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Amblyopia and Non-human Animal Research

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Summary

This paper discusses the claim that the use of non-human animals in amblyopia research has led to our understanding and treatment of this condition. It is shown that such use was not important, that our understanding was based on human experience and that the non-human animal research actually confused the situation.

Keywords: amblyopia, cataract, lazy eye, non-human animal, ocular media opacification, research, species differences, squint, strabismus

Amblyopia is defined generally as a unilateral or bilateral decrease in visual acuity caused by form vision deprivation, abnormal binocular interaction, or both, for which no organic cause can be detected by the physical examination of the eye and which, in some cases, is reversible by therapeutic measures (57). It often occurs as the result of congenital conditions that do not permit both eyes to focus simultaneously. For example, if there is congenital strabismus (squint), and the child utilizes one eye only, the unused eye will become amblyopic. The same holds true for congenital opacification of the ocular media as in cataract or anisometropia (unequal refraction between eyes of the same individual). The reason for reduction in vision appears to be due to a lack of proper connections from the retinal ganglion cells to other neurons in the central nervous system during postnatal development.

Since around the 1960s, there has been considerable experimental work aimed at trying to understand the processes which lead to amblyopia by using non-human animals (animals3). Cats and non-human primates have been the most studied, but chickens and tree shrews also have been used. Experimental manipulations have included perturbations such as: suturing the eyelids closed; removing an eye; causing artificial strabismus, either surgically or through the use of prisms; or, rendering the ocular media opaque. There have been numerous assertions by those presently doing this sort of work that these manipulations have led to significantly greater understanding of amblyopia and that the results have been used to develop treatment methods for affected human beings. Nevertheless, in reviews of treatment regimens in 2016, authors did not mention any animal studies (27, 53). Authors promoted continued clinical research involving human patients and did not mention any reliance on or need for animal research (28, 53). Another review author only mentioned that animal research reached the same conclusions as that done in clinical trials with patients (55).

There are, however, major differences in the development and structure of the visual systems of human beings and other animals (42, 43, 47, 56). The cat, who is widely used, does not have a macula or fovea, two regions of the retina of primary importance for human vision. These areas account for essentially all useful vision occurring in the human being and it is the development, or lack thereof, of their connections in the brain that are of the utmost importance in amblyopia (57). Although there are some general similarities between human beings and cats with respect to neuroanatomy, the differences are so great that the results obtained in this work do not appear to have had any meaning for the human situation based upon a lack of references to this work in reports on human clinical conditions. The cat ‘model’ cannot predict what changes may occur in human beings when vision is deprived either monocularly or binocularly. Furthermore, the experimental situation in the cat and other animals is entirely artificial, a perturbation of an otherwise normal animal. Spontaneously occurring visual deprivation in human children, however, 1

1 The intent of this review is to demonstrate that reliance on animal research is unnecessary to understand or treat amblyopia in people. Although some of the references may be considered 'dated', this only serves to show just how much understanding and management has remained unchanged over the decades despite thousands of animals being subjected to some of the worst privation imaginable. In addition to the lack of scientific credibility or necessity, there are strong moral arguments against subjecting non-consenting beings to harm and death; this subject is addressed in another manuscript (8).

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3 Purely for the sake of convenience, I may refer to animals other than human beings as "animals", recognizing that all are animals of one kind or another; there is no intention to imply that any, even a human being, is morally superior or intrinsically more valuable than another.
often is associated with other developmental defects which tend to modify and confound the situation.

Although there are many structural and physiological similarities between certain non-human primates and human primates, there may still be problems in extrapolating the information to the human situation. In some cases, for example with myopia, there is considerable difference between similar non-human primate species with respect to the results following similar experimental manipulations (46,5). Because of the considerable similarity to human beings, the use of non-human primates also raises greater ethical concerns for many people, concerns which may make the use of these animals inappropriate.

There has been considerable concern expressed by vision scientists other than just myself that the experimental work is either not relevant or may be misleading with respect to the human condition and its treatment (19, 34, 35, 54, 57, 59, 60, 62.5).

When evaluating the claims for the importance of animal work, one also must bear in mind that this work largely is neurophysiological dealing with single cell recordings. This work does not measure vision, which has a large psychological component in people, and actually has little to do with vision in terms of behavior and function. This is even alluded to by some investigators in their own publications (5). One cannot adequately study vision in non-human animals because there is no meaningful and relevant communication with them, and cellular recordings do not tell you whether and how these animals see.

In addition, some of this work has involved some rather serious suffering on the part of the animals. For example, in one study, monkeys were deprived of sight in one eye for periods up to five years (52). In at least one case, one monkey was deprived of her or his sight in both eyes for a period of one year (6). In many cases, the eyes themselves have been removed in these and other sentient creatures (22).

Animals also have been subjected to neuromuscular blocking agents such as gallamine triethiodide, sometimes with what appeared to be inadequate attention to anesthesia. These agents paralyze most of the muscles in the body, but leave the animal conscious and able to feel pain and anxiety even though they cannot respond by moving. In some cases, the experimenters did not appear to be aware that these agents do not provide any anesthesia or analgesia.6

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4 When atropine was used in one eye of either rhesus or stump-tailed macaques, different results were obtained with respect to the production of myopia. There also was a difference in the effects of artificially closing one eye between these otherwise similar primates.

5 Hoyt reported that animal work had suggested that binocular patching, as done in phototherapy of jaundiced children, might be harmful (19). The data from children, however, suggested that binocular patching was not harmful. Marg pointed out that the results of examination of amblyopic children were at odds with some of the experimental work and that, along with the conflicting findings between animal species, this seemed to demonstrate that one could not extrapolate animal results to children with confidence (34). He stated that the animal “models” were not entirely valid for children. Metz noted that the type of occlusion done in experimental work was different from that used therapeutically in children with amblyopia (35). He was concerned because the experimental work done on cats could be interpreted to suggest that amblyopic children should not be patched. Such an interpretation, based on animal studies, would be most unfortunate for amblyopic children. von Noorden and Maumenee were critical of the classical work of Wiesel and Hubel because of the substantial difference in neuroanatomy and neurophysiology between cats and human beings (60). von Noorden later commented on how data from animals could not be applied directly to human beings, and that there were differences between monkeys and cats in the various studies done (57). In his Jackson Memorial Lecture (59), he again was critical of animal experiments with regard to infantile esotropia (convergent strabismus). He pointed out that the monkey work was not analogous. He concluded that there is no animal “model” for infantile esotropia, despite all the work which had been done making infant monkeys strabismic.

6 In a letter to Richard Whitehead, dated 8 June 1987, Colin Blakemore, who uses gallamine triethiodide extensively in his work, made the following statement: “...there is the possibility that muscle relaxants themselves may have some anaesthetic or analgesic action...”. This, of course, is preposterous in that it has long been known that these agents have no anesthetic or analgesic properties (17).
Blakemore, who is one of the leading defenders of experimental work involving animals, has made the claim that amblyopia “...was poorly understood until about 25 years ago when experimental research involving animals began to tackle the question of its origin...in the absence of any real knowledge of the cause of the disease there was no single agreed method of treatment.” This is at serious odds with the available facts. Treatment for, or prevention of amblyopia had been successfully accomplished many years before the experimental work was even considered (1, 7, 11, 44, 60).

There is no evidence that there has been any improvement in the treatment or prevention of amblyopia since the early part of the 1900s. Abraham (1) made the following comments concerning Claud Worth, who retired from practice almost 50 years before experimental work began: “It is surprising how little...has been added to the major store of knowledge as he presented it, at least from the practical viewpoint...Worth's emphasis on early treatment of the error of refraction and the amblyopia is still the keynote of the most rational approach to the treatment of the strabismic child...”

Blakemore also has claimed that “...before the animal research began it was not known whether squint could cause amblyopia or whether the existence of poor vision in one eye causes the squint.” This simply is not true. For example, Claud Worth had made the proper association in the nineteenth century (1). Even as early as the 18th century, George Louis Leclerc Comte de Buffon pointed out that amblyopia leads to strabismus (34).

Blakemore also has stated that there was “...no clear view about the time of onset or duration of the period of sensitivity to the disease,” the implication being that the animal work had provided the answer. This sensitive period is species-specific and is very different in non-human primates, cats and human beings, both qualitatively and quantitatively (7, 18, 34, 44, 54, 57); experimental work on animals could not shed light on the human situation. Furthermore, the fact that earlier ophthalmologists had been recommending early correction of strabismus, and early diagnosis and correction of anisometropia, indicates that they had known and understood the concept of a sensitive period long before the experimental work using animals. Nevertheless, although studies in animals also suggested that changes were permanent some time after the critical period, this has not been always been the case with human patients (62).

When the situation surrounding amblyopia is reviewed, it is found that all the work which has been done on animals has been on the basis of information derived from human observations or which could have been done on human patients (1, 7, 9, 11, 16, 37, 38, 44, 48, 51, 60). All the hypotheses so far examined by experimental work were known by physicians in this field years before the experimental work was done. The available history also seems to indicate that there has been essentially no change in concepts or in treatment methodologies since the 1800s at least. Modern day experimental work, therefore, appears to have had no significant effect on how amblyopia is managed today. Patching of the dominant eye, which started before animal experimentation, is still the most common

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7 This is from a document entitled, “A reply to criticism of experiments involving visual deprivation,” dated September 1987, and written and distributed by Blakemore.
8 Cibis recounted that Paulos of Aegina, in the seventh century, was the first to attempt what now is considered rational treatment of strabismus and amblyopia by using masks in an attempt to force the deviated eye to look straight ahead (11). She also pointed out that this concept was improved upon by von Graefe. Donders and other influential ophthalmologists in the nineteenth century because they correctly believed that strabismus caused amblyopia. Abraham noted that Claud Worth, a nineteenth century ophthalmologist, was recommending early treatment of anisometropia because he knew this condition could lead to strabismus and amblyopia (1). In a symposium on the subject, Peter and others recommended early treatment of strabismus or anisometropia, and early patching of the problem eye to prevent amblyopia (44). They also cautioned that the good eye cannot be continuously patched or else the amblyopia would transfer to it. They, therefore, recommended alternate patching of the normal and abnormal eyes, which still is being done today.
9 “A reply to criticism of experiments involving visual deprivation,” September 1987.
treatment despite decades of animal experiments (32).

Can we continue to learn more about amblyopia without resorting to experimentation on other animals? Keep in mind that any information we obtain from experimental work must still be confirmed in human beings. Moreover, there are many ways to humanely study human beings to get the answers we need with respect to understanding brain function as it may relate to amblyopia or treating amblyopia (2, 3, 12, 13, 14, 15, 20, 21, 24, 25, 26, 29, 30, 31, 32, 33, 36, 41, 45, 50, 61). By carefully studying the human situation in the first place, we not only derive information that is more meaningful in caring for human patients, we also save the resources that would have been expended upon animal studies and we prevent suffering and loss of life of the animals who would have been used.

Many of the hypotheses based upon observation of spontaneous cases of amblyopia or other similar vision disturbance in people have since been confirmed in contemporary studies of human patients (4, 10, 20, 23, 39, 40, 49, 58, 60, 61, 63). Situations such as those seen in these human studies can be considered ‘nature’s experiments.’ By taking advantage of these, it is not unreasonable to predict that we will continue to improve our understanding of amblyopia and similar conditions. By studying people who have lost an eye early in life, who have had untreatable or untreated opacification of the ocular media early in life, or who have had other perturbations of their developing visual system for reasons unrelated to the eye, we can learn a tremendous amount. These situations are not uncommon and they provide the necessary conditions to understand how vision develops in the human being. These, not the experimental studies in other animals, have led, and will continue to lead, to the most important information on how to manage vision disorders in people.

References:


11 In addition to the references on human studies already cited, there have been other studies utilizing contemporary technology to further our understanding of naturally occurring amblyopia in people (14) or vision in normal volunteers (15, 25).
12 The list of references is not intended to be exhaustive on any particular subject. Rather, I have provided just a few examples to emphasize certain points.
Amblyopia and non-human animal research

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31. Liang, Minglong; Xie, Bing; Yang, Hong; Yu, Longhua; Yin, Xuntao; Wei, Luqing and Wang, Jian. 2016. "Distinct patterns of spontaneous brain activity between children and adults with anisometropic amblyopia: a resting-state fMRI study." Graefe's Archive for Clinical and
32. Lunghi, Claudia; Morrone, Maria Concetta; Secchi, Jacopo and Caputo, Roberto. 2016. "Binocular rivalry measured 2 hours after occlusion therapy predicts the recovery rate of the amblyopic eye in anisometropic children." Investigative Ophthalmology & Visual Science 57(4):1537-1546.xvi


The eyelids of the children in this report had been closed for various medical reasons. "ultrasonic data for eight infants who developed monocular axial myopia associated with prolonged eyelid closure in early infancy." relationship between neonatal eyelid closure and axial myopia in monkeys studied in their laboratory. We report clinical and observations of non-human animal work "prompted us to challenge the safety of binocular patching in our nursery. Yet, the data "...occlusion of the eyes of infants undergoing [phototherapy] is now standard practice in most neonatal units." The experimental growth in the LGN." "In the primate, unlike the cat, the period of maximum sensitivity to visual deprivation does not correspond to a period of rapid cell degeneration of certain cells in the retina after damage to similar parts of the brain was similar and could be determined easily in human beings. Human beings with lesions similar to those experimentally caused in the monkeys were also used and compared. It was found that "Nineteen cases of unilateral amblyopia, 10 males and 9 females, were examined: their age ranged from 4 to 16 years. All of them had a history of unilateral occlusion of the eye, in 16 cases within 13 months and in 3 cases within 36 months after birth. Fifteen cases underwent occlusion of about one week due to lid surgery for entropion and 4 cases had a longer occlusion period due to hemangioma, eczema and burns of the lid. The role of unilateral occlusion in the development of amblyopia was discussed and the term 'stimulus deprivation amblyopia' was thought to apply to the cases." "It is surely the performance of visual neurones, not their mere number, that determines an animal's acuity." With respect to VEPs being recorded by Sokol, "In adults and verbal children, there is good correlation between what the patient says he sees, in terms of his own acuity or resolution, and what the brain puts out in terms of electrical stimulus." With respect to VEPs being recorded by Sokol, "In adults and verbal children, there is good correlation between what the patient says he sees, in terms of his own acuity or resolution, and what the brain puts out in terms of electrical stimulus." With respect to VEPs being recorded by Sokol, "In adults and verbal children, there is good correlation between what the patient says he sees, in terms of his own acuity or resolution, and what the brain puts out in terms of electrical stimulus." With respect to VEPs being recorded by Sokol, "In adults and verbal children, there is good correlation between what the patient says he sees, in terms of his own acuity or resolution, and what the brain puts out in terms of electrical stimulus." With respect to VEPs being recorded by Sokol, "In adults and verbal children, there is good correlation between what the patient says he sees, in terms of his own acuity or resolution, and what the brain puts out in terms of electrical stimulus." With respect to VEPs being recorded by Sokol, "In adults and verbal children, there is good correlation between what the patient says he sees, in terms of his own acuity or resolution, and what the brain puts out in terms of electrical stimulus." With respect to VEPs being recorded by Sokol, "In adults and verbal children, there is good correlation between what the patient says he sees, in terms of his own acuity or resolution, and what the brain puts out in terms of electrical stimulus." With respect to VEPs being recorded by Sokol, "In adults and verbal children, there is good correlation between what the patient says he sees, in terms of his own acuity or resolution, and what the brain puts out in terms of electrical stimulus." With respect to VEPs being recorded by Sokol, "In adults and verbal children, there is good correlation between what the patient says he sees, in terms of his own acuity or resolution, and what the brain puts out in terms of electrical stimulus." With respect to VEPs being recorded by Sokol, "In adults and verbal children, there is good correlation between what the patient says he sees, in terms of his own acuity or resolution, and what the brain puts out in terms of electrical stimulus." With respect to VEPs being recorded by Sokol, "In adults and verbal children, there is good correlation between what the patient says he sees, in terms of his own acuity or resolution, and what the brain puts out in terms of electrical stimulus." With respect to VEPs being recorded by Sokol, "In adults and verbal children, there is good correlation between what the patient says he sees, in terms of his own acuity or resolution, and what the brain puts out in terms of electrical stimulus."
The type of occlusion in the cat study to which this letter referred was different than usually used in amblyopic humans. "Lid occlusion eliminates form but considerable light can still reach the eye and might have a different effect upon the eye behind the lid closure than would be produced by a patch. The concern about acuity in the formerly nondeprived eye not reaching normal levels after lid occlusion was removed may therefore be due to a different type of deprivation than is usually produced by clinical patching therapy. I...would hope that their results, based on the experimental technique described, were not interpreted to suggest that patching may do more harm than good, and would not influence clinicians to be less vigorous with their patching therapy. ...I think work will be necessary to more closely simulate the human clinical situation before further conclusions can be reached."

"Thus by keeping cats in the dark except during monocular deprivation, the modelers have been asking a question that has no counterpart in the clinically important monocular deprivation of infants. The monkey data have been similarly misleading in this regard."

"There is new evidence from man that the optic nerve may be involved in some human stimulus deprivation amblyopias... contrary to the classical model originated by Wiesel and Hubel...

The feline limits of fusion and qualitative stereopsis reported here are quite different from those reported from human psychophysical experiments."

The cat's visual acuity is "...about one-sixth that of..." the human.

The experiment also was repeated, in essence, on human subjects to determine if the difference between the results in the cats and those previously reported for humans was due to species differences. Those results argued that it was due to species differences.

"[W]e attempted to measure the limits of fusion and qualitative stereopsis on human subjects, using the same procedures we used in the cat experiments."

"The treatment of squint should begin when the diagnosis is made."

"...central amblyopia which is found in the squinting eye...all phases of treatment yield the best results before the sixth year of life...it is disastrous to delay treatment until the child is of school age...the fight against amblyopia may be begun even in a child six months of age."

"The deprivation and the central scotoma can be transferred from one eye to the other by forced occlusion of the fixing eye in children up to 5 or 6 years of age. The younger the child, the easier it is to transfer the squint and the lowered vision. The time required in young children, about the age of three, for amblyopia to develop after squint becomes fixed, is brief. It is probable that it develops even more rapidly in infants."
“...methods of preventing and of correcting amblyopia...either atropine can be used in the fixing eye, or the fixing eye can be occluded for a time each day. Atropine is least satisfactory... it is partly through this method, which in instances was carried on indefinitely without consulting the physician, that squint was shown to be transferable from one eye to the other.”

With respect to occlusion therapy, “If amblyopia has not developed, a two-hour session each day usually is sufficient to prevent deterioration of vision.”

“Amyloidia rarely if ever develops after the seventh year in any form of squint. For the same reason (perfectly formed and developed maculae), amyloidia and squint cannot be transferred from one eye to the other after the seventh year.”

“Our attack upon the problem of squint is made on the same principles as it was thirty years ago.”

“Then again an evolutionary theory of squint brings with it more than ever the conviction that prevention is better than cure... there is...a whole group of causes -- the refractive errors -- the correction of which, before the time when the infant's visual reactions assume primatinal characteristics, would prevent the development of squint. Wholesale refraction of every child reaching the age of, say, 12 months, might in this regard be a reasonable and powerful preventative of squint...or simply if there is a squint in the family, it should be refracted under complete mydriasis at a very early age...”

“...in order to appreciate correctly the appearance of objects in space...the centres of the other sensory organs must be developed, and the transcortical fibres connecting these with the visual centres must be also developed. Probably a period of some two or three years is passed during childhood before the centres and their communications one with another are fully matured.”

“If then we are correct in assuming that the eyes are not anatomically or functionally complete at birth, and that the stimulus of light, form, movement, etc., is necessary to normal development of full visual capacity, any interference with the clarity of the media in one eye will produce a definite delay in the completion of the development, and the retardation may be such that improvement is delayed beyond the time when development is possible.”

“...studying the effect of lid fusion after section of the optic nerve. Again, we obtained different results in M. mulatta and M. arctoides.”

“...the experiments with atropine administration suggest that the mechanism of eye elongation is different in rhesus and stump-tailed macaques: accommodation seems to have a role in M. arctoides but not in M. mulatta.”

“...there are methods of obtaining essentially the same information from people.

“...There are established methods of obtaining essentially the same information from people.”

“...Two children had toxic bilateral cataracts at the ages of 36 months and 41 months and were deprived of treatment for the next 15 and eight years, respectively. After successful surgery the visual results were about 20/40 in both eyes. This visual recovery suggests that the susceptibility to bilateral stimulus deprivation at this age is slight but not absent, and...longtime deprivation beyond the sensitive period does not effect [sic] greatly the ultimate outcome of the treatment.”

“...These results are in agreement with the known electrophysiological effects of these recovery conditions and are also similar to the effects of reverse occlusion or loss of the nonamblyopic eye in human amblyopes.”

“...areas timely for developing research Impact of amblyopia on education and quality of life; optimal screening timing and tests; optimal administration of conventional treatments; development of child-friendly, effective and safe binocular treatments.

“...However, the critical period for the effects of strabismus may not be the same as that for visual deprivation, which is how the animal critical period has been defined.”

“Burian (1966) found, as we have done, that occlusion amblyopia is most likely before age 3.”

“Thus the effect of deprivation occurs more slowly and remains possible for a longer period in children than in animals.”

“In unilateral congenital cataract, surgery [sic] and optical correction, if indicated, should be completed within the first 4 months of life. Our experience indicates that, at all ages before adolescence, optical correction after the onset of cataract should be treated as a matter of urgency and combined with vigorous occlusion treatment.”

“...Amblyopia has now been produced successfully in models of various species, but data from cats, squirrels, and dogs cannot be applied automatically to man. There are differences in the anatomic and functional organization of the visual system of cats and primates. Human amblyopia involves primarily foveal vision rather than peripheral vision...”

“Moreover, in spite of many similarities of the visual deprivation syndrome in the different species, results from our studies in monkeys are different in some respects from those obtained in cats. For instance, unlike in the cat, unilateral lid closure in the monkey affects not only the binocularly innervated portion of the lateral geniculate nucleus but also the monocular portion...In addition, we have been unable thus far to show that the morphology of different classes of neurons in the lateral geniculate nucleus of the monkey is selectively affected by visual deprivation as it is in cats...”

“...Amblyopia is now defined as a unilateral or bilateral decrease of visual acuity caused by form vision deprivation, abnormal binocular interaction, or both, for which no organic cause can be detected by the physical examination of the eye and which, in appropriate cases, is reversible by therapeutic measures.”

“Research in ambyopic animal models has confirmed many older concepts regarding human amblyopia based solely on clinical observation and psychophysical experimentation.”

“...unilateral atropinization during visual immaturity may actually cause amblyopia. Three reported cases demonstrate this point.”
“Finally, we must ask whether animal experiments have helped us to better understand the pathophysiology of essential infantile esotropia. It is true that the so-called binocular cells in the striate cortex are permanently lost in infant monkeys after artificial strabismus... However, these cells also disappear in nonstrabismic monkeys after eyelid suture... or after experimentally induced anisometropia... Thus far the loss of binocularly innervated striate neurons has only been linked to an absence of stereopsis... There is no evidence from animal research that binocular functions other than stereopsis, such as sensory and motor fusion, are similarly affected by abnormal visual experience early in life. There is currently no animal model for essential infantile esotropia.”

One patient in this report had corneal scarring of the right eye at two years of age. Penetrating keratoplasty was done at 26 years of age, but visual acuity did not improve and convergent strabismus was present when left eye was occluded. The other patients had similar types of histories.

“Juler [1921] emphasized the close relation between the functional result and the age at occurrence of cataract. Similar observations have been reported by Broendstrup [1944]...”

“It has been known for a long time that normal development of the visual system depends to a certain extent on adequate stimulation of the retina during early infancy and childhood.”

Concerning the experiments of Wiesel and Hubel, “...it is not appropriate to transfer these data uncritically, to similar situations in humans, since the morphologic and functional organization of the visual system in cats is substantially different from that in man.”

“Histologic study of the LGNs from a patient with ophthalmologically confirmed anisometric amblyopia shows a decrease of cell sizes in the parvocellular layers innervated by the amblyopic eye. This decrease was more pronounced in laminae receiving crossed fibers.”

“From these results we conclude that following a sequential management plan for treatment of anisometric amblyopia can yield substantial long-lasting improvement in visual acuity and binocular function for patients of any age.”

Bilateral occlusion during critical period extends the critical period and does not lead to loss of visual acuity. Unilateral occlusion results in amblyopia.