4-1984

A report on amblyopia research at Pacific University College of Optometry

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Abstract

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Degree Type

Thesis

Degree Name

Master of Science in Vision Science

Committee Chair

Steven J. Cool

Subject Categories

Optometry

A REPORT ON AMBLYOPIA RESEARCH AT PACIFIC UNIVERSITY COLLEGE OF OPTOMETRY

Research Project
As partial fulfillment of the
Doctor of Optometry Degree at
PACIFIC UNIVERSITY COLLEGE OF OPTOMETRY

April 1984

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AKNOWLEDGEMENTS

I would like to thank Sharon Lorton and Karl Cloyd for their assistance in collecting data on the corneal curvature of kittens.

To Dr. Steven J. Cool goes a special thank you for giving me the opportunity to work with him the past three years. His insights on the behavioral aspects of vision have been valuable.

INTRODUCTION

The bulk of neurophysiological research on the mammalian visual system has been built on the cat. Experiments have shown that postnatal development of the visual system is inextricably related to the early visual experience of the animal. Functional amblyopia has been produced in cats through manipulation of their postnatal visual environment. Morphologic and physiologic studies of these animals have produced a large, complex, and steadily growing data base on the possible mechanisms of amblyopia. One goal of this research is to gain an understanding of amblyopia that will allow improvements in the prevention and treatment of functional amblyopia in the human population.

In this laboratory we are working with cats in an attempt to extend the data base. Currently, we are maintaining a breeding colony of research animals, developing experimental support systems such as computerization of experimental procedures, and conducting preliminary data gathering experiments. The later portion of this paper will describe our work in these areas. The first section of the paper will be a review of the literature on this subject.

VISUAL PATHWAYS OF THE NORMAL CAT

Before an interpretation of the abnormal visual system can be made, an understanding of the morphology and physiology of the normal visual system is necessary. A review of the retina--LGN--cortex pathway of the normal cat is the place to begin.

Ganglion cell axons leaving the eye project to many areas of the brain. The largest number terminate in the dorsal lateral geniculate nucleus (LGN). Six layers A, A1, C, C1, C2, and C3 have been recognized in the LGN.[1] Layers A and A1 are the largest and best understood. Layer A receives input from the contralateral eye and layer A1 receives input from the ipsilateral eye. Two subdivisions of the LGN, the medial interlaminar nucleus and the geniculate wing also receive ganglion cell axons.

The basic elements within the LGN are; the axons of the ganglion cells (retinogeniculate axons), the geniculate cells that project to the cortex (geniculocortical cells), the geniculate cells that do not send axons out of the LGN (the interneurons), and afferent axons returning from the visual cortex (corticogeniculate axons).[3] Incoming retinogeniculate axons terminate on the dendrites of the geniculocortical cells and on the dendrites and cell bodies of the interneurons. Fibers from the interneurons terminate on the dendrites and cell bodies of the geniculocortical cells. Axons returning from the cortex to the LGN terminate on the interneurons and the geniculocortical neurons.

Geniculocortical axons leaving the LGN project mainly to areas 17 and 18 in the visual cortex. The lateral suprasylvian cortex also receives direct input from the LGN. Axons from different layers of the LGN project to different layers in the visual cortex. Axons from the A laminae terminate in cortical layer IV. The corticogeniculate axons return to the LGN from cortical layer VI.

PHYSIOLOGY OF THE VISUAL CORTEX

Based on receptive field properties, the following types of cells have been identified in area 17 of the cat visual cortex:

Concentric cells--- The receptive fields of concentric cells resemble the familiar center-surround pattern found in ganglion cells and LGN cells. This similarity indicates that little transformation of the LGN input has occurred.[2] Concentric cells are found in layer IV where most of the LGN axons terminate.

Simple cells--- Receptive fields of simple cells have parallel bands of excitatory and inhibitory regions. The cells are most sensitive to properly oriented bars of light. The orientation of the stimulus must match the orientation of the excitatory region of the field for maximum response. When the stimulus is moved across the field many simple cells show a directional sensitivity, responding more to one direction than the opposite direction. Most simple cells are found in layer IV, but some

are found above and below that level.

Complex cells--- These receptive fields do not have distinct excitatory and inhibitory regions. Complex cells respond to a stimulus anyplace in their field. Many complex cells show both orientation and directional sensitivity. These cells are found above and below layer IV.

Hypercomplex cells--- These cells retain all the properties of complex cells and also require the stimulus to be a certain length to obtain maximum firing rate. A second class of hypercomplex cells require a second bar of light oriented at a specific angle to the first for optimum response. Hypercomplex cells are found above and below layer IV.

Considering the increasing complexity of receptive field properties as the distance from the layer IV LGN inputs increases, it is clearly indicated that a great deal of information processing occurs in area 17.

Two other features of the visual cortex are orientation columns and ocular dominance columns. One of the major features of the receptive fields of cortical cells is sensitivity to the orientation of the stimulus. It has been shown that cells with receptive fields of the same orientation sensitivity are grouped together. An electrode penetration perpendicular to the cortical surface will encounter cells with similar orientation properties as the electrode is advanced. This group of cells is known as an orientation column. Adjacent orientation

columns differ slightly in their angle of maximum sensitivity in a systematic way so that all 360 degrees are represented in a small area.[2]

Most (80%) of visual cortex cells receive inputs from both eyes.[8] These binocular cells have a similar receptive field in each eye. Input from one eye usually has a stronger influence on the binocular cell that the input from the other eye. A stimulus presented to the dominant eye produces a greater reponse than when the same stimulus is presented to the other eye. Groups of dominant cells are arranged in alternating left eye, right eye columns. Hypercolumn is a term applied to an area 1 to 2 mm^2 that contains a left and right dominance column and orientation columns covering 360 degrees.[2]

NEURAL MECHANISMS

The primary role of the nervous system is to control body function. To achieve this the nervous system gathers information from the environment and from within the body itself. This information is transmitted, stored, changed, and used in any way that can be advantageous to the organism. Throughout the nervous system certain neural circuits and mechanisms are used to process information. One facet of the research on the cat visual system has been an attempt to understand the development of neural mechanisms on a synaptic level.

Competitive and noncompetitive mechanisms are two possible ways that the visual system can develop. Consider two neurons

A and B that are genetically programmed to innervate neuron C. If this development was controlled by a noncompetitive mechanism, the synaptic development from neuron A to neuron C would be independent of the development of neuron B to neuron C. A competitive mechanisms implies that neurons A and B would actively compete for synaptic spaces on neuron C.

If neuron A developed normally while for some reason neuron B did not, neuron A would have relatively more synapses on neuron C. This would be true under the conditions of either competitive or noncompetitive mechanisms. The effect would be greater in a competitive system.[8]

If competitive and/or noncompetitive mechanisms are at work in the developing visual system, abnormal innervation patterns may develope when the organisms visual experience is abnormal.

The development of binocular cells in the cat visual cortex has been studied using various methods to create an abnormal visual environment. One method used in kittens to produce abnormal visual development is monocular lid suture. One eye is sewn shut before it has a chance to open. The animal is allowed to pass through its critical developmental period (4th week through 3rd or 4th month)[4] with only one usable eye.

Studies on these kittens have demonstrated striking changes in visual cortex physiology. The percentage of binocular cells drops from around 80% (normal) to only 5 - 10%.[5] Few area 17 cells respond to stimulation of the deprived eye, and those that do have abnormal visual field properties.

Another method of producing monocular abnormalities is to make the kitten artificially strabismic by cutting the medial or lateral rectus muscle. Exotropic kittens appear to have normal visual acuity in each eye. A survey of their visual cortex cells shows few binocular cells and approximately equal numbers of monocular cells driven by each eye. Esotropic kittens have reduced acuity in the deviating eye. The area 17 cell population shows few binocular cells and few cells driven by the deviated eye. As in the monocular suture experiments, the majority of active visual cortex cells were driven only by the good eye.

The unexpected physiological changes in visual cortex cells in monocular experiments led to other deprivational studies in an attempt to understand what was occuring. Binocular deprivation during the critical period has been produced through binocular suture and total darkness techniques. In the visual cortex of these animals, fewer than normal cells respond to light stimulation, however, the cells that do respond have approsimately normal ratios of monocular and binocular cells.[6]

Alternating occlusion experiments where the animals are always monocular and the occluder is switched daily throughout the critical period produce results similar to those seen in exotropic animals. Both eyes have good acuity and there are few binocular cells in the visual cortex.[7]

These types of deprivational studies have dramatically demonstrated the influence of the environment on the development of the physiology of the visual system. In relating this

line of research to the problem of amblyopia in humans an important question to be considered is how these physiological changes in binocularity are produced. Are the changes due to irreversible synaptic abnormalities caused by competitive or noncompetitive mechanisms or are they the result of other, possibly reversible, neural mechanisms? Is there an actual loss of input to the cortical cells from the deprived eye because the proper synapses are not there? Do normally formed synapses atrophy from disuse? Could it be that normal synaptic connections are extant but the information is being inhibited from reaching the cortical cell?

The next section of this paper will explore the evidence supporting inhibition as the mechanism responsible for the physiological changes seen in deprivational studies.

EVIDENCE FOR INHIBITION IN THE VISUAL SYSTEM

Several lines of evidence suggest that inhibition in the cat visual system maybe mediated by gamma-aminobutyric acid (GABA).[9] In 1974, Duffy administered the GABA-receptor blocker, bicuculline, intravenously to monocularly deprived kittens. Before the bicuculline was introduced, recordings from the cortex showed few binocular cells which is consistant with other monocular deprivation studies. After the bicuculline was injected more than 50% of the sampled cortical cells showed binocular properties. These results led Duffy to conclude that dominance of cortical cells by the good eye in monocularly deprived cats was the result of active inhibition of the input from the de-

prived eye.[9] This indicates that the normal neural connections are intact in a large percentage of area 17 cells. Since the drug was given intravenously it was not possible to determine where in the visual system the inhibition releasing effects were located.

A similar study (Sillito, Kemp, & Patel - 1980) produced the same kind of results by applying bicuculline directly to the visual cortex cells being studied. Evidence is presented to suggest that for some of the cells there is a selective GABA-mediated inhibitory process suppressing the non-dominant eye input.[10]

However, in a follow up study (Sillito, Kemp, & Blakemore - 1981) using the same direct cortical bicuculline application method found that 70% of the cells failed to show an input from the deprived eye. They conclude that intracortical GABA-mediated inhibition makes no significant contribution to the domination of cortical cells by the normal eye and propose that a redistribution of excitatory synaptic terminals on these cortical cells is a more significant factor.[12]

Based on these experiments it does seem clear that there is an inhibitory mechanism involved in the physiological changes produced by monocular deprivation. More work is needed to define the location of the inhibition releasing actions of bicuculline. Since Duffy was able to greatly increase the percentage of binocular cortical cells with intravenous application of bicuculline and Sillito et al. are currently unable to do so with direct cortical bicuculline application perhaps the location of the inhibition is not in the visual cortex.

Kratz, Spear, and Smith approached the inhibition question from another perspective. They raised monocularly deprived kittens for several months. In agreement with previous studies 0 - 10% of the striate cortex cells were driven by visual stimulation of the deprived eye. After these findings were taken the good eye was enucleated. Recordings made after the enucleation showed that up to 45% of the cortical cells could be driven by the deprived eye.[13] The authors concluded that the most likely mechanism producing these results is a release from inhibition. They feel that geniculocortical projections of the deprived eye are inhibited by the good eye.[13] Removal of the good eye releases the inhibition.

Considering the above studies it appears that a large percentage of cortical cells in monocularly deprived kittens retain normal or nearly normal synaptic connections from both eyes. Active inhibition of the input from the deprived eye mediated by the good eye seems a probable mechanism for the reduced performance of the deprived eye. An insight to the possible location of this inhibitory process comes from a study conducted by Marrocco, McClurkin, and Young on macaque monkeys. A rotating grating stimulus was used to assess the effects of stimulation of the region outside the classical center-surround receptive field of LGN cells, In conjunction with the rotating grating a cryogenic blockade of the visual cortex was performed by circulating ice water through a metal chamber cemented to the skull above area 17. Cryogenic blockade can eliminate activity in cortical layer VI, where corticogeniculate afferents are located. They found a definite corticogeniculate feedback

mechanism and have shown that cells in area 17 can have a direct effect on the ability of the LGN cells to transmit information.[14]

Reviewing the LGN connections discussed earlier, it is possible that corticogeniculate axons returning from cortical layer VI could have a influence on the passage of information through the LGN on its way to the visual cortex.

USE OF HARD CONTACT LENSES AS A MEANS OF PRODUCING DEPRIVATIONAL AMBLYOPIA IN KITTENS

INTRODUCTION

Studying the neurophysiology of amblyopia in cats requires that some of these animals be made amblyopic in one eye while the fellow eye is allowed to develop normal vision. Common procedures employed to achieve this goal are:

1- Monocular occlusion by lid suture. The upper and lower lids of one eye are sewn together before the eyes open. The covered eye is deprived of all form vision but recieves some diffuse light.

2- Monocular occlusion by goggle type filter devices of various densities from translucent to totally dark.

3- Esotropia produced by severing the lateral rectus muscle of one eye which produces a degree of amblyopia in the strabismic eye.

Rigid contact lenses are a seldom used alternative to the lid suture and goggle type occlusion techniques. In this laboratory we would like to use darkened hard contact lenses as our preferred method of monocular occlusion. To do this in an effective, practical and non-traumatic fashion we will need a set of contact lenses with base curves that closely correspond to the corneal curvatures of young kittens as they pass through their critical developmental periods.

The following section of this paper contains the preliminary data on the relationship between corneal curvature and age that will define the range of base curves needed in our set of contact lens occluders.

RELATIONSHIP BETWEEN CORNEAL RADIUS AND AGE

Corneal power readings were taken weekly on two groups of young kittens born to different mothers in the feline research colony at Pacific University College of Optometry.

Group one- Three kittens followed weekly from age 4 weeks to age 18 weeks. Measurements were not taken on weeks 8,9 and 14.

Group two- Five kittens followed weekly from age 2 weeks to age 18 weeks. Measurements were not taken on weeks 6 and 17.

Corneal power measurements were taken with a standard Bausch and Lomb keratometer. Initially, the power readings were beyond the range of the instrument. A series of plus lenses was used to extend the range. A plus lens placed at the aperture of the keratometer magnifies the image of the mires and allows measurement of short corneal radii. These accessory lenses were used during most of the data collection process. All of these measurements were corrected using constants determined by measurements taken on steel balls of known radii.

Measurement of the corneal power in each of the two principal meridians was taken on both eyes weekly. The orientation of the meridians was not recorded.

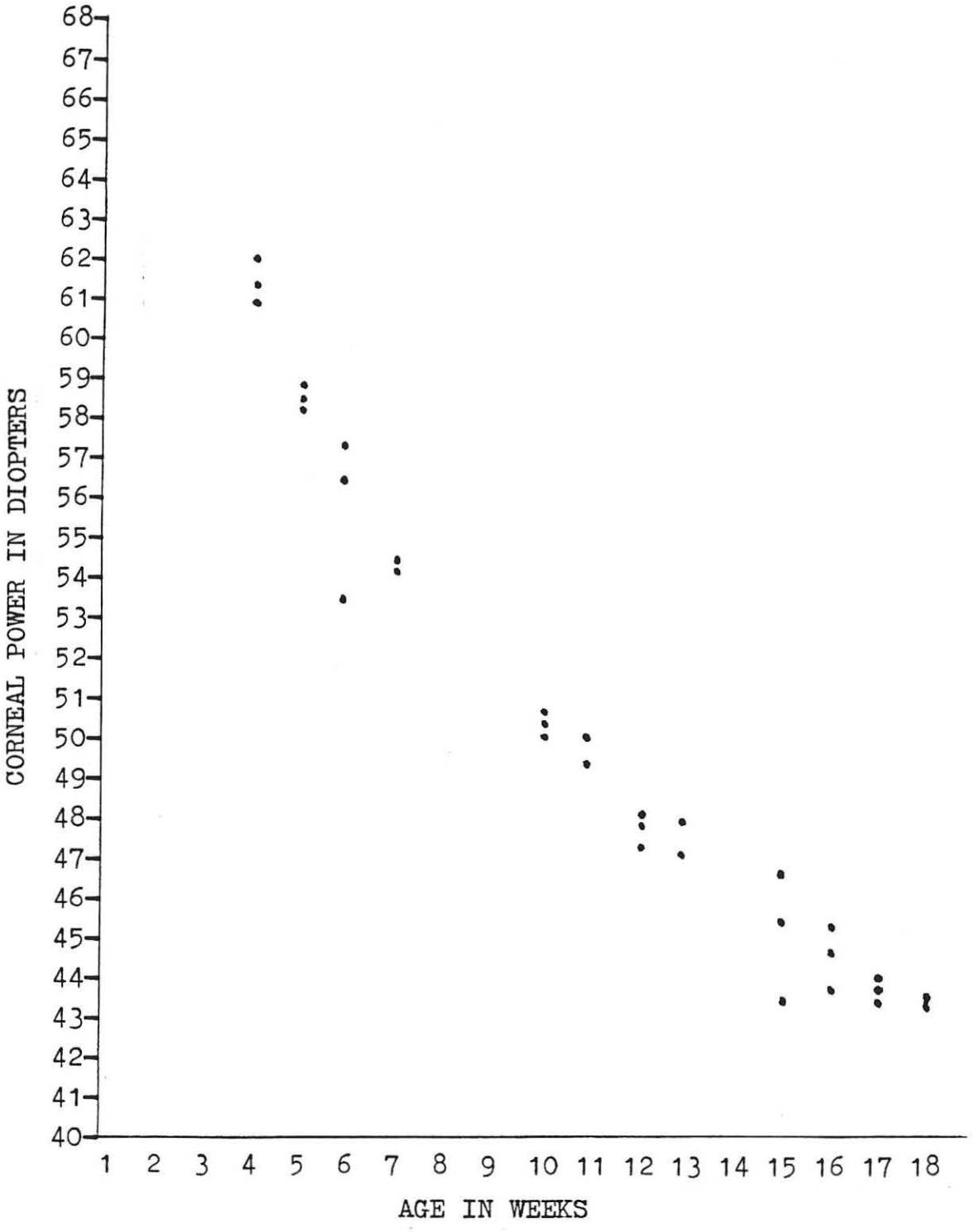
The following graphs show separate and combined data from groups one and two.

GRAPH A

Distribution of the data from the three kittens in group one. Corneal power in diopters is plotted against age in weeks.

In the following four graphs, each point represents the average of the four readings (two principal meridians per eye) taken at the given age.

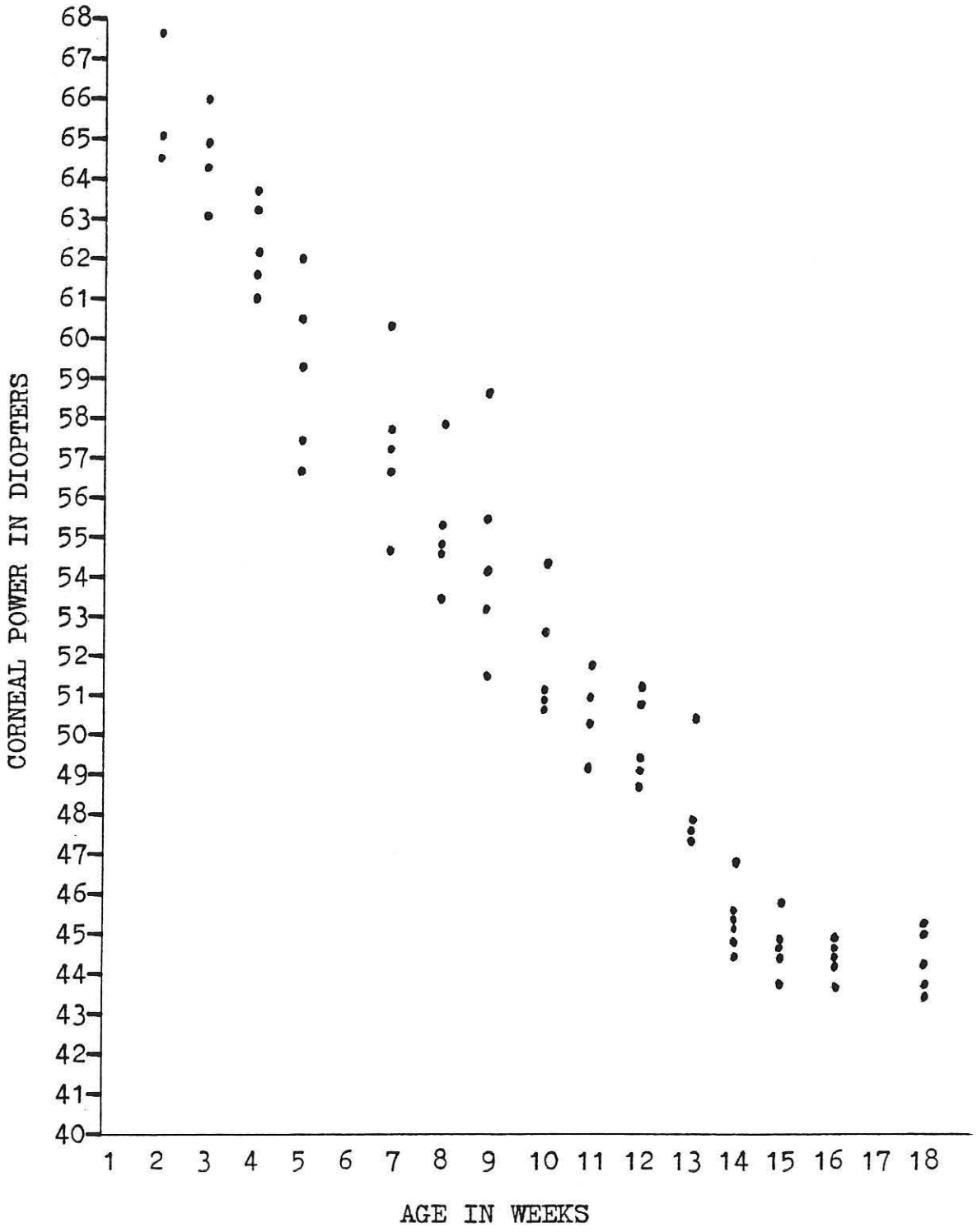
GRAPH A


CORNEAL POWER IN DIOPTERS
68
67
66
65
64
63
62
61
60
59
58
57
56
55
54
53
52
51
50
49
48
47
46
45
44
43
42
41
40
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
AGE IN WEEKS

GRAPH B

Distribution of the data from the five kittens in group two. Corneal power in diopters is plotted against age in weeks.

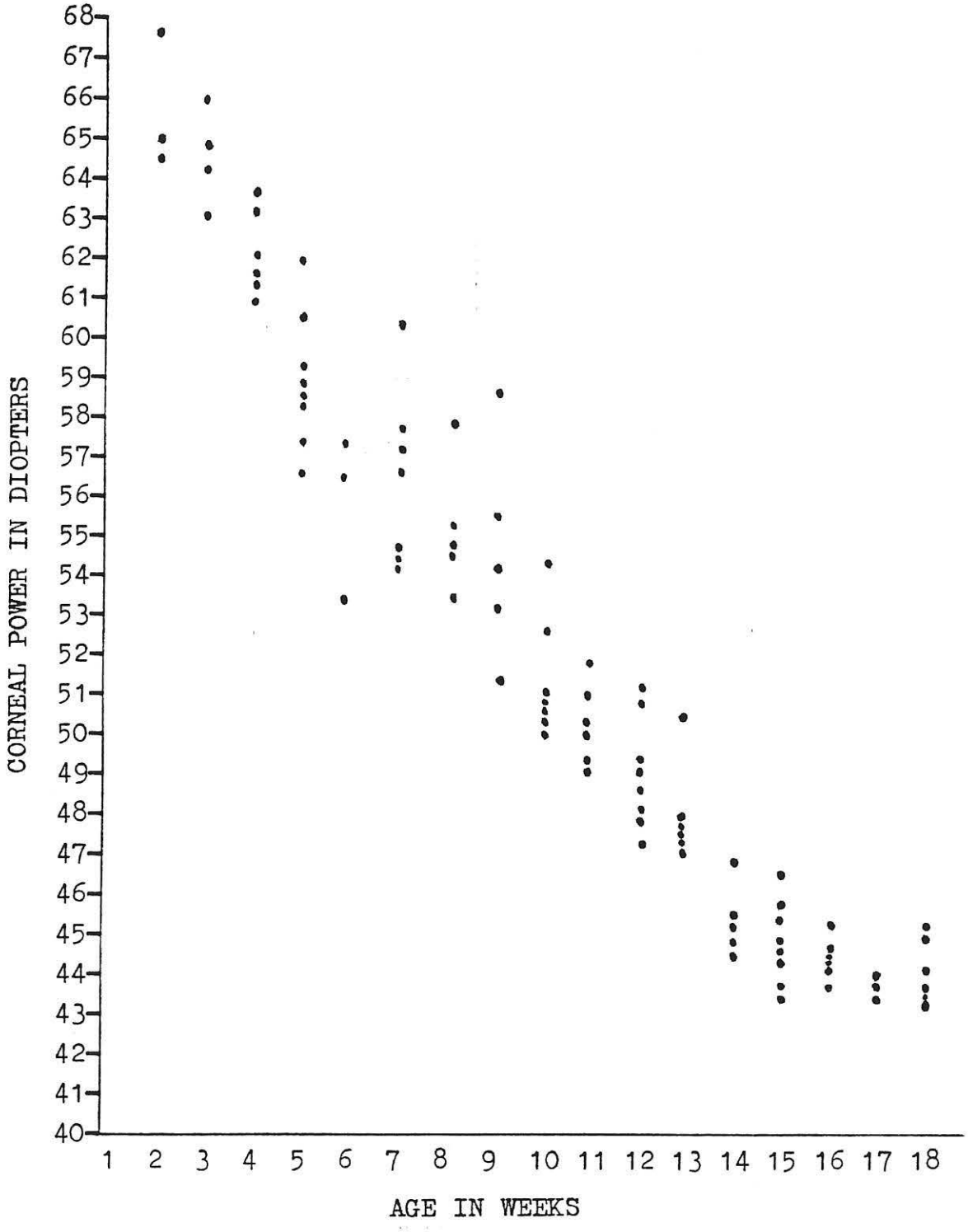
GRAPH B


CORNEAL POWER IN DIOPTERS
68
67
66
65
64
63
62
61
60
59
58
57
56
55
54
53
52
51
50
49
48
47
46
45
44
43
42
41
40
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
AGE IN WEEKS

GRAPH C

Distribution of combined data from the eight kittens in groups one and two. Corneal power in diopters is plotted against age in weeks.

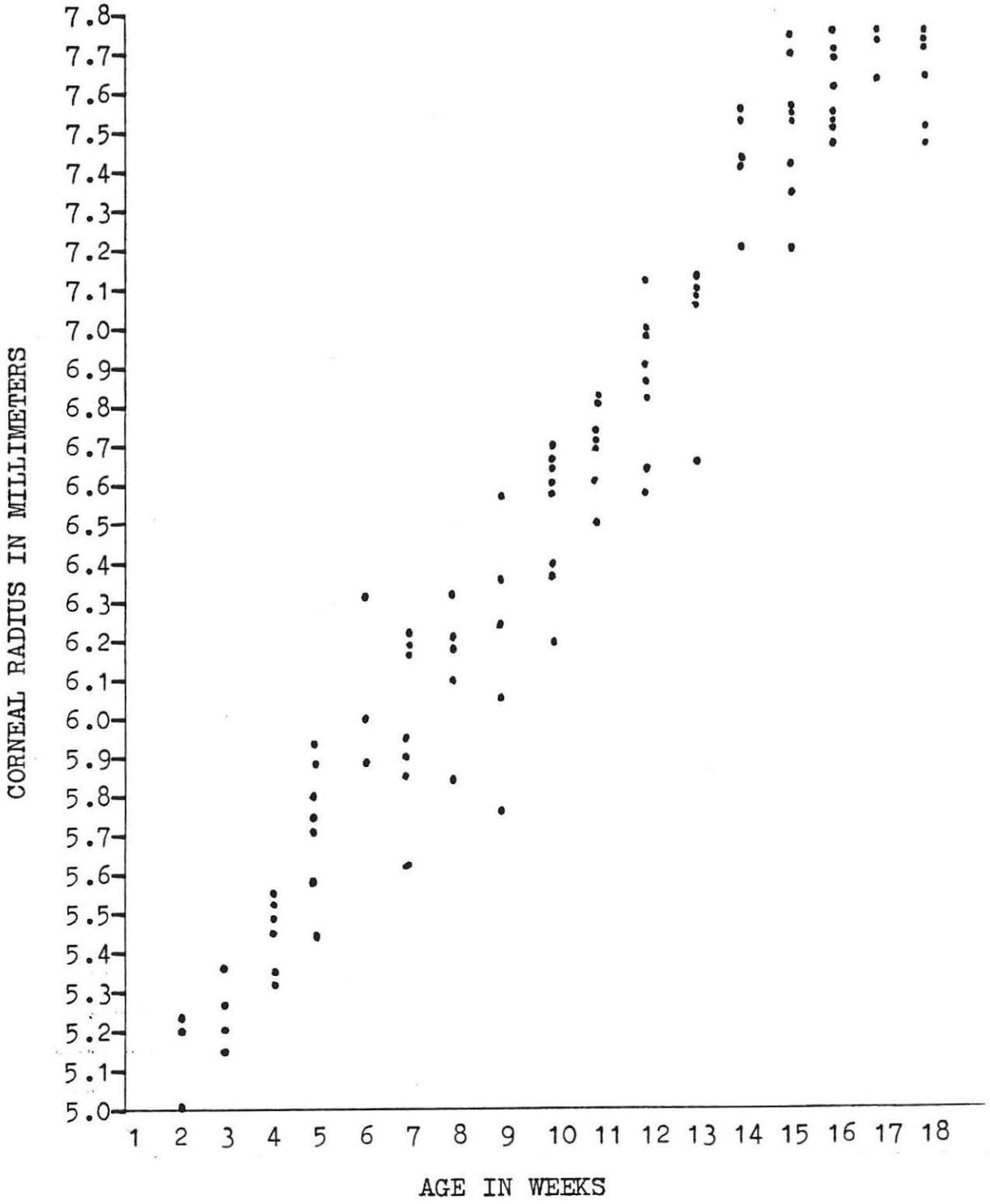
GRAPH C


CORNEAL POWER IN DIOPTERS
68
67
66
65
64
63
62
61
60
59
58
57
56
55
54
53
52
51
50
49
48
47
46
45
44
43
42
41
40
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
AGE IN WEEKS

GRAPH D

Distribution of combined data from the eight kittens in groups one and two. Corneal radius in millimeters is plotted against age in weeks.

GRAPH D


CORNEAL RADIUS IN MILLIMETERS
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
6.5
6.4
6.3
6.2
6.1
6.0
5.9
5.8
5.7
5.6
5.5
5.4
5.3
5.2
5.1
5.0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
AGE IN WEEKS

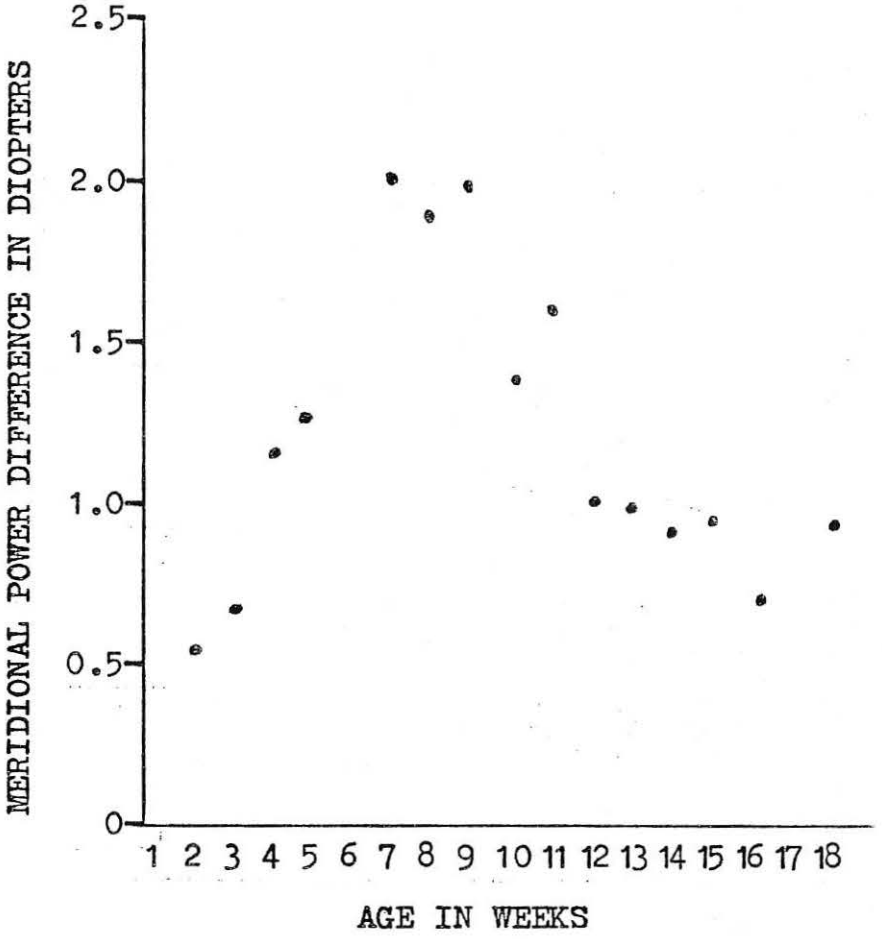
GRAPH E

Distribution of the average power difference in the two principal meridians from the eight kittens in groups one and two.

Each point represents the average difference in the powers of the two principal meridians of all eight kittens at the given age.

Meridional power difference in diopters is plotted against age in weeks.

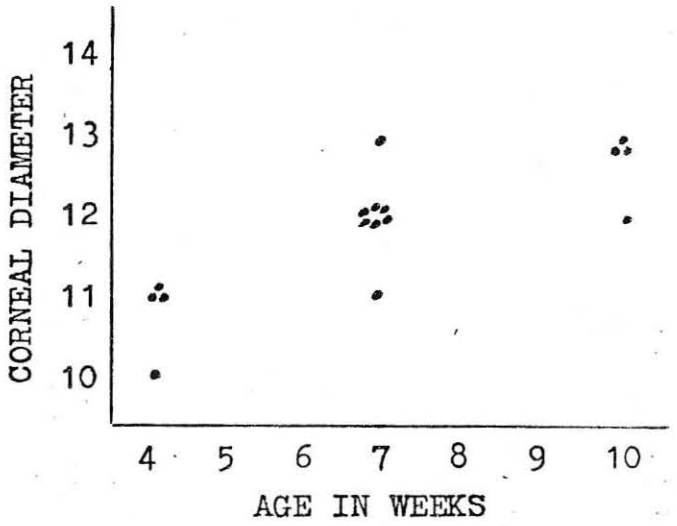
GRAPH E


MERIDIONAL POWER DIFFERENCE IN DIOPTERS
2.5
2.0
1.5
1.0
0.5
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
AGE IN WEEKS

ESTIMATED CORNEAL DIAMETER

Measurements of corneal diameter (to the nearest millimeter with a hand held ruler) were taken on two separate litters of kittens at three different ages. This information will be used to determine the diameters needed in our set of contact lens occluders.

	4 weeks	7 weeks	10 weeks
GROUP 3		11 mm	12 mm
		12 mm	13 mm
		12 mm	13 mm
		12 mm	13 mm
GROUP 4	10 mm	12 mm	
	11 mm	12 mm	
	11 mm	12 mm	
	11 mm	13 mm	



DISCUSSION

This preliminary information on the change in corneal curvature with age indicates a fairly constant rate of corneal flattening between 2 and 18 weeks of age. The rate of flattening appears to decrease around the 15th week. Corneal curvatures in the first 10 to 12 weeks are steeper than commonly available base curves. Standard base curves fall in the 7.0 mm to 8.5 mm range. Lenses used in the first 3 months of age will have to be custom made in order to get the correct base curves. Once the cornea is flat enough, standard lenses may be used.

The data on meridional power differences (corneal astigmatism) indicates that there will not be a serious problem in the use of spherical base curve lenses on most kittens. The average corneal astigmatism for the first 18 weeks is about 1 diopter with a peak of 2 diopters at 7 weeks of age.

Initial estimates of corneal diameter indicate that in order for the occluding lenses to cover the entire corneal surface, they must have overall diameters in the 10 mm to 13 mm range.

Further measurements on these corneal parameters would be useful as the number of kittens represented in this report is small. It would be useful to relate corneal changes to body weight as well as to age.

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