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Optic Nerve Size in Blind and Normal Mice[1]

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Abstract. Measurements of eyes and optic nerves of blind and normal mice were taken at ages ranging from 1-60 days. The mice used were from a Bagg albino strain in which a dominant mutation for blindness had occurred. The size of the optic nerve appears to be dependent upon the development of the eye. Optic nerves from blind eyes are smaller than those from normal eyes, and optic nerves from blind eyes without a lens and with a folded retina are smaller than those from eyes with a lens, even though the lens is vacuolated and the cornea is thickened.

The purpose of this investigation was to determine whether the optic nerve from the blind eye of a mouse undergoes degeneration or if the development of the nerve from the blind eye is blocked at some stage. This is part of a larger problem of the effect of a peripheral organ upon the central nervous system.

In enucleation experiments performed upon four- to six-day old mice, a complete or nearly complete degeneration of the optic nerve had occurred when the animal was sacrificed at 3-11 weeks of age (Terry, Roland, and Race, 1962).

In an anophthalic strain of mice, the optic nerve was absent or underdeveloped (Chase, 1945). In this case, the eye was also underdeveloped.

Mice raised in total darkness for 20-30 days showed a decrease in thick fibers of the optic nerve, and a delay in myelinization. There was no significant difference in the cross-sectional area of optic nerves of mice raised in darkness or reared under normal laboratory conditions (Gyllensten and Malmfors, 1963).

In the teleost, *Fundulus heteroclitus*, when the eye was completely removed, no retinal tissue or optic nerve was present. But when varying degrees of retinal tissue developed, then an optic nerve grew into the brain at the normal point of entry (White, 1948).

In this investigation, the animals used were from a Bagg albino strain in which a mutation for blindness had occurred. The mutation was first observed in the laboratory of Dr. Ernst W. Casperi, then of Wesleyan University at Middletown, Connecticut. The mutation is dominant, and lethal when homozygous.

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In the normal mouse, the eyelids are fused at birth, and opening occurs at about the thirteenth day after birth. In the strain of mice we were using, blind animals typically were born with their eyelids open. Soon after birth, the eyes appear dry, then fluids are secreted around the eye, sometimes hemorrhaging occurs, and scabs are formed over the eye (Watson, Orr and McClure, 1961). Later the eyes of these mice may have one of the following: (1) opaque corneas often vascularized, (2) opaque vacuolated lenses, (3) rosette formations in the retina, or (4) no lens at all with the folded retina filling the complete eye region. These abnormalities may be unilateral or bilateral.

Methods

Two methods of examination were used: (1) gross observation and (2) prepared cross sections.

For gross observation, with forceps and scissors the fresh brain was dissected from the skull of sacrificed animals. With experience, the olfactory lobes, optic nerves and eyes could be removed intact with the brain. Because of the soft consistency of the brain of the very young mice, it was necessary to fix those tissues in 10% formalin prior to removal from the skull. After the brain was removed, the optic nerves were observed and photographed.

For the cross sections, whole heads, with the lower jaw and top of the skull removed, were fixed in Bouin's solution, embedded in paraffin, sectioned at ten microns, and stained with hematoxylin and eosin or with Luxol Fast Blue P. A. S. Hematoxylin (Armed Forces Institute of Pathology, 1960).

From these slides, using an ocular micrometer, we measured the diameter of the optic nerves from both normal and blind eyes. The measurements were taken eight to ten sections anterior to the optic chiasma. If a true cross section had not been obtained, then to insure accuracy, we measured the nerve at its minor axis.

The measurement of the eye was taken across the eye from the outside of the retina, across the lens, to the outer part of the retina on the other side. This was usally the longest dimension of the eye. When no lens was present, the diameter in a comparable location was measured.

Results of Macroscopic Observation

In the adult mouse, the optic nerve and chiasma are opaque white, well defined and prominent on the ventral aspect of the brain (Figure 1). This photograph shows the brain of a 12-month old normal male mouse with eyes attached.

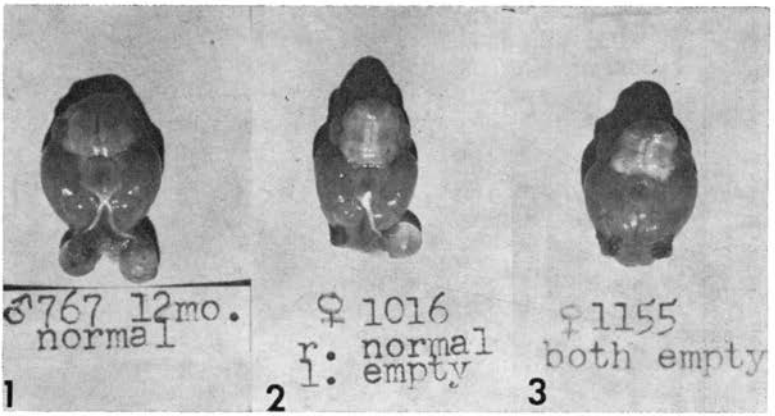

Figure 1. Ventral view of normal adult showing eyes, optic nerves and chiasma.
Figure 2. An adult with one normal eye and one extremely small eye, showing one normal nerve and one threadlike nerve.
Figure 3. An adult with both eyes very small and optic nerves almost invisible.

The optic nerves that arise from adult blind eyes are smaller than nerves from normal eyes. In most cases, nerves from eyes with opaque corneas were reduced in size and were white, but nerves from very small eyes, in which the lens was missing and retinal tissue folded, appeared to be clear thin threads. An animal with one normal eye and one blind eye will show one normal nerve and one nerve which may be threadlike (Figure 2). An animal with both eyes severly affected will have two such threadlike nerves (Figure 3).

In the observation of young normal mice we found that the optic nerves appear clear for about the first ten days, then the nerves begin to turn milky white, and by the twelfth or thirteenth day they are completely white, due to myelinization. At about this time the eyes open.

Until the time of eye opening, the optic nerve looks much the same in blind and normal mice. Later, in the case of an eye with no lens and folded retina, the nerve remains small and relatively clear, showing little if any myelinization. In the less severe forms, where a lens is present and the eye is of nearly normal size, but with perhaps an opaque cornea, the optic nerve becomes myelinated and seems to grow in proportion to the amount of eye tissue present.

Results of Microscopic Observations

In the scatter diagram of eye growth with age of the mouse, it is apparent that the blind eye is retarded in growth and typically does not reach normal size (Figue 4). The more severely affected remain much smaller than normal or opaque eyes. Nerve

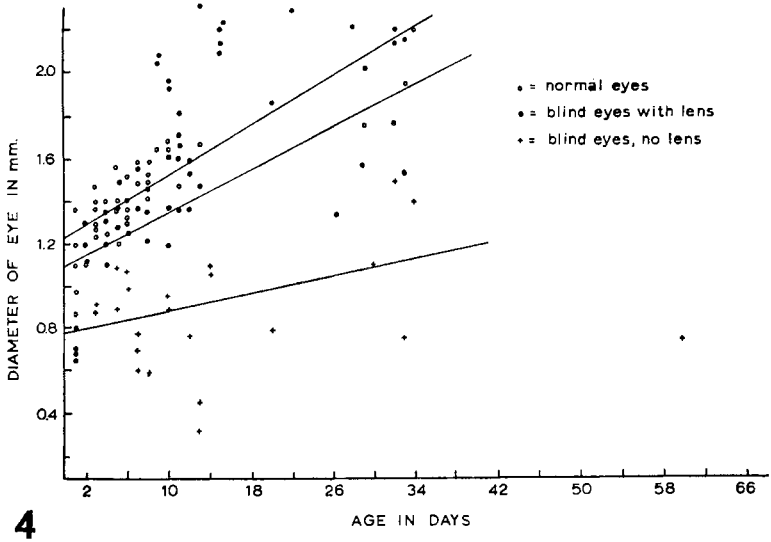

Figure 4. Scatter diagram showing the growth of the eye with increasing age of the mouse. Blind eyes, particularly those with no lens, grow more slowly and remain smaller than normal eyes.

growth shows a similar pattern (Figure 5). The nerve from an opaque eye is smaller than that from a normal eye, and the nerve from an eye without a lens is extremely small. The relationship of the optic nerve size to the diameter of the eye is shown in Figure 6. It appears that the optic nerve grows in direct proportion to the eye. The coefficient of correlation for these measurements, using data from both blind and normal eyes and nerves, is significant at the 1% level ($r = 0.63$ with 100 degrees of freedom).

Table 1 shows the average diameter in millimeters of the optic nerve in normal and blind mice. The optic nerves from blind eyes are decidedly smaller than those from normals, and the more severely affected eyes have smaller optic nerves than those less severely affected. The greatest growth occurs from about the ninth to the fifteenth day.

Figures 7-15 illustrate the abnormalities in the eyes and the attendant nerves that we see in this strain of mice. At five days of age, the nerves from blind and normal eyes are about the same size, by 12 days, there is a decided difference in size between nerves from opaque eyes, those from eyes without a lens, and those from normal eyes.

Discussion

In former work on the influence of the eye on the optic nerve, the observations started at about three weeks after eye enuclea-

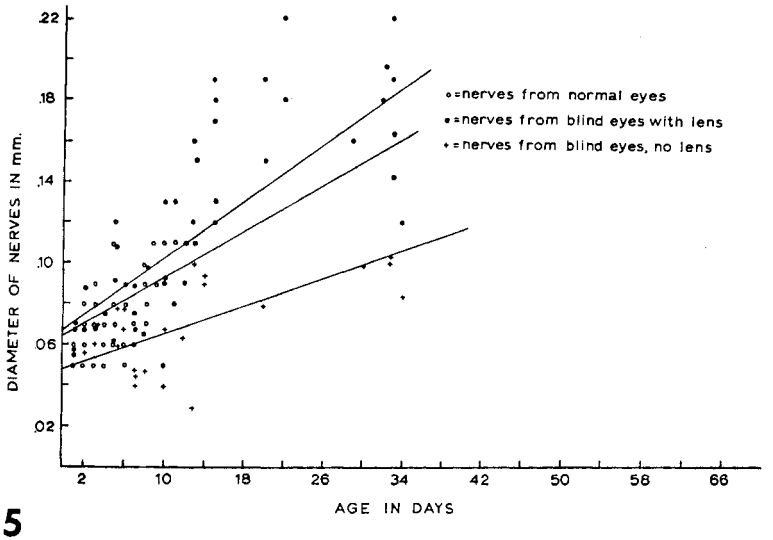

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Figure 5. Scatter diagram showing the growth of the optic nerve with increasing age of the mouse. Nerves from blind eyes remain smaller than nerves from normal eyes.

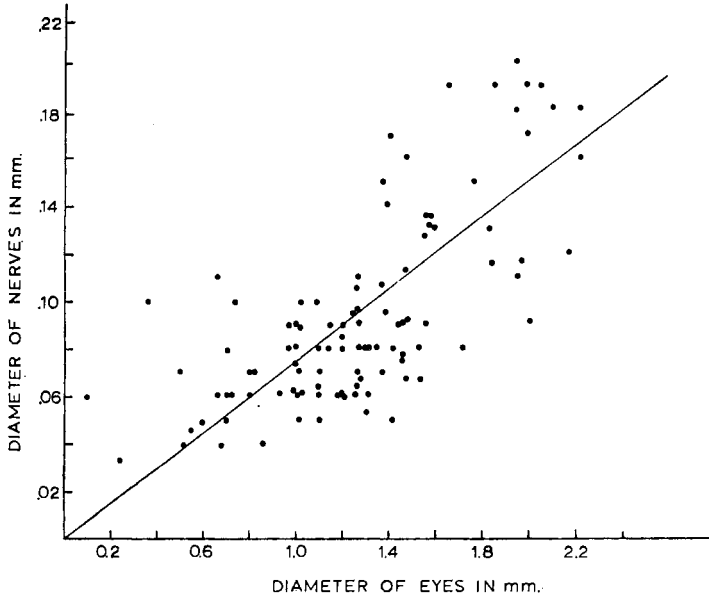

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Figure 6. Scatter diagram showing the relationship of the size of the optic nerve with the size of the eye.

Table 1. Average Size of Optic Nerves in mm.

Age in days	No.	Normal	Blind, with Lens	Blind, no Lens
1	6	.0590	.0616	
2	8	.0726	.0780	.0570
3	8	.0774		.0710
4	7	.0634	.0740	
5	16	.0844	.0896	.0696
6	8	.0800		.0760
7	9	.0690	.0770	.0450
8	9	.0826	.0882	.0470
9	3	.1052		
10	9	.1244	.0780	.0510
11	7	.1184	.0940	
12	4		.1100	.0640
13	6	.1450	.1270	.0734
14	2			.0916
15	6	.1642		
20	4	.1720		.0810
22	1	.1800		
30	1			.1050
32	4	.1860	.1960	.1760
33	6	.1880	.1534	.1120
34	2	.1260		.0840
60	2	.0950		

tion (Terry, Roland, and Race, 1962). In this investigation, we have measured the optic nerves of genetically blind mice at daily intervals from birth. We have taken the diameter of the eye to an index of the total development of the eye.

Our data indicate that though some degeneration probably occurs in the nerves from blind eyes, particularly at older ages, a greater factor is that nerve growth is retarded. We think that the optic nerve reflects the condition of the eye, for where the eye is severely damaged with no lens, folded retina, etc., this diameter is very small. Where the lens is present, though vacuolated, it is usually larger, and where only an opaque cornea is present, it may be close to normal size.

A count of the fibers present in the optic nerves from normal and blind eyes would be more accurate than the measurements we have taken, we hope to be able to accomplish this in the future by means of electron microscopy.

Summary

1. Eyes and optic nerves of blind and normal mice were observed and measured at ages ranging from 1-60 days.

2. Blind eyes were classified as opaque eyes with a lens, and reduced eyes without a lens.

3. Gross observation showed that myelinization of the optic nerves of normal animals occurs at about the time of eye opening. Myelinization of optic nerves from blind eyes is retarded

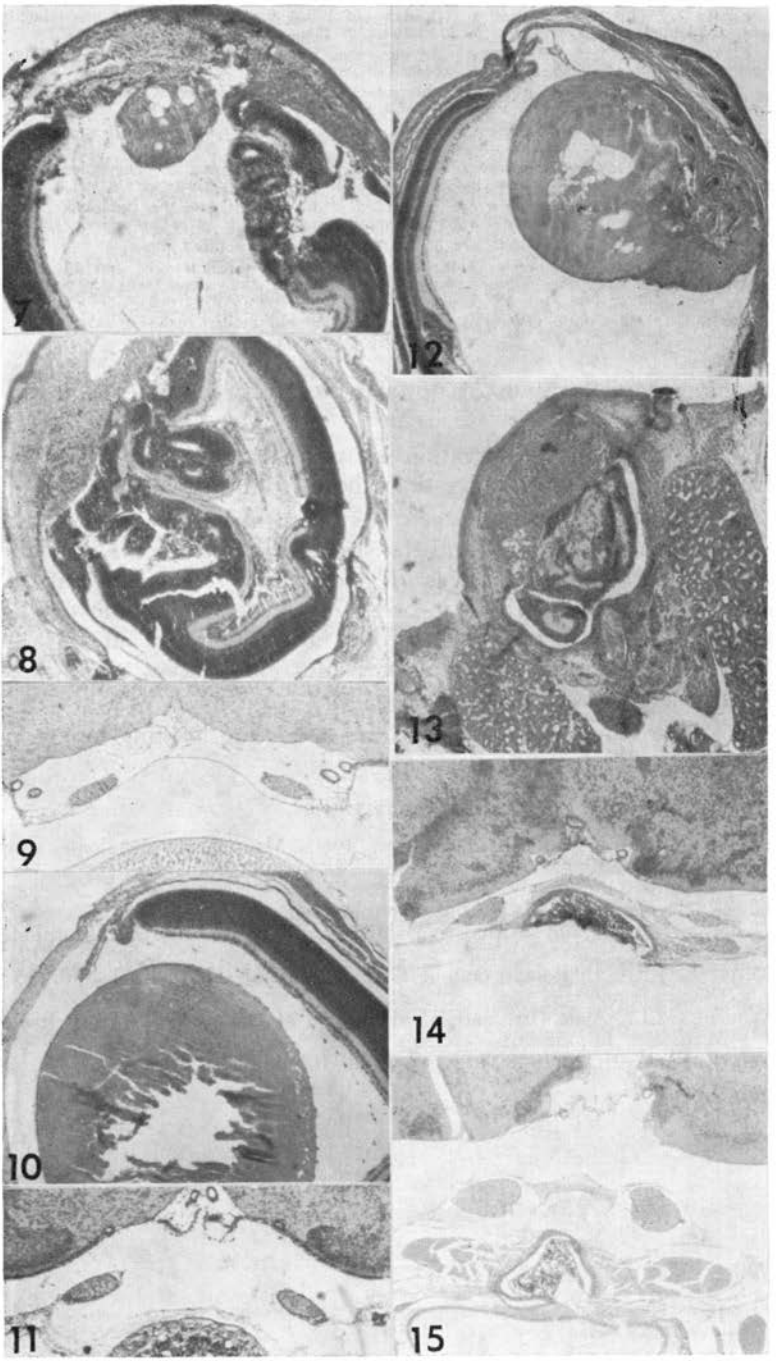
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Figure 7. The right eye of a five day old blind mouse. Notice the vacuolated lens, thickened cornea and rosette formations in the retina. (x45)

Figure 8. The left eye of the same mouse as Figure 7. Notice that this eye has no lens, the retina is folded, and the cornea is very thick. (x 42)

Figure 9. The optic nerves just anterior to the chiasma. This is from the same five-day old blind mouse as Figures 7 and 8. (x37)

Figure 10. The eye of a five-day old normal mouse. The normal lens is so hard at this stage that it shatters in cutting. (x50)

Figure 11. The optic nerves of a normal five-day old mouse. They are quite similar in size to those of the five-day old blind mouse. (x 42)

Figure 12. The opaque right eye of a 12-day old mouse. Note the vacuolated lens with a large exudate, thickened cornea and small rosette in the lower left corner. (x38)

Figure 13. The reduced left eye of the same 12-day old blind mouse. (x38)

Figure 14. The optic nerves of the 12-day old mouse of Figures 12 and 13. Note that the nerve from the reduced eye is much smaller than that from the opaque eye. (x30)

Figure 15. The optic nerves of a normal 15-day old mouse. (x33)

opening. Myelinization of optic nerves from blind eyes is retarded.

4. Microscopic observation showed that the optic nerves from blind eyes are smaller than those from normal eyes.

5. The diameter of the eye was taken to be an index of the development of the eye, and the size of the optic nerve appears to be dependent upon this development. The coefficient of correlation between the size of the optic nerve and the eye is 0.63, with 100 degrees of freedom and significant at the 1% level. Both blind and normal eyes and optic nerves were used in this calculation.

6. The size and condition of the eye is the limiting factor in the growth of the optic nerve.

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