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AMERICAN JOURNAL
OF OPTOMETRY
& PHYSIOLOGICAL OPTICS
Vol. 59, No. 6, pp. 451-464
June 1982
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Academy of Optometry
Printed in U.S.A.

Prentice Memorial Lecture: Is the Animal Model for Stimulus Deprivation Amblyopia in Children Valid or Useful?

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Abstract

The animal models are not, strictly speaking, valid for clinical application to children, primarily because of the large differences in the duration of the critical or sensitive period. However, they do provide a useful conceptual framework to follow, especially while determining the waxing and waning of the amblyopia in each eye by preferential looking or visual evoked potential acuity methods. These methods allow us to detect or determine the degree of amblyopia and guide the treatment or prevention of stimulus deprivation amblyopia in each child by direct measurement. The reciprocal effect of amblyopia found by Thomas, Mohindra and Held in infants by the preferential looking method and confirmed and extended in age by our group with the visual evoked potential acuity method could have been predicted by the animal modelers from the cross-suturing experiments. It appears that more harm than good may be done by patching infants for the treatment of amblyopia without measuring the acuity of each eye to avoid the significant loss of connections to the patched eye and to both eyes (binocular units).

Key Words: stimulus deprivation, amblyopia, critical period, animal models, preferential looking, visual evoked potential

There is a curious clinical binocular phenomenon in young children. If one eye is occluded, its visual acuity falls while at the same time if the other eye is amblyopic, its vision improves. This reciprocal effect has been shown by two completely different

methods of measuring visual acuity in infants. One method uses pattern visual evoked potentials.¹⁻⁶ Another method is the preferential looking technique as modified and used by Held and his group,⁷⁻¹¹ who originally discovered the phenomenon in infants.¹²⁻¹⁶ This finding in babies came as a surprise because of tacit assumptions in the application of the animal findings to the clinical situation, as will be explained later. The animal experimenters have not asked identical questions of their prepara-

Charles F. Prentice Award Lecture presented at the Annual Meeting of the American Academy of Optometry, Orlando, Florida, December 13, 1981.

Received November 12, 1981.

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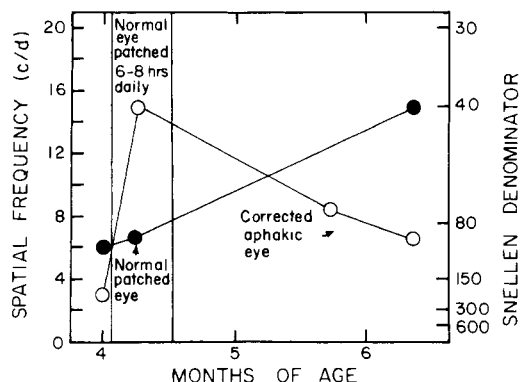


FIG. 1. Patient had a congenitally dense polar cataract which was extracted at 6 weeks of age. After the final contact lens correction at 4 months, visual acuities were measured. Patching had been intermittent for 1½ months before testing. Closed circles represent the normal patched eye. Redrawn from Odom et al.⁵ The reciprocal effect is clearly seen after the patch is removed at 4½ months and is better shown, occurring several times, in Fig. 4.

tions. When they do, they will likely find a similar phenomenon.

As may be seen in Fig. 1, the acuity of a 4-month-old infant who has just been fitted with a correcting contact lens over an aphakic eye shows about 6/30 (20/100) in the normal eye and 6/90 (20/300) in the corrected aphakic eye, which had been deprived of a clear optical image since birth. This previously deprived eye shows a marked increase of visual acuity to 6/12 (20/40) when the normal eye is occluded by a patch. The patched normal eye often shows a fall in acuity, although in this instance there is no significant change. When the patch is removed, a reverse, reciprocal phenomenon takes place. The normal, formerly patched eye gaining and the originally deprived but now corrected aphakic eye falling so that their acuities are once again reversed. (The reciprocal effect occurs several times in Fig. 4.) Could this have been predicted by the animal model? Because the discounting of this reciprocal phenomenon by clinicians conflicts with the animal model, it seems time to question it and ask whether this model is valid or even useful. It is also time to question whether our understanding of the prevention and treatment of amblyopia can be more efficiently and effectively learned in the clinic than in the laboratory.

STIMULUS DEPRIVATION AMBLYOPIA

Amblyopia, a reduction of visual acuity (which can be considered a partial blindness), afflicts 1 to 5% of people.¹⁷ Based in part on animal models, the bulk of this anomaly is believed to be caused by a deprivation of normal pattern or form stimulation early in life (exanopsia, occlusion, strabismus, anisometropia, etc.). The deprivation can be total or partial. It can be monocular, because of a patch over one eye or because of other monocular visual stimulus deprivation, for example, that caused by a cataractous lens. It is not yet clear whether stimulus deprivation amblyopia can be binocular because of a therapeutic bandage over both eyes, or, for example, because of dense bilateral cataracts or even nondense partial ones. The animal model is equivocal. The commonly observed nystagmus in children which supervenes makes assessment of visual acuity difficult. The deprivation can be spherically refractive because of, for example, the large refractive error resulting from the removal of the crystalline lens to eliminate a cataract, or even from moderate anisometropia. It can be meridional,^{18, 19} although the animal model of meridional amblyopia is less than clean-cut.^{20, 21} (Optical correction may eliminate it in animals,²² but at least it does not occur before the 1st year or so in a baby's life, according to Held.⁷) Finally, it may be directional at least in cats.²³

The thesis of the animal model is that visual deprivation during a neurally modifiable period, the so-called sensitive or critical period, will have a deleterious effect on the visual synapses or neurons, causing a reduction of acuity or, in a word, amblyopia.

While measuring amblyopia objectively in children, we have found an amazing modifiability or sensitivity of the neurovisual system. It does not seem to be directly comparable to experiments performed on cats and monkeys, which form the bases of the animal model. This may be because the animal physiologists (with one notable exception discussed later) have not seemed to try to design their experiments in a form where the application to clinical problems would be readily apparent. (In all fairness, many of the early animal experiments were directed toward other issues.) It may also

be a matter of species differences. At the present time the questions to ask are: is the current animal model appropriately applied for children, and is it useful?

The Animal Model of Monocular Stimulus Deprivation Amblyopia in Cats

In a series of papers starting in 1963, Wiesel and Hubel²⁴ demonstrated how a loss of visual function in kitten may be caused by various kinds of stimulus deprivation. Monocular deprivation caused a lack of response by striate cortical neurons normally stimulated through the deprived eye. Artificially induced strabismus did the same through the deviating eye.²⁵ Binocular deprivation by means of binocular patching or dark rearing did increase the number of abnormally responding cells, although the two eyes responded well and equally.²⁶ Alternating strabismus or alternating patching of the eyes provided a picture of the loss of binocular neurons, that is, a loss of striate cell activity which responds to both eyes.

Although there was some cell shrinkage in those layers of the lateral geniculate nucleus which are associated with the deprived eye,²⁷ the deprivation-induced deficit was placed in or shortly after the first synapse in the visual cortex where the pathways from the two eyes join synaptically. It is important to note that in order for the deprivation to have an effect it must occur during the kitten's sensitive period. This period of neurovisual system pliability appears to start at the 3rd week and disappears at the 3rd month after birth, after which there is little change,^{28, 29} even behaviorally.³⁰ As will be discussed later, the period has been extended somewhat.

Of special concern is the method of determining function in these animal experiments. Activity of single neural units was measured rather than functional visual acuity. The active neurons of the striate cortex were represented by a histogram showing the number of units vs. the degree of representation of input to each of the two eyes, one bin for each of the eyes alone or monocular response (numbers 1 and 7), one bin for an equal binocular response (number 4), and the rest graded in between (bin numbers 2, 3, 5, 6), as seen in Fig. 2A, panel L.

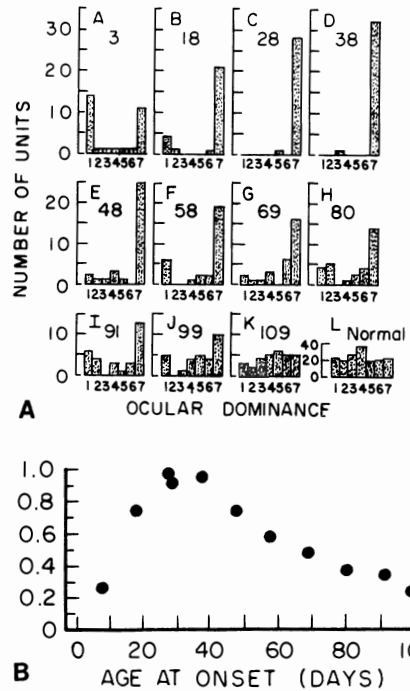


FIG. 2. Eye dominance, deprivation, and the sensitive period in cats. (Redrawn from Vaegan et al.⁶⁶ which was redrawn from Olson and Freeman.¹⁰⁷) A: panels A to K are eye dominance histograms for cats raised normally until they were monocularly deprived from 9 to 11 days at progressively later ages and recorded immediately after the deprivation. The age at onset of deprivation in days is on each graph. The right eye was deprived in all kittens and recordings were from the left hemisphere. Neurons in bin 1 were driven only by the contralateral eye, which had been deprived; neurons in bin 7 were driven by the ipsilateral eye. Bin 4 contains those neurons which responded equally to both eyes. The other bins are graded in between. L shows the pooled data from four normal cats recorded at 45, 48, 55, and 135 days. B: the sensitive or critical period for monocular deprivation derived from the data in Fig. 2A. The "deprivation effect" is the normalized proportion of cells not responding from stimulation of the deprived eye relative to the normal controls. The peak sensitivity comes at about the 29th day and falls rapidly after 38 days.

This is called an ocular or eye dominance histogram.

Binocular cells (dominance bins 2 through 6) most likely govern binocular functions such as stereopsis and fusion. They suffered most from alternating occlusion, almost as much from alternating strabismus, much from monocular deprivation as seen in Fig. 2A, panels A to K, and relatively little if any from binocular occlusion.

It was postulated that deprivation of one eye provides an advantage to the fellow eye in the binocular competition for synaptic representation where the paths from the two eyes meet synaptically in the striate cortex. This has been abundantly confirmed, most recently by Smith,^{31,32} to whom the reader is referred for a discussion of the evidence and references.

What does a sample of the active single neuron population in the striate cortex tell about visual acuity or amblyopia? If there is a normal population of cells it is a reasonable assumption that functional acuity is normal. But even when the count is absolute rather than relative it does not measure the visual acuity nor the degree of amblyopia, inasmuch as the quantitative relation of neural unit populations to acuity is unknown, although this problem is being investigated.^{31,32} Thus the eye dominance histogram is undoubtedly related to acuity and therefore to amblyopia but the quantitative relation is not known.

Since the pioneering work of Hubel and Wiesel,²⁴⁻²⁹ there has been abundant confirmation of the sensitive period in cats as seen in Fig. 2B, followed by some modification and much cogent addition. It is clear that the critical period for different functions is not exactly the same even in the same species.^{33,34} The sensitive period for monocular deprivation (one eye patched) may well be different from that for binocular vision deprivation (alternate eye patching). Environmental factors can modify the period as pointed out in a thorough review by Mitchell.³⁵

Although most of the data have come from cats, monkey experiments have further added to our understanding, providing a primate model which can perhaps be more accurately extrapolated to man. The "animal model" should be referred to, then, as the "animal models." We will concentrate both on the cat because most work has been done on it, and the monkey because of its closeness to man, rather than on numerous other species such as lambs.³⁶ A recent review of animal data is found in Movshon and Van Sluyters.³⁷

THE HISTORY OF AMBLYOPIA

In medieval times it was believed that strabismus was caused by the muscles of

the eye. In the 16th century, Georg Bartisch³⁸ of Saxony, in one of the first books on ophthalmic surgery, devised a mask to force the squinting eye to look straight ahead or not see at all (Fig. 3). The mask is said to have been first developed by the ancient Greeks.

However, in the 18th century, the great French naturalist George Louis Leclerc, Comte de Buffon,³⁹ suggested that unequal vision in the two eyes, or amblyopia, leads to squint, which is not a result of neuromuscular dysfunction. As he said almost poetically, "... l'inégalité de force dans les yeux est une espèce de strabisme innée ..." (Inequality of acuity in the two eyes is a kind of innate strabismus.) Treatment called for patching "... il me paroît que le plus simple, le plus naturel, et peut-être le plus efficace de tous les moyens, serait de couvrir le bon oeil pendant un temps ..."

The 19th century introduced modern and rational concepts of amblyopia and squint through Louis Emile Javal (née Jacob). Their development from the last century to modern times has been summarized by Duke-Elder and Wybar.⁴⁰

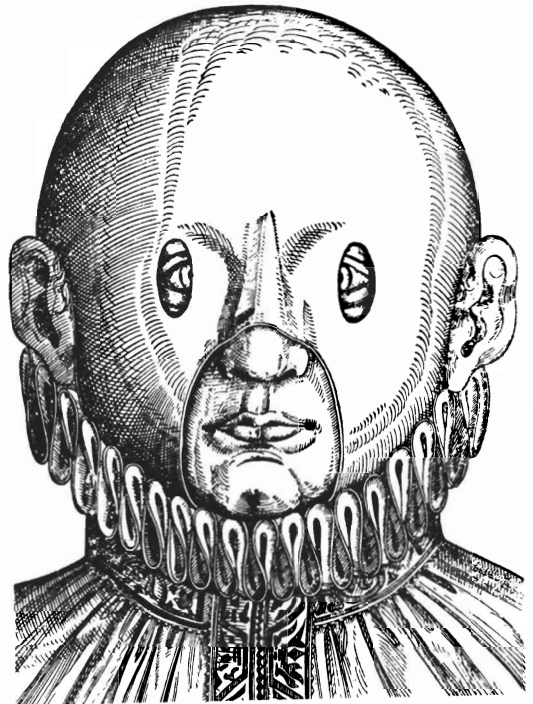


FIG. 3. Strabismus mask of Bartisch.³⁸

THE MODERN CONCEPT

According to Duke-Elder and Wybar,⁴⁰ the object is to gain normal binocular vision by whatever means necessary and possible: good refraction, prevention or cure of amblyopia, and/or eccentric fixation. Of course, the measurement of visual acuity and the application of orthoptics must wait until the child is old enough to cooperate. They relate that the treatment of amblyopia should begin not later than 2 years of age. If fusion is not achieved during the first 3 years of life, it never will be. It is progressively harder to treat amblyopia after the age of 5, and especially after age 7 or 8. In amblyopia, the normal eye is occluded (as was first enunciated by Lelerc³⁹) at the earliest possible age. In alternating occlusion between the two eyes, the goal is to maintain equal vision in the two eyes inasmuch as prolonged occlusion of one eye causes amblyopia, which can be corrected by shifting the occluder to the other eye. Overcoming the amblyopia but not the squint may, when occlusion is removed, induce anomalous correspondence, so orthoptics or surgery must be applied to straighten the eyes.

A distinction is made between the amblyopia of "arrest," which is the visual acuity that developed before stimulus deprivation stopped further development, and amblyopia of "extinction," which is the fall of visual acuity from some higher value. (It can be seen from the animal model that there is no simple amblyopia of arrest because there is always amblyopia of extinction).

Ophthalmologists have been divided in adopting animal models. For example, Jampolski⁴¹ has been skeptical of the classical animal models. This may have arisen in part because his original proposal of a distinction between occlusion and diffusion amblyopias was not supported in the early animal studies. von Noorden⁴² is the leading ophthalmologist in applying the animal model to the prevention and treatment of amblyopia in children. He has been able to extract data from both children in the clinic and monkeys in the laboratory. He says that "Amblyopia is a unilateral or bilateral decrease of visual acuity caused by form visual deprivation and/or abnormal binocular interaction for which no organic cause

can be detected by physical examination of the eye and which in appropriate cases is reversible by therapeutic measures."

von Noorden⁴² is careful to point out that "the interpretation of the animal data cited and its application to human amblyopia is still speculative." But he expects that an experimental model will eventually lead to a better understanding of amblyopia as well as to more effective models of therapy. He observes that the sensitivity in children is greatest during the first 2 years of life, although it extends to perhaps age 4¾. He suggests patching the sound eye 3 days out of 4 during the 1st year of life, then 4 days followed by 1 day of patching the amblyopic eye during the 2nd year. In 3- to 4-year-old children the occlusion period of the fixating eye can be lengthened, provided the visual acuity of each eye is monitored at frequent intervals. According to von Noorden,⁴² the value in occluding the amblyopic eye (which is not in accord with the animal model) is, first, it reinforces the dominant eye and, second, the amblyopiogenic factors become active when both eyes are open and prevented from reversing any gains made by the therapy. This point is difficult to understand in light of the way binocular units are lost in cats and monkeys.

The Cat Model and Modern Clinical Concepts

With one notable exception, the animal models agree qualitatively with modern clinical concepts of stimulus deprivation amblyopia. (This agreement does not, of course, necessarily mean that the model is a valid one for children.) The animal models can provide a quantitateness that the clinical concept lacks, especially in the timing of the period of neurovisual modifiability, the sensitive period.

The original sensitive period of kittens, from the end of the 3rd week to the end of the 3rd month, has been both confirmed and also modified in both directions, even to 1 year in the cat,³⁵ but these modifications do not seem to be very significant for our purpose, which is to determine the sensitive period in children. It is important to know this sensitive period, the argument goes, in order to apply an animal model. It is clear to clinicians that the sensitive period of children must be longer than that of

kittens. On the basis of clinical experience and experiments, this period lasts until 5 to 10 years of age (von Noorden,⁴³ 5¾ years; Vaegan and Taylor,⁴⁴ 9 to 10 years; and Awaya,⁴⁵ 8 to 9 years), although some clinicians think this period lasts longer.

While the original animal investigations were made on cats, the animal modelers had long felt that a more valid estimate for children could be obtained from species closer to man, such as the monkey.

The Monkey Model

Monkey data are less plentiful than those from cats.⁴⁶⁻⁴⁹ Strabismus occurs naturally in this species,⁵⁰ and presumably so does amblyopia. Strabismus induces strabismic amblyopia.⁵¹ It is now fairly well established that the monkey sensitive period is stable from birth to 7 weeks, after which it declines, and is virtually ended at 9 weeks.^{49, 52} This is based on changes in cortical layer IVc because the period may extend to at least 1 year in other cortical layers.^{49, 52} There is a need for behavioral data to clarify these functions.

Can this mean that the infant's sensitive period is similar to that of the monkey, only a couple of months long? There is, after all, a difference in the rate of development of the two species. Teller et al.⁵³ have shown that the development of visual acuity takes 4 times longer in infants than in the monkey. Using this factor, the human sensitive period would be (4 × 9) about 36 weeks, or roughly 9 months. These data do not seem to be in accord with clinical observations and experiments, which give a value of 5 to 10 years.

There may be differences in the response to deprivation between cats and monkeys. Crawford et al.⁴⁶ found that the monkey striate cortex is even more vulnerable to binocular deprivation than that of Hubel and Wiesel's cats²⁴⁻²⁹ (but monocular deprivation showed no apparent differences). After 4 weeks of binocular deprivation, not only were there fewer binocular units, but 51% of all cells tested were visually unresponsive. This could be the basis of a kind of binocular amblyopia if visual acuity were reduced. Recently, Kaye et al.⁵⁴ found that if the dark-reared cat is recorded immediately after deprivation, the ocular domi-

nance histogram is normal, but binocular units suffered if recorded after a subsequent year or two of light rearing. Monkeys need to be tested under similar conditions.

Hyvärinen et al.⁵⁵ showed that in the parietal cortex of monkeys there is a cross-sensory model deprivation effect in dark-reared animals. Little recovery was observed after several months. This too is in contrast to the recovery observed in cats.⁵⁶⁻⁵⁷ Mitchell et al.⁵⁸ have demonstrated in the cat that cross-suturing is not necessary to obtain almost complete recovery of visual acuity in the originally deprived eye, closed from birth to 40 or 60 days. In the monkey, however, reverse suturing is essential for histological⁴⁸ or physiological recovery.⁵⁹ These experiments demonstrate that there is at least one important species difference between cat and monkey other than the obvious ones of hue discrimination and resolution. They also demonstrate that extrapolation of these conflicting models to children cannot be done with confidence.

DEPRIVATION PERIODS IN ANIMALS AND CHILDREN

The early work on cats showed that monocular deprivation, usually by suturing closed the lids of one eye, need be for only a matter of days²⁹ or even hours^{60, 61} during the height of the sensitive period to produce an irreversible deficit of active cortical neural units. This finding has been confirmed and also subjected to some modification. If the cats are allowed a normal visual environment before and after the deprivation, the effect is not as severe⁶² and may even show no effect.⁶³ 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. A monkey monocularly deprived for 14 days beginning at 1 month of age by Harwerth et al.⁶⁴ and then allowed a normal visual environment exhibited a deep and lasting amblyopia. However, simple conclusions cannot be drawn from this experiment, as will be discussed later.

As mentioned earlier, Teller et al.⁵³ found

that the ratio of development of visual acuity in macaque monkeys relative to children is about 1:4; that is, the development of monkey acuity at 6 weeks is similar to that of a child of 6 months. Using this factor of 4 for the difference in the rate of development would translate the Harwerth data to a model of a child of 4 months, deprived for 2 months, resulting in a severe loss of acuity in the occluded eye. What evidence is available to support this model?

Effect of Monocular Deprivation on Visual Acuity in Children

Most evidence for stimulus deprivation amblyopia is retrospective. One exception is seen in Jacobson et al.¹⁵

Awaya and his colleagues⁶⁵ found in cases of sequential patching after entropion surgery that about 2% of the infants became amblyopic as a result. This figure is based on one amblyopic child (out of a sample of 51 children) who was operated on at the age of 6 months. The 2% statistic has been widely misinterpreted to be 100% of those children patched for 1 week at less than 1 year of age.^{4, 43, 66} In a much larger sample (which was the basis of the misinterpretation), Awaya and his colleagues⁶⁵ did not have complete statistics but did note that the eye patched last always corresponded to the amblyopic eye, providing evidence of cause and effect. Furthermore, according to Awaya et al.,⁶⁵ the 2% figure is higher than would be expected in the normal population when one considers that all types of stimulus deprivation amblyopia comprise about 3% of the population (including form deprivation, strabismus, anisometropia, and ametropia). The 2% value is from form deprivation alone (Awaya et al.^{67, 68}; personal communication, 1981.) Hartwig et al.⁶⁹ also found about a 3% incidence. They examined the records of the duration of unilateral occlusion in 32 children from 11 days to 3½ years of age who had been bandaged after surgery, burns, or trauma of the lids and conjunctiva. The children were recalled and 30 of them were found to have good visual acuity and binocular vision. One had normal acuity but was an intermittent alternating exotropia. Only one child had amblyopia, a 6½-year-old boy who was monocularly occluded at 2½ years of age for 9

weeks. Vision was 6/24 (20/80) and was not improved by pleoptics. Squint was not observed, although eccentric fixation developed afterwards. The authors concluded that unilateral occlusion at least up to 10 days duration does not lead to deprivation amblyopia.

Mackensen⁷⁰ records a case where, in error, there occurred 7 months of continuous monocular occlusion of the previously sound eye of a 5-year-old boy. Subsequently, with patching of the originally amblyopic eye, the previously sound eye jumped from 6/60 (20/200) or less to 6/6 (20/20) in 4 days. Apparently, the severe deprivation amblyopia here was easy to overcome, even at 5 years of age.

Based on his clinical records, von Noorden⁷¹ concluded that the sensitive period in children lasted from birth to 4½ years as compared to his finding of about 2 months in monkeys. Recently, von Noorden⁴³ has concluded that amblyopia can develop up to 5¾ years of age when deprivation lasts for 1 to 36 months. Patching the nondeprived eye brings improvement in acuity if the original deprivation began after the age of 30 months.

Held and his colleagues^{7, 9-11} have measured visual acuity of infants by their version of the preferential looking method, originated by Fantz⁷² and also developed by Teller⁷³ and her colleagues.^{74, 75} The primary limitation of this technique is that it is generally restricted to children up to about 1 year of age because of the development of changes in the child's behavior, although the age limitation has been somewhat extended.⁷⁵ Held's group¹²⁻¹⁶ has shown that the neurovisual system is highly modifiable during this period. The changes in acuity caused by deprivation are extraordinarily transient. In fact, although these infants may have considerable astigmatism, there seems to be no evidence of the development of meridional amblyopia during this period.⁸

Jacobson et al.¹⁵ have clearly demonstrated that amblyopia can result not only from anisometropia in infants,⁷⁶ but also from esotropia. Four infants with alternating esotropia from birth or shortly after had equal or nearly equal monocular acuities upon first measurements at an average age

of about 15 weeks. A significant acuity difference was first found at an average of about 20 weeks of age. At this age it took only a few weeks to develop a clear difference in the acuities of the two eyes.

There is some indication in children that the formerly deprived eye will recover its acuity without occluding the normal eye (Jacobson et al.,¹⁶ case no. 7) under what is termed "biocular" viewing conditions. If this is so, the cat rather than the monkey model may be more applicable.

We have been measuring the visual acuity of infants and children by means of pattern visual evoked potentials (VEP).⁴ The age of the child has no bearing on our ability to record these measurements. In children monocularly deprived until 3 to 5 months after birth, patching the sound eye causes a marked increase in acuity in the formerly deprived eye.

The patched eye rapidly loses acuity as the formerly deprived eye gains, in a reciprocal way. Is this loss of acuity in the previously nondeprived eye originally observed by Held and his group,¹²⁻¹⁶ amblyopia? Because it is in accord with the definition, it can be called "patching amblyopia." It can occur at least to 8 years of age, although the improvement of acuity in the formerly deprived eye may occur only to about 4 or 5 years.^{5, 6}

A major test of the animal model is to see whether it predicts quantitatively what we have been able to measure on infants. As mentioned earlier, patching a monkey at one month of age for 15 days elicits a deep amblyopia.⁶⁴ If the development of the infant's visual system takes four times longer than does the monkey,⁵² then a child of 4 months deprived for 2 months or more should be severely amblyopic. Fig. 4 shows a child of 5 months who had been deprived in one eye by a congenital cataract and upon its removal at 3 days of age by a large hypermetropia until corrected by a contact lens starting at 2½ months. Measurements starting at 5 months before patching show that the amblyopia, about 6/24 (20/80), is not very severe despite months of deprivation compared with that of the monkey,⁶⁴ shown as an open triangle. This monkey at the end of deprivation was about 6 weeks old, at which time the sensitivity was beginning to fall. Perhaps the remaining duration

and effectiveness of the sensitive period did not permit recovery or perhaps it was the lack of cross-patching. It also had a sizable anisometropia, which in the event that all other conditions for recovery were favorable, would still have precipitated the amblyopia. Another example of extreme modifiability in a very young child was seen in Fig. 1.

Hence, it may well be that the primary difference in vision between monkey and baby is only in the duration of the sensitive period. This could account for the discrepancies observed, except for recovery without cross-patching in infants.¹⁶

Let us assume that the main, highly sensitive part of the sensitive period in children as indicated by both VEP acuity measurements^{5, 6} and clinical evidence⁴³⁻⁴⁵ lasts to about 5 or 10 years. During this period, amblyopia could occur but it would be readily reversible, neglecting the binocular units. Then the animal model would indeed be useful as long as we did not use it to predict the sensitive period duration in children.

There is an early period of high sensitivity in the monkey as seen in the geniculate innervation of striate cortical layer IVc after monocular deprivation. As mentioned earlier, sensitivity of the cells above and below layer IV may show some remaining neural sensitivity for more than a year,^{49, 51} or even as long as 1½ to 2 years (T. N. Wiesel, personal communication).

Based on the phylogenetic ratio of 4, this could extrapolate to a sensitive period in children lasting 6 to 10 years. We are comparing a neurohistophysiological effect in the striate cortex of monkey with the visual acuity effect in children. Measurement is needed of the duration of the sensitive period of visual acuity to monocular deprivation in the monkey. However, now that data are being obtained directly from children, the need for animal experiments is less pressing. Nevertheless, cross-patching experiments in the monkey^{49, 52} show a reciprocal effect of eye dominance and the histology shows a similar reciprocal expansion and contraction of geniculate afferents, both of which at 1 year have lost their plasticity.⁵² It may be that there are correspondingly two different kinds of sensitive periods to monocular deprivation in chil-

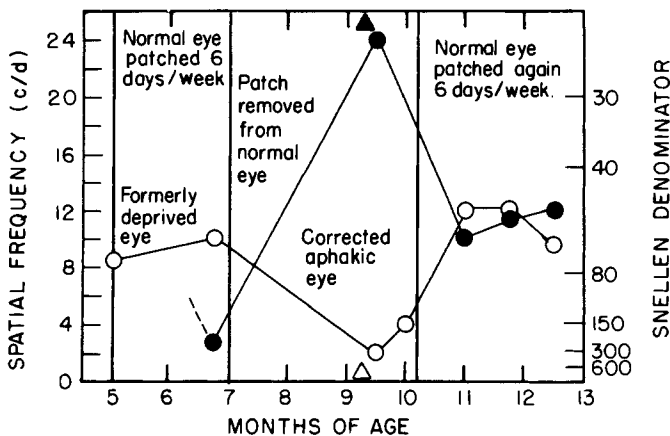


FIG. 4. Visual evoked potential acuity measurements in monocularly deprived infants. Redrawn from Odom et al.⁵ Congenital cataract of the right eye removed at 3 days of age. Contact lens was fitted between 2.5 and 5 months. It was not possible to measure the normal eye at the first session at 5 months of age. The dashed line indicates an assumption of good acuity at that time. The triangles show the acuity of the two eyes of a monkey, which was monocularly deprived for 2 weeks at 1 month of age.⁶⁴ This age corresponds to about 4 months in the child in terms of acuity development.

dren, an early and a late, but we have no evidence for it as yet.

BINOCULAR FUNCTIONS

The animal models paint a dismal picture of the effect of patching on binocular unit activity. Monocular patching is bad and alternating patching is worse. The latter is still practiced by clinicians, apparently with little justification. Cross-patching in animals does bring back some binocular unit function, but only after most or all of it has been destroyed by the initial occlusion. The cat model predicts that dark rearing (or binocular patching) destroys stereopsis.⁵⁴ Until we can get data directly from children, it would seem wise and prudent to follow the animal models and avoid both patching the amblyopic eye and also binocular patching.

Binocular function and unit activity await more measurements of the kind now possible in children.⁷⁶⁻⁸² There is evidence that the sensitive period in children for these units is of the order of 2 to 4 years.^{83, 84} It now appears possible to record VEP correlates of Poggio-Fischer binocular units to analyze the responses of the kinds of cells involved in stereo and fusion problems.⁸⁵

NEUROTRANSMITTERS AND VISUAL DEPRIVATION

A neurochemical model of visual modifiability has been worked out in cats for

catecholamines (norepinephrine and its toxin, 6-hydroxydopamine)⁸⁶ and for bicuculline, an antagonist of γ -aminobutyric acid), which is an inhibitory transmitter.⁸⁷ Although it may not be a transmitter, 4-aminopyridine can produce a recovery during the first 3 days of monocular deprivation in lambs.³⁶ These biochemical models might be more elegant than the deprivation ones, but they do not yet lead to a clinically useful course of prevention or treatment. They might provide a rational basis for some of the widespread values reported for the sensitive period in children.

ANOTHER KIND OF DEPRIVATION AMBLYOPIA

With clinical problems in mind, it has been shown by Ikeda^{88, 89} and her colleagues in their cat models that anisometric amblyopia can be caused by a loss of functional X-type retinal ganglion cells, "X-cell amblyopia."⁹⁰ This has been supported in part by other cat experiments,⁹¹⁻⁹⁴ despite excellent evidence to the contrary in cats⁹⁵ and in monkeys.⁹⁶

The distinction may hinge on possible differences between losses caused by blur, and losses caused by pattern deprivation.⁶⁶ Ikeda⁸⁸⁻⁹⁰ (or peripheral) amblyopia does not occur with total pattern deprivation (as in Hubel and Wiesel^{124, 29} or central amblyopia) but does occur with blur, the most

common clinical condition for amblyopia (Vaegan, personal communication).

There is new evidence from man that the optic nerve may be involved in some human stimulus deprivation amblyopias,⁹⁷ contrary to the classical model originated by Wiesel and Hubel.²⁴

The most complete and extensive evidence has been provided by the Moorfields Eye Hospital Electrodiagnostic Clinic of Geoffrey B. Arden and his group in London. In a convincing series of papers, they show that the malfunction of the optic nerve, including perhaps other proximal cells of the retina, may be the cause of a kind of human stimulus deprivation amblyopia.^{66, 98-100} It is not successfully treated by patching the other eye nor by orthoptics, as is the amblyopia which is more centrally seated. The condition is determined by the pattern electroretinogram. It has also been clearly shown in the cat.¹⁰¹ The pattern electroretinogram is a specific electroretinographic wave responding to pattern with a time to peak of about 50 msec. Arden and his colleagues' work on patients has now been confirmed.¹⁰²

Siegfried¹⁰³ has found visual evoked potentials from the region of the human temple, which may reflect activity of the optic nerve. Early wavelets in the visual evoked potentials may reflect precortical activity in the visual pathway.¹⁰⁴ These, along with new tests of binocular function, will help to make us even less dependent on animal models, allowing direct evidence of specific function or lack of it in each patient.

CLINICAL APPLICATION

The clinician has a dilemma after he has removed the deprivation by surgery and/or contact lenses. Will the vision of the formerly deprived eye now improve spontaneously? As previously mentioned, evidence from cat experiments indicate it will,⁵⁸ but that from monkey, the opposite will occur.⁵⁹ In either case, one must be wary of applying an animal model, especially about those aspects where there are abrupt species differences; that is, the cat appears to fall between monkey and man.

It may be preferable to avoid any patching if possible because the animal models tell us (and we have no reason as yet to be

skeptical) that binocular neurons will always suffer. If patching is necessary, the degree can be minimized and titrated to maintain equal acuity in the two eyes, albeit at less than the maximum possible acuity value for the sound eye. This widely used strategy^{76, 105, 106} seems to work well. In the Beller⁷⁶ study, there was an aniseikonia from the contact lens-corrected aphakic eye. This may amount to as much as 7 to 18% (J. M. Enoch, personal communication). Thus good simultaneous binocular stimulation was not possible and binocular cells presumably would be sacrificed anyway.

A mechanical model of stimulus deprivation amblyopia based on VEP acuity measurements of amblyopic children is being offered by Jastrzebski et al.⁶ Changes induced by patching or its cessation are considered in terms of sensitivity and elastic and plastic effects. The same mechanism seems to be involved in both amblyopic and normal eyes. This analysis suggests that patching part-time rather than 12 or more hours per day elicits asymmetries between eyes in terms of the elastic and plastic characteristics of the visual system's sensitivity to patching, which forms the basis for successful treatment. It also points to a sensitive period of about 6 or 7 years for this function.

CONCLUSION

The evidence generates some skepticism of the animal models of the development of stimulus deprivation amblyopia for children, despite the powerful, qualitative conceptual framework with which we have been enriched. We have little framework on which to base a rational clinical treatment other than direct and frequent monitoring of visual evoked potentials. The latter are not limited by the age of the child. Without monitoring, it is possible that "therapeutic" patching may do more harm than good.

Foremost is the large disparity in the monocular deprivation sensitive periods of the monkey or cat acuity, 2 to 4 months vs. 5 to 10 years in children. Furthermore, one might expect a progression in the length of the period from cat to monkey to man, but the monkey appears to have the shortest one. Furthermore, cats show remarkable

recovery when simply released from monocular deprivation, but monkeys show none unless the other eye is (cross) patched. In this respect, infants appear to be closer to cats than to monkeys.

There is so little direct evidence as yet of the effect of deprivation of binocular cells in children that we must continue to use the animal model qualitatively until quantitative data are obtained from clinical measurements in infants. The means and techniques to do so are now becoming available.

The animal models, strictly speaking, are not entirely valid for children but they have powerful and useful concepts that have not been fully used by clinicians nor fully interpreted by animal physiologists. These concepts may be applied as our knowledge of human visual function continues to grow and until the models are superseded by direct knowledge from children gained by new electrophysiological and behavioral techniques.

ACKNOWLEDGMENTS

This paper is a result of the efforts of Dr. Creig S. Hoyt, Director of the Children's Eye Clinic, Department of Ophthalmology, University of California, San Francisco, and George B. Jastrzebski, doctoral candidate. Earlier, Dr. J. Vernon Odom also collaborated. Appreciation and gratitude for helpful discussions also go to Drs. D. E. Mitchell, Vaegan, R. Held, S. Awaya, and T. N. Wiesel.

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