Total retinal degeneration in apparent anophthalmos of the Syrian hamster.

CHAI H. YOON.

Anophthalmia in the Syrian hamster was found to result from an extensive degeneration of retinal tissue and tissues derived from the retina. Eyes of affected animals were normal at the twelfth day of gestation (the average gestation period in the Syrian hamster is 16 days). However, the retina of these eyes showed rapid and extensive degeneration during the first two weeks after birth. In adults, the sclera-choroid complex was the only recognizable structure of the original eye, with an occasional remnant of deteriorated lens.

Anophthalmia has been reported in every class of vertebrates. Some of these forms are known to be hereditary, but the number of well-established forms of hereditary anophthalmia, in which the eyes are the primary target of mutations, is relatively small. Mammalian species, where the hereditary nature of anophthalmia has been established, include mice, hamsters, and guinea pigs. Some forms of anophthalmia reported in man are apparently hereditary. Of these, the developmental process of the anomaly has been worked out only in mice. Chase and Chase concluded, after their investigation of the embryology of anophthalmia in mice, that there was an inhibition of growth of the eye vesicle and that a failure of the eye vesicle to induce the lens led to the anophthalmic condition. However, anophthalmia in the Syrian hamster was found to have a completely different etiology.

Anophthalmia in the Syrian hamster was first described by Knapp and Polivanov. The condition is transmitted by a pair of incompletely dominant genes (gene symbol, Wh). Affected homozygotes never open their eyelids, although they are not fused. Also, these animals appear to be deaf. In adults, a mass of muscular tissues and Harderian glands are seen inside a thin and transparent conjunctiva. The fur of the affected animal is invariably white. Thus, the effects of the genes are apparently pleiotropic. Heterozygotes are normal except for their light-colored bellies.

It was found that affected animals do have normal eyes at the twelfth day of gestation, when the development of the eye proper is practically complete. However, the retinal components of these animals undergo rapid and extensive degeneration from around the time of birth. In adults, the sclera-choroid complex is the only recognizable sign of the eye, with an occasional remnant of deteriorated lens. Changes are brought about by a total degeneration of the retina and the tissues that are immediately derived from the retina. Thus, anophthalmia in the Syrian hamster resembles the retinal degeneration found in various species of animals and man rather than the anophthalmia in mice.

Materials and methods. Hamsters carrying the Wh gene in a heterozygous condition were obtained from an inbred line, BIO 72.29. In order to increase reproductivity, these animals were outcrossed to another inbred line, BIO 4.24 (wild type). Both lines are maintained at Bio-Research Institute, Cambridge, Mass. Matings were made between heterozygotes obtained from this outcross to produce anophthalmic animals, which are poor breeders.

In order to obtain embryos of known age, matings were made between heterozygotes. When embryos were removed, anophthalmic animals were identified by lack of pigment in their eyes. In the mating system used, anophthalmic animals were always white, and white animals were always anophthalmic.

Embryos and young animals were killed with chloroform and fixed in 10 per cent formalin. In the case of fully grown animals, only the eye and its accessory organs were removed and fixed. Some specimens were frozen in a cryostat after chloroform fixation. Both longitudinal and cross-sections were cut either at 8 μ or 16 μ. They were stained with cresyl echt violet.

Results. At the twelfth day of gestation, when most of the major components of the eye proper were present, the mutant hamsters were found to have normal eyes, except for the reduced number of pigment granules in the pigment layer. No apparent differences were detected between the normal and affected eyes.

However, significant differences were clearly
visible in the affected eyes immediately after birth, as shown in Fig. 1. Fig. 1, A shows a normal eye immediately after birth. The eyelids, cornea, ciliary body, and iris were present. The inner and outer nuclear layers could be distinguished. Fig. 1, B shows an affected eye of the same age. The shape of the eyeball was grossly distorted. The retina showed signs of disorganization, especially at the central region. Both the pigment and nuclear layers were irregularly shaped. The ciliary body and iris also showed signs of deterioration.

Progressive changes were evident at the sixth day as shown in Fig. 2. Figs. 2, A and C show a normal eye of six days. The inner and outer nuclear layers were further differentiated, but the ganglionic cells were barely recognizable. Figs. 2, B and D show an affected eye of the same age. The size of the eye as a whole was much smaller than that of the normal eye, although there was little difference in the size of the orbit. The entire retina was broken into numerous irregular groups and the pigment layer had lost its identity at many places. The lens occupied the entire space within the retina. The ciliary body and the iris were no longer recognizable.

Some specimens of this age showed a detached lens, displaced to the rear of the eyeball, but not occupying the entire space within the retina. It appeared that the lens was first detached from its normal position, displaced to the rear of the eyeball, and subsequently became surrounded by retinal tissue as the space within the retina diminished.

The destruction of the eye was nearly complete by the fifteenth day when photoreceptor cells were prominent in the normal eye. Small patches of broken retinal tissue were buried deep inside the fibrous growth of the sclera. The lens was shrunken and in a process of further deterioration. The optic nerve was thin and tortuous in its route.

At nine months the sclera-choroid complex was the only prominent structure of the original eye as shown in Fig. 3. Fig. 3, A shows the retina of a normal eye at nine months. The layer of photoreceptor cells, the inner and outer nuclear layers, the inner plexiform layer, and the layer of ganglionic cells were of similar size. In order to avoid an obstruction of view by thick pigment granules, a normal nonpigmented eye of a hamster obtained from one of the inbred lines at Bio-Research Institute was used for this figure. Figs. 3, B and C show an affected eye of the same age. The sclera-choroid complex was thicker than that of the normal eye and was invaded at places by cells that appeared to be of retinal origin. The optic nerve was but a thin thread with little nerve tissue. There was some degree of hyperplasia of Harderian glands and ocular muscles. However, the eyelids were normal and the conjunctiva was present.

Discussion. The retina, including the pigment layer, arises from the original eye vesicle. In
anophthalmos of the Syrian hamster, this structure is completely destroyed. The ciliary body and the iris derive parts of their structures from the pigment layer, and they are also completely destroyed. The lens has its immediate origin not in the eye vesicle but in the ectoderm. However, the suspensory ligaments of the lens are believed to arise from retinal cells. It appears that the lens loses its suspensory ligaments when the retina degenerates and is displaced into an abnormal position where it deteriorates. Thus, the changes observed in the affected eye may be explained as

Fig. 2. Normal (A) and affected (B) eyes of six days. ×20. Retina of normal (C) and affected (D) eyes of the same age. ×200. in = inner nuclear layer; on = outer nuclear layer; p = pigment layer; c = choroid.
Fig. 3. (A). Retina of a nonpigmented, normal eye of a nine-month-old nonpigmented animal from one of the inbred lines of Bio-Research Institute. ×120. G = ganglionic cell layer; IN = inner nuclear layer; ON = outer nuclear layer; IP = inner plexiform layer; OP = outer plexiform layer; PH = photoreceptor cell layer; SC = sclera-choroid complex. (B). Remnants of an affected eye of the same age. ×50. (C). Magnified view of a portion of sclera-choroid complex of the same affected eye. Remnants of retinal tissue are seen buried inside the sclera-choroid complex. ×120.
a result of the degeneration of retinal tissue and its derivatives.

The optic nerve, which is an outgrowth of ganglion cells, was affected as expected. However, the sclera, choroid, and ocular muscles arise from the mesenchyme that surrounds the original eye vesicle. As expected, they were relatively normal until the retinal degeneration reached its final stage. Most changes observed in these structures appear to be secondary to changes in the retina and the lens.

The pathologic pictures of the retinal degeneration in mice, rats, and dogs appear to be quite different from those of the Syrian hamster. One of the bases of these differences appears to lie in the difference of the time of onset of the degenerative process, which sets in relatively early in mice, beginning before the rods complete their differentiation. In rats the degeneration sets in after the rods and cones have attained their normal length. The situation in cats, dogs, and man resembles that in rats. Degeneration in the Syrian hamster, however, sets in even earlier than in mice, beginning before the appearance of any sign of the photoreceptor cells. This early onset of the degenerative process appears to be, at least partially, responsible for the more extensive destruction of the eye.

The apparent pleiotropism of the Wh gene presents an intriguing problem. However, it is difficult to determine at this time whether the Wh gene in the Syrian hamster is truly pleiotropic or whether it is a set of very closely linked genes. Only a large-scale breeding experiment can clarify this problem.

The basis for the deafness observed in the Syrian hamster is not known. However, it is interesting to note that no deafness has been mentioned in mice or rats in connection with hereditary retinal degeneration, while deafness often accompanies retinitis pigmentosa in man.

The author expresses his gratitude to Mrs. J. Yoon and J. Peterson for their preparation of histological slides, and to Mr. J. Coughlin for photography. He also expresses his thanks to Mr. J. Campbell for his assistance during the course of this investigation.

From Department of Biology, Boston College, Chestnut Hill, Mass. 02167. This work was supported by author's Grants 5R01 NSO2267-13, 14 of the National Institute of Neurological Diseases and Blindness. Animal breeding was carried out at Bio-Research Institute, Cambridge, Mass., and this portion of the work was supported by General Research Support Grant SO1 RR05525 of the National Institutes of Health. Submitted for publication Oct. 11, 1974. Reprint requests: Dr. C. H. Yoon, Department of Biology, Boston College, Chestnut Hill, Mass. 02167.

Key words: retina, retinal degeneration, anophthalmia, Syrian hamster.

REFERENCES


Ocular effects of diacetyl morphine and lysergic acid diethylamide in rabbit.

KEITH GREEN.

Intravenous lysergic acid diethylamide (LSD) given to rabbits in doses from 1 to 100 μg per kilogram of body weight produced a dose-related increase in intraocular pressure and outflow facility. Minor changes in systemic blood pressure were observed, but respiration rate was accelerated, and mydriasis became pronounced at higher doses. Diacetyl morphine (heroin) was given intravenously in doses from 0.1 to 2 mg. per kilogram of body weight. A dose-related decrease in intraocular pressure and an increase in outflow facility was found. A dose-related miotic was observed and at higher doses respiration became markedly depressed. Neither drug alters the permeability of the isolated ciliary epithelium. Both drugs appear to increase capillary blood pressure and, hence, aqueous humor inflow to cause the intraocular pressure to be maintained at approximately normal levels in face of increases in outflow facility of 50 per cent.