopthalmia-cyclopia (top), whereas removal of mesoderm subjacent to neural plate (folded back) produced synophthalmia-cyclopia (bottom). This experiment suggests that the locus of the primary defect in synophthalmia-cyclopia is in the mesoderm. Chromosomal abnormalities and various cytotoxic agents may selectively damage the mesodermal organizer or interfere with its growth.

prechordal mesoderm and to cyclopia (Holtfreter & Hamburger, 1955). In this case, deficient anterior neural plate formation results from inadequate induction and/or growth support.

An alternative model for developmental alterations leading to cyclopia has been presented by Rogers (1964B), and similar results have been obtained by Schowing (1965) and Toerien (1975). In Rogers and Toerien's experiments neural tube (fold) material was removed from between the optic vesicles in chick embryos (Fig. 30).

Finally, a group of toxic agents can injure the anterior neural plate and eye fields, but by and large they do not produce synophthalmia-cyclopia. Environmental agents that interfere almost exclusively with anterior neural plate development result in anophthalmia and microphthalmia, as in the case of Adelmann's experiments, but not in cyclopia (Johnston et al. [in

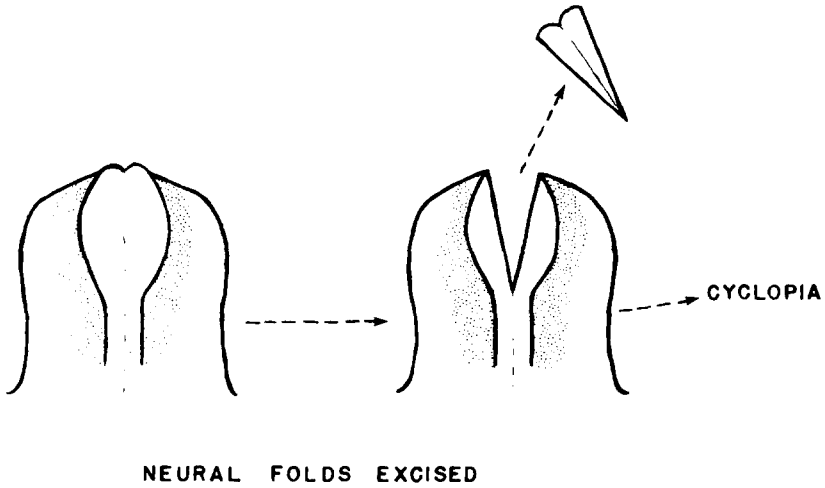

Fig. 30. Dissection of wedge of telencephalic area and part of the diencephalic region during the 6- to 7-somite stage of chicken embryos resulted in cyclopia. Neural folds are stippled (redrawn from Rogers, 1964b).

press]). X-irradiation during anterior neural plate formation causes cell death throughout this structure and results in microphthalmia and anophthalmia but, again, not cyclopia (Bhakdinaronk [in prep.]; Murakami et al., 1961; Murakami et al., 1962). Drugs such as cadmium that selectively destroy neural crest cells (Kushner et al. [in prep.]) also do not cause synophthalmia or cyclopia. In lithium-induced cyclopia, the anterior mesoderm as well as portions of the neural tube are affected, each tissue manifesting decreased RNA and protein synthesis (Rogers, 1964A).

Presence or absence of the pituitary gland may be of significance in synophthalmia-cyclopia. Rogers (1957) has emphasized the fact that the pituitary was present in his specimens; it was absent in most of Adelmann's specimens. Adelmann attributed the absence of the anterior pituitary to the presence below the eye of an abnormal mass of presumptive eye muscle tissue that may have interfered with normal brain-oral ectoderm interaction (Adelmann, 1936).

The pituitary is variably absent in magnesium-induced cyclopia, and Rogers attributed this absence to the more ventral position of the eye rudiment, which consequently impinges on the pituitary area in these cases. It is now apparent (Hammond, 1974) that the anterior pituitary is induced by prechordal mesoderm and that deficiency of this tissue could explain pituitary absence in Adelmann's specimens as well as in magnesium-induced cyclopia.

The pituitary is variably absent in human synophthalmia-cyclopia (Ed-

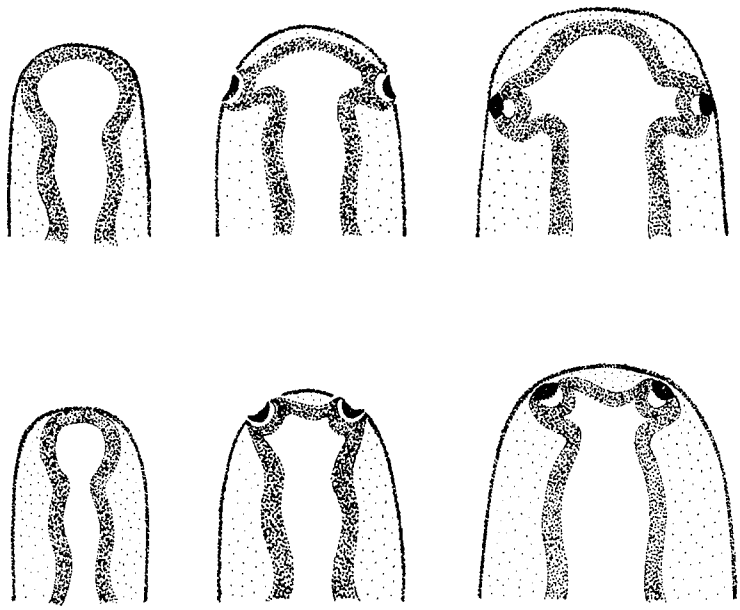

Fig. 31. The sequence above depicts an adequate mesodermal induction of the presumptive ocular anlagen, which grow outward to establish complete bicentricity. The hypothetical sequence below depicts inadequate induction, creating a shared zone in the fields of the presumptive ocular anlagen medially and posteriorly.

monds, 1950; Rogers, 1957) and in the related conditon of arhinencephaly (Hintz et al., 1968; Haworth et al., 1961; Yakovlev, 1959). In familial arhinencephaly the pituitary may be absent in other wise unaffected siblings (Romshe & Sotos, 1973). In the only case of otocephalic cyclopia that the authors were able to locate, the pituitary was present.

There are some animal models of synophthalmia-cyclopia, e.g., spontaneous cyclopia in the chick (Landauer, 1956) and cyclopia resulting from ingestion of veratrum alkaloids in ruminants (Binns et al., 1960; Bryden et al., 1971; Evans et al., 1966). These conditions show a range of synophthalmic-cyclopic malformations closely resembling those found in man. The pathogenesis and histopathology of these defects have not been studied thoroughly. Some limited inferences about the animal disorders can be drawn from the known actions of other drugs producing cyslopia. For example, the vinca alkaloid vinblastine can also produce cyclopia in the rat (De Myer, 1964A): this drug is known to affect cytoplasmic microfilaments and microtubule formation, and hence its adverse influence on cell division and cell movement could mediate teratogenicity (Yamada, 1976). vitamin A produces

cyclopia in the rat (Giroud, 1963) and affects both cell migration and cell division (Johnston et al. [in press]). Such agents would be expected to have effects both on the migration of prechordal mesoderm and directly on neural plate formation. Understanding the precise mechanisms underlying the different forms of synophthalmia-cyclopia requires further study (Figs. 31 & 32).

Synophthalmia, rather than cyclopia, was found more frequently in the present series, in which the smallest fetus (case 3) was 5 cm. in length and the majority weighed more than 1,500 gm. This series is therefore biased; cyclopia, the more extensive malformation, is highly lethal and probably reuslts in early fetal death, as suggested by Nishimura et al. (1966, 1968), who studied elective abortuses. They found a much higher frequency of cyclopia and other malformations associated with holoprosencephaly than expected.

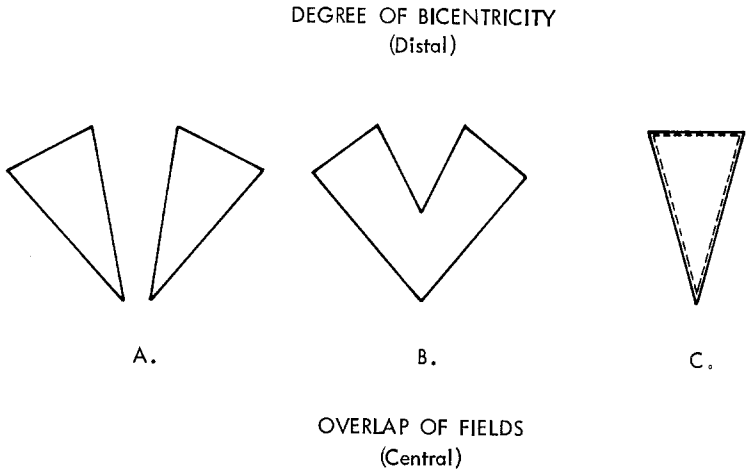

Fig. 32. Simplified diagrammatic comparison of normal ocular fields (A) with hypothetical eye fields in synophthalmia (B) and cyclopia (C). (A) The successful induction of and/or growth support for the anterior neural plate by the mesoderm allows complete bicentricity to emerge as the presumptive ocular anlagen grow outward. (B) Limited induction of and/or failure of growth support for the neural plate entails an incompletely developed median zone in the eye fields. The shared median region may result in single structures proximal to the brain, but some degree of bicentricity usually emerges in the ocular structures most distal from the brain (paired anterior segments and synophthalmia). (C) Minimal induction of and/or growth support for the presumptive ocular anlagen prevents any degree of bicentricity from emerging and results in true cyclopia.

To introduce the discussion on the malformed brain that accompanies synophthalmia-cyclopia, a review of cerebral embryogenesis will be given. During the early somite stage as the neural tube is closing, the optic vesicles evaginate ventrally in the region of the neural tube destined to become the diencephalon. The olfactory buds evaginate in the late somite stage (Yakovlev, 1959). After closure of the neural tube, the rostral end expands and two constrictions occur caudally, segmenting the neural tube into the prosencephalon (forebrain), mesencephalon (midbrain), and the rhombencephalon (hind brain, including the pons, cerebellum, and medulla oblongata). The prosencephalon later segments transversely into the diencephalon (the hypothalamus, thalamus, and optic chiasm) posteriorly and the median nonpaired telencephalon (a holosphere) anteriorly (Yakovlev, 1968). Bilateral evagination from the telencephalon results in the telencephalic vesicles separated by a median plane of cleavage. With continued growth the telencephalic vesicles balloon outward dorsally, laterally, and posteriorly, covering the diencephalon (Hamilton & Mossman, 1972; Yakovlev, 1968).

In synophthalmia-cyclopia, the brain is often designated arhinencephalic, a term first used by Kundrat (1882). Arhinencephaly, in the strict sense, is defined as an absence of rhinencephalon and the olfactory bulbs and tracts. Yakovlev (1959) noted that the rhinencephalon is present in these brains, although the olfactory bulbs, tracts, and tubercles are absent; he pointed out that failure of prosencephalic cleavage is the major defect.

In necropsy examination of 22 infants described as arhinencephalic, Karseras & Laurence (1975) found only three brains in which the absence of the olfactory apparatus was the only cerebral defect. Further, in 1,735 consecutive autopsies studied by Karseras & Laurence (1975), absence of the first cranial nerve was not found. Hence, *arhinencephaly*, in this restricted sense, is extremely rare. *Arhinencephaly* is used more frequently in a less restricted meaning to describe the brain associated with a variety of anomalies including cyclopia (Duke-Elder, 1964; Warkany, 1971), cebocephaly, and ethmocephaly (DeMyer, 1964B; Warkany, 1971; Yakovlev, 1959). The term is also used in an even broader sense clinically to categorize a variety of patients with facial anomalies such as the *'arhinencephalic syndromes'* (Kundrat, 1882; Yakovlev, 1959; Warkany, 1971; DeMyer et al., 1964B; Karseras & Laurence, 1975). The 'arhinencephalic syndromes' usually include prosoporhinal malformations (harelip, cleft palate). Harelip and cleft palate were not found in any of our cases.

The arhinencephalic brain consists of a horseshoe-shaped bank of cerebral

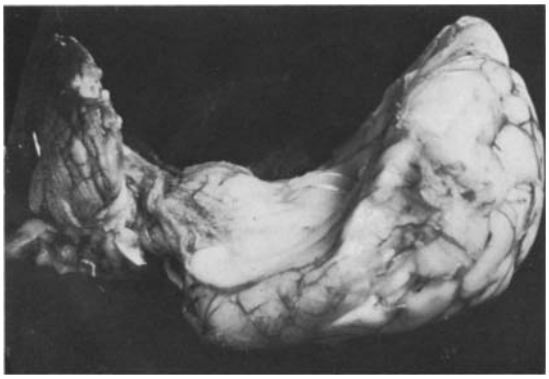

Fig. 33. Lateral aspect of the brain in Yakovlev's case of arhinencephaly shows abortive development of the telencephalon (holotelencephaly) (Yakovlev Collection, #HPC-1-52) (reprinted from Yakovlev, 1959, with permission of the author and publisher).

cortex covering a single ventricular cavity; the olfactory apparatus, corpus callosum, septum pellucidum, and fornix are absent. Yakovlev (1959) described 10 brains in children with arhinencephalic syndromes, none of whom were cyclopic, and termed these brains holotelencephalic to emphasize that the defect is a failure of bilateral evagination of the telencephalic vesicles and of midline cleavage. The defects were variable in the diencephalon; in some specimens the thalami were represented by a single midline mass of poorly differentiated tissues, but the optico-chiasmic structures

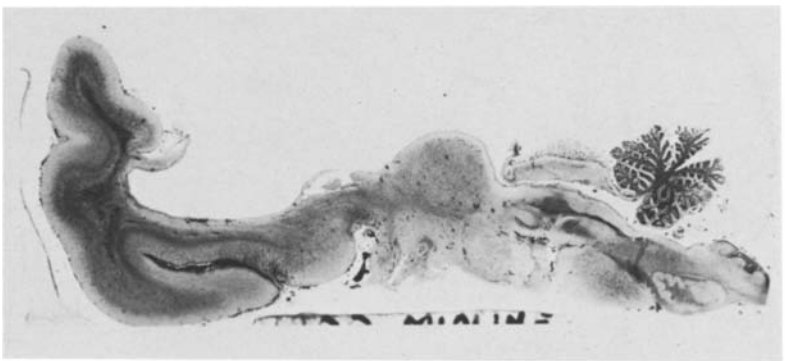

Fig. 34. Sagittal section through the forebrain and anterior neuraxis in a case of holotelencephaly of Yakovlev (1959) discloses primitive development of telencephalic and nearly normal diencephalic structures without synopthalmia (Yakovlev Collection, #HCP-16-54R, level 1200 midline).

of the diencephalon were present. Throughout our discussion we use the term *holoprosencephaly* to designate the brain associated with synophthalmiacyclopia. *Holoprosencephaly* specifies the anatomic region involved, that is, both telencephalon and diencephalon. Holotelencephaly is the term used when the failure of cleavage is limited to the telencephalon. Holotelencephaly and holoprosencephaly are types of arhinencephaly according to the broader use of this term.

Kundrat (1882) postulated that arhinencephaly and cyclopia are related, and their presence in the same sibships (Cohen et al., 1971; DeMyer et al., 1964B) has provided strong support for this idea. Further, the most common chromosomal anomaly in both conditions is trisomy 13. Yakovlev (1959) in his classic paper on holotelencephaly (arhinencephaly) emphasized the bicentric nature of the events underlying telencephalic cleavage. Holotelencephaly and holoprosencephaly are examples of various degrees of failure of cleavage and differentiation of the telencephalic vesicles. Median dorsal structures are more severely affected than ventral structures.

The holoprosencephalic brain reflects a failure of both the hemispheres and the optic vesicles to develop fully bilaterally (Yakovlev, 1968). The interhemispheric fissure does not develop (Figs. 33, 34, & 35). Nonetheless,

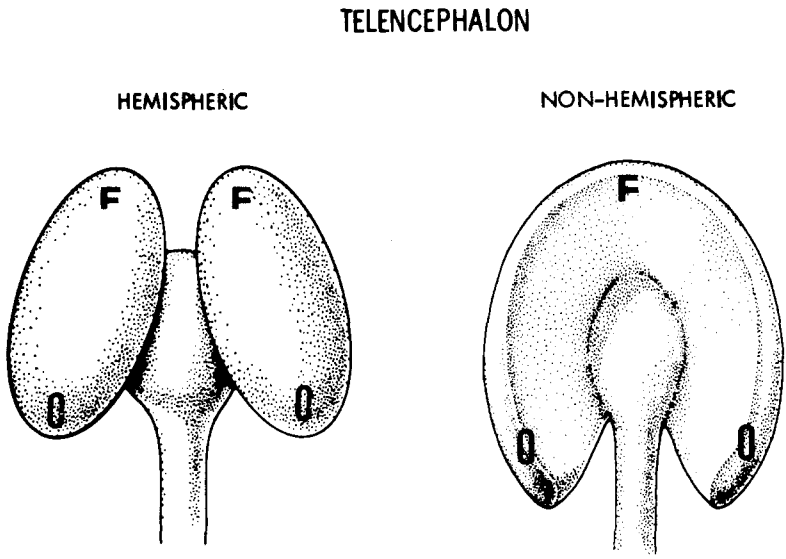

Fig. 35. Diagram of dorsal view of normal hemispheric development of telencephalon is shown on left. The nonhemispheric brain (holoprosencephaly, holotelencephaly, or arhinencephaly) is shown on right (based on Yakovlev, 1959). Corresponding telencephalic areas include frontal cortex (F) and occipital cortex (O).

some degree of advanced histogenetic (vs. organogenetic) differentiation does occur bilaterally.

The dorsal border of the holospheric vesicle – the latter being the cavity in the holoprosencephalic brain that represents the combined lateral and the third ventricles – is rimmed by the arc of the hippocampus and, more ventrally, by a strip of praepiriform cortex (Yakovlev, 1959).

Bilateral evagination of supralimbic cortex-associated areas is invariably missing in holotelencephalic and holoprosencephalic brains. Instead, a single median mass of telencephalic tissue grows outward, producing the holosphere without the appearance of the median hourglass constriction that creates the paired hemispheres. Chronologically, evagination of the telencephalic vesicles occurs as the optic vesicles induce the lens placode in the surface ectoderm at the 30 somite stage (Duke-Elder & Cook, 1963; Hamilton & Mossman, 1972). Thus, the emergence of hemispheric (telencephalic) bicentricity lags behind optico-diencephalic bicentricity (Yakovlev, 1959).

At the summit of the orbital wall of the holosphere, some evidence of cortical differentiation (frontal cortex) is present; the motor cortex (Brodman's areas 4 and 6) is usually present in the midpoint of the bend of the horseshoe-shaped brain (Yakovlev, 1968). Posteriorly and bilaterally on each limb of the horseshoe, parietal, temporal, uncal, and visual cortices are present (Fig. 35). Thus, minimal degrees of bicentric differentiation and cleavage do occur posteriorly. The major defect is the lack of full bilateral evagination, expansion, and differentiation of the cortex-associated areas of the frontal lobes and lack to a lesser degree of the parietal and temporal lobes. Consequent upon this arrest in outward growth is the presence of modest degrees of cortical differentiation more anteriorly and medially than normal (Yakovlev, 1959, 1966). In our case 25, normal movements of the extremities and body were noted, indicating that, despite the severe organogenetic defect and the paucity of neurons in the corticospinal tract histologically, motor and sensory neuronal differentiation was functional to a detectable degree.

Yakovlev (1959) succinctly summarized the findings in holotelencephalic brains by noting an anteroposterior gradient in the failure of evagination and differentiation. He stressed that the prosencephalon or anterior-most part of the neural plate originates from a 'single germinal fountainhead of neuroblasts in the dorsal lip of the anterior neuropore.' Failure of growth and bilateral evagination of this median progenitor mass – that is, non-emergence of bicentricity caused by insufficient outgrowth – results, in Yakovlev's terminology, in a 'telencephalon impar' (impar = nondivided). The median germinal mass containing the material of the presumptive hemispheres fails to produce the hemispheric evaginations and undergoes only

the more limited rhinic differentiation – rhinic tissue being essentially a median (ventral) substrate that in organogenesis develops without bicentricity (i.e., without lateralization) (1968). In 'telencephalon semipar' (semipar = partially divided), there is evidence of prosencephalic bicentricity with the development of bilaterally identifiable limbic lobes (calloso-marginal and parahippocampal gyri and orbital cortex). Finally, in 'telencephalon totopar' (totopar = completely divided), supralimbic cortical differentiation is achieved bilaterally, i.e., two complete cerebral hemispheres develop.

The spectrum of disorders represented by synophthalmia-cyclopia is therefore mirrored in the spectrum of brain malformations represented in 'telencephalon impar' (nondivided) and 'telencephalon semipar' (partially divided). Despite the lack of organogenetic bicentricity in the holoprosencephalic brain caused by the absence of interhemispheric fissuring, the tissue that does grow outward farthest from the midline telencephalic-progenitor mass displays relatively normal histogenetic differentiation (temporal, uncal, and visual cortex bilaterally); medial tissues (frontal cortex) are the most severely affected. Similarly we have documented the striking degree of ocular differentiation (anteriorly and laterally) in synophthalmic-cyclopic eyes. The dificiency of frontal cortex corresponds to the faulty opticochiasmatic differentiation. Median rhinic cortical (rhinencephalon) differentiation occurs, but the bilateral sensory apparatus (olfactory bulbs, tracts, and tubercles) does not develop.

In his studies, Yakovlev (1959) pointed out that the mesodermal induction of the optic anlagen occurs somewhat earlier than that of the presumptive olfactory and telencephalic vesicles. Consequently, comparatively normal eye development can occur despite the failure of the emergence of telencephalic bicentricity. On the other hand, a failure of bicentricity in the optic anlagen obligates a telencephalon semipar or impar (holoprosencephaly). The reason for this linkage is that involvement of the relatively caudal areas of the presumptive optic anlagen generally implies an extensive failure of induction of the entire median prechordal neural plate. In our cases the brains were always abnormal, and in no case were paired telencephalic vesicles recorded. The face in synophthalmia-cyclopia thus predicts holoprosencephaly or more poorly developed brain tissue, but a more normal-appearing face does not negate the occurrence of holotelencephaly. The organization of the anterior neural plate according to its prospective derivatives is illustrated in Fig. 36. It seems logical that a profound defect in ocular organogenesis might interfere with telencephalic growth, as witnessed by the holoprosencephaly seen with cyclopia. In holotelencephaly of trisomy 13, the eyes are usually microphthalmic, indicating a failure of induction of the more rostral neural plate that does not extend more caudally to the dien-

cephalon (holoprosencephaly); the microphthalmos most likely is caused by histogenetic defects stemming from the abnormal genome.

Three important points must be made in comparing the brain with the ocular maldevelopments: First, the eyes in synopthalmia-cyclopia reach a comparatively higher degree of differentiation than the diencephalon from which they developed, as is evidenced by the eventual emergence of bicentricity of forebrain primordium, so that the structures that differentiate later are more severely affected, since there may be insufficient germinal tissue remaining. In Melian's case 15 (1964) both a pupillary response and blinking of the lids were reported in response to light stimulus, proving that in at least some cases synapses in the diencephalon do occur, on a limited scale.

Second, it appears that early and serious derangements in ocular organogenesis will influence prosencephalic development adversely. Holoprosencephaly represents the most advanced cerebral development that is obligated in conjunction with the anlagen of the synophthalmic-cyclopian eye. Lesser degrees of cerebral malformation such as mild hypogenesis or dysgenesis of the cerebral hemispheres did not occur in our series (Table 3), and to our knowledge has not been reported in a case of synophthalmia-cyclopia (Duke-Elder & Cook, 1963). Whether the defect is primarily a failure of mesodermal induction and support of the neural plate (Adelmann type) or a massive loss or underdevelopment, the eyes and brain in cyclopia-holo-

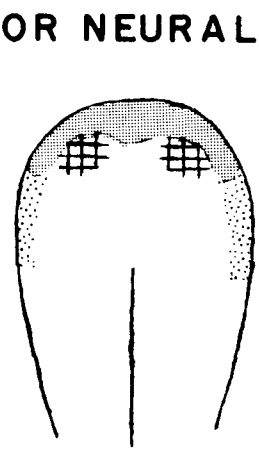

Fig. 36. Neuroectoderm destined as telencephalon (fine stipple) lies rostral to eye fields (crosshatch). Neural crest cells (coarse stipple) are laterally situated (diagram based on work with amphibians by Nieuwkoop et al., 1958).

prosencephaly seem linked together by a shared embryologic disaster that awaits further elucidation.

Third, the defect in cerebral development may be restricted to the presumptive telencephalic primordia, resulting in holotelencephaly. In the arhinencephalic syndromes deficiencies of the neural crest and neural folds produce the cleft lips and palates (Johnston & Listgarten, 1972). Two eyes, often microphthalmic usually occur with these lesser cerebral defects, rather than synophthalmia-cyclopia.

A final word should be said about the subject of arhinencephaly and synophthalmia-cyclopia. Karseras & Laurence (1975) examined the eyes of 22 infants with arhinencephaly and found 8 cases in which there were significant ocular anomalies. Three of the eight cases displayed the restricted form of arhinencephaly, i.e., only the olfactory bulbs and tracts were absent. The associated ocular abnormalities varied and included microphthalmia and hypoplasia of the optic nerves and chiasm, but a tendency toward synophthalmia-cyclopia was not found. These cases, therefore, represent narrow field defects in midline differentiation probably of neural fold development, reflected in both the opticochiasmic and olfactory systems.

The remaining five cases with ocular findings reported by Karseras & Laurence (1975) were instances of arhinencephaly in its broader sense, i.e., holoprosencephaly or holotelencephaly. In two cases there was a suggestion of synopthalmia-cyclopia. Their case 3 was an example of 'ocular fusion,' and the authors stated that a chiasm was present. The globes, although described as fused, appeared separate on the photomicrograph. The case exhibits two rudimentary optic nerve stalks with dysplastic neural and mesenchymal elements, merging into an abortive chiasm. The karyotype was 47 XX, D^+, and the severe dysplasia probably reflects the chromosomal abnormality. Furthermore, the proboscis was not located above the eyes but rather was situated between them. This feature together with the presence of one naris conforms to ethmocephaly rather than cyclopia. The palpebral fissures appeared separated, and the orbits were not described. In view of the presence of rudimentary optic nerves and chiasm, this case shows greater bicentricity than any of our cases listed in Table 7. All of our cases in Table 7 belong in grade 1 (cyclopia) of the classification of median facial anomalies proposed by DeMyer et al. (1964B), while case 3 of Karseras & Laurence (1975) would fall in grade 2, ethmocephaly.

In case 1 of Karseras and Laurence the 'cyclops tendency' was evidenced by a posterior deficiency of the sclera. The photomicrograph of this globe suggested a colobomatous cyst, that is, a failure of closure of the embryonic fissure permitting the extraocular protrusion of a uveal-neural continuous with the intraocular contents, rather than an associated second eye. A colo-

bomatous cyst is not an unusual occurrence in a microphthalmic eye.

Case 2 of Karseras & Laurence (1975) is quite fascinating. There was complete bilateral anophthalmia, absence of the optic foramina, the pituitary and sella turcica, and the oculomotor nerves, and hypoplasia of the cerebellum. The orbits were not described. A small proboscis was present. In our view this case represents a massive and more widespread disorder of the neural plate extending more caudally than usual (oculomotor and cerebellar disorders) and a more profound disorder than was usually encountered in this series (see Table 7).

A variety of other ocular abnormalities was seen in Karseras & Laurence's (1975) spectrum of arhinencephaly. Four out of eight cases in this series showed trisomy D, and two did not; in two cases cytogenetic studies could not be performed because of failure of the tissue cultures. Trisomy D was associated with both the restricted and more global forms of arhinencephaly.

Karseras & Laurence (1975) reached two major conclusions. First, that the appearance of the face does not always predict the condition of the brain, as suggested by DeMyer et al., (1964B), since either holoprosencephaly or restricted arhinencephaly may coexist with a wide range of facial and ocular malformations. On the other hand, our data, based on the analysis of this series of 35 cases of synophthalmia-cyclopia, support the position of DeMyer et al. (1964B) that the appearance of the face is a reflection of the type of brain malformation. In the majority of our cases of synophthalmia-cyclopia, a clear relationship exists between the appearance of the eyes and the upper facial region and the holoprosencephalic brain. Only four cases (Table 8, cases 26, 27, 34, and 35) do not easily fit into the usual pattern. Thus there appear to be two groups of cyclopia-synophthalmia. One is a more frequently occurring group in which development of the eyes and brains results from a quantitative deficiency in anterior neural plate induction with secondary alterations in neural crest migrations (see section C) into the upper facial region; the other group is quite bizarre and occurs less frequently in our series and probably results from a combination of embryonic mishaps (see section D).

Secondly, Karseras & Laurence (1975) concluded that normal chromosomal studies do not necessarily exclude an underlying chromosomal disorder, since the latter may have not been discovered with earlier methods and may still escape detection by current methods. Familial cases of arhinencephaly must in some way be chromosome-associated; yet, often karyotyping has been unrevealing, further underlining the shortcomings in present methods of chromosomal analysis. It should be noted, however, that the maternal environment in subsequent pregnancies may affect offspring similarly, and this nonchromosomal factor may explain some familial cases. Nonetheless,

from a clinical point of view, multiple associated somatic and visceral anomalies in cases of synophthalmia-cyclopia are still a good guide to the possibility of an underlying chromosomal disorder.

Facial anomalies

In the case reported in detail, the gradient of development and differentiation noted in the ocular structure and the brain was also present in the bones, teeth, and soft tissues of the upper facial region. The radiographs in this case (Fig. 22) (see also Currarino & Silverman, 1960; Kurlander et al., 1966; Sedano & Gorlin, 1963; Zingesser et al., 1966) demonstrate that the osseous structures are poorly developed medially but again are highly symmetric and well differentiated temporally. Striking hypoplasia of the ethmoidal, frontal, zygomatic, central sphenoidal, and maxillary bones is evident, as is the absence of the medial facial bones – the nasal, vomer, and lacrimal. Laterally, the greater wings of the sphenoidal bone are only mildly hypo-plastic but slightly displaced medially and inferiorly. The central incisors are absent, in agreement with the findings of others (Lathan, 1971; Sedano & Gorlin, 1963). Various cranial foramina, more laterally placed, are present and paired. Similarly, the appearance of the face reflects the symmetry and gradient of development of the deeper structures of the upper head region (Fig. 1).

In the development of the upper facial region, it is the structures derived from neural plate – the brain and eyes – that are largely responsible for organizing the mesenchyme into bones, teeth, and soft tissues. The embryonic tissue from which the facial mesenchyme derives has, in the past, been ascribed to both mesoderm and cranial neural crest cells (Mann, 1957; Duke-Elder & Cook, 1963; Duke-Elder, 1964; Gilbert, 1957; Bartelmez, 1962; Bartelmez & Blount, 1954). It is not our purpose to review the literature on this subject but rather to summarize recent experimental work on the contributions of cranial crest cells to the development of the upper facial region. Although some helpful general reviews on the ontogenetic fates of the axial neural crest are available (Horstadius, 1950: Weston, 1970; Hamilton & Mossman, 1972), the rather extensive and dispersed literature on the cranial neural crest has not been reviewed recently (Bartelmez & Blount, 1954; Bhakdinaronk et al., in preparation; Brihaye-Van Gertruyden, 1962; Cohen & Hohl, 1976; Conel, 1942; Coulombre, 1975; Coulombre et al., 1974; Johnston, 1966, 1974; Johnston & Listgarten, 1972; Johnston et al., 1973, in press; Johnston & Krames, in preparation; Le Lièvre & Le Douarin, 1975; Noden, 1973; Toerien, 1974, 1975).

In the ophthalmic literature, mesoderm is usually listed as the embryonic precursor of orbital and ocular mesenchyme, but recent investigations (Johnston, 1966, 1974; Johnston et al., 1973; Johnston & Listgarten, 1972; Johnston et al., in press; Noden, 1973) have shown that with the exceptions of the vacular endothelia and the extraocular muscles the orbital mesenchyme derives mostly from cranial neural crest (Figs. 37, 38, & 39) (Jakobiec & Tannebaum, 1975). Experimental work has utilized transplanted neural crest cells either labeled with tritiated thymidine (Johnston, 1966; Noden, 1973, 1975; Le Lièvre & Le Dourin, 1975) or identificable by distinctive nuclear markers – the most commonly employed being the large chromosomal mass in the nuclei of transplanted crest cells of the Japanese quail (Le Douarin, 1973). Similar studies in rat embryos in culture (Johnston & Krames, in preparation) extend the observations to mammalian embryos.

Cranial neural crest cells originate from the ectoderm located between the neural plate and the surface ectoderm. Neural crest cells are not found, however, in the most rostral part of the neural plate or tube (Nieuwkoop et al., 1958). Usually at about the time the neural folds close, crest cells begin extensive migrations. Crest cells migrate ventrally and anteriorly in a layer underneath the surface ectoderm. As they encounter the eye, the sheet of crest cells splits into two components, one migrating between the eyes to form the mesenchyme of the maxillary processes and visceral arches (Fig.

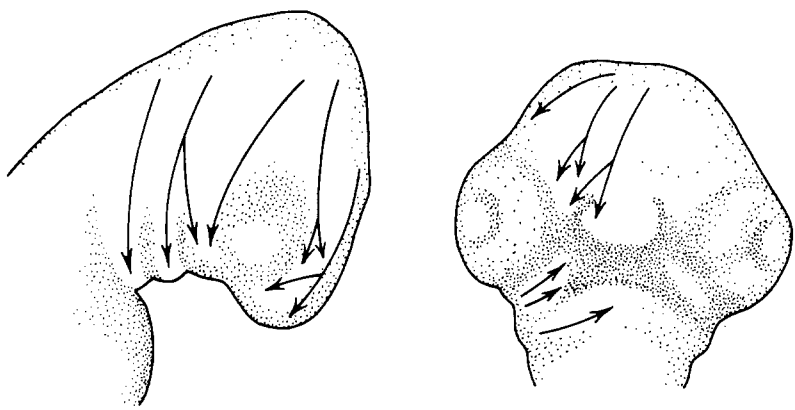

Fig. 37. Neural crest cells sweep ventrally around the ocular anlage (left) into the maxillary and frontonasal processes (right) as depicted in chick embryos. (Arrows indicate direction of sweep). Normal development of the nose and central facial structures is contingent upon the continued growth and eventual fusion of the maxillary and frontonasal processes around the eye (reprinted from Johnston, M.C., 1966, with permission of the publisher).

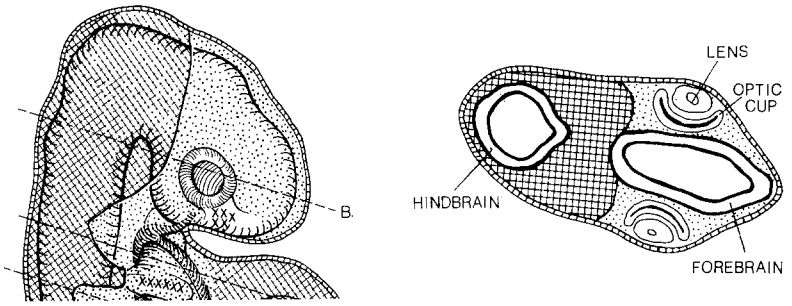

Fig. 38. Extensive migration of neural crest cells (stippled area) causes them to occupy a position ventral to the mesoderm (crosshatch). Section through a chick embryo (left) illustrates the envelopment of the ocular anlagen by neural crest descendants (right) (reprinted from Johnston, M.C., et al., 1973, with permission of the publisher).

37). The crest mesenchyme initially forms all the tissue between the overlying surface epithelium and underlying forebrain and eye in the upper facial region, i.e., the frontonasal and maxillary processes (Johnston et al., in press). Once in their new location, the crest cells multiply and differentiate in situ to supply the supporting tissues and osseous structures of the central face and orbit (Figs. 38 & 39). In the eye, crest cells supply the subepithelial corneal stroma and endothelium, the ciliary muscle, the uveal stroma (Johnston et al., in press), the uveal melanocytes (Brihaye-Van Geertruyden, 1962), and the meningeal sheaths and connective tissue columns of the optic nerve. In the upper facial region they form the connective and skeletal tissues, including the deep facial and basal skull bones that were noted to be absent in the radiographs of our case of synophthalmia. Odontoblasts also arise from crest cells (Horstadius, 1950; Weston, 1970; Hamilton & Mossman, 1972). The lacrimal gland, medial lacrimal apparatus, and cilia and sebaceous glands of the lids and caruncles derive from surface ectoderm.

One other embryologic event that affects the sequence of neural crest cell migration and the subsequent formation of the upper facial processes is the induction of the olfactory placodes. Neural fold formation during the closure and forward growth of the neural tube brings the surface ectoderm into close apposition to neural tube material. This prospective forebrain material induces the olfactory placodes in the surface ectoderm. The formation of the nasal placodes is similar to the induction of the lens placodes from the surface ectoderm by the evaginating optic cups. The olfactory placodes are first located above and medial to the optic vesicles and become separated from the forebrain by cranial crest cells. The frontonasal processes surround the olfactory placode and grow downward between the eyes to form the

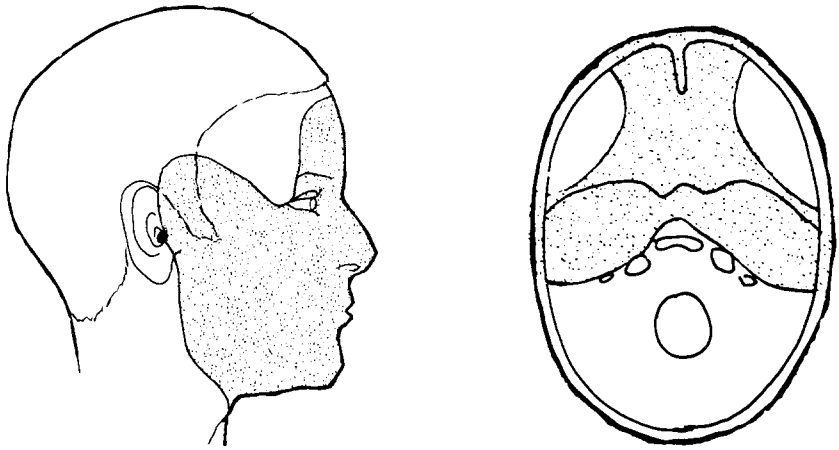

Fig. 39. (Left) Stippled area represents neural crest component of the connective and osseous tissues of the face (figure primarily based on information derived from avian studies). (Right) Cranial neural crest cell contribution (stippled area) to the bones of the orbit and base of skull (reprinted from Johnston, M.C., et al., 1973, with permission of the publisher.

nose as well as portions of the upper lip and the anterior maxilla (Fig. 40, top). The crest cells supply the cartilage, connective tissues, and smooth muscle of the wall of the nose as well as the median facial bones and portions of the incisor teeth. The cilia and glandular elements of the nose derive from the surface ectoderm.

The facial and bony defects in synophthalmia-cyclopia can now be ascribed in part to the central synophthalmic structure preventing neural crest migration and the subsequent descent of the facial processes (Fig. 40, bottom). The olfactory placode and crest cells remain stranded above the eye. Only one olfactory placode is usually induced in synophthalmia-cyclopia, as evidenced by the single naris in the proboscis; the downward movement of the proboscis is impeded by the median ocular rudiment, creating the supraocular tubular structure (Fig. 41). The single olfactory placode seems to reflect insufficient ectodermal induction by the holoprosencephalic brain.

In keeping with defective induction of the olfactory placode, we were unable to find any ganglion cells in the roof of the proboscis. The tissues derived from both the crest cells and the surface ectoderm in the proboscis are, nonetheless, histologically mature. The absence of the median facial bones and the hypoplasia of the orbit and anterior cranial fossa, all of which are derived from cranial neural crest cells, reflect incomplete crest cell migration and deficient secondary differentiation caused by the inadequate

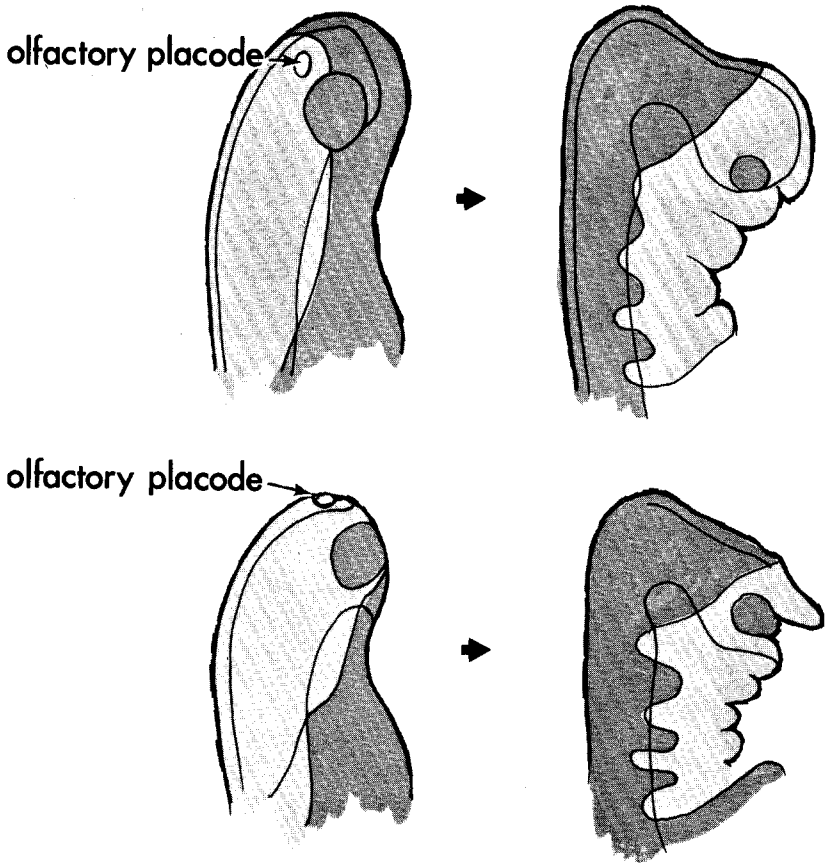

Fig. 40. (Top) The normal forebrain induces two olfactory placodes above and between the more lateral optic vesicles. Neural crest cells (light area) migrate into the frontonasal area (upper right) and contribute to the formation of the frontonasal processes. With flexing of the neural tube and migration of the neural crest, the olfactory placodes and frontonasal processes move ventrally and downward between the optic vesicles. Mesoderm is represented as dark area. (Bottom) In synophthalmia-cyclopia, the forebrain tissue frequently induces only a single olfactory placode (lower left). The centrally located synophthalmic-cyclopic rudiment impedes the migration of neural crest cells into the medial facial area (lower right). The fusion of the frontonasal and maxillary processes is prevented, so that the midline proboscis fails to descend and remains above the ocular structure. Maxillary crest cells complete the upper lip.

induction of the holoprosencephalic brain. The cranial bones posterior to the squamous temporal bone were, on the other hand, relatively normal, in line with the observed contribution of crest cells to the middle cranial fossa

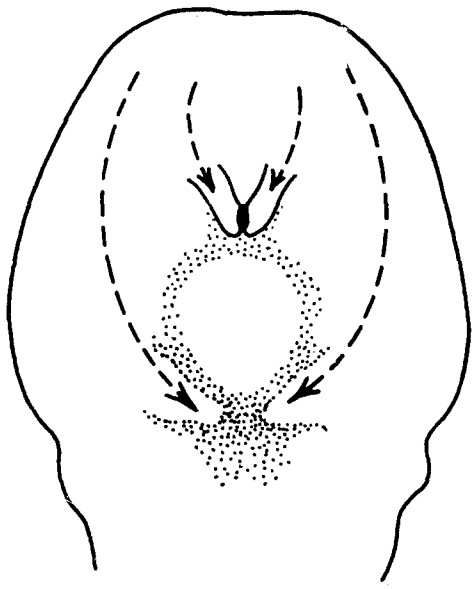

Fig. 41. Frontal view of sequence of neural crest cell migration as occurs in Fig. 40, bottom. Optic rudiment, located centrally, prevents migration and descent of neural crest cells, frontonasally. Compare with normal in Fig. 37.

and their relatively unencumbered migration to this site (Fig. 39). Crest cells fated to become odontoblasts in the lateral segments of the maxilla were also able to complete their migration and differentiation, as witnessed by the presence of teeth in the radiographs. In contrast, absence of incisor teeth in the maxilla in this and other studies (Latham, 1971; Sedano & Gorlin, 1963) reflects the inability of the frontonasal mesenchyme cells to reach the oral epithelium, with which they normally interact for incisor tooth formation.

No cleft palates were recorded in this series, but the upper lip was generally hypoplastic, indicating that the maxillary processes can only partially compensate for the failure of descent of the frontonasal processes.

The presence or absence of the pituitary glands was not recorded in this paper because of very limited data. We were not able to identify pituitary cells in our own specimen. Cells of the anterior pituitary gland derive from oral ectoderm and cranial neural crest cells (Johnston et al., 1974), while the cells of the posterior pituitary arise from neural plate.

The constellation of features that emerge from most of our cases of synophthalmia-cyclopia includes the median (deficient) ocular structure, the single orbit, the absent chiasm, the proboscis, the holoprosencephalic brain, and the absence of major malformations in the neuraxis below the diencephalon and in the remainder of the body. A small group of cases in this series combined features of synophthalmia-cyclopia with an other defect.

In two cases in which the proboscises were rudimentary (cases 5 and 31), the cerebral tissues had been specifically listed as hypoplastic. In case 5, no proboscis was found, and there was a meningo-encephalocele with a defect in the frontal bone. These data, though fragmentary, suggest that if no proboscis is formed, the cerebral tissue most likely will be profoundly deficient. In case 7, craniorachischisis occurred with synophthalmia.

In case 12, the optic nerve was aplastic. The mother in this case had been treated for syphilis during the pregnancy. The failure of differentiation of the optic nerve may have been secondary to degenerative changes in the neural retina. Infoldings of the neural retina were found in this case and many others. Coulumbre (1956) has shown that when such infoldings occur as a result of experimental manipulations, the retinal tissues undergo degeneration, apparently as a result of being removed from their blood supply. Such secondary changes could explain the presence of retinal rosettes, poor development of the optic nerve, and failure of formation of the optic chiasm.

Case 11, in which there were asymmetric synophthalmia and unilateral hypoplasia of the cerebrum and face, most likely represents synophthalmia with a secondary unilateral disaster occurring slightly later in gestation. There was a higher degree of histogenetic as well as organogenetic disorder on the affected side.

In case 35, no derivatives of the anterior neural plate were found in the orbit, but a rudimentary optic nerve was found intracranially, indicating that a synophthalmic-cyclopic rudiment had at least been transiently formed. Sections of the optic stalk showed collections of primitive retinal cells intracranially that had not remained in the orbit. The bony canal of the optic nerve had not formed. The cause of this total failure of the outward growth of the optic rudiment is unknown.

In case 32, 'gray' tissue was found in the orbit, and no proboscis was present. The anterior end of the neural tube was nonexistent, implying total failure of the most anterior neural plate but yet an early and partial induction of a median ocular structure more caudally, Apparently the anterior prosencephalic defect was so profound and the cerebral tissue was so limited

that no olfactory placode (no proboscis) was induced and the impoverished prosencephalic environment, possibly including inadequate neural crest substrate, was unable to further support the incipient eye tissues that consequently underwent secondary degeneration.

Cases 16, 17, and 19 (proven or possible trisomy 13) and case 26 (cyclopia with cryptothalmus) have been discussed.

SUMMARY

Synopthalmia-cyclopia represents a spectrum of ocular anomalies that result from a deficiency of the presumptive ocular fields in the anterior neural plate. With outward growth from the neural plate, the ocular anlagen are eventually able to achieve some degree of bicentricity distal from the brain (anterior segments of the eyes), while there is a persistent sharing of the eye fields more proximal to the brain (posterior segments of the globe and optic nerve). Unless there is an associated chromosomal defect, the neural plate that is successfully induced will, with continued growth, display a high degree of orderly histogenesis. The holoprosencephalic brain, lacking hemispheric cleavage and demonstrating incomplete bicentricity, indicates that the deficiency in the neural plate includes the region destined to produce the forebrain. The proboscis, bony defects, and central facial anomalies in synophthalmia-cyclopia are due to interference with migration of neural crest cells and the development of facial processes around the central optic rudiment. The inadequate induction of the olfactory placode leads to abnormal interaction between neural crest cells and facial processes, resulting in the formation of a proboscis. The primary defect in generating adequate neuroectoderm may reside in a failure of the underlying mesoderm, as observed by Adelmann in amphibians; synophthalmia-cyclopia would then be a failure of two complete eye fields to emerge and separate. Synophthalmia- cyclopia in man may result from destruction of the anterior neural folds, as recorded in chicks by Rogers. In either case, the high degree of symmetry of the ocular tissues suggests that the defect occurs before the eye fields are fully established, but once established the eye anlagen follow the orderly program of ocular differentiation, producing mature tissues.

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