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CLINICAL, STRUCTURAL, and BIOCHEMICAL ADVANCES IN HEREDITARY EYE DISORDERS

EDITOR: **Donna L. Daentl**

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CLINICAL, STRUCTURAL, AND BIOCHEMICAL ADVANCES IN HEREDITARY EYE DISORDERS

Based on the Proceedings of the Third Annual Symposium of the Society of Craniofacial Genetics Held in New York City

Editor

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CLINICAL, STRUCTURAL, AND BIOCHEMICAL ADVANCES IN HEREDITARY EYE DISORDERS

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Preface

Entry into the decade of the 80s has been accompanied by a tremendous expansion of possibilities for the prevention and treatment of a variety of inherited diseases. However, the application of new technology to many other hereditary disorders will come only after they have been defined more completely in molecular terms. Toward this end, certain hereditary disorders affecting the structures of the eye have been subjected to renewed research interest. Fresh directions to pursue answers to old questions have received impetus from studies of neural crest cell migration, advances in the biochemical study of connective tissues, intermediary metabolism, and lysosomal storage diseases, and from experiments pointing to the important influence of the extracellular matrix on cellular migration, proliferation and differentiation. In the case of some eye disorders, molecular approaches are not yet possible. However, careful clinical, genetic and structural studies have been illuminating heterogeneities not previously appreciated.

It was for the purpose of reviewing these recent investigations pertinent to the pathogenesis of some genetic eye diseases and of pinpointing questions which remain to be answered, that the symposium "Clinical, Structural, and Biochemical Advances in Hereditary Eye Disorders" was held on June 8, 1980, in New York City on the occasion of the 1980 March of Dimes Birth Defects Conference. The symposium was sponsored by the Society of Craniofacial Genetics with assistance from the March of Dimes Birth Defects Foundation and The Johns Hopkins University School of Medicine. Papers in this volume derive from presentations of the speakers at that symposium, in some cases with additions updating to the time of publication. This symposium was the third in an annual series on clinical

problems affecting structures of the craniofacial complex and sponsored by the Society of Craniofacial Genetics. The organization is composed of clinicians and basic scientists with special interest in the study of disorders affecting the head and neck.

It has been a primary aim of these symposia to promote much-needed communication between basic scientists and clinicians, with the belief that integration of the perspectives of both groups will maximize the potential for advancement of knowledge. Subjects covered in this volume are thus a reflection of that philosophy. It is hoped that these pages will provide both basic scientist and clinician with fresh vantage points from which to view still-unsolved problems.

Donna L. Daentl
Editor

Contents

Clinical, Structural, and Biochemical Advances in Hereditary Eye Disorders, pages 1-15

The Distribution of Cranial Neural Crest Cells During Ocular Morphogenesis

Stephen Meier

ORIGIN AND DISPERSION OF OCULAR CREST

The neural crest of vertebrate embryos arises from a population of ectodermal cells along the dorsal surface of the neural tube. These cells migrate extensively and ultimately form a variety of differentiated cell types (reviewed by Hörstadius [1] and Weston [2]). The relocation of crest cells is characterized by migration through the embryo, which is spatially and temporally patterned. In the trunk region, the entire length of the neural tube contributes crest cells [3,4], which are released in a cranial to caudal sequence coordinate with neurulation. In the cranial end [5, 6], crest cells emerge as discrete populations at different times during development. For instance, mesencephalic crest originates first, with more anterior prosencephalic and more posterior rhombencephalic populations emerging later.

Much of the experimental evidence for the precision and timing of cranial crest migration comes from transplantation of labeled segments of neural tube into host embryos (Fig. 1 A–C). Avian or amphibian neural segments can be labeled with tritiated thymidine [5–7], permitting crest derivatives of the explant to be located in the embryo by autoradiography. For analysis of avian embryos, it is also possible to use quail tissue as the source of the graft [8,9]. Crest cells derived from quail can be distinguished from those of the host chick by a histochemical technique specific for the nucleolus of quail cells [10]. By examining serial sections of operated embryos sacrificed at various stages of development, the migratory behavior of crest cells can be monitored.

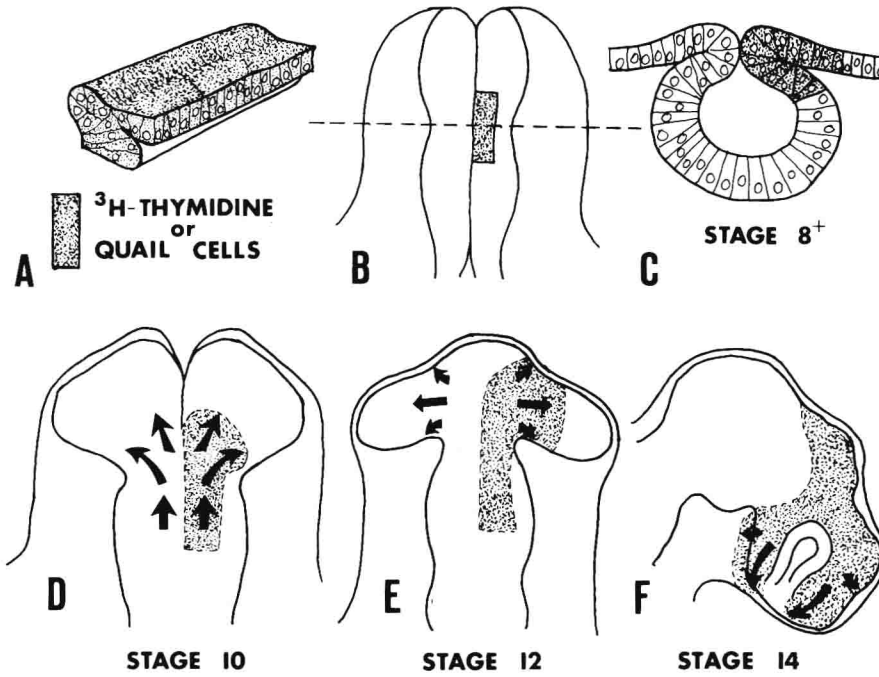

Fig. 1. The major migratory routes of avian cranial neural crest cells have been mapped by cell marking experiments, summarized here in diagrammatic form after Noden [6]. A. Explants of quail tissue or ^{3}H-thymidine-labeled chick tissue are grafted (B) in place of host tissue. Subsequent distribution of labeled crest in the embryo is monitored by fixing and serially sectioning embryos (B,C) at various stages of development after transplantation. Ocular crest is derived principally from the prosencephalic region (D), and spreads anteriorly over the surface of the optic stalk (E), finally encircling the eye rudiment (F).

Most of the cranial crest that participates in avian ocular development is derived from prosencephalon, particularly the diencephalic region [5,6]. By stage 10 [11], migrating crest cells emerge along the dorsal surface of the diencephalon and migrate over the surface of the optic vesicle (Fig. 1 D–F). Initially, the caudal surface of the optic vesicle is colonized as crest cells migrate in a dorsal-ventral, medial-lateral sequence. By stage 12, some cells have migrated far enough cranially to spread over the rostral surface of the optic vesicle, so that by stage 14, the optic stalk is nearly encircled by crest. Crest is excluded from the region of contact between surface ectoderm and optic vesicle (the

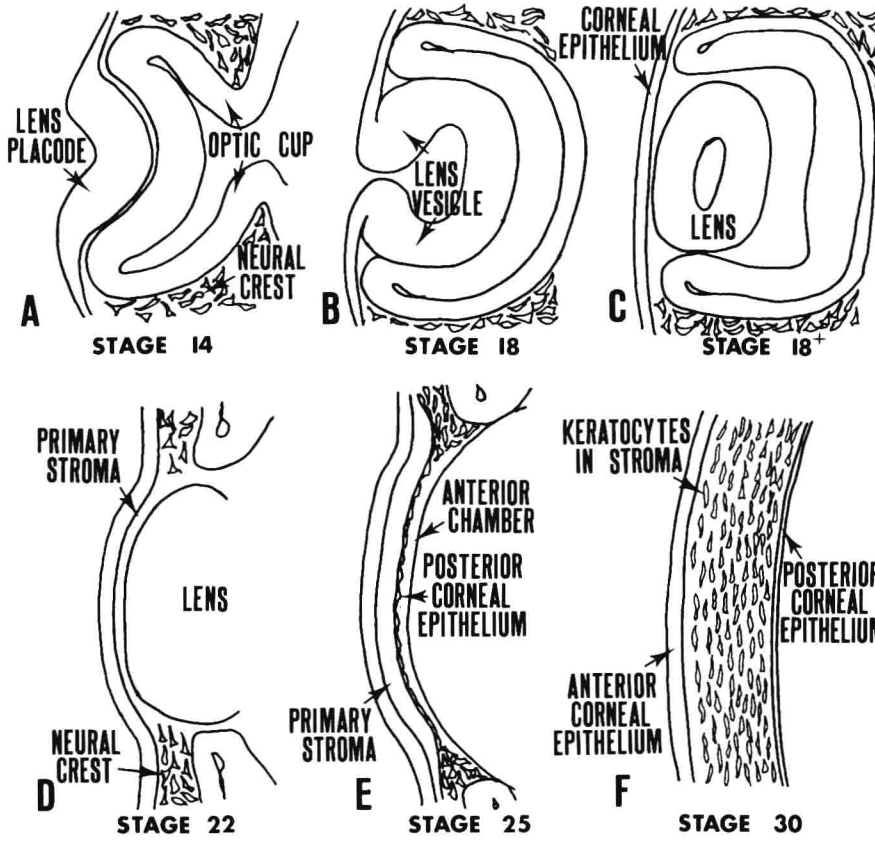

Fig. 2. Diagrammatic representation of the early stages in development of the avian cornea (after Hay [12]). A. When the lens placode begins to invaginate, the corneal epithelium lies over the rim of the optic cup. B,C. When lens invagination is complete, corneal epithelium spreads over the lens to renew the continuity of the surface ectoderm. D. Corneal epithelium secretes the primary stroma and neural crest cells begin to invade it. E. The first wave of crest cells separates the primary stroma from the lens and differentiates into the posterior corneal epithelium. F. A day later, a second population of crest colonizes the acellular primary stroma and differentiates into keratocytes.

site of lens placode formation) and along the ventral surface of the optic stalk, where the choroid fissure will develop.

CREST CONTRIBUTIONS TO OCULAR TISSUES

The cranial crest that surrounds the optic cup first participates in corneal development. During stage 14 the pseudostratified lens placode invaginates into the optic cup (Fig. 2). This morpho-

genetic movement causes the ectoderm circumferentially adjacent to the lens placode to eventually become positioned above the lens as the corneal epithelium (reviewed by Hay [12]). The optic cup closely approximates the surface ectoderm at the corneal margin, and cranial crest cells accumulate (Fig. 3). The corneal epithelium secretes a collagenous stroma that is deposited as an organized extracellular matrix between itself and the lens (Fig. 2D). Leaving the margin of the eye cup, neural crest cells [9] spread between the lens and the primary stroma to form a contiguous sheet, the posterior corneal epithelium (Fig. 2E). The separation of the cornea from the lens creates the anterior chamber of the eye. The newly formed posterior corneal epithelium secretes hyaluronate into the primary stroma [13], effectively hydrating it and causing it to swell. A second population of crest cells residing at the margin of the eye cup then invades the primary stroma. The crest cells that colonize the layers of the primary stroma differentiate into keratocytes, which are responsible for producing and maintaining the adult corneal stroma (Fig. 2F).

In addition to participating in corneal development, cranial crest cells also contribute to a variety of other ocular tissues [14]. These include the pigment cells of the iris and the choroid, most of the sclera, and many cartilages and bones of the jaw, face, and cranium. In birds, some crest cells adjacent to the presumptive pigmented epithelium undergo local condensation and begin chondrogenesis. These scleral ossicles are usually 14 in number and serve to support the eye at the cornea-sclera junction [15]. Crest cells also contribute to the connective tissues of the ocular muscles and give rise entirely to the ciliary muscle.

DEVELOPMENT OF SEGMENTED MESODERM IN THE CRANIAL REGION

Recently [16] it was discovered that the mesodermal layer of chick embryos is segmented from head to tail. Furthermore, the organization of the segmental pattern is initiated very early in development (stage 4). It can first be noted in the region of Hensen's node at the anterior end of the primitive streak (Fig. 4A). At the cranial-most end of the embryonic axis a circular domain of mesoderm condenses into the prechordal plate. As Hensen's node regresses down the streak, it connects the prechordal plate to the notochord along the midline. In the paraxial

Fig. 3. A scanning electron micrograph (SEM) of a frontal section taken through the developing eye of a stage 18 chick embryo. The lens has invaginated and the corneal epithelium has spread over it. × 555.

mesoderm on either side of Hensen's node, thin cylinders of mesoderm called somitomeres are also established. It is the tandem addition of pairs of somitomeres that forms the morphogenetic basis for segmentation of the mesoderm. In the trunk region, somitomeres condense and undergo morphogenesis into somites

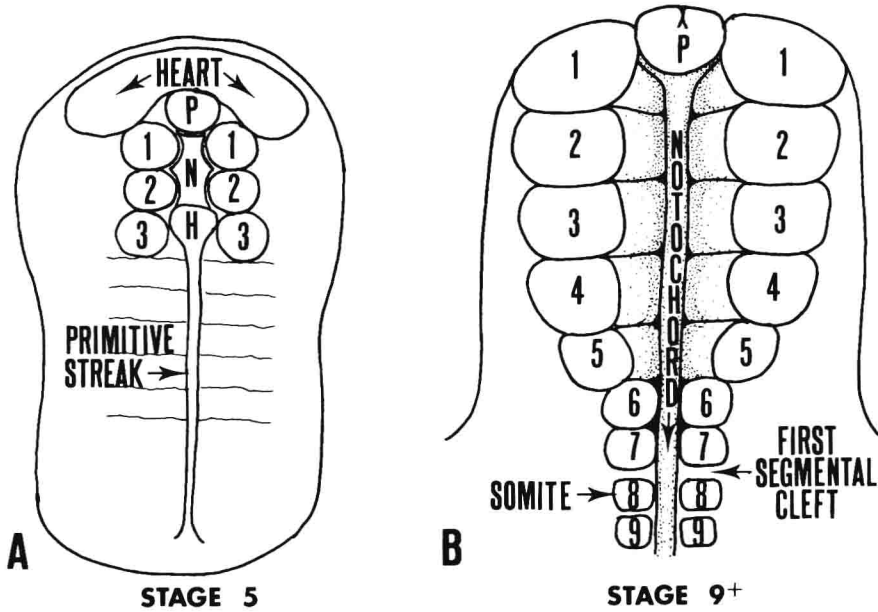

Fig. 4. A diagrammatic representation of the patterned mesoderm of a chick embryo viewed dorsally (ectoderm removed). A. At the cranial-most end of the axis at stage 5 sits the circular prechordal plate, P. Extending along the midline from the plate to Hensen's node (H) is the notochord (N), flanked on either side in the paraxial region by the first three tandem pairs of somitomeres (1,2,3). B. While more pairs of somitomeres are added posteriorly as the node regresses down the streak, those established earlier undergo morphogenesis. By stage 8+, just prior to cranial neural crest migration, seven tandem pairs of somitomeres can be distinguished ahead of the first segmental cleft. The first "somite" visible at the light level is actually the eighth metameric segment.

[16, 17], whereas in the cranial region, somitomeres undergo morphogenesis but do not condense and remain contiguous [18]. In fact, there are seven pairs of somitomeres ahead of the first somite, which were previously unrecognized. By stage 9+, just prior to the emergence of the cranial crest, the entire mesodermal layer adjacent to the neural tube is patterned (Fig. 4B).

Since the mesodermal pattern is visible from a dorsal view, stage 10–14 chick embryos were fixed, dissected free of surface ectoderm, and processed for observation with the scanning electron microscope (SEM), as previously described [16]. Exposed mesoderm was repeatedly washed to remove granular extracellular matrix, presumably hyaluronate [18–20], so that the outlines of mesodermal cells were not obscured. Patterned mesoderm in

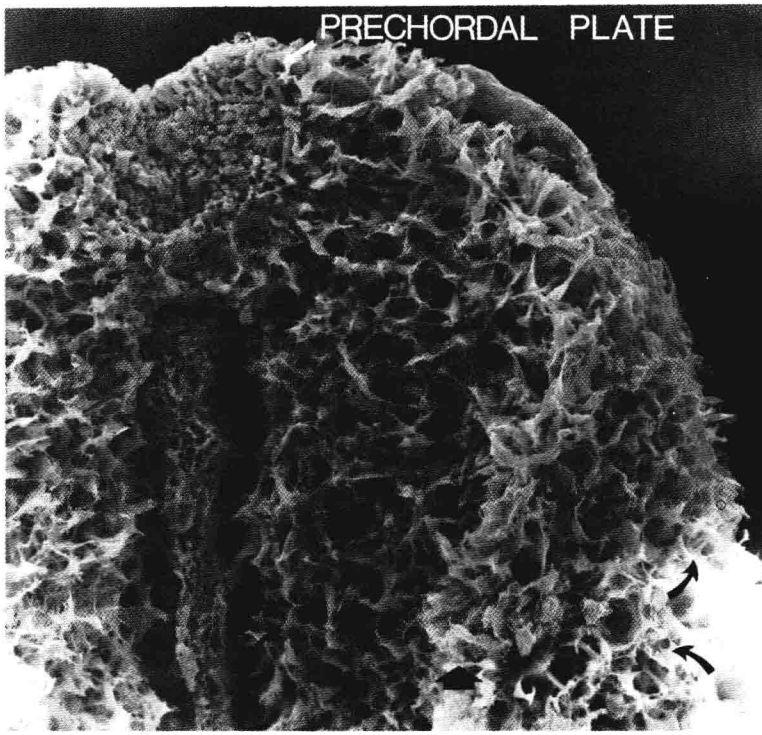

Fig. 5. A dorsal view of the mesoderm of the cranial-most end of a stage 8 chick embryo. The first, right somitomere is oval shaped (curved arrows), its axial border merging with the prechordal plate and a stretch of notochord (removed). Its caudal border interfaces with the second somitomere (double curved arrows). The first somitomere is composed of dispersed cells, swirled about a central point (star) within the mesodermal core. The large arrow head points out a question-mark-shaped ridge which reflects the outline of the expanding optic vesicle. × 214.

the region of optic vesicle formation includes the prechordal plate and the first pair of somitomeres. The prechordal plate mesoderm lies at the anterior tip of the notochord and is delineated from the adjacent paraxial somitomeres by the density of its component cells (Fig. 5). Although the prechordal plate originates at stage 4 as a circular domain of columnar cells, by stage 9, the cranial-most half has been bent ventrally and caudally, causing the plate to fold back underneath itself and assume a rather elliptical shape.