Comparative ophthalmic pathology

The comparative study of animal eyes has been a primary source of knowledge in understanding normal embryology, anatomy, physiology, and biochemistry of the human eye. The field of comparative pathology has recently enjoyed a “renaissance” but has been exploited only to a limited extent by ophthalmologists and visual scientists. The comparative pathologist is in a special position to make significant contributions to the understanding of human eye disease.

Historically, in the latter part of the nineteenth and early twentieth century, great achievements in comparative pathology were made by Jenner, Pasteur, Calmette, Guerin, Osler, Rous, Shope, and others who made important contributions to human medicine through the study of animal diseases. Then followed a half century during which comparative pathology was ignored for a variety of reasons. However, in the past 15 years, there has been a renewal of interest and a rise in the quality of research and training in this field largely because government funds are available for basic research and training. For the field of visual science an important step forward has been the establishment of Veterinary Ophthalmologists. This has quantitatively influenced the interest in ocular diseases of animals reported by veterinarians.

Two specialized journals which report studies of comparative disease are the Comparative Pathology Bulletin, published quarterly by the Registry of Comparative Pathology, and Comparative Pathology. Also useful to visual scientists are two registries of comparative pathology, one at the National Academy of Sciences and one at the Armed Forces Institute of Pathology. These have been established in recent years to record and disseminate information about potential animal models to be used in the study of human disease. “The Handbook of Animal Models” is published by the Registry of Comparative Pathology and describes 60 animal models. The aim of this publication is “to provide investigators with a readily accessible, critically prepared but succinct reference to animal disease, experimentally induced or occurring naturally, which could be used for comparison with human disease.” Four fascicles of this excellent work are available and an examination of its contents reveals many diseases of interest to the ophthalmologist, including acute toxoplasmosis (monkey); Klinefelter’s syndrome (cat); globoid cell leukodystrophy (dog); amyloidosis (mice); Lafora’s disease (dog); kuru and Creutzfeldt-Jacob disease (mink); Down’s syndrome (chimpanzee); lupus erythematosus (dog); Waardenburg’s syndrome (cat); G_m gangliosidosis (cat); G_m gangliosidosis (dog); rheumatoid arthritis (rats and swine); malignant lymphoma (monkeys, cattle, sheep, horses, and pigs); hereditary fructose intolerance (rats); and gross congenital anomalies of a variety of species. In reviewing these cases it becomes evident that the study of the ocular aspect of most of these diseases is lacking.

The study of induced experimental models with regard to glaucoma, cataract, retinal disease, herpetic and other forms of corneal disease, and many other entities forms a major portion of the research effort currently being undertaken in ophthalmol-
ology and the visual sciences. Extrapolation of information from animal models to humans has, of course, its hazards and pitfalls. The effort to discover, preserve, and exploit naturally occurring or spontaneous animal models relevant to ophthalmic disease is much more limited. Individual reports regarding a sickle-cell anemia–related disorder (deer); Chediak-Higashi disease (cattle, mink, mice); ocular tumors (fowl), and other examples can be found. Of these studies the most impressive deal with cataract and retinal degeneration.

The attempt to understand the biochemical and morphologic changes occurring in cataract formation has led to the utilization of a number of animal models, many of which depend on cataractogenic agents, such as sugars (glucose, galactose, and xylose), other chemicals (naphthalene, triparanol, and BUdR), x ray, microwave, near-UV light and ultraviolet, cold, anoxia, laser, and viral induction. However, among the most fascinating of cataractogenic mechanisms are those associated with hereditary cataracts. In the Nakano Cataract Strain a pinhead nuclear opacity is noted to develop 3 weeks after birth. These mice were crossed with the Charles River strain and a new colony was developed and studied biochemically and histologically in the United States. It was found that the development of the lens opacity is accompanied by a sudden increase in the lens hydration and a sudden rise in the lens sodium. There is convincing evidence that this imbalance of the “pump-leak system” appears to be initiated by a deficiency of Na-K ATPase, a component of the active pump mechanism. Other strains of mice with both recessive and dominant modes of cataract inheritance have been described but studied less completely. In rats, a hereditary cataract mutation has been induced by x irradiation and the mutation has been inherited as a simple recessive factor. The predominant chemical change observed in the lens proteins during formation of the hereditary rat cataract was the oxidation of cysteine sulfhydryl (–SH) groups to cystine disulfide (–S–S–) groups. The process was accompanied by the formation of high-molecular-weight protein aggregates composed of various species of lens protein. Spontaneous cataract formation in various breeds of fish have also been studied. It would appear from these models that a number of genetic abnormalities may result in enzyme defects responsible for interrelated abnormalities of sodium and potassium equilibrium, sugar metabolism, free amino acids, lens protein, and lipoprotein components of cell membranes. Hereditary congenital or juvenile human cataracts may depend on abnormalities similar to those found in the animal models. Aging changes in the lenses of animals comparable to the senile human cataract have yet to be studied in an organized way.

Spontaneously occurring, inherited retinal abnormalities in animals are being studied from both the morphological and functional standpoints. These investigations are leading to correlations with observations in human retinal diseases in which specimens for histopathological examination are not readily available, especially at early stages of disease. Canine “retinopathies” have provided models for retinitis pigmentosa–like diseases; central, as well as peripheral, retinal anomalies and dystrophies; and retinal dysplasia. But work to elucidate the morphology and delineate the function in these animals must continue, deriving more exact analogies to human diseases which will enhance the visual scientist’s understanding of disease processes and eventually let him put a therapeutic handle on human retinal abnormalities. The retinal physiologists have shown us the elegance of “simplifying” a functional problem in normal retinas by picking an appropriate animal; e.g., by the choice of an animal with large, easily penetrated retinal units, individual cells can be studied; or by the selection of an animal with a single class of receptors, results remain free of the confounding effects of other classes of cells. To some extent the comparative pathologist can simplify his...
study by choosing an animal whose dystrophy clearly affects rods before cones or vice versa, or retinal pigment epithelium before receptors.\(^2\) But the main simplification given the comparative pathologist by his animal models is the more rapid development of the animal and its disease. This leads to the obvious advantage of opportunities to observe the course of morphological and functional changes, the range of severity of the abnormality, and the modes of inheritance. These advantages are most easily exploited in the rodent models of retinal disease, e.g., the RCS rats, the C\(_3\)H mouse and the more recently described WAG-RIJ rat.\(^2\)

There are other advantages of animal models in ophthalmic comparative pathology. Animals constitute an "early warning system" for man because they are lower on the food chain; this is important as new chemical compounds for weed control, insect control, and other purposes are introduced. The ophthalmologic aspects of such surveillance are important and the study of congenital anomalies as those occurring in deer may be pertinent to this. Yet another specific example may be found in the microsporidian parasite *Encephalitozoon (Nosema).* This organism, under consideration for use in insect control, has recently been shown to cause ocular pathology, including cataract formation in lower species.\(^2\)\(^7\)\(^-\)\(^8\) In addition, as human research restrictions become more stringent, the availability of animal models takes on increasing importance.

Comparative pathology probably had its beginning with the regulations concerning meat inspection in the Babylonian Empire of Hammurabi about 2100 B.C.\(^1\) Its next mention in history is with regard to the first and perhaps largest of all government research grants to be awarded: that given by Alexander the Great to Aristotle in 350 B.C., when he commissioned him "to learn the nature of animals. . . . For this end he placed at his disposal some thousands of men in every part of Asia and Greece among them hunters, scholars, park keepers, herdsmen, bee wards, as well as keepers of fish ponds and aviaries in order that no creature might escape his notice."\(^2\)^{21}

The importance of this type of investigation continues. Renée Dubois stated, "if we look carefully enough, we will eventually find an animal model for every disease."\(^2\) This applies to ophthalmology.

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