
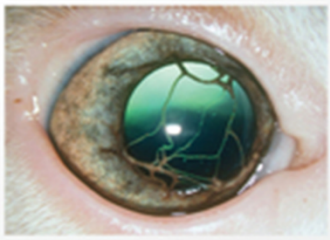
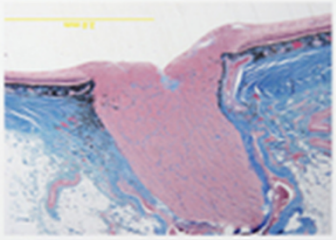
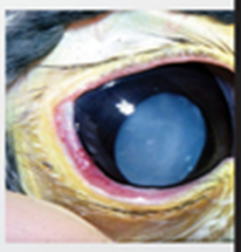

VETERINARY OPHTHALMOLOGY

EDITED BY **KIRK N. GELATT**

SIXTH EDITION

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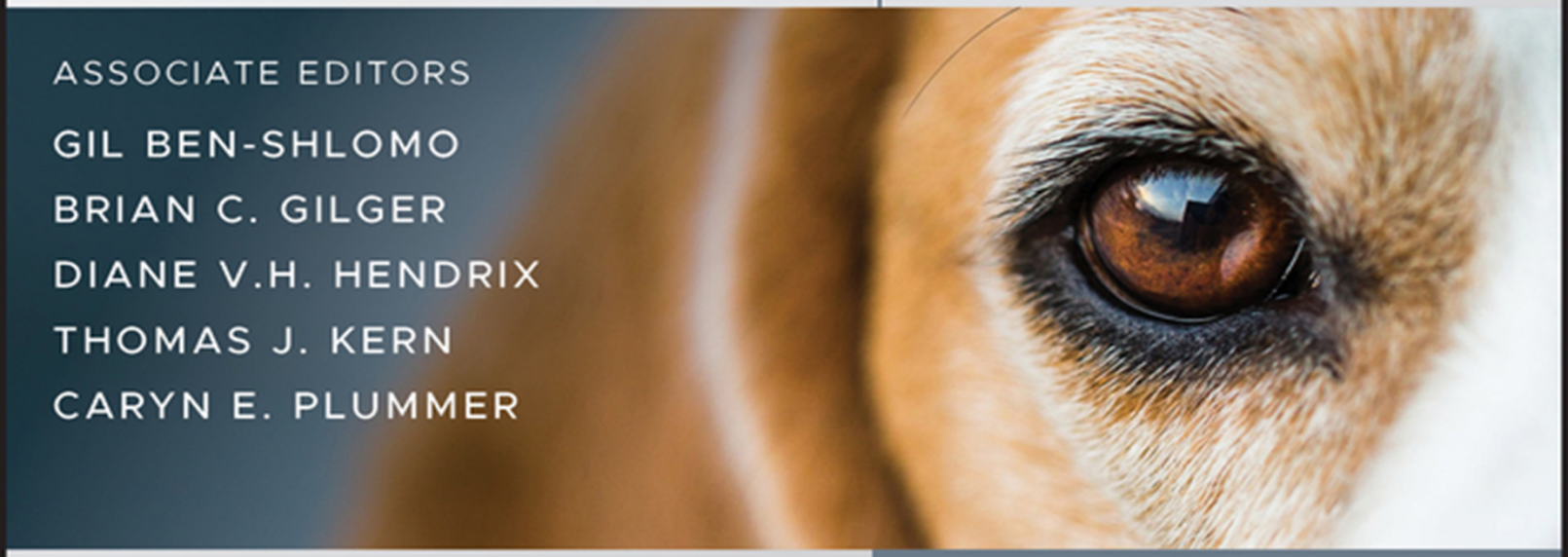

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Veterinary Ophthalmology

Volume I and Volume II

Editor
Kirk N. Gelatt

Associate Editors
Gil Ben-Shlomo
Brian C. Gilger
Diane V.H. Hendrix
Thomas J. Kern
Caryn E. Plummer

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This book is dedicated to the memory of Dr. Gil Ben-Shlomo, an exceptional scholar, teacher, father and friend. The veterinary ophthalmology community has lost a gentle doctor and a gentleman.

Contents

Contributors

Gil Ben-Shlomo, DVM, PhD
Diplomate ACVO, Diplomate ECVO
Associate Professor of Ophthalmology
Departments of Clinical Sciences
College of Veterinary Medicine
Cornell University
Ithaca, NY, USA

Ellison Bentley, DVM
Diplomate ACVO
Clinical Professor, Comparative Ophthalmology
Department of Surgical Sciences
School of Veterinary Medicine
University of Wisconsin-Madison
Madison, WI, USA

Michael H. Boevé, DVM, PhD
Diplomate ECVO
Staff Ophthalmologist
Department of Clinical Sciences of Companion Animals
Faculty of Veterinary Medicine
Utrecht University, The Netherlands

Alison Clode, DVM
Diplomate ACVO
Port City Veterinary Referral Hospital
Portsmouth, NH, USA

Cynthia S. Cook, DVM, PhD
Diplomate ACVO
Veterinary Vision
San Carlos and San Francisco, CA, USA

Cheryl L. Cullen, DVM
Diplomate ACVO
CullenWebb Animal Eye Specialists
Riverview, NB, Canada

Emma Dewhurst, MA, VetMB, MRCVS
Diplomate ECVCP, FRCPath
IDEXX Laboratories
Wetherby, West Yorkshire, UK

David Donaldson, BVSc(Hons), MRCVS, MANZCVS
Diplomate ECVO
European Specialist in Veterinary Ophthalmology
Senior Clinician in Ophthalmology
Langford Vets
University of Bristol Veterinary School
Langford, Bristol, UK

Seth Eaton, VMD
Diplomate ACVO
Clinical Assistant Professor, Comparative Ophthalmology
Department of Surgical Sciences
School of Veterinary Medicine
University of Wisconsin – Madison
Madison, WI, USA

Björn Ekesten, DVM, PhD
Diplomate ECVO
Professor of Ophthalmology
Department of Clinical Sciences
Faculty of Veterinary Medicine
Swedish University of Agricultural Science
Uppsala, Sweden

Robert English, DVM, PhD
Diplomate ACVO
Animal Eye Care of Cary
Cary, NC, USA

Heidi J. Featherstone, BVetMed, DVOphthal, MRCVS
Diplomate ECVO, Diplomate RCVS
Head of Ophthalmology
The Ralph Veterinary Referral Centre;
Honorary Associate Professor
Nottingham Veterinary School
Marlow, Buckinghamshire, UK

Kirk N. Gelatt, VMD
Diplomate ACVO
Emeritus Distinguished Professor of Comparative Ophthalmology
Department of Small and Large Animal Clinical Sciences
College of Veterinary Medicine
University of Florida
Gainesville, FL, USA

Brian C. Gilger, DVM, MS
Diplomate ACVO, Diplomate ACT
Professor of Ophthalmology
Department of Clinical Sciences
College of Veterinary Medicine
North Carolina State University
Raleigh, NC, USA

Juliet R. Gionfriddo, DVM
Diplomate ACVO
Professor Emeritus of Ophthalmology
Department of Clinical Sciences
College of Veterinary Medicine
Colorado State University
Fort Collins, CO, USA

Elizabeth A. Giuliano, DVM, MS
Diplomate ACVO
Associate Professor of Ophthalmology
Department of Veterinary Medicine and Surgery
College of Veterinary Medicine
University of Missouri
Columbia, MO, USA

Mary Belle Glaze, DVM
Diplomate ACVO
Gulf Coast Animal Eye Clinic
Houston, TX, USA

David Gould, BSc (Hons), BVM&S, PhD, DVOphthal, FRCVS
Diplomate ECVO
RCVS and European Specialist in Veterinary Ophthalmology
Head of Ophthalmology
Davies Veterinary Specialists
Manor Farm Business Park
Higham Gobion, Hertfordshire, UK

Bruce H. Grahn, DVM
Diplomate ACVO
Professor Emeritus of Veterinary Ophthalmology
Western College of Veterinary Medicine and
Prairie Ocular Pathology of Prairie Diagnostic Laboratories
University of Saskatchewan
Saskatoon, SK, Canada

Glenwood G. Gum, MS, PhD
Director of Ophthalmology
Absorption Systems
San Diego, CA, USA

Ralph E. Hamor, DVM, MS
Diplomate ACVO
Clinical Professor of Comparative Ophthalmology
Departments of Small and Large Animal Clinical Sciences
College of Veterinary Medicine
University of Florida
Gainesville, FL, USA

Claudia Hartley, BVSc, CertVOphthal, MRCVS
Diplomate ECVO
European Specialist in Veterinary Ophthalmology
Head of Ophthalmology
Langford Vets
University of Bristol Veterinary School
Langford, Bristol, UK

Christine L. Heinrich, DVOphthal, MRCVS
Diplomate ECVO
RCVS and European Specialist in Veterinary Ophthalmology
Eye Veterinary Clinic
Leominster, Herefordshire, UK

Diane V.H. Hendrix, DVM
Diplomate ACVO
Professor of Ophthalmology
Department of Small Animal Clinical Sciences
College of Veterinary Medicine
University of Tennessee
Knoxville, TN, USA

Ian P. Herring, DVM, MS
Diplomate ACVO
Associate Professor of Ophthalmology
Department of Small Animal Clinical Sciences
Virginia-Maryland College of Veterinary Medicine
Virginia Tech
Blacksburg, VA, USA

Allison R. Hoffman, DVM
Diplomate ACVO
Eye Care for Animals
Pasadena, CA, USA

Thomas J. Kern, DVM
Diplomate ACVO
Associate Professor of Ophthalmology
Department of Clinical Sciences
College of Veterinary Medicine
Cornell University
Ithaca, NY, USA

Patrick R. Kircher, Dr.Med.Vet., PhD
Diplomate ECVDI, Exec. MBA, UZH
Professor of Veterinary Diagnostic Imaging
Clinic for Diagnostic Imaging
Department of Clinical Diagnostics and Services
Vetsuisse Faculty, University of Zurich
Zurich, Switzerland

András M. Komáromy, DrMedVet, PhD
Diplomate ACVO, Diplomate ECVO
Professor of Ophthalmology
Department of Small Animal Clinical Science
College of Veterinary Medicine
Michigan State University
East Lansing, MI, USA

Marta Leiva, DVM, PhD
Diplomate ECVO
Professor Associate
Hospital Clinic Veterinari
Fundació Universitat Autònoma de Barcelona;
Departament de Medicina i Cirurgia Animal
Facultat de Veterinària
Universitat Autònoma de Barcelona
Bellaterra, Barcelona, Spain

David J. Maggs, BVSc
Diplomate ACVO
Professor of Ophthalmology
Department of Surgical and Radiological Sciences
School of Veterinary Medicine
University of California – Davis
Davis, CA, USA

Bianca C. Martins, DVM, MSc, PhD
Diplomate ACVO
Clinical Associate Professor of Ophthalmology
Department of Surgical and Radiological Sciences
School of Veterinary Medicine
University of California - Davis
Davis, CA, USA

Gillian J. McLellan, BVMS, PhD, DVOphthal, MRCVS
Diplomate ECVO, Diplomate ACVO
Associate Professor of Comparative Ophthalmology
Department of Surgical Sciences
School of Veterinary Medicine *and*
Department of Ophthalmology and Visual Sciences
School of Medicine and Public Health
University of Wisconsin-Madison
Madison, WI, USA

Richard J. McMullen, Jr., Dr.Med.Vet, CertEqOphth (Germany)
Diplomate ACVO, Diplomate ECVO
Associate Professor of Equine Ophthalmology
Department of Clinical Sciences
Auburn University
JT Vaughan Large Animal Teaching Hospital
Auburn, AL, USA

Jessica M. Meekins, DVM, MS
Diplomate ACVO
Associate Professor of Ophthalmology
Department of Clinical Sciences
Veterinary Health Center
College of Veterinary Medicine
Kansas State University
Manhattan, KS, USA

Tammy Miller Michau, DVM, MS, MSpVM
Diplomate ACVO
Vice President, Medical Affairs Operations
Mars Veterinary Health
Vancouver, WA, USA

Nicholas J. Millichamp, BVetMed, PhD, DVOphthal, MRCVS
Diplomate ACVO, Diplomate ECVO
Eye Care for Animals-Houston
Houston, TX, USA

Freya Mowat, BVSc, PhD
Diplomate ECVO, Diplomate ACVO
Assistant Professor of Ophthalmology
Department of Surgical Sciences
School of Veterinary Medicine
University of Wisconsin-Madison
Madison, WI, USA

Ron Ofri, DVM, PhD
Diplomate ECVO
Professor, Veterinary Ophthalmology
Koret School of Veterinary Medicine
Hebrew University of Jersualem
Rehovot, Israel

Kostas Papasouliotis, DVM, PhD, MRCVS
Diplomate RCPath (Vet.Clin.Path.), Diplomate ECVCP
EBVS® European Specialist in Veterinary Clinical Pathology
Senior Clinical Pathologist
IDEXX Laboratories
Wetherby, West Yorkshire, UK

Robert L. Peiffer, Jr., DVM, PhD
Diplomate ACVO
Professor Emeritus of Ophthalmology and Pathology
School of Medicine
University of North Carolina
Chapel Hill, NC, USA

Teresa Peña, DVM, PhD
Diplomate ECVO
Professor
Hospital Clinic Veterinari
Fundació Universitat Autònoma de Barcelona;
Departament de Medicina i Cirurgia Animal
Facultat de Veterinària
Universitat Autònoma de Barcelona
Bellaterra, Barcelona, Spain

Simon M. Petersen-Jones, DVetMed, PhD, DVOphthal, MRCVS
Diplomate ECVO
Myers-Dunlap Endowed Chair in Canine Health
Professor of Comparative Ophthalmology
Department of Small Animal Clinical Sciences
College of Veterinary Medicine
Michigan State University
East Lansing, MI, USA

Christopher G. Pirie, DVM
Diplomate ACVO
Associate Professor of Ophthalmology
Department of Small Animal Clinical Sciences
College of Veterinary Medicine
Michigan State University
East Lansing, MI, USA

Stefano Pizzirani, DVM, PhD
Diplomate ACVO, Diplomate ECVS-inactive
Associate Professor of Ophthalmology
Department of Clinical Science
Tufts Cummings School of Veterinary Medicine
North Grafton, MA, USA

Caryn E. Plummer, DVM
Diplomate ACVO
Professor of Comparative Ophthalmology
Departments of Small and Large Animal Clinical Sciences
College of Veterinary Medicine
University of Florida
Gainesville, FL, USA

Simon A. Pot, DVM
Diplomate ACVO, Diplomate ECVO
Ophthalmology Section
Equine Department
Vetsuisse Faculty, University of Zurich
Zurich, Switzerland

Amy J. Rankin, DVM, MS
Diplomate ACVO
Associate Professor of Ophthalmology
Department of Clinical Sciences
Veterinary Health Center
College of Veterinary Medicine
Kansas State University
Manhattan, KS, USA

Alain Regnier, Dr.Med.Vet, PhD
Emeritus Professor of Ophthalmology
Department of Clinical Sciences
School of Veterinary Medicine
Toulouse, France

Don A. Samuelson, PhD, MS
Professor of Comparative Ophthalmology (Retired)
Department of Small Animal Clinical Sciences
College of Veterinary Medicine
University of Florida
Gainesville, FL, USA

Lynne S. Sandmeyer, DVM, DVSc
Diplomate ACVO
Associate Professor of Ophthalmology (Retired)
Department of Small Animal Clinical Sciences
Western College of Veterinary Medicine
University of Saskatchewan
Saskatoon, SK, Canada

Erin M. Scott, VMD
Diplomate ACVO
Assistant Professor of Ophthalmology
Department of Small Animal Clinical Sciences
College of Veterinary Medicine and Biomedical Sciences
Texas A&M University
College Station, TX, USA

Frans C. Stades, DVM, PhD
Diplomate ECVO
Emeritus Professor of Veterinary Ophthalmology
Department of Clinical Sciences of Companion Animals
Faculty of Veterinary Medicine
Utrecht University
Utrecht, The Netherlands

Sara M. Thomasy, DVM, PhD
Diplomate ACVO
Professor of Comparative Ophthalmology
Department of Surgical and Radiological Sciences
School of Veterinary Medicine;
Department of Ophthalmology & Vision Science
School of Medicine
University of California
Davis, CA, USA

Samuel J. Vainisi, DVM
Diplomate ACVO
Animal Eye Clinic
Denmark, WI, USA

Lucien V. Vallone, DVM
Diplomate ACVO
Assistant Clinical Professor of Comparative Ophthalmology
Department of Small Animal Clinical Sciences
College of Veterinary Medicine
Texas A&M University
College Station, TX, USA

Alexandra van der Woerdt, DVM, MS
Diplomate ACVO, Diplomate ECVO
The Animal Medical Center
New York, NY, USA

Katrin Voelter, DVM, Dr.Med.Vet., PhD
Diplomate ECVO
Equine Department
Vetsuisse Faculty, University of Zurich
Zurich, Switzerland

Kenneth R. Waller III, DVM, MS
Diplomate ACVR
Clinical Associate Professor of Diagnostic Imaging
Department of Surgical Sciences
School of Veterinary Medicine
University of Wisconsin-Madison
Madison, WI, USA

Aubrey A. Webb, DVM, PhD
CullenWebb Animal Eye Specialists
Riverview, NB, Canada

R. David Whitley, DVM, MS
Diplomate ACVO
Gulf Coast Veterinary Specialists
Houston, TX;
Departments of Small and Large Animal
Clinical Sciences
College of Veterinary Medicine
University of Florida
Gainesville, FL, USA

David A. Wilkie, DVM, MS
Diplomate ACVO
Professor of Comparative Ophthalmology
Department of Veterinary Clinical Sciences
College of Veterinary Medicine
The Ohio State University
Columbus, OH, USA

David L. Williams, MA, VetMB, PhD, CertVOphthal, MRCVS
Senior Lecturer, Veterinary Ophthalmology
Department of Clinical Veterinary Medicine
University of Cambridge
Cambridge, UK

Joseph C. Wolfer, DVM
Diplomate ACVO
Toronto Animal Eye Clinic
Toronto, ON, Canada

Preface

In 1965 when I entered veterinary ophthalmology, it became very quickly apparent that there was a very limited information base or knowledge in veterinary ophthalmology. If this new clinical discipline was to grow and develop into a respected clinical specialty, we would need to develop our own scientific base, and compete with the other emerging clinical specialties in veterinary medicine. And we have! With our limited English-language books of *Veterinary Ophthalmology* by R.H. Smythe (1956), W.G. Magrane's first edition of *Canine Ophthalmology* (1965; Lea and Febiger), and *Diseases of the Canine Eye* by F.G. Startup (1969; Williams and Wilkins), and the chapter in *Advances in Veterinary Science* called 'Examination of the Eye' and 'Eye Operations in Animals' by Otto Überreiter (1959; Academic Press), we needed to "roll up our sleeves" and get to work big time!

We have available now (2021) a large number of veterinary ophthalmology books concentrating on the dog, cat, exotic animals, horses, ophthalmic pathology, and ophthalmic surgery. Two veterinary ophthalmology journals have proven invaluable to our success as a discipline. The first journal, *Veterinary and Comparative Ophthalmology*, was published by Fidia Research Foundation and Veterinary Practice Publishing (1991–1998), and our second journal was *Veterinary Ophthalmology* (published by Blackwell and Wiley-Blackwell, 1998 to present); they greatly assisted our development and proved critical for the distribution of new scientific information. In fact, the current journal provides more than 90% of animal ophthalmic literature annually worldwide.

In the late 1950s and extending into the 1970s, professional groups of budding veterinary ophthalmologists organized scientific societies to gather and exchange their knowledge and clinical experiences, which rapidly evolved to Colleges of Veterinary Ophthalmologists whose primary missions were to train new veterinary ophthalmologists (termed residents), and foster (and fund) research to "grow" the clinical discipline long term and worldwide. Nowadays these significant changes have greatly enriched veterinary ophthalmology, and markedly improved the quality of our ophthalmic animal patients.

The advances in this text, *Veterinary Ophthalmology*, have paralleled and documented the changes in veterinary ophthalmology, and has become our symbol of where we are today. In 1981, the first edition was released, consisting of 21 chapters (788 pages) by 22 authors, and was well received. As a result, subsequent editions followed: second edition (1991; 765 pages and 19 authors), and then in 1999 our last single-volume release (1544 pages, 37 chapters, and 44 authors). The third edition was markedly expanded and had color illustrations throughout the text.

The last two editions were two-volume sets: for 2007, volume one 535 pages, 9 chapters, and 45 authors, and for the second larger volume 1672 pages, 20 chapters, and 36 authors; and in 2012 for volume one 789 pages, 12 chapters, and 26 authors, and for the second volume 1479 pages, 22 chapters, and 39 authors. All editions were well referenced; in fact, a great value of this text is that it documents the advances in veterinary ophthalmology during the past half of the twentieth century, and the first two decades of the twenty-first century!

The sixth edition again consists of two volumes, 37 chapters, and 64 contributors. Like the last two editions, the first volume contains the basic science and foundations of clinical ophthalmology chapters and the first part of the third section on canine ophthalmology. Basic vision science courses in veterinary medical colleges are often an afterthought, and our veterinary ophthalmic basic sciences are frequently documented by veterinary ophthalmologists (rather than anatomists, physiologists, pharmacologists, etc.).

The first volume of the basic sciences and foundations of veterinary ophthalmology is designed to provide the base of those subjects that underpin the clinical sciences. They include embryology, anatomy, ophthalmology physiology, optics and physiology of vision, and fundamentals of vision in animals. In the foundations of clinical ophthalmology section, the chapters include immunity, microbiology, clinical pharmacology and therapeutics, ophthalmic pathology, ophthalmic examination and diagnostics, ophthalmic genetics and DNA testing, fundamentals of microsurgery, and photography. The third section starts with the chapters for

the first part of the canine ophthalmology including orbit, eyelids, nasolacrimal system, lacrimal secretory system, conjunctiva and nictitating membrane, cornea and sclera, and glaucoma.

The second volume focuses on clinical ophthalmology in the different species, and starts with the second part of canine ophthalmology (chapters- anterior uvea, lens and cataract formation, surgery of the lens, vitreous, ocular fundus, surgery of the posterior segment, and optic nerve), and continues with feline, equine, food and fiber-producing animals, avian, New World camelids, laboratory animals, pocket pet animals, and exotics, and concludes with comparative neuro-ophthalmology, ophthalmic manifestations of systemic diseases, and the index. The sixth edition more or less has devoted space relative to the amount of time based on different animal species encountered in veterinary ophthalmology practice.

Now, in 2021, the sixth edition of *Veterinary Ophthalmology* continues to document this discipline's advances. The magnitude of this edition has now required five associate editors, who devoted their time and expertise to make it happen. Like for me, I'm certain it was a learning experience! They are Drs. Brian C. Gilger, Diane V.H. Hendrix, Thomas J. Kern, Caryn E. Plummer, and Gil Ben-Shlomo. Each editor chose their authors and respective chapters, based on their expertise and preferences. A book like this is a huge undertaking, and all of us have devoted hundreds of hours to make it a successful product for the profession. Our 64 authors contributed hundreds of hours to this edition, taking time away from family and practice, and we thank them.

When all the chapters had been submitted and production had started, the COVID-19 pandemic spread across the world like a massive hurricane. Terms like "face masks," "social distancing," "isolation," and "quarantine or shelter at home" became common terms, and our daily personal and professional routines were markedly disrupted. But progress in the production of the sixth edition continued uninterrupted.

We thank Erica Judisch, Executive Editor, Veterinary Medicine and Dentistry, and Purvi Patel, Project Editor, of Wiley-Blackwell for their expertise and assistance in making the sixth edition of *Veterinary Ophthalmology* a reality. Our copyeditors, Jane Grisdale and Sally Osborn, and project manager Mirjana Misina were superb. And lastly, we thank and appreciate the continued support and encouragement of our spouses and family members who bear with us as we struggle to meet our time schedules and other life priorities.

Distinguished Professor of Comparative Ophthalmology, Emeritus

Kirk N. Gelatt, VMD, Diplomate, American College of Veterinary Ophthalmologists

About the Companion Website

This book is accompanied by a companion website:

www.wiley.com/go/gelatt/veterinary

The website includes:

- PowerPoints of all figures from the book for downloading
- References linked to CrossRef

Section I

Basic Vision Sciences

1

Ocular Embryology and Congenital Malformations

Cynthia S. Cook

Veterinary Vision, San Carlos and San Francisco, CA, USA

An understanding of normal and abnormal ocular development is essential to the broader subjects of anatomy, physiology, and pathology. Embryology provides both insight into the development of structures such as the cornea, iridocorneal angle, and retina and their normal and pathologic functions, as well as a means of understanding how congenital malformations occur.

Investigations of ocular development have often used rodents as animal models. Comparison with studies of humans and other animals demonstrates that the sequence of developmental events is very similar across species (Cook, 1995; Cook & Sulik, 1986; Hilfer, 1983; O'Rahilly, 1983). Factors that must be considered when making interspecies comparisons include duration of gestation, differences in anatomic end point (e.g., presence of a tapetum, macula, or Schlemm's canal), and when eyelid fusion breaks (during the sixth month of gestation in the human versus 2 weeks postnatal in the dog; Table 1.1).

This chapter describes normal events and abnormalities in this developmental sequence that can lead to malformations. Bearing in mind the species differences alluded to earlier, the mouse is a valuable model in the study of normal and abnormal ocular morphogenesis. In particular, studying the effects of acute exposure to teratogens during development has provided valuable information about the specific timing of events that lead to malformations.

Gastrulation and Neurulation

Cellular mitosis following fertilization results in transformation of the single-cell zygote into a cluster of 12–16 cells. With continued cellular proliferation, this morula becomes a blastocyst, containing a fluid-filled cavity. The cells of the blastocyst will form both the embryo proper and the extraembryonic tissues (i.e., amnion and chorion). At this early stage, the embryo is a bilaminar disc, consisting of hypoblast and epiblast. This embryonic tissue divides the blastocyst space into the amniotic cavity (adjacent to epiblast) and the yolk sac (adjacent to hypoblast; Fig. 1.1).

Gastrulation (formation of the mesodermal germ layer) begins during day 10 of gestation in the dog (day 7 in the mouse; days 15–20 in the human). The primitive streak forms as a longitudinal groove within the epiblast (i.e., future ectoderm). Epiblast cells migrate toward the primitive streak, where they invaginate to form the mesoderm. This forms the three classic germ layers: ectoderm, mesoderm, and endoderm. Gastrulation proceeds in a cranial-to-caudal progression; simultaneously, the cranial surface ectoderm proliferates, forming bilateral elevations called the neural folds (i.e., the future brain). The columnar surface ectoderm in this area now becomes known as the neural ectoderm (Fig. 1.2).

As the neural folds elevate and approach each other, a specialized population of mesenchymal cells, the neural crest, emigrates from the neural ectoderm at its junction with the surface ectoderm (Fig. 1.3). Migration and differentiation of the neural crest cells are influenced by the hyaluronic acid-rich extracellular matrix. This acellular matrix is secreted by the surface epithelium as well as by the crest cells, and it forms a space through which the crest cells migrate. Fibronectin secreted by the noncrest cells forms the limits of this mesenchymal migration (LeDouarin & Teillet, 1974). Interactions between the migrating neural crest and the associated mesoderm appear to be essential for normal crest differentiation (LeDouarin & Teillet, 1974; Noden, 1993). The neural crest cells migrate peripherally beneath the surface ectoderm to spread throughout the embryo, populating the region around the optic vesicle and ultimately giving rise to nearly all the connective tissue structures of the eye (Table 1.2; Hilfer & Randolph, 1993; Johnston et al., 1979; Noden, 1993). The patterns of neural crest emergence and migration correlate with the segmental disposition of the developing brain.

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Companion website: www.wiley.com/go/gelatt/veterinary

Table 1.1 Sequence of ocular development (Cook, 1995; O'Rahilly, 1983).

Human (Approximate Postfertilization Age)				Dog (Day Postfertilization)	
Month	**Week**	**Day**	**Mouse (Day Postfertilization)**	**Postnatal (P)**	**Developmental Events**
1	3	22	8	13	Optic sulci present in forebrain
	4	24	9	15	Optic sulci convert into optic vesicles
			10	17	Optic vesicle contacts surface ectoderm
					Lens placode begins to thicken
		26			Optic vesicle surrounded by neural crest mesenchyme
2	5	28	10.5		Optic vesicle begins to invaginate, forming optic cup
					Lens pit forms as lens placode invaginates
					Retinal primordium thickens, marginal zone present
		32	11	19	Optic vesicle invaginated to form optic cup
					Optic fissure delineated
					Retinal primordium consists of external limiting membrane, proliferative zone, primitive zone, marginal zone, and internal limiting membrane
					Oculomotor nerve present
		33	11.5	25	Pigment in outer layer of optic cup
					Hyaloid artery enters through the optic cup
					Lens vesicle separated from surface ectoderm
					Retina: inner marginal and outer nuclear zones
			11.5	29	Basement membrane of surface ectoderm intact
					Primary lens fibers form
					Trochlear and abducens nerves appear
					Lid folds present
	6	37	12		Edges of optic fissure in contact
			12	30	Tunica vasculosa lentis present
					Lens vesicle cavity obliterated
					Ciliary ganglion present
		41	12	32	Posterior retina consists of nerve fiber layer, inner neuroblastic layer, transient fiber layer of Chievitz, proliferative zone, outer neuroblastic layer, and external limiting membrane
			17	32	Eyelids fuse (dog)
	7				Anterior chamber beginning to form
			12.5	40	Secondary lens fibers present
		48	14	32	Corneal endothelium differentiated
	8	51			Optic nerve fibers reach the brain
					Optic stalk cavity is obliterated
					Lens sutures appear
					Acellular corneal stroma present
		54		30–35	Scleral condensation present
	9	57	17	40	First indication of ciliary processes and iris
					Extraocular muscles visible

Table 1.1 (Continued)

Human (Approximate Postfertilization Age)			Mouse (Day Postfertilization)	Dog (Day Postfertilization)	
Month	**Week**	**Day**		**Postnatal (P)**	**Developmental Events**
				—	Eyelids fuse (occurs earlier in the dog)
	10			45	Pigment visible in iris stroma
					Ciliary processes touch lens equator
					Rudimentary rods and cones appear
				45–1 P	Hyaloid artery begins to atrophy to the disc
3	12			—	Branches of the central retinal artery form
4				51	Pupillary sphincter differentiates
					Retinal vessels present
				56	Ciliary muscle appears
				—	Eye axis forward (human)
—				56	Tapetum present (dog)
				2–14 P	Tunica vasculosa lentis atrophies
					Short eyelashes appear
5				40	Layers of the choroid are complete with pigmentation
6				—	Eyelids begin to open, light perception
				1 P	Pupillary dilator muscle present
7				1–14 P	Pupillary membrane atrophies
				1–16 P	Rod and cone inner and outer segments present in posterior retina
				10–13 P	Pars plana distinct
9				16–40 P	Retinal layers developed
				14 P	Regression of pupillary membrane, tunica vasculosa lentis, and hyaloid artery nearly complete
					Lacrimal duct canalized

Data from Aguirre et al. (1972), Akiya et al. (1986), Cook (1995), and van der Linde-Sipman et al. (2003).

It is important to note that mesenchyme is a general term for any embryonic connective tissue. Mesenchymal cells generally appear stellate and are actively migrating populations surrounded by extensive extracellular space. In contrast, the term *mesoderm* refers specifically to the middle embryonic germ layer. In other parts of the body (e.g., the axial skeletal system), mesenchyme develops primarily from mesoderm, with a lesser contribution from the neural crest. In the craniofacial region, however, mesoderm plays a relatively small role in the development of connective tissue structures. In the eye, mesoderm probably gives rise only to the striated myocytes of the extraocular muscles and vascular endothelium. Most of the craniofacial mesenchymal tissue comes from neural crest cells (Johnston et al., 1979).

The neural tube closes initially in the craniocervical region with closure proceeding cranially and caudally. Once closure is complete, the exterior of the embryo is fully covered by surface ectoderm, and the neural tube is lined by neural ectoderm. Neural segmentation then occurs to form the specific parts of the brain: forebrain (i.e., prosencephalon), midbrain (i.e., mesencephalon), and hindbrain (i.e., rhombencephalon; see Fig. 1.3 and Fig. 1.4). The optic vesicles develop from neural ectoderm within the forebrain, with the ocular connective tissue derivatives originating from the midbrain neural crest.

Formation of the Optic Vesicle and Optic Cup

The optic sulci are visible as paired evaginations of the forebrain neural ectoderm on day 13 of gestation in the dog (see Fig. 1.3, Fig. 1.4, Fig. 1.5, Fig. 1.6, and Fig. 1.7). The transformation from optic sulcus to optic vesicle occurs

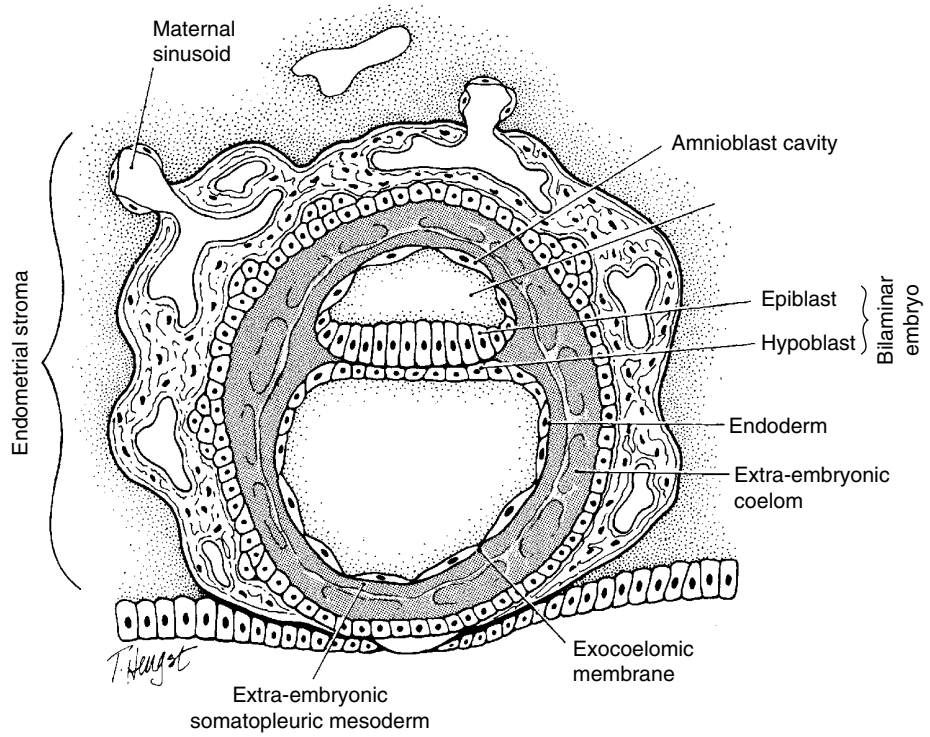

Figure 1.1 A blastocyst that has penetrated the maternal endometrium. An embryoblast has formed and consists of two cell layers: the epiblast above, and the hypoblast below. (Reprinted with permission from Cook, C., Sulik, K.K., & Wright, K.W. (2003) Embryology. In: *Pediatric Ophthalmology and Strabismus* (eds. Wright, K.W. & Spiegel, P.H.), pp. 3–38. New York: Springer.)

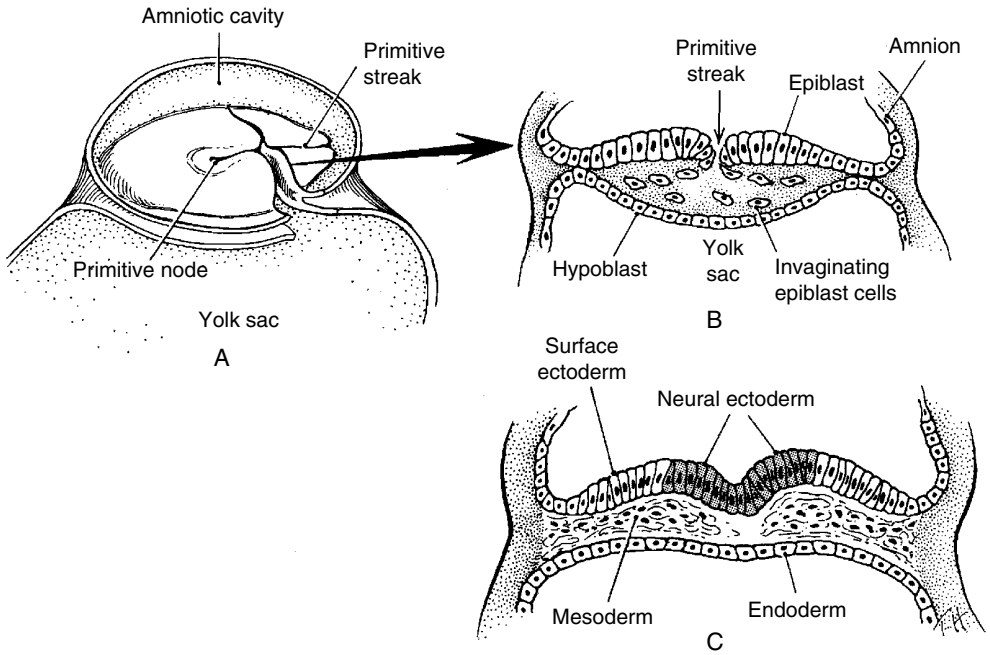

Figure 1.2 **A.** Dorsal view of an embryo in the gastrulation stage with the amnion removed. **B.** Cross-section through the primitive streak, representing invagination of epiblast cells between the epiblast and hypoblast layers. Note that the epiblast cells filling the middle area form the mesodermal layer. **C.** Cross-section through the neural plate. Note that the ectoderm in the area of the neural groove (shaded cells) has differentiated into neural ectoderm, whereas the ectoderm on each side of the neural groove is surface ectoderm (clear water cells). (Reprinted with permission from Cook, C., Sulik, K.K., & Wright, K.W. (2003) Embryology. In: *Pediatric Ophthalmology and Strabismus* (eds. Wright, K.W. & Spiegel, P.H.), pp. 3–38. New York: Springer.)

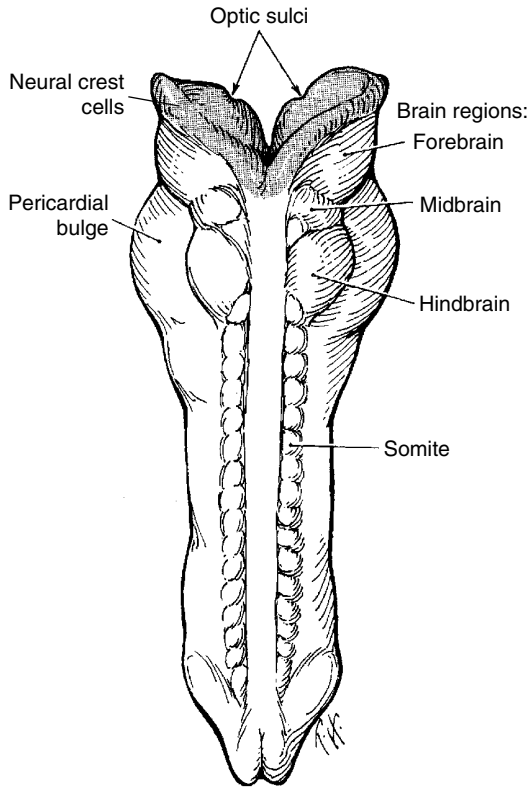

Figure 1.3 Dorsal view showing partial fusion of the neural folds to form the neural tube. Brain vesicles have divided into three regions: forebrain, midbrain, and hindbrain. The neural tube, groove, and facing surfaces of the large neural folds are lined with neural ectoderm (shaded cells), whereas surface ectoderm covers the rest of the embryo. Neural crest cells are found at the junction of the neural ectoderm and surface ectoderm. Neural crest cells migrate beneath the surface ectoderm, spreading throughout the embryo and specifically to the area of the optic sulci. Somites have formed along the lateral aspect of the closed cephalic neural tube. On the inside of both forebrain vesicles is the optic sulci. (Reprinted with permission from Cook, C., Sulik, K.K., & Wright, K.W. (2003) Embryology. In: *Pediatric Ophthalmology and Strabismus* (eds. Wright, K.W. & Spiegel, P.H.), pp. 3–38. New York: Springer.)

concurrent with the closure of the neural tube (day 15 in the dog). Intracellular filaments and microtubules within the cytoskeleton alter cell shape and allow for cell movement. In addition to the mechanical influences of the cytoskeleton and the extracellular matrix, localized proliferation and cell growth contribute to expansion of the optic vesicle (Fig. 1.5; Hilfer & Randolph, 1993; Hilfer et al., 1981).

The optic vesicle enlarges and, covered by its own basal lamina, approaches the basal lamina underlying the surface ectoderm (Fig. 1.5). The optic vesicle appears to play a significant role in the induction and size determination of the palpebral fissure and of the orbital and periocular structures (Jones et al., 1980). An external bulge indicating the presence of the enlarging optic vesicle can be seen at approximately day 17 in the dog.

Table 1.2 Embryonic origins of ocular tissues (Johnston et al., 1979; Noden, 1993; Yamashita & Sohal, 1987).

Neural Ectoderm	Neural Crest
Neural retina	Stroma of iris, ciliary body, choroid, and sclera
Retinal pigment epithelium	Ciliary muscles
Posterior iris epithelium	Corneal stroma and endothelium
Pupillary sphincter and dilator muscle (except in avian species)	Perivascular connective tissue and smooth muscle cells
	Striated muscles of iris (avian species only)
Bilayered ciliary epithelium	Meninges of optic nerve
	Orbital cartilage and bone
	Connective tissue of the extrinsic ocular muscles
	Endothelium of trabecular meshwork
Surface Ectoderm	**Mesoderm**
Lens	Extraocular myoblasts
Corneal and conjunctival epithelium	Vascular endothelium
Lacrimal gland	Schlemm's canal (human)
	Posterior sclera (?)

Data from Ashton (1966), Cook et al. (1991a), and Cook and Sulik (1986, 1988).

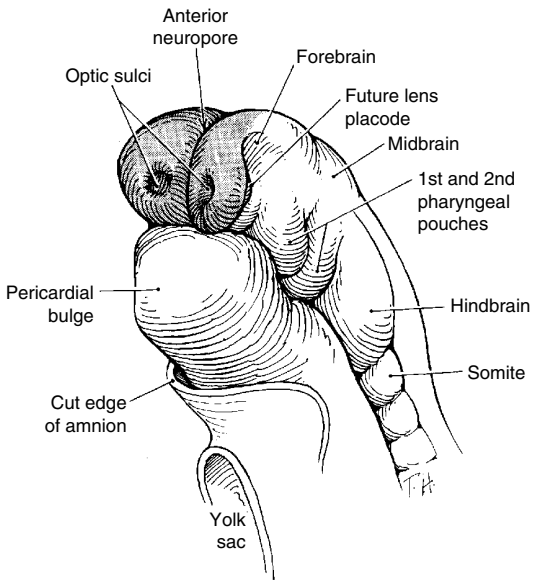

Figure 1.4 Development of the optic sulci, which are the first sign of eye development. Optic sulci on the inside of the forebrain vesicles consisting of neural ectoderm (shaded cells). The optic sulci evaginate toward the surface ectoderm as the forebrain vesicles simultaneously rotate inward to fuse. (Reprinted with permission from Cook, C., Sulik, K.K., & Wright, K.W. (2003) Embryology. In: *Pediatric Ophthalmology and Strabismus* (eds. Wright, K.W. & Spiegel, P.H.), pp. 3–38. New York: Springer.)

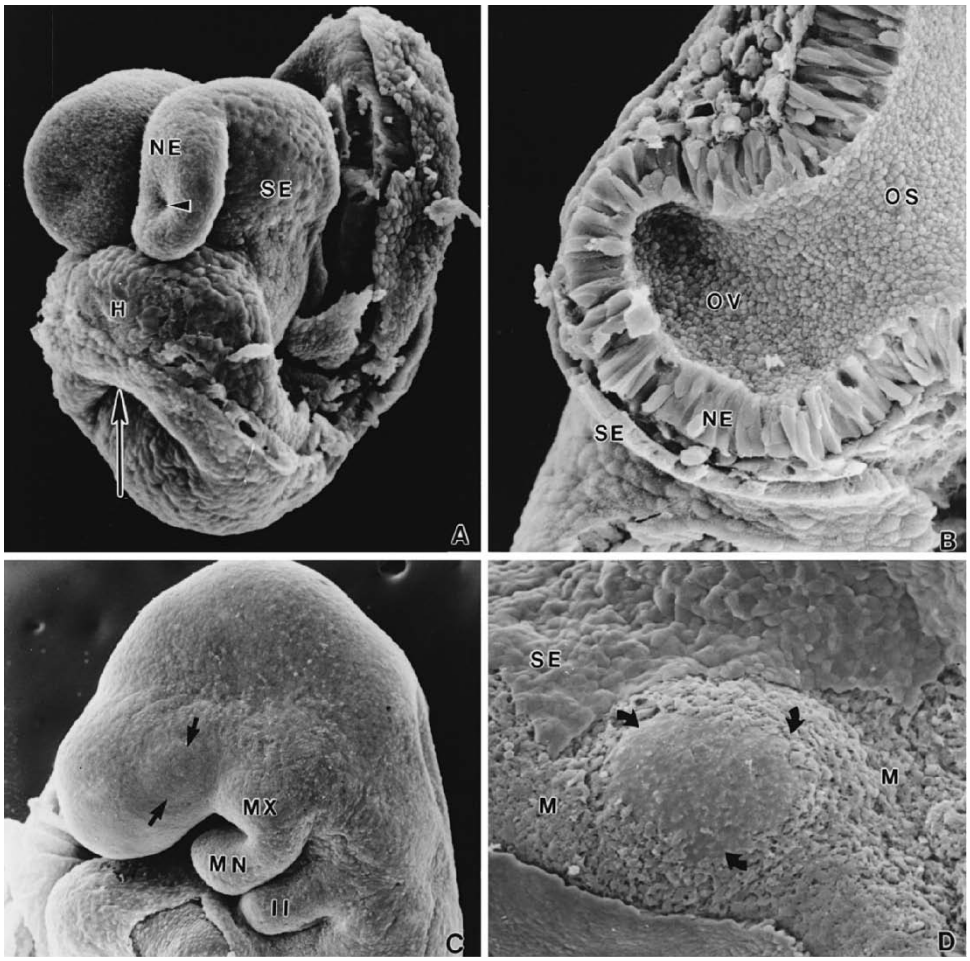

Figure 1.5 **A.** Scanning electron micrograph of a mouse embryo (six somite pairs) on day 8 of gestation, equivalent to day 13 of canine gestation. The amnion has been removed, and the neural folds have segmented into a forebrain region containing the optic sulci (arrowhead), which are evaginations of neural ectoderm (NE). The close proximity to the developing heart (H) can be seen. The area where the NE meets the surface ectoderm (SE) is where the neural fold will meet and fuse; this area also gives rise to the neural crest cells. The entrance to the foregut is indicated by the arrow. **B.** Scanning electron micrograph of the optic vesicle on day 9 of gestation in the mouse (day 15 in the dog). Expansion of the optic sulcus results in an optic vesicle (OV) that approaches the surface ectoderm (SE). A thin layer of mesenchyme is still present between the NE and the SE. The optic stalk (OS) is continuous with the ventricle of the forebrain. **C.** The bulge of the enlarging OV (arrows) can be seen externally. MN, mandibular prominence of the first visceral arch; MX, maxillary prominence of the first visceral arch; II, second visceral arch. **D.** Partial removal of the SE from an embryo of 25 somite pairs (day 17 in the dog; day 19 in the mouse) reveals the exposed basal lamina of the OV (arrows). Enlargement of the optic vesicle has displaced the adjacent mesenchyme (M) so that the basal lamina of the SE is in direct contact with that of the OV. (Reprinted with permission from Cook, C.S. & Sulik, K.K. (1986) Sequential scanning electron microscopic analyses of normal and spontaneously occurring abnormal ocular development in C57B1/6J mice. *Scanning Electron Microscopy*, **3**, 1215–1227.)

The optic vesicle and optic stalk invaginate through differential growth and infolding (Fig. 1.6 and Fig. 1.7). Local apical contraction (Wrenn & Wessells, 1969) and physiologic cell death (Schook, 1978) have been identified during invagination. The surface ectoderm in contact with the optic vesicle thickens to form the lens placode (Fig. 1.6, Fig. 1.7, and Fig. 1.8A, B), which then invaginates with the underlying neural ectoderm. The invaginating neural ectoderm folds onto itself as the space within the optic vesicle collapses, thus creating a double layer of neural ectoderm, the optic cup.

This process of optic vesicle/lens placode invagination progresses from inferior to superior, so the sides of the optic cup and stalk meet inferiorly in an area called the optic (choroid) fissure (Fig. 1.8F). Mesenchymal tissue (of primarily neural crest origin) surrounds and fills the optic cup, and by day 25 in the dog, the hyaloid artery develops from mesenchyme in the optic fissure. This artery courses from the optic stalk (i.e., the region of the future optic nerve) to the developing lens (Fig. 1.9 and Fig. 1.10). The two edges of the optic fissure meet and initially fuse anterior to the optic stalk, with fusion then progressing anteriorly and posteriorly.