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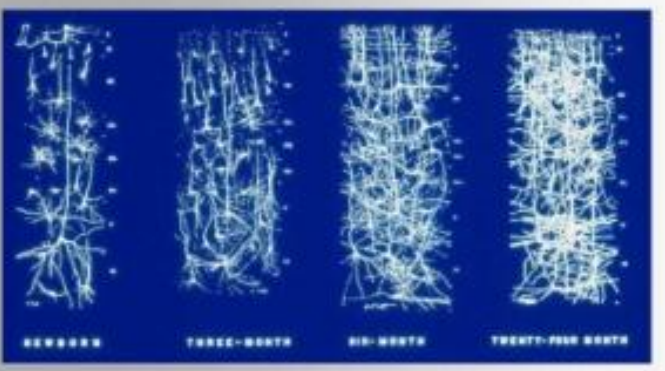

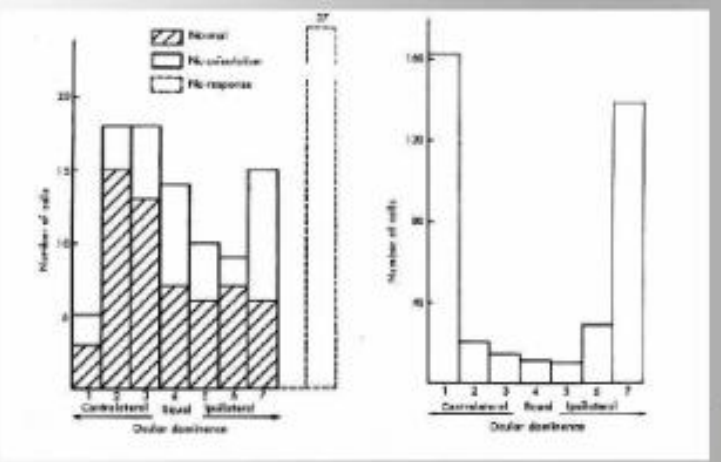

# Visual

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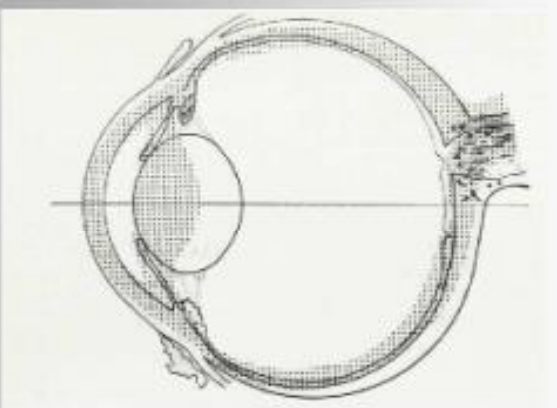

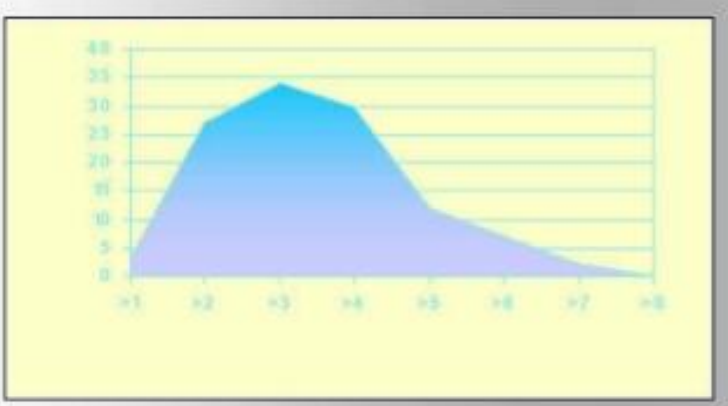

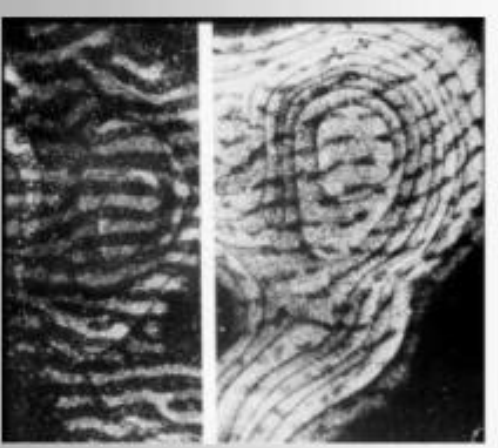

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# THE SENSITIVE PERIOD IN THE DEVELOPMENT OF THE HUMAN VISUAL SYSTEM AS INDICATED BY TRANSFER OF FIXATION

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Dedicated to the memory of

the late Alan Stanworth, M.D., Ph.D.,

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who supervised the research work for this thesis.

## SUMMARY

### THE SENSITIVE PERIOD IN THE DEVELOPMENT OF THE VISUAL SYSTEM AS INDICATED BY TRANSFER OF FIXATION

A.A. Assaf, FRCS

It has been recently established that sensory systems, particularly the visual system, in experimental animals possess a sensitive period during which functional deprivation can result in biochemical, anatomical and physiological changes in the affected system. This period largely corresponds to the period of the post-natal anatomical growth and physiological maturity in the newborn animals.

This thesis is an attempt to delineate the sensitive period for the development of the visual system in man. It consists of three parts. Part I is a review of animal work indicating post-natal growth of the visual system in kittens and monkeys. This is foll owed by describing work indicating plasticity and the presence of a sensitive period in such animals. Part II is a review of the anatomical and physiological growth in the human visual system and the clinical evidence pointing towards the presence of a sensitive period. The third part is the author's investigation and consists of a review of patients with strabismic amblyopia who had occlusion therapy involving visual deprivation of the non-strabismic eye.

Occlusion has long been used in the management of different forms of amblyopia in children. It occasionally occurs that infants and young children having occlusion treatment for strabismic amblyopia switch fixation to the originally strabismic eye. This switch of fixation indicates that the neurological mechanisms of fixation must be of sufficient plasticity to allow such switch. Analysis of switch of fixation and its relation to age of occlusion and many other factors was used to indicate the sensitive period during which transfer of fixation is possible. The sensitive period for such reversal extended up to 7 years of age. This period can be subdivided into intervals of decreasing sensitivity, ranging from a critical period, during which switch of fixation can be produced by brief periods of occlusion, to one of minimal sensitivity during which switch of fixation occurred only after prolonged occlusion and tended to be transient. This sensitive period roughly paralleled the period of post-natal growth and physiological maturity in the human visual system.

## CONTENTS

## ACKNOWLEDGEMENTS

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## PREFACE

Recently it has been established that the visual system in young experimental animals is plastic. It responds to visual deprivation and other alterations in the visual experience with biochemical, anatomical, physiological and behavioural changes. These occur to a varying degree depending on the animal and the part of the visual pathways involved. This plasticity is confined to a certain age which is called the "sensitive period". This sensitive period or age largely corresponds to the period of postnatal anatomical growth and physiological maturity in the newborn animals.

For humans the concept of a sensitive period has the potential of important clinical application in the prevention and management of amblyopia in children. It might indicate that there is a specific period of development during which the visual system is susceptible to different forms of visual deprivation leading, clinically, to amblyopia. In addition this amblyopia might be preventable or reversible if removal of the causative factors or management is carried out within this sensitive period. It is founded on the belief that the human visual system like that of certain animals undergoes a period of post-natal development in the first few years of life. Deprivation of adequate stimuli during this period can affects its normal functioning, extending into adult life. In this thesis

evidence for the presence of a sensitive period in the human visual system will be presented; and in addition, analysis of how its sensitivity correlates with normal anatomical growth and physiological maturisation of the visual apparatus.

The thesis is in three parts. Part one is a review of animal work indicating post-natal growth of the visual system in animals, mentioning which factors are innate and which can be modified by visual experience. This is followed by describing work indicating plasticity and the presence of a sensitive period in such animals. Part two is a review of the anatomical and physiological growth in the human visual system and the clinical evidence pointing towards the presence of a sensitive period. The third part is the author's investigation and consists of a review of patients with strabismic amblyopia who had occlusion therapy, involving visual deprivation of the nonstrabismic eye. Occlusion therapy often leads to improvement in the visual acuity and fixation of the strabismic eye. The group of patients reviewed not only had improvement in their visual acuity, after occlusion, but actually switched, or reversed, fixation to the previously strabismic eye, i.e. the strabismus was transferred to the originally fixing eye, sometimes with amblyopia in this newly deviating eye. This effect occurred up to a certain age. Analysis of switch of

fixation and its relation to the age of occlusion, and many other factors, will be used to indicate the sensitive period during which the fixation mechanisms are still plastic to allow such strabismus of squint and fixation. The number of patients switched at a certain age and the type of switch produced reflects the sensitivity to occlusion.

The present thesis does not aim at an exhaustive study of the vast literature in parts I and II, dealing with animal and human evidence for the presence of a sensitive period, but rather a general look with the hope of extracting some conclusions.

# PART ONE

## EVIDENCE FOR A SENSITIVE PERIOD OF DEVELOPMENT OF THE VISUAL SYSTEM IN ANIMALS

- REVIEW -

"Monocular deprivation experiments indicated that neural connections present early in life can be modified by visual experience. Such neural plasticity was not observed in the adult cat but existed only during the first three post-natal months" [T. Weisel, Acceptance Lecture for Nobel Prize in Medicine, 1981; Wiesel 1982].

## I. INTRODUCTION: STRUCTURE, FUNCTION & EXPERIENCE

The concept that experience by an individual, especially when young, might alter the way it perceives and reacts to events later in life is not a new one. Much recent experimental work suggests that the sensory input in the post-natal period might play a crucial role in the formation and maintenance of functional activity of specific sensory centres. It indicates that the development of many aspects of different sensory systems including visual, auditory, olfactory and somatic sensory depends upon normal function.

Individuals are the product of inheritance and environment. The environmental influences play a vital, but poorly understood, role in the development of the nervous system. Only recently scientists are beginning to discover how the environment affects the sensory development of the organism.

The influence of the peripheral sensory organs on the central nervous system structures differs in different periods of development of the latter. At an early embryonal stage experimental changes in the mass of peripheral sensory organs cause great changes in the gross anatomy of the corresponding centres as has been frequently demonstrated by means of extirpation or transplantation of eye primordia, limb buds and other neuronally connected rudiments [Gyllensten et al, 1965]. At later stages the

central changes following interference with peripheral organs are more subtle, most often manifested as quantitative disturbances in the normal histology or cytology, e.g. scarcity of fibres, delayed myelination, decrease in growth of the dendritic processes, changes in the content of nucleic acid, cholinesterases and many other enzymes and proteins. These quantitative cytologic and histochemical alternations constitute a gradual transition from morphologic to a physiologic character and to normal functional influences of sensory stimuli on the centres.

The visual system has frequently been used as a test system for studies of the significance of different stimuli on the development and maintenance of neural structures [Gyllensten, 1965; Chow, 1973]. It offers good conditions for experimental research in this field. It also provides an opportunity to compare and contrast the intrinsic genetic control of neural development with the highly variable controls imposed by the animal's environment and experience, [Hirsch & Leventhal, 1978], since it is possible to modify and quantify the sensory inputs and to record physiological responses from different parts of the visual systems with a high degree of precision. The neuroanatomy of the visual pathways is also fairly well known and the afferent supply of centres is exclusively or mainly restricted to optic fibres.

From a mass of experiments in this field it became clear that the visual system depended heavily upon early experience for its normal structure as well as function [Hirsch & Leventhal, 1978]. Disuse produces altered brain structure and chemistry and over- stimulation produces exaggerated neural growth patterns and restructuring of function [Rosenweig et al, 1969, 1972]. The age dependence of these modifications in many animals is well marked; it is essentially confined to a stage in the early post-natal period. Imbalance of environmental input during this critical stage of early development may subsequently produce uneven function from which recovery is difficult or impossible.

## II. EVIDENCE FROM THE NON-VISUAL SYSTEMS

Evidence from many experiments on the sensory systems, other than the visual system, points to some effect of sensory deprivation on the structure and function of the affected centres. It also indicates that these effects can occur only during a defined sensitive period.

### A. AUDITORY SYSTEM

Sound deprivation has been found to alter the structure, function and responses of different auditory centres.

The morphological effects were recorded by different authors. Feng and Rogowski [1980] reported an increase in the number of cells with dominant dendritic patterns on the side receiving input from the non-deprived ear in rats. Reduction in the size of neurons was also reported in rats, after auditory deprivation, in the brain stem auditory nuclei [Webster and Webster, 1977; 1979]; of the cells of the antero-ventral cochlear nucleus [Coleman and O'Connor, 1979; Blatchley et al, 1983] and dorsal and ventral cochlear nuclei [Coleman et al, 1982].

Auditory performance was also affected by auditory deprivation according to Wolf [1943], Gauron and Becker [1959], Batkin et al, [1970], Tees [1967] and Patchett [1977]. These authors showed that deprivation of patterned

sound at an early stage of development in rats reduces the adult animal's ability to make auditory pattern discrimination.

After studying unit activity responses in the inferior colliculus in rats Silverman & Clopton [1977] demonstrated complete loss of binaural interactions after unilateral auditory deprivation, while this was little affected by bilateral deprivation. Such changes were also demonstrated in cats [Moore & Irvine, 1981].

A sensitive period for binaural interaction was found to be between 10 - 60 days after birth. The plasticity of these developmental processes is maximal at 10 - 30 days and is greatly reduced from 30 - 60 days of age (Clopton & Silverman, 1977).

## B. SOMATOSENSORY

Experiments with several sensory modalities in animals confirmed the observation that restriction of stimulus during the early post-natal weeks has significant effects upon adult abilities; and that early experience is critical for the achievement of well-coordinated responses to stimulation [Held, 1965; Riesen & Zilbert, 1975]. Nissen et al [1951] demonstrated the effect of sensory deprivation from the limbs on the chimpanzee, resulting in poor coordinated movement.

## III. EVIDENCE FROM THE VISUAL SYSTEM

### A. HISTORICAL BACKGROUND

The question of the influence of function and the environment on structure is an old question. It is one of the basic questions of nature. Only recently among the mass of experimental work on the subject a trickle of answers started flowing through.

One of the first scientific experiments to be performed in this field was by von Gudden [1870], who found slight reduction in the size of one optic nerve in rabbits that had been raised with one eyelid sutured. This occurred on the sutured side. Spalding [1873] studied the behaviour of hooded newly hatched chicks after a period of visual deprivation. After 1-3 days he removed the hoods and noted their behaviour immediately thereafter. For six minutes they sat chirping and looking about; at the end of that time, they performed following head-eye movements and movements consisting of a snap-seize swallow of a fly which was flying close by. His observations on 20 visually deprived chicks convinced him they had a sense of visual direction. Their behaviour was conclusively against the theory that the perceptions of distance and direction by the eye are the result of experience. von Gudden [1874] removed the eye from infant rabbits and subsequently studied the adult nervous system. In 1889 he sectioned the optic nerve or destroyed the retina in young rabbits and observed an extremely thin

optic nerve, grey instead of white on the operated side; the opposite anterior colliculus was much reduced in size; the lateral geniculate body showed little if any change and the cerebrum was unchanged.

Held [1896] claimed that myelin formation in the optic nerve could be hastened by exposing the prematurely opened eye of a young rabbit or dog to light over a period of a few days. In 1900 Berger studied young cats and dogs after they had been raised with both eyes sutured and examined them several months later. No changes in the retina, optic nerve or lateral geniculate body were found. But the visual cortex showed reduced gyri and cortical thickness; and on Golgi preparations showed that the cells were smaller than normal with fewer processes. These features were interpreted as arrest of development due to lack of function. He suggested that complete lack of light would result in marked atrophy of the optic nerve and primary centres. Other authors studied the effects of visual deprivation in the same period such as Mann [1895], Bach [1895] and Birch-Hirschfeld [1900]. Mann studied the retina, lateral geniculate nucleus and occipital lobes in dogs and rabbits, after uniocular occlusion of a few hours duration and found increased chromatin material in the cells of the deprived side.

Von Monakow [1914] studied the effect of enucleation on

the primary optic centres in rabbits and noted that secondary degeneration never extended beyond them. After many years the main cells of the lateral geniculate body showed some reduction in size, but no other obvious structural changes. He found an equal reduction of gray and white matter diffusely throughout the occipital cortex of dogs, six months after bilateral enucleation at birth. If the neurons of the third order are affected so little by the absence of the optic nerve, it is hardly to be expected that they would be seriously affected by the removal of impulses coming over the optic nerve.

Minkowski [1920] showed the lateral geniculate nuclei were affected by removal of the eye even when it is done in adult animals, resulting in transneuronal atrophy or degeneration.

Detwiler [1932] found no measurable difference in the development of the retina in the light and dark-reared rats. Goodman [1932] raised rabbits in the dark from birth to six months and found no changes in the retina, optic nerve, superior colliculus lateral geniculate body, pulvinar or striate cortex. Clark and Penman [1934] found cell loss in the lateral geniculate body after removal of one eye in adult animals. Tsang [1937] enucleated eyes of infant and adult rats and found the optic nerve to be reduced in size in both. The lateral geniculate nucleus was thinned to 55-65% of the normal size with loss of cells. The visual cortex was thinned and the superior colliculus was reduced

in size to 76% of normal. These changes were more marked in infant than adult rats.

In the nineteen-forties and -fifties, research is next concentrated on the behavioural and psychological effects of visual deprivation, some of which will be mentioned later, the most prominent of which is the work of Riesen and co-workers. It was not until the early nineteen-sixties that definite neurophysiological and anatomical effects were demonstrated.

Summary:

Up to the early nineteen-forties little or no concrete evidence was available in support of the theory that visual deprivation can affect the structure or function of the visual pathways. In the nineteen-forties and -fifties research concentrated on behavioural and psychological effects of visual deprivation the most prominent of which was the work of Riesen and co-authors. Not until the early sixties were definite anatomical and neurophysiological effects demonstrated.

## B. TYPES OF VISUAL DEPRIVATION

Earlier experiments involved more drastic techniques of deprivation such as enucleation of one or both eyes, optic nerve section or dark rearing in infant and adult animals. It became obvious that enucleation and optic nerve section would soon be followed by axonal degeneration towards the lateral geniculate body and retrograde degeneration towards the ganglion cells in the retina, more marked in young animals than adults.

Experimental data on dark-rearing resulted in the conclusion that it eventually caused atrophic changes in the retina with loss of ganglion cells together with other local morphological changes [Chow et al, 1957; Rasch et al, 1961]. Also, light deprivation from birth severely retarded the development of visual abilities in chimpanzees [Riesen, 1947], monkeys [Fantz, 1965], and kittens [Held & Hein, 1963; Ganz & Fitch, 1968].

Soon it became apparent that enucleation and optic nerve section were less than satisfactory physiological methods of studying visual deprivation and that even dark-rearing could result in more than ocular effects. Moreover, it appeared that diffuse light itself was not sufficient for visual development, and that stimulation by visual patterns was essential if animals were to develop normally. So more specific methods of deprivation were developed.

Attempts have been made to simulate in animals known clinical entities in humans which, if occurring in infancy or early childhood, could result in amblyopia. Stimulus deprivative amblyopia was modelled by the old method of lid suture in addition to opaque contact occluders [Mishkin et al, 1959; Hubel & Wiesel, 1965; Ganz & Fitch, 1968; Berger & Meier, 1968] or other methods of patterned vision and light deprivation [von Noorden & Crawford, 1981b]. Artificial strabismus was produced in animals by surgery; convergent [von Noorden & Dowlight, 1970; Yinon et al, 1975; Ikeda & Wright, 1976], or divergent [Hubel & Wiesel, 1965; Baker et al, 1974] or by the use of prisms [Shlaer, 1971; Crawford & von Noorden, 1980]. Experimental anisometropia was produced with atropine [Ikeda & Tremain, 1978a; Boothe et al, 1982] or with high powered lenses [Blakemore & Eggers, 1977], or artificial astigmatism by cylindrical lenses [Freeman & Pettigrew, 1973; Freeman, 1977; Cynader & Mitchell, 1977; Thibos & Levick, 1982]. The effects of experimental aphakia were studied in monkeys by von Noorden & Crawford [1977].

Monocular, binocular or alternate total deprivation was used [Wiesel & Hubel, 1965a; Hubel & Wiesel, 1965]; The extent of recovery from the effects of visual deprivation was assessed after deprivation, monocular or binocular, followed by binocular viewing or reverse closure [Wiesel &

Hubel, 1965b; Blakemore & van Sluyters, 1974; Movshon, 1976a,b; Mitchell et al, 1977; Giffin & Mitchell, 1978]. This was performed at different ages in different animals to outline the age at which the animal could be affected maximally by the altered visual experience.

Summary :

Different methods of visual deprivation were used, many can be compared to recognised clinical entitities in man.

Enucleation and optic nerve section though resulting in total loss of sensory input, will produce more than a physiological response to loss of function. Thus such cases were excluded from the review. In contrast, dark-rearing experiments, being a more physiological method of deprivation, though resulting in a more than visual effect, were included.

## C. ANIMAL MODELS - POSTNATAL DEVELOPMENT OF THE VISUAL SYSTEM

The most frequently used animal models for research in visual deprivation are monkeys, cats, rabbits and mice. Of these only two possess visual capabilities approaching those of man - monkeys and, to a much less extent, cats.

The Macaque monkey provides a good animal model for human vision at behavioural level. Spectral sensitivies, colour vision, acuity, frequency response functions, stereopsis and other visual functions are very similar to the corresponding visual capacities in humans [Bough, 1970; Devalois et al, 1974a,b; Sarmiento, 1975; Merigan, 1976; Crawford, 1977; Teller et al, 1978; von Noorden, 1978b]. Given these similarities of visual capacities of adult monkey and man, it seems likely that the infant monkey will provide a good model for human visual development (for studies on visual behaviour in monkeys see Ordy et al, 1962, 1965; Weiskrantz, 1972; Teller et al, 1978; Teller, 1981). Jampolsky [1978] challenged the adequacy of the Macaque monkey as an animal model for strabismic amblyopia due to the absence of naturally occurring strabismus. But Kiorpes and Boothe [1981] reported 2% incidence of naturally occurring strabismus in Macaca nemestrine monkeys.

Cats also possess many visual capabilities as found in adult humans, e.g. stereopsis and binocularity. In addition contrast sensitivity function displays findings

similar to human function [Blake et al, 1974a].

In monkeys and cats the visual system is not fully developed at birth, but continues to develop over the first few months of post-natal life at the behavioural, anatomical and physiological levels.

1) Development of visual acuity

In Macaque monkeys there is at least a rough correspondence between the period during which acuity normally develops and the period during which the visual system is most sensitive to the effects of visual deprivation. Using optokinetic nystagmus [Ordy et al, 1964] and preferential

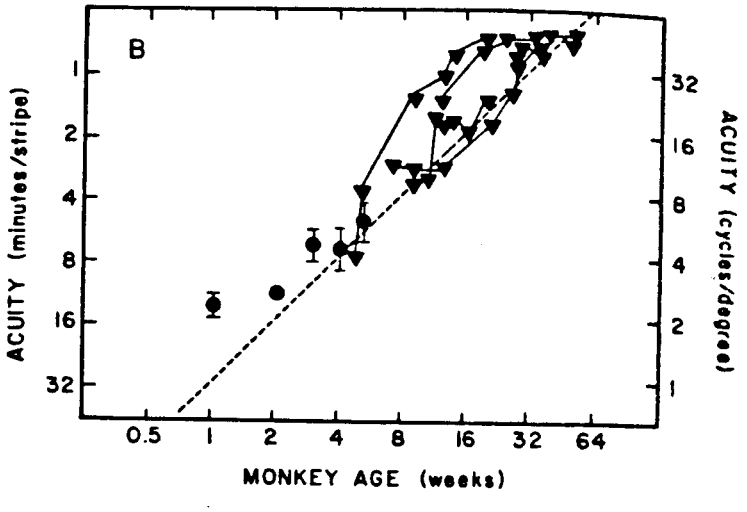



Fig. 1 Development of the visual acuity in pigtail macaque (Macaca nemestrina) monkey infants. Acuity is plotted against the age [Teller, 1981].

looking [Teller et al, 1978], the grating acuity in the newborn monkey has been found to be about the same as the human infant at birth (20/300) [Bishop, 1981], but subsequently the monkey's acuity develops more rapidly. The improvement takes place over approximately the same range in the two species, but it does so in six weeks in the monkey rather than the six months needed by human infants (Fig. 1).

In kittens normal eye opening occurs at about the 8th day of age [Sherman, 1972a; Blakemore & Cummings, 1975]. At eye opening kittens appear behaviourally blind. This lasts until the 4th postnatal week. Improvement occurs gradually until all kittens show some vision by their seventh post-natal week [Sherman, 1972a]. The visual acuity reaches adult value by the age of 3-4 months, which coincides with the completion of the sensitive period [Freeman & Marg, 1975; Mitchell et al, 1976]. In addition, the development of spatial resolution power of the lateral geniculate neurons receiving from the area centralis of the retina runs parallel with the development of the visual acuity from 3-12 weeks of post-natal life [Ikeda & Tremain, 1978b].

2) Anatomical growth

Maturational changes in the dioptric mechanisms, the retina, final myelinization and biochemical changes occur in the visual pathways. All these changes occur post-natally

and might influence the development of vision in primates [Ordy et al, 1965].

In kittens development of the optics in the cat's eye corresponds with the sensitive period [Thorn et al, 1976]. In addition, development of all cell types in the central region of the retina is complete between 4-5 weeks after birth, and the more peripheral regions by 9 weeks after birth [Donovan et al, 1966] and myelination of the optic nerve is completed by 12 weeks of age [Moore et al, 1976]. This corresponded well with the period of post-natal development of the visual acuity of the lateral geniculate neurons, Fig. 2 [Ikeda, 1980].

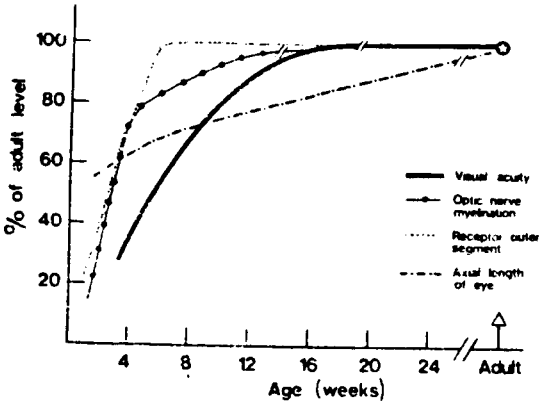



Fig. 2 Development of cellular visual acuity in kittens [Ikeda & Tremain, 1978b] compared with that of optic nerve myelination [after Moore et al, 1976], length of the outer segments of the photoreceptors [after Donovan, 1966] and the axial length of the eye [after Thorn et al, 1976]. Note that optic nerve myelination reaches the adult level at approximately the same time as visual acuity [Ikeda, 1980].

In monkey visual cortex all neurons have been generated, reached their final positions and formed their basic connections subserving ocular dominance before birth, i.e. before visual experience. In the superior collicular and lateral geniculate nucleus monocular segregation is well established before birth, whereas in the visual cortex it is not fully developed at birth [Rakic, 1977].

Columnar organisation in visual cortex is mixed between right and left at one week of age. Later these columns segregate into separate columns for the two eyes, forming periodic bands. At 3 weeks the columnar pattern resembles that seen in adults. By six weeks an adult degree of columnar segregation is established [Wiesel, 1977; Levay et al, 1980]. In addition, there was a marked increase in the number of dendritic spines on the surface of the cells of the visual cortex. All neurons showed spine population decreases between nine months of age and adult, suggesting continuing long term maturational changes [Boothe et al, 1979].

In kittens there is considerable growth in the lateral geniculate nucleus cells post-natally [Sherman, 1972b]. During the first week of life, geniculate cells are still immature and lack dendrites. An active phase of dendritic extension occurs during the second postnatal week [Mason, 1983]. On the other hand, geniculate cells cross-sectional area increased by about 50-60% from birth to 15 weeks of

life [Kupfer & Palmer, 1964]. Later studies showed rapid growth to about half the size in the first 2-4 weeks of post-natal life [Hubel & Wiesel, 1970; Hickey, 1980]. Garey et al [1973] demonstrated differential cell growth in the monocular and binocular segments of the lateral geniculate nucleus. There is a pronounced rapid phase of cell growth, especially marked between 2-5 weeks and is over by 2 months of age. After this there is relatively little growth of monocular cells, but binocular cells continue to grow until about 4 months, when they reach adult size.

The kitten, by the 8th post-natal day, has many of its functional geniculostriate system connections. Sadlack [1972] studied the dendritic branching and spine density in the visual cortex in kittens and concluded that until day 20, neuronal development is mainly under genotypic control, but after this period environmental manipulation can affect the morphology of the visual cortex in kittens. Few synapses are present at birth. In fact, less than 1% of synapses in the primary visual cortex develop before eye-opening [Cragg, 1975a]. Synapses increase rapidly in number between 8-37 days of life. The timing of synaptic development in the visual cortex has been compared quantitatively with that in the lateral geniculate nucleus and qualitatively with synaptogenesis in the retina. Synapses develop in the lateral geniculate nucleus and cortex in a

parallel fashion, with the main increase in synapses in the lateral geniculate nucleus and cortex taking place four weeks after the eye is being used [Cragg, 1975a] (Fig. 3). Thus it appears that the period of synaptic development in kittens coincides with the normal time of eye-opening, as does the burst in the development of dendritic spines in the visual cortex of the mouse [Hirsch & Leventhal, 1978].

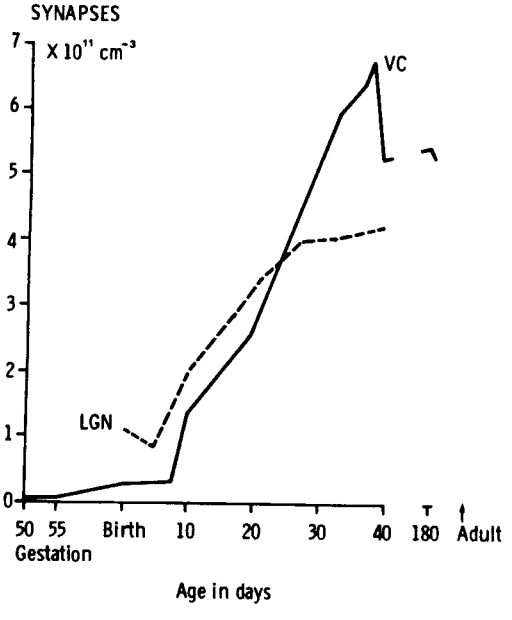



Fig. 3 The density of synapses in the visual cortex and the lateral geniculate nucleus in kittens [Cragg, 1975a].

3) Physiological maturity

In their early experiments on visual development in kittens, Hubel & Wiesel [1963] reported that they had found cortical neurons with normal adult type specificity of responsiveness in animals that had not opened their eyes. They therefore concluded that much of the complex organisation of the visual cortex responsible for the receptive field properties, binocular interaction and functional architecture is developed solely under genetic control and is present in the very young kittens without visual experience. They therefore suggested that the effects of visual deprivation are due to a disruption of connections that were there from the start, rather than a failure to develop. This view was supported by the findings of Sherk and Stryker [1976].

This concept was challenged by others who found no or few cortical cells selective for stimulus orientation [Barlow & Pettigrew, 1971; Blakemore & Mitchell, 1973; Pettigrew, 1972, 1974; Blakemore & van Sluyters, 1975; Singer & Trettor, 1976]. They concluded that diffuse binocular connections and the mechanism for directional movement selectivity appear to be innately determined, but the mechanisms for disparity and orientation require visual experience. Later it became clear that binocularity and orientational selectivity are present when the eyes first open, but visual experience is still necessary to maintain

and develop these specifities [Buisseret & Imbert, 1976; Blakemore, 1977; Fregnac & Imbert, 1978]. This disagreement, at least partly, arose after comparing binocularly deprived kittens post-natally to newly born undeprived kittens, which is inappropriate. By the 4th-5th week of age the cortical neurons are virtually adult in their physiology [Pettigrew, 1974; Blakemore & van Sluyters, 1975; Imbert & Buisseret, 1975]. At this time geniculocortical and intracortical transmission of neuronal impulses is still immature, in spite of the systems for orientation and direction selectivity in the visual cortex being almost fully developed [Beckman & Albus, 1982]. Also by 5-6 weeks, the proportion of binocular neurons tuned for retinal disparity begin to approach adult level, with very rapid improvement in stereo acuity over the same period [Pettigrew, 1974; Timney, 1981]. In adult cats four-fifths of all neurons of the visual cortex are binocular with highly complex receptive field organisation [Hubel & Wiesel, 1962].

Cortical neurons in the adult monkey in layer IV C are organised in columns according to ocular dominance; these are called ocular dominance columns [Hubel et al, 1977; Hubel, 1979]. At birth there is some physiological mixing of left and right inputs. The basic columnar pattern is evident and some small regions are already monocular.

At 3 weeks of age the columnar pattern resembles that seen in the adult except for a suggestion that the borders between columns are not so sharply demarcated. By 6 weeks an adult degree of columnar segregation is established [Hubel et al, 1977; Levay et al, 1980]. In kittens this segregation occurs during the first few months of life [Levay et al, 1978].

In rabbits, rats and mice there is considerable evidence that much of the cortical development is completed successfully in the absence of post-natal visual stimulation, but at a reduced rate. These animals basically depend on monocular vision [van Sluyters & Stewart, 1974].

4) Summary:

It appears that behaviourally and anatomically (especially at the dendritic level) adult standards are not reached until the first few months of life in both monkeys and kittens. At the cortical level it appears that neurons of all types of selectivity are present in the area 17 at birth, except those required for binocular disparity. The question of whether they have as high a degree of selectivity as those of the adult is still open and there does seem to be a possible role of experience in 'tuning up' these selectivities. So it appears that innate mechanisms give the visual system highly specific connections, but visual experience early in life is necessary for their maintenance and full development.

## D. EFFECTS OF VISUAL DEPRIVATION

As mentioned above the visual system has many unique features that make it a suitable model for the effects of sensory deprivation. There is extensive literature on this subject, but it was not until the elegant work of Wiesel & Hubel on the visual cortex in the early sixties that the way was opened for electrophysiological studies which led to more specific physiological results being achieved. The present review although not exhaustive discussed the main concepts and findings. Other authors have review articles on the subject, e.g.: Barlow, 1975; Bishop, 1981; Blake, 1979: Blakemore, 1978; Brattgard, 1952; Chow, 1973; Ganz, 1975, 1978; Globus, 1975; Grobstein & Chow, 1975; Guillery, 1974; Hirsch & Leventhal, 1978; Mendelson & Ervin, 1962; Riesen, 1961, 1965a,b, 1966, 1975; Riesen & Zilbert, 1975; Rosenzweig, 1966; Scheibel & Scheibel, 1968; Tees, 1976; Walker et al, 1975; Wickelgren 1972; Wiesel, 1982].

### 1) Retina

Effects of visual deprivation on the retina are more subtle than those in higher structures. These include biochemical, histological and electrical responses.

a. Biochemical effects

Biochemical effects of visual deprivation were reviewed by many authors, e.g. Chow [1973] and Walker et al [1975].

1. Proteins and nucleic acids synthesis and turn-over: Dark-rearing was found to produce a decrease in the protein and/or RNA levels in young animals' retina, especially affecting the ganglion cell layer. This was demonstrated in monkeys [Winsberg & Riesen, 1966]; chimpanzees, cats and mice [Rach et al, 1961]; kittens [Sankova & Arefeva, 1973] and in rabbits [Brattgard, 1952]. On the other hand, lid suture produced no difference from normal in the rats' retina [Mariani et al, 1967].

2. Tissue metabolism: Dark-rearing in young rabbits produced some decrease in the activity of malic dehydrogenase, lactic dehydrogenase, and acid phosphatase; this is contrasted with an increase in glucose-6-phosphate dehydrogenase activity [Schimke, 1959]. These findings were not confirmed by Liberman [1962], who found no changes in the enzymatic activity in the rat's retina after dark-rearing.

3. Neurotransmitters A decrease in cholinesterase activity was found in adult rats after dark-rearing

[Glow & Rose, 1964]. This was also demonstrated in young rats after lid suture or opaque occluders [Glow & Rose, 1966] and in dogs after bilateral lid suture and blindfolding [Chang et al, 1941].

b. Histological Effects

It is possible to alter the structure of the retina by dark rearing or lid suturing. Most morphological studies have been concerned with the retinal ganglion cells or their processes. Only a few observations were made of changes in other neural elements of the retina, but the evidence is mainly contradictory.

Dark-rearing in earlier studies produced no retinal effects, especially in rabbits [Goodman, 1932] or kittens [Detwiler, 1932; Hellestrӧm & Zetterstrӧm, 1956]. Later it was found to produce varying effects in different animals.

In rabbits De Robertis and Franchi [1956] and De Robertis [1958] reported that the synaptic vesicles in the retina could be altered by exposure to light. Furthermore, Tucker et al [1982] found a delay in the maturation of the photoreceptors; this returned to normal adult characteristics by 4 weeks of age.

In rats Cragg [1969a] found wide receptor terminals along with a lower density of synaptic

vesicles, but the vesicle size was not altered. On the other hand, no effect on the synapses was demonstrated in the guinea-pig retina.

Monkey's retina showed no obvious changes [Chow, 1955; Hendrickson & Boothe, 1976]. But in kittens there was cytoplasmic atrophy in the bipolar and ganglion cell layers, with a comparative decrease in the size of the ganglion cells [Rasch et al, 1961] and the inner plexiform layer was thinner with less dense population of Müller cell fibers [Weiskrantz, 1958]. By far the most dramatic change occurred in the chimpanzee retina with pronounced loss of ganglion cells [Riesen, 1950, 1960; Chow et al, 1957; Rasch et al, 1961].

Earlier studies with lid suture and other forms of pattern deprivation showed no effect, e.g. after bilateral lid suture in young cats and dogs [Berger, 1900], in kittens [Wiesel & Hubel, 1963a], or monkeys [Baker et al, 1974].

But von Noorden et al [1977] demonstrated a decrease in the size and density of the parafoveal retinal ganglion cells after long term visual deprivation in monkeys. Other changes were described in rats by Sosula & Glow [1971] using contact lens occluders; these authors demonstrated an increase in

the number of amacrine synapses and larger than normal synaptic vesicles in the inner plexiform layer.

c) Electrophysiological effects:

Dark-rearing produced a delayed or subnormal b-wave component of the electroretinogram in kittens [Zetterström, 1955; Hellström & Zetterström, 1956; Baxter & Riesen, 1961; Cornwell & Sharpless, 1968], and monkeys [Riesen, 1970]. This effect is opposite to that which occurred in rabbits, where a larger b-wave was found [Bonaventure et al, 1971; Reuter et al, 1971]. Monocular occlusion, on the other hand, produced no effects on the electroretinogram in monkeys [von Noorden et al, 1970a; Baker et al, 1974], but a reduced b-wave in kittens [Ganz et al, 1968].

Studies of the cell physiology on the whole were concerned with the ganglion cell responses. Sherman & Stone [1973] found normal properties of sustained and transient ganglion cells after monocular or binocular deprivation. However, Ikeda & Tremain [1979] found a loss of spatial resolution of sustained X-retinal ganglion cells, at or near the area centralis (visual axis) in kittens raised with esotropia and which had lost the ability to fixate. Sustained cells in the area centralis were normal in kittens with esotropia, which retained the ability to fixate with the esotropic

eye. These findings were supported by Chino et al [1980], but contrasted with the findings of Cleland et al [1980]. These authors failed to demonstrate any loss of spatial resolution power of either class of retinal ganglion cells in the vicinity of area centralis in kittens deprived by lid-suture. Similarly, no changes were demonstrated in kittens after astigmatism-rearing [Thibos & Levick, 1982].

d) Summary:

Retinal effects of visual deprivation appear to be concerned mainly with the ganglion cells. These effects vary in different animals. Their severity varied from a biochemical level as a decreased RNA and protein synthesis to the extreme case of cell death. Furthermore, the functional activity of the retina is affected differently in different animals. It appears that amblyopia, at least strabismic amblyopia, is associated with loss of the spatial resolution power associated with the X-type or sustained retinal ganglion cells.

## 2. Optic Nerve, Chiasm and Tract

### a) Chemical and physiological

Iida & Scheibler [1968] studied the optic chiasm and optic tract in rats after dark-rearing and found no effects on glycolysis. Other authors studied axoplasmic transport after dark-rearing in the optic nerve in rabbits [Karlsson & Sjostrand, 1971] - there was no difference from normal.

### b) Histological

Dark-rearing was reported to result in fewer thick optic nerve fibres and retarded myelination in mice [Gyllensten & Malmfors, 1963]. However, a prolonged stay in the dark did not prevent the eventual normal myelination [Gyllensten et al, 1966]. Furthermore, Held [1896] found that myelination of the optic nerve fibers could be hastened by exposing a prematurely opened eye of a young rabbit or dog to light over a period of a few days. Packing density is also affected by dark-rearing; this was demonstrated by Weiskratz [1958] in dark reared kittens.

Lid suture produced a decrease in the size of the optic nerves in rabbits [von Gudden, 1870]. This was confirmed by Wendell-Smith [1964] who demonstrated about 10% decrease in the cross sectional area of the optic nerve in mice. This contrasts with the normal

optic tracts found in dark-reared young rats [Fifkova & Hassler, 1969].

c) Summary:

Dark-rearing delays the myelination of the optic nerves, but this eventually proceeds to normality. In some animals lid-suture reduces the thickness of the optic nerve, the significance of which is far from clear.

3. Lateral Geniculate Nucleus

a) Biochemical effects

1) Proteins and Nucleic Acids Synthesis and Turnover

No studies aimed at studying protein changes in the lateral geniculate nucleus after visual deprivation were found, apart from those following enucleation.

2) Tissue Metabolism A decrease in the metabolic activity occurred in rats after dark-rearing [Iida & Scheibler 1968]. On the other hand, lid-suture in kittens produced no changes in the lateral geniculate nucleus cell activity [Kupfer & Palmer, 1964]. Later Wong-Riley [1979] demonstrated a decrease in the cytochrome oxidase staining of the binocular segment of the deprived geniculate laminae in kittens after monocular lid-suture. The monocular segment appeared to be unaffected.

3) Neurotransmitters: Dark-rearing produced a decrease in the acetylcholinesterase and cholinacetyltransferase activity in rats [Maletta & Timiras, 1967]. These changes were absent after lid-suture [Maletta & Timiras, 1968]. Iida & Scheibler [1968] on the other hand failed to confirm any changes in the neurotransmitter activity in such animals after dark-rearing.

b) Histological

The effect of dark-rearing on the histology of the lateral geniculate nucleus is uncertain. While some authors reported no marked cellular changes, e.g. in monkeys [Chow, 1955; Hendrickson & Boothe, 1976], cats [Burke & Hayhow, 1968] or rabbits [Goodman, 1932], others found about 20% decrease in volume of internuclear material in lateral geniculate nucleus of growing mice [Gyllensten et al, 1965]. Cragg [1969b] studied the axon terminals in the lateral geniculate nucleus in rats reared in the dark and found them to be larger and less numerous than in light-reared animals. Furthermore, Clark [1943] found laminar atrophy in some young monkeys lateral geniculate nucleus after a long stay in red monochromatic light.

It is well known that the extreme method of removal of the sensory input by enucleation on optic nerve section is soon followed by transneuronal cell atrophy involving the lateral geniculate nucleus, e.g. [Cook et al, 1951; Kalil, 1980]; for review see Cowan [1970]. Lid-suture is a more physiological method of visual deprivation with no structural damage or injury to the visual pathways. Lid-suture is also found to be associated with well-marked cellular changes in the lateral geniculate nucleus. After monocular eyelid suture in young kittens, the cells of the laminae in

lateral geniculate nucleus supplied by that eye grew less and were smaller than normal [Wiesel & Hubel, 1963a; Kupfer & Palmer, 1964; Guillery, 1973; Hickey et al, 1977]. Similar findings were later described in monkeys [von Noorden, 1973b; Headon & Powell, 1973; Baker et al, 1974; von Noorden and Middleditch, 1975], and in other animals [Guillery & Kaas, 1974a; Guillery, 1974; Chow & Spear, 1974; Fifkova & Hassler, 1969]. This is only seen if the eye is sutured in the first few weeks of life and these changes were irreversible [Wiesel & Hubel, 1963a, 1965b; Hubel & Wiesel, 1970; von Noorden & Crawford, 1978a], or partially reversible [Chow & Stewart, 1972]. However, Dürsteler et al, [1976] found that they could correct or even reverse the cell size differences in kittens by reverse suture. In general, a reduction in the cell size that varies from between 25-40% has been reported after such experiments [Wiesel & Hubel, 1963a: Guillery & Stelzner, 1970; Headon & Powell, 1973; Hickey et al, 1977]. This difference in lateral geniculate nucleus cell size is smaller when using a translucent contact lens rather than lid suture. Finally, lid suture in adult cats produces no cytological effects on the lateral geniculate nucleus [Wiesel & Hubel, 1963a]. Monkeys rendered aphakic [von Noorden & Crawford, 1977]

during the first month of life had lateral geniculate nucleus effects comparable to those obtained by lid suture techniques.

After electronmicroscopic studies on the lateral geniculate nucleus of visually deprived dogs, using lid-suture, Szentagothai & Hamori [1969] concluded that most marked changes occurred in the dendritic spikes of the geniculate cells.

Ikeda et al [1977] studied kittens with convergent squint and found the lateral geniculate nucleus cells in the laminae supplied by the convergent eye to be smaller. Their density was higher than normal and there was a decrease in the size of all classes of cells, not only large cells. Monkeys with esotropia also showed a decrease in the cell size in the lateral geniculate nucleus involving the laminae receiving input from the deprived eye [von Noorden, 1973b; Crawford & von Noorden, 1979a; von Noorden & Middleditch, 1975]. Exotropia without amblyopia showed the least severe changes. No changes were detected in monkeys raised wearing dissociating prisms [Crawford & von Noorden, 1980].

This difference in cell size among the deprived and the non-deprived laminae may be due to normally innervated cells growing larger than normal, while deprived cells grow less, or it might be due to an

arrest in development, or shrinking of such cells. On the other hand, it might be due to visual deprivation affecting preferentially the large cell (Y-cell) population in the deprived laminae. [Wiesel & Hubel, 1963a; Sherman et al, 1972; Sherman & Wilson, 1975; Hickey et al, 1977; Wilson et al, 1977; Crawford, 1978].

This marked effect of unilateral visual deprivation is in contrast with binocular deprivation, where little or no effect on cell growth was demonstrated after bilateral lid suture in kittens [Chow & Stewart, 1972; Guillery, 1973] and in cats and dogs [Berger, 1900]. A 5% difference between normal and binocularly deprived kittens was demonstrated [Guillery, 1973]. Other authors found a slightly higher difference from normal in bilaterally deprived kittens [Kupfer & Palmer, 1964; Hickey et al, 1977]. Others stated that the effect is widespread throughout the lateral geniculate nucleus, resulting in general shrinkage or loss of cells [Wiesel & Hubel, 1965a], or a preferential loss of larger Y-cells from all layers of lateral geniculate nucleus on binocular deprivation [Sherman et al, 1972]. In general it is agreed that this size difference is much less marked in binocular deprivation than in monocular deprivation.

Geniculate cells compete during their development,

probably for available synaptic surfaces upon the cortical cells. Success in this competition depends upon the nature of the visual input [Wiesel & Hubel, 1965a; Guillery & Stelzner, 1970], or on the interactions between the geniculate cortical axons that involve translaminar inhibition through interneurons [Suzuki & Kato, 1966]. Success or failure in this competition might be reflected by changes in the cell size.

Some authors pointed out that the effects of monocular deprivation were mostly limited to the binocular segment with smaller or no involvement of the monocular segment. This was demonstrated in kittens [Guillery & Stelzner, 1970; Guillery, 1972; Hickey et al, 1977; Spear, 1977] and monkeys [Headon & Powell, 1973], but monkeys had also involvement of the monocular portion [von Noorden & Middleditch, 1975]. It was thought to be due to binocular competition, which only affected the binocular segment; the monocular segment being spared such effect. Guillery [1972] demonstrated the effect of binocular competition by producing a lesion in the temporal retina; this resulted in an area of transneuronal atrophy in the lateral geniculate nucleus. He then deprived the opposite eye. The segment in the deprived eye, opposite the injured segment in the non-deprived eye, was spared the effects of

visual deprivation; i.e. it had normal size cells [Guillery, 1972; Sherman et al, 1974]. Using identical procedures, von Noorden et al [1976] have reported similar results in the monkey.

In rats and mice, binocular interaction plays a relatively minor role in the functional organisation of the lateral geniculate nucleus. This nucleus differs from that of carnivores and primates, and one might expect the effect of visual deprivation to reflect this difference.

c. Physiological

Earlier studies showed none or only subtle physiological abnormalities in the cat's lateral geniculate nucleus following visual deprivation [Wiesel & Hubel, 1963a; Chow & Stewart, 1972; Sherman & Sanderson, 1972; Hamasaki et al, 1972]. Later it was reported that while, in kittens, many geniculate cells receiving input from the deprived eye continue to respond normally, many cells showed changes in their response properties [Hamasaki & Winters, 1973; Eysel et al, 1979].

The cells of lateral geniculate nucleus can be classified according to their receptive field properties into sustained (X) cells which are smaller and

have a slow linear response; and a bigger transient (Y) cell with fast non-linear response. Some authors suggested that the Y-cells are more selectively affected by visual deprivation, monocular or binocular in kittens and tree shrew [Sherman et al, 1972; Hoffmann & Cynader, 1975; Garey & Bakemore, 1977; LeVay & Ferster, 1977; Lin & Sherman, 1978]. But after monocular deprivation, the monocular segment in the lateral geniculate nucleus appeared to suffer no such loss of Y-cells [Sherman et al, 1972, 1975; Hoffmann & Cynader, 1975]. This suggested selective loss of Y-cells is not in satisfactory accord with the physiologic evidence based on the relative frequency of recording from X and Y cells in normal and pattern deprived animals [Eysel et al, 1979]. In addition, Shapley and So [1980] found that the usual consequences of monocular deprivation are not necessarily associated with a loss of geniculate Y-cells in monocularly deprived cats.

Visual acuity of the geniculate cells (as estimated in terms of the highest spatial frequency of a sinusoidal grating stimulation to which the cells respond with modulated firing) had been measured in kittens with artificial squint and anisometropia [Ikeda & Wright, 1975, 1976; Ikeda & Tremain, 1978a,c]. These authors found that in artificial divergent squint

the "visual acuity" of the geniculate cells were normal because they adopt the strategy of alternate fixation [Ikeda & Tremain, 1977]. In convergent squint, the 'sustained'cells connected to the central retina of the esotropic eye had a significantly poorer acuity than those with their afferents from the central retina of the normal eye. The major defect was suffered by the sustained cells (X cells) and the loss of visual acuity was restricted to central vision. The peripheral retina of the esotropic eye had normal spatial resolution. The loss of the visual acuity in the esotropic eye depended on the age at which the squint was produced. The visual acuity was arrested at its level of development at about the age of the squint onset. In artificial anisometropia, produced by instilling atropine in one eye, there was, also, a significant loss in the visual acuity of the sustained cells from the area centralis segment as compared to normal. This occurred in one or both eyes depending on whether there was monocular or binocular deprivation produced by blurring the image and defocus. This reduction in the spatial resolution was much less than with esotropic eyes. So gross unilateral or bilateral defocus during development in kittens has been shown to produce changes in spatial resolution of the geniculate cells.

Reduced spatial resolution was also confirmed in kittens after deprivation from patterned vision by Maffei and Fiorentini [1976a]. When lateral geniculate nucleus cell amblyopia was present in kittens with strabismus or atropinisation, the degree of amblyopia and 'shrinkage' of lateral geniculate nucleus cells was correlated with the degree of loss of binocularity among the cells of the visual cortex [Tremain & Ikeda, 1982]. Monkeys, on the other hand, do not show abnormal spatial resolution of lateral geniculate nucleus cells after complete and prolonged uniocular deprivation of pattern vision. This suggests that monkeys might differ in this respect from kittens [Blakemore, 1979].

d) Summary:

The lateral geniculate nucleus appears to be affected more severely by visual deprivation than the retina.

While little or no biochemical effect occurred, the physiological changes were more marked. These were essentially concerned with the loss or reduction of spatial resolution of the geniculate cells in the deprived laminae. This has especially occurred in kittens reared with artificial strabismus or ametropia, and primarily affected the central retina subserved by the X- or sustained geniculate cells.

By far the most marked changes are anatomical. Between 25-40% neuronal cell loss is reported after monocular deprivation, the monocular segment appeared to be spared of such cell loss. Furthermore, cell loss is much less marked after binocular deprivation.

The differential cell loss between deprived and non-deprived laminae and relative minimal cell loss after binocular, as compared to monocular deprivation, might be a reflection of cell competition. Cell competition was proved to occur, but deprivation factors per se appear to be operative as well. In addition to this reported cell loss, the dendritic spines of the geniculate cells appear to be markedly affected by visual deprivation indicating loss of cell communication.

4. Visual Cortex

a) Biochemical effects

1) Proteins and Nucleic Acids Synthesis and Turnover

The visual cortex in rats showed no changes after dark-rearing [De Bold et al, 1967] or lid-suture [Maraini et al, 1967]. On the other hand, an increase in the RNA levels was described in monkeys after exposure to flickering light [Singh & Talwar, 1969] and in rats and chicks on light stimulation after a period of dark rearing [Apple et al, 1967; De Bold et al, 1967; Dewar & Reading, 1970].

Levay [1977] found that polysomes were lacking in the visual cortex of pattern deprived kittens examined by the electron microscope. This might reflect a deficit in the synthesis of axonally transported proteins.

2) Tissue Metabolism After monocular deprivation the kitten's visual cortex showed a reduction in the cytochrome oxidase activity [Wong-Riley, 1979]. This was located in the form of alternating columns reflecting the distribution of dominance columns.

3) Neurotransmitters No changes were found in rats after light deprivation [Maletta & Timiras, 1967, 1968]. But an increase in the acetylcholinesterase activity was described in rats after enriched visual

experience [Bennett et al, 1964]. In addition, the loss of cortical binocularity which occurs after monocular visual deprivation could be preserved by treating kittens with 6-hydroxydopamine (6-O HDA) [Kasamatsu & Pettigrew, 1979].

b. Histological

In contrast to the well-marked histological changes in the lateral geniculate nucleus, minimal or no changes were described in the visual cortex. Changes described could be classified into those affecting cell-communication involving the dendritic pattern and/or synaptic vesicles and those affecting the neuronal cells themselves. These occurred either after dark-rearing or monocular and binocular deprivation.

Dark-rearing Reduced number, length, branching or distribution of dendrites or their spines were described in different animals, e.g. kittens showed a decrease in the length and dendritic branching patterns in layer IV of the visual cortex [Coleman & Riesen, 1968]. Rabbits showed deformed dendritic spines [Globus & Scheibel, 1967] and mice had loss of dendritic spines [Valverde, 1967, 1971; Ruiz-Marcos & Valverde, 1969; Valverde & Ruiz-Marcos, 1970]. In this last animal these changes were produced by shorter

periods of dark-rearing (1-2 months) but showed partial normalisation after 4 months of dark-rearing [Gyllensten et al, 1965].

A reduction in the number of synaptic vesicles occurred in dark-reared kittens [Gary & Pettigrew, 1974] and rabbits [Vrensen & de Groot, 1974].

Cellular changes occurred in dark-reared mice, reflected as a decrease in the nuclear size and the amount of internuclear material in layers II-IV [Gyllensten, 1959]. Swindale [1981] was unable to detect ocular dominance columns in the visual cortex of dark-reared kittens; he concluded that visual experience is necessary for their proper formation. These changes described were contrasted with the dark-reared monkeys. These animals showed no changes in their visual cortex [Chow, 1955].

Monocular and binocular deprivation The visual cortex in cats and dogs raised with bilateral lid suture showed smaller cells in Golgi preparations. In addition, these cells had fewer processes than normal. These findings were confirmed by Cragg [1975b], who reported some 30% decrease in the synaptic density, particularly in layer IV and V after bilateral deprivation in kittens. Others failed to show any changes in the kitten's visual cortex [Mitra, 1958; Wiesel &

Hubel, 1963b, 1965b].

Callosal neurons (neurons which send their axons through the corpus callosum) in the visual cortex were dramatically decreased in number and had a narrower region of distribution after binocular deprivation in kittens [Innocenti & Frost, 1980]. This probably reflects the disturbance of binocularity in such animals.

More marked changes were described after monocular lid suture. Thorpe & Blakemore [1975] found that, after monocular deprivation in kittens, the axons from the deprived laminae of the lateral geniculate nucleus have less extensive distribution of the visual cortical cells.

The monkey's visual cortex appeared normal with Nissl's stain after monocular visual deprivation. But other histological methods showed marked changes in the relative sizes of the ocular dominance stripes in layer IVc with shrinkage of stripes receiving input from the deprived eye and corresponding expansion of those receiving from the normal eye. These changes were much more severe when closure was done at 2 weeks of age rather than later, but the cell body size and packing density appeared normal in the shrunken stripes [Hubel et al, 1977; Blakemore et al, 1978; Levay

et al, 1980]. Similar changes were described in kittens [Movshon, 1976a; Movshon & Dürsteller, 1977]. On the other hand changes that occurred after visual deprivation in monkeys were absent after artificial esotropia [von Noorden, 1973b].

Other authors studied cortical changes after lid suture in rats [Fifkova, 1968, 1970; Fifkova & Hassler, 1969; Rothblat & Schwartz, 1979], and squirrels [Guillery & Kaas, 1974b]. After unilateral lid suture there was a decrease in cortical thickness which is most pronounced in layers II-IV, with a decrease in the cell density on the side of the deprived eye.

In general, different authors studied different changes, in the visual cortex following visual deprivation; e.g. cell density (Gyllensten et al, 1965; Fifkova & Hassler, 1969; Boas et al, 1969]; synaptic density [Cragg, 1967, 1972, 1975a,b; Fifkova, 1970, 1974; Vrensen & de Groot, 1974]; density of dendritic spines [Fifkova, 1968; Valverde, 1967, 1971; Globus & Scheibel, 1967; Ruiz-Marcos & Valverde, 1969; Szentagothai & Hamori, 1969; Valverde & Ruiz-Marcos, 1970; Parnavelas et al, 1973; Rothblat & Schwartz, 1979]; synaptic vesicle density [Vrensen & deGroot, 1974; Garey & Pettigrew, 1974] and dendritic branching patterns [Globus & Scheibel, 1967; Coleman & Riesen, 1968; West & Greenough, 1972; Sadlack, 1972;

Greenough & Volkmar, 1973; Spencer & Coleman, 1974]. There were some obvious disagreements between published statements, and there are likely to be important differences between species studied and methods used, suggesting a multitude of factors that influence cortical development.

In general, the anatomical changes in the visual cortex, though not marked, reflect the loss of function experienced after visual deprivation. These changes were manifested by absence of cell communication evident as abnormalities in the dendritic tree and the synaptic junctions. These channels of communications are under-developed, atrophied or not formed, following reduction of inflow of sensory information. Absence of visual stimulation might not totally suppress the development of communication channels in the visual cortex, some development still occurs in the absence of function, but probably never reaches normal levels.

In addition, it appears that competition seen at the geniculate level is at least partially operative on the cortical level. This is reflected in the changes in the sizes of ocular dominance columns, resulting in shrinking of those supplying the deprived eye and a parallel expansion of those serving the viewing eye.

c) Physiology

It was not until the elegant work of Wiesel and Hubel on the neurophysiology of the visual cortex and the effects of visual deprivation [1962, 1963, 1965, 1970] that substantial progress in the field was achieved. They won the Nobel prize for 1981 for their work. The visual cortex is the most extensively studied part of the visual pathways in normal and visually deprived animals.

Monocular deprivation Wiesel and Hubel discovered that visual deprivation during infancy has prolonged and permanent effects on the cat's visual cortex. In the normal kitten 4/5th of the striate cortex cells are driven binocularly [Hubel & Wiesel, 1962] (Fig.4). When pattern vision was excluded from the eye during development, the ability of that eye to activate cortical cells was severely reduced [Wiesel & Hubel, 1963b, 1965b; Ganz et al, 1968] the binocular mechanism was disturbed and most of the cortical cells that respond to stimulation could be driven only by the normal eye. There was loss of synaptic input from the deprived eye to the cells of the visual cortex, in addition to changes in ocular dominance. Few of the striate cortex cells can be driven only by the deprived eye and virtually none of these have normal receptive field

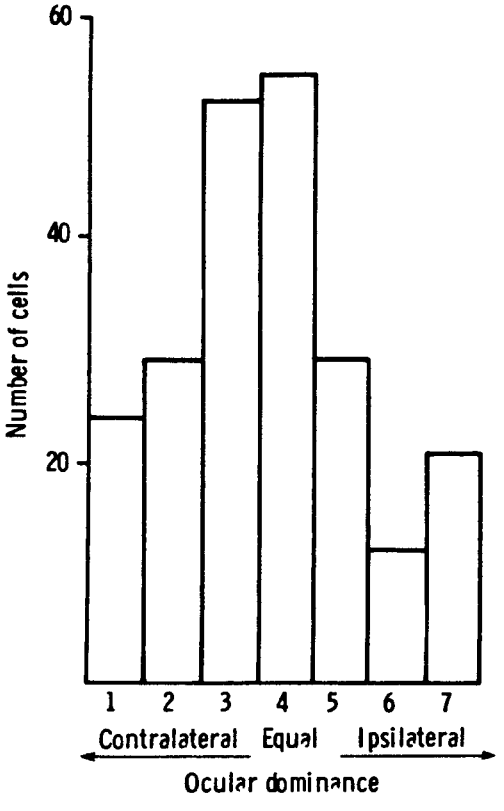



Fig. 4 Ocular-dominance distribution recorded from striate cortex of adult cats. Cells of group 1 were driven only by the contralateral eye; for cells of group 2 there was marked dominance of the contralateral eye, for group 3, slight dominance. For cells in group 4 there was no obvious difference between the two eyes. In group 5 the ipsilateral eye dominated slightly, in group 6, markedly; and in group 7 the cells were driven only by the ipsilateral eye [Hubel & Wiesel, 1962].

characteristics. A few cells did not respond to either eye and few had binocular input [Wiesel & Hubel, 1963b; Hubel & Wiesel, 1970; Blakemore & van Sluyters, 1974; Movshon & Blakemore, 1974; Olson & Freeman, 1975; Kratz et al, 1976] (Fig. 5). This

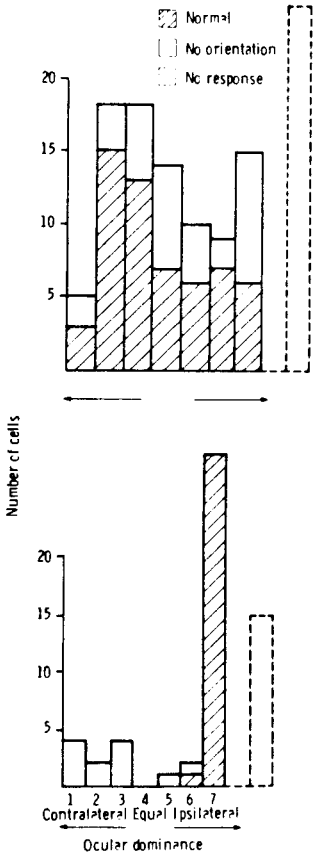



Fig. 5 a) Ocular dominance distribution of cortical cells recorded from binocularly deprived kittens [Wiesel & Hubel, 1965a].
b) Ocular dominance distribution of cells recorded in the visual cortex of monocularly deprived kittens. The animals were 8-14 weeks old and all had monocular lid suture [Wiesel & Hubel, 1965a].

inexcitability of cortical cells after monocular deprivation even for electrical stimulation of the optic nerve of the deprived eye [Blakemore & Hillman, 1977], can be interpreted in terms of withdrawal from the cortical synapses of the afferent axons of deprived geniculate neurons. This effect of binocularity is also extended to the associated visual cortical areas

(areas 18 and 19), which are even more severely affected than the primary visual cortex [Leventhal & Hirsch, 1983; Hirsch & Leventhal, 1983].

In monkeys, visual deprivation in the new-born resulted, as in kittens, in a marked shift in ocular dominance and non-responsiveness to stimulation of the deprived eye [Wiesel & Hubel, 1971; Baker et al, 1974; Crawford et al, 1975; Blakemore et al, 1978; von Noorden & Crawford, 1978a].

Rabbits seemed to be almost totally uninfluenced by their early visual deprivation. There was a marginal effect of monocular deprivation on ocular dominance in the binocular segment [van Sluyters & Stewart, 1974]. The receptive field characteristics of the cortical cells in deprived eye of rabbits can be affected by abnormal visual experience [Chow & Spear, 1974; Grobstein & Chow, 1975].

Binocular deprivation Both dark-rearing and bilateral lid-suture lead to relatively less marked changes in the activity of cortical cells than monocular lid-suture.

In kittens both lead to breakdown of binocularity,

but most cells, continue to respond to either eye. This effect on binocularity is variable. While some authors reported a decrease in the proportion of the binocularly driven cells [Kratz & Spear, 1976], others found the effect on binocularity to be small, or even undetectable [Wiesel & Hubel, 1965a; Pettigrew, 1974; Blakemore & van Sluyters, 1975; Leventhal & Hirsch, 1977], especially after short periods of binocular lid-suture (Fig.5).

While many cells responded normally with normal receptive field properties, there were many cells that responded non-specifically, lacking orientation or directional properties and many were still completely unresponsive [Wiesel & Hubel, 1965a; Pettigrew, 1974; Blakemore & van Sluyters, 1974, 1975; Imbert & Buisseret, 1975].

In dark-reared kittens, most visual cortical cells were binocularly activated and had non-specific receptive field properties. This is contrasted with prolonged lid-suture, with a high incidence of unresponsive cells and cells with unmappable receptive fields, and a low proportion of binocularly responsive cells [Wiesel & Hubel, 1965a; Singer & Tretter, 1976; Kratz & Spear, 1976; Leventhal & Hirsch, 1977; Mower et al, 1981]. In addition, binocular lid-suture produced permanent developmental effects on cortical physiology,

whereas dark-rearing leaves the cortex in a state which can be modified by subsequent visual experience.

Binocular deprivation in monkeys also resulted in large numbers of unresponsive neurons and severe reduction in proportion of binocular units [Wiesel & Hubel, 1974; Crawford et al, 1975]. Many of the remaining binocular cells had abnormal properties of receptive fields. In general, monkeys appeared to be more susceptible to binocular deprivation than cats [Kratz & Spear, 1976; Wiesel & Hubel, 1974].

In rabbits after binocular deprivation, the cells of the visual cortex did not exhibit response selectivity and most aspects of cortical function would develop eventually in animals deprived of vision [Grobstein & Chow, 1975].

Alternate occlusion After alternate occlusion in kittens there was a sharp reduction in the binocular activated neurons and there was a failure of development of binocular connections. This only occurred when alternate occlusion began before 12 weeks of age. The cells of the visual cortex continued to respond normally, but were driven monocularly [Hubel & Wiesel, 1965; Blake et al, 1974b; Blake & Hirsch, 1975; Blakemore, 1976; Presson & Gordon, 1979].

Binocular competition In contrast to lateral geniculate nucleus, many cells in the monocular portion of the visual cortex serving the deprived eye did not have normal receptive fields, but it was less seriously affected than the binocular portion [Sherman et al, 1974; Guillery & Kaas, 1974b, Wilson & Sherman, 1977]. Since the monocular segment was affected by visual deprivation it followed that binocular competition was not the only factor in the cortical development, but it played some role, since the binocular portion was more severely affected than the monocular portion after monocular deprivation. In addition, the effects of binocular deprivation in which the binocular competition was not operative, were much less severe [Wiesel & Hubel, 1965a; Kratz & Spear, 1976]. Complex cells at least in the monocular segment appeared to be more seriously affected by the deprivation than simple cells. Binocular competition for the synaptic space between the axons from the eyes [Wiesel & Hubel, 1965a; Sherman et al, 1974] may lead, in some cases, to additional synapses for the non-deprived eye which might give the cell unusual or abnormal receptive field properties; hence deprivation also appeared to affect the central connections related to the non-deprived eye.

So it appeared that deprivation had its effect in two main ways, a direct effect, which is passive or related to failure of development, in which relatively mild morphological changes occurred in the retina lateral geniculate nucleus, but may be more extensive modifications in the cortex, especially the upper layers: and a competitive effect in which no changes occurred at the retina, a drastic effect on the lateral geniculate nucleus cell growth and an altered balance of geniculate inputs in the visual cortex leading to an abnormal ocular dominance.

Selective visual experience More specific experimental procedures to answer how and to what extent the brain can respond to specific changes in the visual input were done by rearing kittens in a "striped environment" of vertical or horizontal orientation [Hirsch & Spinelli, 1970; Blakemore & Cooper, 1970; Blakemore & Mitchell, 1973; Blakemore & van Sluyters, 1974a; Leventhal & Hirsch, 1975; Blasdel et al 1977; Hirsch & Leventhal, 1977; Stryker et al, 1978;]. Most cortical neurons responded selectively to elongated stimuli with orientation at or near the viewed axis.

This method of rearing is essentially different from other methods of deprivation. It provides the

animal with static, fixed and repetitive environment. It provides further evidence of the effect of early experience on the development of the visual cortex.

Artificial strabismus Artificial strabismus produced in experimental animals resulted in drastic alterations in the physiology of the visual cortex. Kittens with artificial divergent strabismus (Hubel & Wiesel, 1965; Blakemore & van Sluyters, 1974a; Ikeda & Tremain, 1977; van Sluyters & Levitt, 1979] had a sharp decline in their normal binocularity and the cells of the visual cortex came to be influenced by one eye or the other, but not both (Figs 6 & 7). This was the result of lack of synergy between the inputs from the two eyes. There was no significant shift in ocular dominance or amblyopia because of the ability of the animal to fixate with either eye alternatively, similar to many cases of extropia in humans. Kittens reared with artifical esotropia lost their binocularity [Ikeda & Tremain, 1977; Blakemore & Eggers, 1977], but in addition, there was amblyopia and shift in ocular dominance in favour of the fixing eye (Fig. 7). (See also Yinon et al, [1975]).

Kittens with artificial strabismus did not always lose their cortical binocularity if they were reared exclusively in an environment of repetitive stripes all

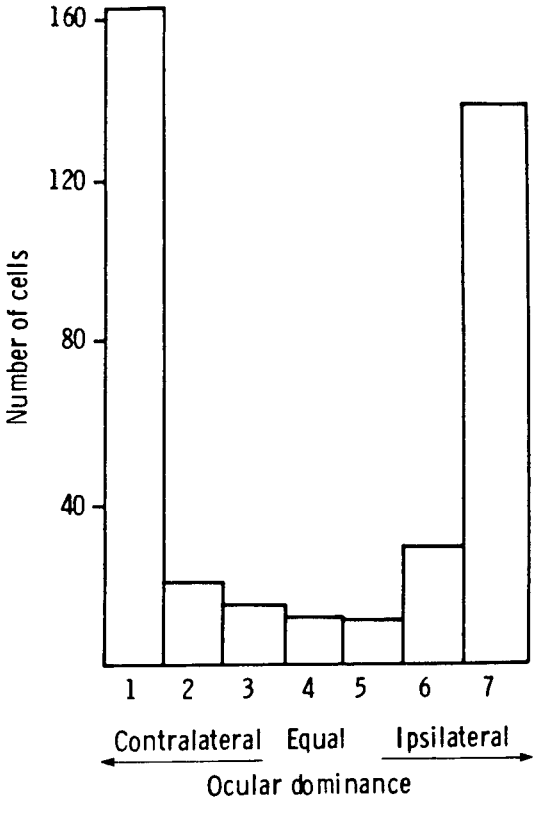



Figure 6 Ocular dominance distribution of cells recorded from kittens with divergent strabismus [Hubel & Wiesel, 1965].

of the same orientation, resulting in the same kind of pattern inputs from both eyes [Blakemore &van Sluyters, 1974a; Blakemore, 1976]. This illustrated that the maintenance of normal synaptic connections seemed not only to depend on the amount of incoming impulse activity, but also on the similarity between the inputs from each eye. These findings were contradicted by von Noorden

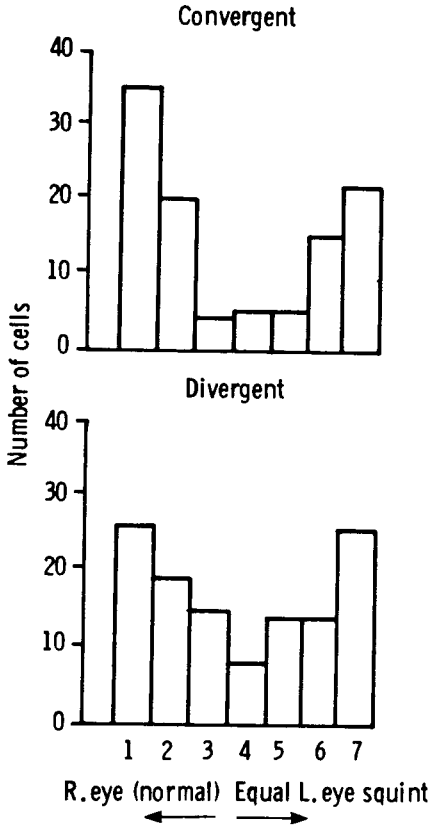



Fig. 7 Comparison of cortical cell responses in kittens with convergent and divergent squint [Ikeda & Tremain, 1977].

& Crawford [1981a] who failed to confirm in strabismic monkeys that binocularly responding cortical neurons can be preserved by exposing the animals to a non-conflicting repetitive visual environment.

Von Noorden [1973b; Barker et al, [1974], and Crawford & von Noorden [1979a] studied monkeys with artificial strabismus and found similar results. There were shifts in cortical dominance in esotropia.

In exotropia there was an equal number of cells driven by each eye, very few binocularly activated neurons and the number of unresponsive neurons was higher than normal, but those driven by the deviated eye had normal receptive field properties.

Immobilization of the one eye, surgically, in kittens produced similar loss of binocularity. Adult cats, after immobilization of one eye, also showed a decrease in the proportion of the binocular units in the cortex, and the receptive fields for the immobilized eye were sometimes abnormal [Fiorentini & Maffei, 1974; Buchtel et al, 1975; Maffei & Fiorentini, 1976b] indicating a possible role of extraocular receptors in maintaining cortical binocularity.

Infant monkeys reared wearing dissociating prisms had similar effects as in squint. The loss of binocularity in the cortex was proportional to the duration of prism wear [Crawford & van Noorden, 1979b, 1980]. Kittens reared wearing prisms had similar findings [Shlaer, 1971; van Sluyters & Levitt, 1979]; this also occurred after rotation of one eye [Blakemore, et al, 1975; Yinon, 1975]. There was a decrease in the binocularity of cortical cells, but the animal had good visumotor coordination when using the rotated eye.

Artifical Ametropia Artifical anisometropia with atropine [Ikeda & Tremain, 1978a] led to loss of cortical binocularity and shift of ocular dominance away from the atropinised eye towards the normal eye; this was much weaker than eyelid suture or strabismus. When instilling atropine in both eyes there was no disturbance in binocularity.

Kittens raised with high minus lenses in front of one eye (-8 to -12D), had effects much like those of brief monocular occlusion. Forty-three per cent of all units excited by stimulation of the deprived eye, 13% were monocularly driven by that eye [Blakemore & Eggers, 1977]. Also cortical cells subserving the deprived eye showed lower contrast sensitivity in kittens wearing high-power lens before one eye [Eggers & Blakemore 1978]. Kittens raised wearing high cylindrical lenses had an induced artificial astigmatism similar to astigmatism in humans [Freeman & Pettigrew, 1973; Cynader & Mitchell, 1977]. This resulted in one clear meridian, while the perpendicular meridian was out of focus. The result was slight but obvious bias in the proportion of neurons favouring the orientation that was originally in clear focus on the retina [Freeman & Pettigrew, 1973; Freeman, 1977]. From that it was obvious that the development of the visual cortex depended not only upon the ability of

either eye to see, but also upon the variety of visual stimuli that are available to the good eye to see [Diamond, 1967; Rosenzweig et al, 1969]. Loss of cortical input from the deprived eye also depended on patterned images in that eye and not just reduced illumination [Blakemore, 1976].

Visual Evoked Potential Dark-rearing was reported to produce longer, or variable, visual evoked potential latencies in young rats [Callison & Spencer, 1968], and rabbits [Fourment & Scherrer, 1961; Scherrer & Fourment, 1964].

Lid-suture also produced longer latencies in the cortex ipsilateral to the deprived eye in infant rats [Yinon & Auerbach, 1973]. Other authors reported absent or reduced visual evoked responses in kittens after lid suture [Glass, 1973; Ganz & Haffner, 1974; Jones & Berkley, 1977; Shapley & So, 1980]. These changes were normalised after a time of light environment or reverse closure in cats and rabbits after dark rearing [Scherrer & Fourment, 1964; Glass, 1973].

d) Summary:

Visual deprivation produces marked effects on the visual cortex. While little or subtle biochemical effects were reported, more marked histological effects occurred. But by far the most marked changes are

physiological.

The histological changes can either affect cell-communication by affecting the dendritic tree and the synaptic junction; or, still more markedly, affect the ocular dominance columns characterised by shrinkage of those serving the deprived eye and expansion of those connected to the viewing eye.

The physiological effects of visual deprivation involve changes in the binocularity and/or the response characteristic of single cortical neurons. Binocularity is drastically affected in conditions which affect binocular co-operation as is monocular occlusion, alternate occlusion, strabismus and anisometropia. On the other hand, inactivity, loss of selectivity or abnormal receptive field characteristics more commonly occur with dark-rearing and binocular deprivation.

Finally, it could be added that the present evidence supports the competitive mechanisms rather than disuse, as the prime factors in the production of the changes observed after monocular deprivation, though deprivation <u>per se</u>, has some additional effects, especially obvious on dark-rearing or binocular deprivation.

5. Superior Colliculus

Few studies analysed the biochemical or histological effects of visual deprivation on the superior colliculus. On the other hand, the physiological effects are more widely covered.

a) Biochemical

Maletta and Timiras [1967, 1968] studied the biochemical effects of visual deprivation in rats. These authors demonstrated a decrease in the neurotransmitter activity after dark-rearing and a decrease in the protein synthesis after lid-suture. On the other hand, Iida and Sheibler [1968] found no effects on glycoslysis in rats after dark-rearing.

b) Histological

Dark-rearing produced no histological changes in the monkey's superior collicular [Chow, 1955]. This is contrasted with Gyllensten et al [1965], who found a 10% decrease in the volume of internuclear material in dark-reared mice.

c) Physiological

Superior colliculus in kittens and monkeys probably plays a role in the control of visual orientation and following responses, because collicular cells are extremely sensitive to stimulus movement, [Apter, 1946;

Sprague & Meikle, 1965; Straschill & Rieger, 1973; Kurtz & Butter, 1980]. The superior colliculus regulates reflex conjugate eye movements. Each point on the superior colliculus is found to regulate movement of the two eyes to a particular part of the visual field. Its charted map for control of localized eye movement compares well with that charted for the projection of the visual field on the colliculus. Each point stimulated determines the eye position with reference to head or body [Apter, 1946]. Stimulation of collicular cells produced shifts in gaze and eye movements, depending on the site of stimulation [Guitton et al, 1980]. In monkeys, impairment in shifting gaze to eccentric stimuli occurred after superior collicular lesions [Kurtz & Butter, 1980].

Following ablation of the visual cortex in cats almost no collicular cells were binocularly driven, as compared to about 75% of cells in the normal animal. Normally, most retinal input to the colliculus is from the contralateral eye and presumably most collicular cells are binocular cells, this occurred only because they receive input from binocularly driven cortical cells [Rosenquist & Palmer, 1971].

After raising kittens with one eye sutured the effect on the colliculus mirrored the effect on the

cortex. Almost all cells in both colliculi are driven only by the normal eye. In addition, units influenced by the deprived eye lack directional selectivity. These effects are limited to the binocular segment of superior colliculus, since the monocular segment has normal physiological properties. [Wickelgren & Sterling, 1969a,b; Hoffmann & Sherman, 1974]. This lack of responsiveness to the deprived eye could result from post synaptic inhibition of superior collicular neurons by corticotectal projections which carry information from the normal eye. Two weeks following cortical removal there was dramatic reversal of ocular dominance. Most cells in the colliculus contralateral to the deprived eye were driven exclusively by that eye, whereas before they had responded only to the stimulation of the normal eye [Sterling & Wickelgren, 1970; Wickelgren & Sterling, 1969a,b; Berman & Sterling, 1974].

After binocular suture in kittens, the receptive fields were very similar to collicular receptive fields in decorticated animals. Almost all cells were driven only by the contralateral eye and only 12% were directionally selective as compared to 75% in the normal [Sterling & Wickelgren, 1970]. Any method decreasing cortical input to the colliculus increases the influence of the retinal input.

After artificial squint, the results were rather ambiguous. Fifty to eighty per cent of cells were binocularly driven. The type of muscle surgery had no striking effect on the number of directionally selective cells or the distribution of preferred directions [Wickelgren 1972; Gordon & Gummow, 1975]. But in time, the cells that were binocularly driven in the colliculus ipsilateral to the squinting eye were less and this colliculus became to be overwhelmingly dominated by this normal eye. There was no change in the colliculus contralateral to the squinting eye, i.e. it remained binocularly driven.

So it appeared that visual experience was necessary for normal collicular development. Visual deprivation retarded the development of directional selectivity, motion sensitivity binocularly activated cells [Hoffmann & Sherman, 1974, 1975]. In addition, monocular and binocular deprivation primarily affected the Y-pathway to the superior colliculus. This appeared to reflect the absence of Y-cells from the lateral geniculate nucleus, and only the slow-conducting W-cell afferent projections to the colliculus could be demonstrated.

d) Summary:

The effects of visual deprivation on the superior colliculus are mainly physiological. These mirror the effects on the visual cortex.

Monocular deprivation in kittens produced shifts in collicular dominance in favour of the non-deprived eye. In addition units still influenced by the deprived eye lacked directional selectivity. On the other hand, binocular deprivation resulted in a marked loss of binocularity with few cells developing directional selectivity.

This lack of responsiveness to the deprived eye appears to result from inhibitory influences on the superior collicular neurons by the cortico-tectal projections which carry information from the normal eye. Removal of the visual cortex resulted in dramatic regain of control by the deprived eye over the contralateral superior colliculus, whereas before they responded exclusively to stimulation of the normal eye.

## 6. Other Effects

### a) Effects on visual behaviour

One of the most prominent features of visual deprivation is amblyopia. Young animals appeared behaviourally blind when using the deprived eye or eyes.

Dark-reared infant monkeys demonstrated poor visual acuity [Riesen, 1950; Chow et al, 1957] with retarded ability to learn visual discrimination. Riesen [1950] concluded that stimulation by visual patterns is essential to normal visual development. In addition, the development of visual discrimination is a matter of maturity as well as learning. Later, other authors [Regal et al, 1976] demonstrated better visual acuity in such animals, using preferential looking, with the lack of performance occurring on the qualitative tests, suggesting that dark-rearing may interfere more with visual and visuo-motor responsiveness than acuity per se.

Dark-reared rabbits also had behavioural deficits [Goodman, 1932]. This was supported by van Hof [1971], who found decreased orientative discrimination in light-deprived rabbits.

After monocular deprivation, kittens [Dews & Wiesel, 1970; Chow & Stewart, 1972; Mitchell et al,

1977] and monkeys [Berger & Meier, 1968; von Noorden et al, 1970a; von Noorden, 1973a] appeared behaviourally blind when first forced to employ the deprived eye. This poor vision in the deprived eye might persist and recovery was suppressed by the action of the normal eye. The greater the competitive disadvantage an eye is placed at during development, by monocular deprivation, the greater the acuity (sensory) deficits. These deficits appear to be more a result of competition than of the effects of deprivation per se [Smith, 1981].

Deprivation for the first 4-6 weeks in kittens resulted in the permanent effect of only lowering the visual acuity. If deprivation extended to the first 16 weeks, the animal showed no indication of visual guidance of paw placement or of pattern discrimination.

Similarly, binocularly deprived kittens [Dews & Weisel, 1970; Wiesel & Hubel, 1965a; Sherman, 1972a; Smith et al, 1980a] appeared behaviourally blind on binocular viewing, the effects were less drastic than might be expected from the knowledge of the effect of monocular occlusion; this is perhaps due to lack of competition between the two eyes. The same findings occurred in bilaterally deprived monkeys [Hyvarinen & Hyvarinen, 1982]. Infant monkeys deprived of patterned vision had low visual acuity when first tested,

but improved with visual experience [Riesen et al, 1964]. Longer periods of binocular deprivation resulted in divergent squint [Sherman, 1972a].

Esotropia induced early in kittens [Ikeda & Wright, 1972; Jacobson & Ikeda, 1979] and monkeys [von Noorden & Dowling, 1970; von Noorden, 1973a; Baker et al, 1974; Kiopres & Boothe, 1980] produced poor vision and amblyopia in the affected eye. In monkeys amblyopia started to occur 4 weeks after the onset of esotropia. In exotropia, on the other hand, if the animal adopted the strategy of alternate fixation, there was no amblyopia in the squinting eye, a situation sometimes occurring in human strabismus. If it is not associated with alternating fixation it can lead to amblyopia in the deviating eye [Ikeda & Tremain, 1977; Grünau & Singer, 1980].

These changes appeared to occur within a definite period. They occurred only if the animal was deprived in the first 2 - 3 months in cats and monkeys. Deprivation at 4 months of age or later produced no effect. [Dews & Wiesel, 1970; von Noorden & Dowling, 1970; von Noorden, 1973a; von Noorden et al, 1970a].

Ikeda and co-workers [Ikeda & Wright, 1976; Ikeda & Jacobson, 1977a; Ikeda & Tremain, 1978b,c; Ikeda et al, 1978; Jacobson & Ikeda, 1979] studied amblyopia after

artificial esotropia in kittens. They concluded that amblyopia in such animals is due to loss of spatial resolution power of the sustained (X) geniculate cell type; these cells are fed from the area centralis of the squinting eye (Fig. 8). The degree of this amblyopia

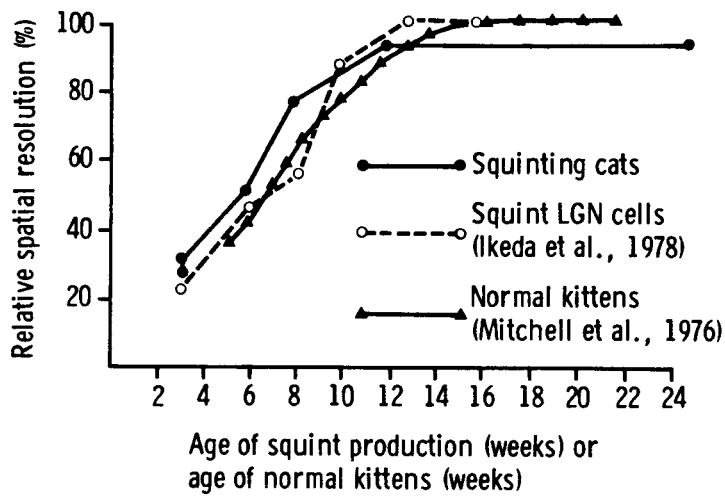



Fig. 8 Visual acuity of adult cat with squint produced at different ages compared to that of lateral geniculate nucleus sustained cells and that of normal kittens [Jacobson & Ikeda, 1979].

correlated well with the degree of cell "shrinkage" of the lateral geniculate nucleus and loss of the binocularity in the visual cortex [Tremain & Ikeda, 1982]. They concluded that the strabismic amblyopia in kittens occurs prior to the visual cortex, i.e. in the retina or lateral geniculate nucleus. Thibos & Levick [1982] showed no loss in spatial resolution occurring at the

level of the retinal ganglion cells in kittens after astigmatic rearing.

Anisometropia in kittens produced by wearing spherical [Blakemore & Eggers, 1977] or cylindrical lenses [Thibos & Levick, 1982] in front of one eye, or by administering atropine in one eye [Ikeda & Tremain, 1978a] resulted in amblyopia in the affected eye. In the case of atropine, this is also associated with reduction in the spatial resolving power of the cells in the lateral geniculate nucleus driven by the atropinised eye. Similarly, amblyopia was demonstrated in monkeys reared anisometropically by the administration of atropine in one eye [Boothe et al, 1982].

b) Effects on Spatial behaviour

Prior to the advances in the electrophysiological studies on the visual cortex of Wiesel and Hubel in the sixties, a large part of the physiological studies on visual deprivation dealt with its behavioural effects. Ganz [1975] and Riesen and Zilbert [1975] had compiled a good summary on such effects.

After dark-rearing in early post-natal weeks, kittens showed retarded visual abilities [Held & Hein, 1963; Ganz & Fitch, 1968]. These effects also occurred in chimpanzees [Riesen, 1947, 1950] and

monkeys [Fantz, 1965]. Such animals showed no visual placement [Riesen & Aarons, 1959; Walk & Gibson, 1961; Wiesel & Hubel, 1963b, 1965b; Wilson & Riesen, 1966], but developed visual placing after a few hours-weeks in a light environment [Ganz & Fitch, 1968; Kalil, 1978]. Poor visually guided behaviour and depth discrimination also occurred in rabbits [Volokhov & Shiljagina, 1972]; rats [Nealey & Riley, 1963; Heller, 1968]; and chicks [Spalding, 1873; Fantz, 1957].

Kittens raised with both eyelids sutured did not avoid obstacles successfully, [Walk & Gibson, 1961; Wiesel & Hubel, 1965a,b;]. This was also true for monkeys [Fantz, 1965; Wilson & Riesen, 1966]. Kittens which had binocular pattern deprivation also showed poor visually guided behaviour, slow locomotion and abnormal gait [Chow & Stewart, 1972; Ganz & Fitch, 1968; Wiesel & Hubel, 1965a,b; Walk & Gibson, 1961]. In addition, such animals failed to blink rapidly to approaching objects when first tested [Walk & Gibson, 1961].

Area 7 contains neurons which respond to various types of visual stimuli related to stimulus movement in addition to discharges triggered by eye movements. The lack of visual orientation behaviour which was observed in monkeys and cats after dark-rearing or binocular deprivation might fit the nearly total lack

of function in association area 7; hence, there was a great reduction in the proportion of cell groups activated by visual stimulation as a consequence of binocular deprivation [Hyvärinen, 1982]. Binocular deprivation has its greatest effect on the visual aspect of integration of visual and somatic inputs needed for orientation in the surroundings and in the immediate extra personal space, which is the role of the association cortex. Recovery from early deprivation in area 7 appeared to be very poor in the monkeys, even after 2 years of visual experience. This author stressed the importance of early detection and correction of visual defects to avoid permanent changes in the neural mechanisms.

After monocular deprivation, kittens when tested with the deprived eye bumped into obstacles and walked hesitantly [Riesen et al, 1953; Riesen & Mellinger, 1956; Wiesel & Hubel, 1963b, 1965b; Ganz & Fitch, 1968; Dews & Wiesel, 1970; Rizzolatti & Tradardi, 1971]. Monocularly deprived cats had very few cells remaining in their visual cortex which are highly selective to motion and contour [Wiesel & Hubel, 1963b, 1965a,b; Ganz et al, 1968] which might reflect their poor spatial behaviour. Similar results were found in kittens with squint on using the affected eye [Ikeda &

Wright, 1972].

Monocularly deprived kittens showed no binocular depth discrimination if the deprived eye was not opened by 30 days of age. Deprivation lasting to 35 days or more completely eliminated the binocular superiority, with no signs of recovery. If deprivation started after 4 months of age there was no effect on depth perception [Timney, 1983].

Some authors argued for the presence of an innate basis for "visual cliff" depth perception in rats [Lashley & Russell, 1934; Walk et al, 1957, 1965; Walk & Gibson, 1961; Nealy & Edwards, 1960]. But visual experience proved to be necessary for this type of depth perception in kittens [Walk & Gibson, 1961; Held & Hein, 1963] and monkeys [Walk & Gibson, 1961; Fantz, 1965; Wilson & Riesen, 1966].

Visual deprivation might cause visuo-motor coordination deficiencies [Riesen, 1965a] or it may induce a form discrimination deficit independent of such coordination deficiencies. In monkeys it appears that experience and learning have their main effects on behavioural processes other than the reception and discrimination of patterned stimulation [Fantz, 1965]. Held & Bauer [1967] described infant monkeys who lacked experience of visual guidance of arm movements and who were unable to use their hands appropriately for a few

weeks after being allowed to use visual guidance. Their reaction to the arm when first seeing it was as though it were a foreign object that they started to become familiar with. Thus it appears that experience of eye-hand coordination is necessary for the perfection of this function. On the whole visual experiments had demonstrated that rats, cats and monkeys, and probably man, all had an innate competence to perform comparatively simple behavioural orientations in space. The absence of normal visual-motor experiences could induce a suppression or extinction of orientation behaviour that was innately provided for. Conversely, normal visual-motor experience sustained and increased the precision of the basic network for such visual motor response competence.

c) Other visual effects

Dark-rearing in kittens was reported to produce cylotorsion, divergence and enhanced pupillary reactions. These effects were transient and later returned to normal (Cynader, 1979).

Dark-reared monkeys showed loss of blink reflex with absent fixation or following movement. The first visual following movements were not smooth, but a series of jerky refixations. In addition, reduced optokinetic nystagmus, spontaneous nystagmus and optic

disc pallor were reocrded [Riesen, 1950, 1958; Riesen et al, 1964].

Neonatal lid-suture, monocular or binocular, was reported to produce myopia and/or an increase in the axial length of the deprived eye in kittens [Gollender et al, 1979; Kirby et al, 1982], monkeys [Wiesel & Raviola, 1977; Raviola & Wiesel, 1978; von Noorden & Crawford, 1978b], or tree shrew [Sherman et al, 1977]. These changes were also reported after optically induced anisometropia in kittens [Smith et al, 1980b].

Meyers & McCleary [1964] showed the presence of interocular transfer from an experienced to a deprived eye in kittens. But other authors did not demonstrate its presence, or were inconsistent in such cases [Ganz & Fitch, 1968; Ganz & Haffner, 1974].

Ikeda & Jacobson [1977b] demonstrated that cats reared with convergent squint had a significant reduction in the extent of the visual field in the squinting eyes. This was located mainly in the nasal field, but in some cases it extended into the temporal field as well.

d) Summary:

Poor visual acuity is one of the main effects of visual deprivation. It occurrs to a varying degree

after all forms of visual deprivation: dark-rearing, monocular and binocular deprivation and induced strabismus and anisometropia. It is most severe in cases of monocular deprivation, This added a competitive element beside the effects of visual deprivation per se. Pure effects of visual deprivation are best seen in dark-rearing or binocular deprivation, where visual acuity is less affected. The main effect in this case is on the visuo-motor behaviour due to lack of visual monitoring on hand and body movements.

Amblyopia, or poor visual acuity appears to occur, at least in strabismic and anisometropic amblyopia, at the level of the lateral geniculate nucleus. This is associated with loss of spatial resolution power of the cells subserving area centralis of the deprived eye.

The effects on visuo-motor co-ordination involved retarded visual abilities, absence of visual placement and poor guided behaviour and depth discrimination. This appeared worse on binocular deprivation.

Such behavioural defects could be explained by the relative absence of highly selective motion and contour cortical cells in the primary visual cortex subserving the deprived eye, especially after monocular deprivation, and the great reduction in the proportion of cell groups in area 7 which respond to stimulus movement. This occurs especially after binocular depri-

vation.

The present general consensus is that experience is necessary for visual motor co-ordination perfection. The absence of normal visual-motor experiences could induce suppression or extinction of orientation behaviour that are innately provided for. Conversely, normal visual experience sustains and increases the precision of the basic network for such visual motor response competence.

## IV. THE SENSITIVE PERIOD

Animals reacted differently to visual deprivation, not only according to the type of occlusion, the part of the visual pathways involved and species, but also according to the age of deprivation. Deprivation at an early age in the post-natal life produced much more drastic effects than at a later age, while adult animals showed no effects, even after prolonged periods of deprivation. This period of heightened sensitivity is called the sensitive period.

### A. VISUAL DEPRIVATION IN YOUNG ANIMALS

#### 1) Kittens

Hubel & Wisel [1970] defined in some detail the sensitive period for the effects of unilateral eye closure in kittens. It began near the start of the 4th week and remained high until some time between 6 and 8 weeks. This sensitivity declined and disappeared finally around the end of the third month. After 4 months, kittens seemed insensitive even to longer periods of monocular deprivation (Table 1).

Sensitivity is greatest (critical period) between 4 and 5 weeks of life, where only 3 to 4 days of occlusion produced the same drastic effects as weeks of occlusion started two weeks later. In one month old kittens, clear changes in the cortical dominance could be detected after about one day of deprivation and marked after 2.5 days [Olson &

**TABLE 1**

**The sensitive age in kittens and monkeys as indicated by studies on the visual cortex**

(Assaf, 1983)

| | Type of occlusion | Age of high sensitivity | Upper end | Authors |
|---|---|---|---|---|
| Kittens | Monocular | 4-8 weeks | End of 3rd month | Hubel & Wiesel [1970] |
| | Monocular | 5th week | 14 weeks | Blakemore & van Sluyters [1974] |
| | Monocular | Before 4-7 weeks | End of 4th month | Olson & Freeman [1980] |
| | Monocular | - | 6-8 months | Cynader et al [1980] |
| | Alternate | 5th week | 12 weeks | Presson & Gordon [1979] |
| Monkeys | Monocular | First 6-8 weeks | - | Wiesel & Hubel [1971] |
| | Monocular | - | $15\frac{1}{2}$ weeks | Von Noorden & Crawford [1978a] |
| | Monocular | First 9 weeks | 3-4 months | Blakemore et al [1978] |
| | Monocular | - | 10 weeks | Hubel [1979]; Levay et al [1980] |

Freeman, 1975; Movshon & Dürsteler, 1977]. In fact very brief monocular deprivation (6 to 20 hours) during this period of heightened sensitivity had been reported to be sufficient to produce modifications in the physiology of the visual cortex [Pettigrew & Garey, 1974; Peck & Blakemore, 1975; Freeman, 1979].

The sensitive period for the anatomical changes in the lateral geniculate nucleus likewise started near the 4th week [Hubel & Wiesel, 1970; Giffen & Mitchell, 1978], 3rd week [Cragg et al, 1976] or even before the 3rd week of life

[Garey et al, 1973]. During the period of high sensitivity (critical period), which extended up to 6-8 weeks, changes in the geniculate cell-size could be produced by only a few days of monocular occlusion. The sensitive period declined to around the end of the 3rd month (Table 2).

**TABLE 2**

**The sensitive age in kittens and monkeys as indicated by studies on the morphology of the lateral geniculate nucleus**

(Assaf, 1983)

| | Type of occlusion | Age of high sensitivity | Upper end | Authors |
|---|---|---|---|---|
| Kittens | Monocular | 4-8 weeks | End of 3rd month | Hubel & Wiesel [1970] |
| | Monocular | Starts before 3 weeks | 4 months | Garey et al [1973] |
| | Monocular | 3-6 weeks | 14 weeks | Cragg et al [1976] |
| | Monocular | 4-6 weeks | 4 months | Giffen & Mitchell [1978] |
| Monkeys | Monocular | - | 3rd month | Headon & Powell [1973] |
| | Monocular | - | 8 weeks | von Noorden & Crawford [1978a] |
| | Monocular | first 6 weeks | 11 weeks | Vital-Durand et al [1978] |

Kittens with monocular deprivation for the first 4-6 weeks showed a permanent defect in vision (Table 3). When closure extended through the first 7 weeks, the visual acuity was further lowered, but the animal still showed good visual guidance of paw placement. Further extension of deprivation through the first 16 weeks led to a still more

severe defect; such animals showed no indication of visual guidance of paw placement or of pattern discrimination [Dews & Wiesel, 1970]. Grading of visual defects with age and length of deprivation, was generally parallelled by a change in proportion of cortical cells driven by stimulation of the deprived eye.

**TABLE 3**

**The sensitive age in kittens and monkeys as indicated by studies on vision and visual behaviour**

(Assaf, 1983)

| | Type of occlusion/ visual deprivation | Age of high sensitivity | Upper end | Authors |
|---|---|---|---|---|
| Kittens | Monocular | 4-8 weeks | end of 3rd month | Dews & Wiesel [1970]; Hubel & Wiesel [1970] |
| | Artificial Strabismus (prism induced) | - | 8th week | Shlaer [1971] |
| | Artificial Strabismus | 3-7 weeks | 12th week | Yinon [1976]; Ikeda & Jacobson [1977a]; Ikeda & Tremain [1978c]; Jacobson & Ikeda [1979] |
| | Monocular | - | 6-8 months | Cynader et al [1980] |
| | Monocular | ? - 8 weeks | 14th week | Wilkinson [1980] |
| | Monocular | ? - 7 weeks | 4 months | Timney [1983] |
| Monkeys | Monocular | - | 3rd month | von Noorden et al [1970a] von Noorden [1973a] |
| | Monocular | - | 8th week | von Noorden & Crawford [1978a] |

More recently it is thought that the sensitive period for monocular occlusion might extend beyond the first 3 months of post-natal life. Olson & Freeman [1980] found that it started earlier than 4 weeks, remained high through

the 48 post-natal day and subsided gradually, probably persisting at least through the end of the 4th month of age. This is supported by Cynader et al [1980] who reported that the sensitive period extends to an even longer period - it lasted until 6-8 months of age.

For alternate monocular occlusion a decrease in the proportion of binocular cells in the visual cortex if it was started before 12 weeks of age was shown to occur over 10 days of alternate occlusion in kittens [Presson & Gordon, 1979].

The period of susceptibility for convergent squint extended from 3-12 weeks of age [Yinon, 1976; Ikeda & Jacobson, 1977a; Ikeda & Tremain, 1978c; Jacobson & Ikeda, 1979]. Strabismus after 3-4 months of age had no effect on binocularity or visual acuity (Fig. 8, p.81). The degree of disturbance of spatial vision in squinting cats was most related to the age of onset of squint, i.e. the earlier the onset, the more profound the amblyopia. When compared to the data on visual acuity in kittens, the pattern of results suggests that convergent squint can arrest the development of spatial vision.

Kittens wearing prisms during the sensitive period could adjust if misalignment was within certain limits. Until the kittens were about 8 weeks old, their behaviour did not alter when prisms were accidentally dislodged. After this period, loss of prism glasses caused an immediate

cessation of activity, cowering and "freezing" [Shlaer, 1971].

The period during which the superior colliculus in kittens is sensitive to the effects of monocular deprivation is probably the same as that of visual cortex. Lund and Lund [1972a,b] found that experience dependent changes for development of synaptic contacts in the superior colliculus for patterned visual stimulation occurred before 30 days and not beyond 40 days. This was thought to be the critical period during which patterned visual stimulation was necessary if synaptogenesis was to be completed in a normal fashion.

2. Monkeys

Monkeys also have a sensitive period for monocular occlusion. Its onset and duration was very similar to those of cats; it started near birth and ended around the 12th week of life. Different authors reported periods around these figures, i.e. first 3 months [von Noorden et al, 1970a; von Noorden, 1973a], high susceptibility during the first 6 weeks, low susceptibility extending to $1\frac{1}{2}$-2 years [Wiesel & Hubel, 1971], first 3-4 months [Blakemore et al, 1978], first 10 weeks [Hubel, 1979]. There was a rapid decline in sensitivity at the end of the 2nd month, although some residual effects of deprivation might still be detectable as late as one year [Wiesel,

1982] (Table 1).

Visual deprivation by monocular lid-suture at the age of 4 weeks (during the critical period) for less than 2 weeks produced a marked shift in ocular dominance to the non-deprived eye [Crawford et al, 1975; Blakemore et al, 1978;]. Strongly binocular cells were preferentially affected. Such short closures during this period also resulted in severe loss of visual acuity, monkeys being more vulnerable to the effects of occlusion than cats, with no physiological or behavioural recovery appearing to take place.

LeVay et al [1980] showed that at 10 weeks, closure had only a mild effect on the size of the ocular dominant columns in layer IVc of the visual cortex. Closure at 7-14 months of age produced no effect. This late deprivation still caused a shift of ocular dominance in the upper cortical layers, but not as extreme as with earlier closures.

The sensitive period for the cellular changes in the lateral geniculate nucleus after monocular lid closure started after that for the changes in the ocular dominance and ended before it, to around the end of the 2nd month. But Headon & Powell [1973] found that it extended up to 3 months of age (Table 2).

All monkeys whose lid was sutured between birth and 9

weeks of age had developed poor vision, none recovered their visual acuity. When lid closure started at 12 weeks, this did not produce any permanent deficit (Table 3).

For strabismic amblyopia, the sensitive period appeared to be similar to that for the production of deprivation amblyopia. Amblyopia was absent in monkeys when made esotropic at 17 months of age [von Noorden & Dowling, 1970].

## B. VISUAL DEPRIVATION IN ADULT ANIMALS

As seen, the effects of visual deprivation can be produced in young animals during a period of heightened sensitivity. This sensitivity declines gradually where it becomes minimal or undetectable later in life.

Many authors deprived adult animals, but little or no effect was demonstrated. Burke & Hayhow [1968] reared adult animals in the dark for many years with no effect. Monocular occlusion for many months also produced no effect on the visual cortex, lateral geniculate nucleus or on the visual behaviour [Hubel & Wiesel, 1970; Dews & Wiesel, 1970; Chow & Stewart, 1972; Hoffmann & Cynader, 1977]. Alternate occlusion for 3 weeks produced no effect on the visual cortex of adult cat [Presson & Gordon, 1979]. In addition, no amblyopia was detected after strabismus produced in cats older than 13 weeks [Ikeda et al, 1978; Jacobson & Ikeda, 1979].

Adult monkeys also seem to be not affected by prolonged periods of deprivation [Wiesel, 1977; Blakemore et al, 1978; Vital-Durand et al, 1978; Levay et al, 1980]. In addition, no amblyopia occurred after strabismus in monkeys older than 15 months [von Noorden & Dowling, 1970].

## C. SUMMARY

The effects of visual deprivation in animals occur exclusively at a certain age, this is called the sensitive period. In kittens the sensitive period extends between 3-12 weeks of age, with the critical age extending between 4-6 weeks. The upper limit might extend to 6 months of age. In monkeys it exends from birth to 12 weeks of age, with the critical period occurring around the 4th week of age; though sensitivity could be detected up to one year of age. This is contrasted with adult animals, in both cats and monkeys, where no effect is demonstrated on prolonged visual deprivation.

## V. REVERSAL OF THE EFFECTS OF VISUAL DEPRIVATION

The non-deprived eye appears to gain an advantage, during the sensitive period, that is still present to some extent after deprivation had been discontinued, thereby tending to suppress the recovery of the re-opened eye.

Many studies have attempted to outline the sensitive period by attempting to reverse the effects of monocular deprivation either by simple opening of the deprived eye or by reverse suture of the good eye. Reversal of such effects indicates that the visual system is still plastic to allow such reversal.

Dark-rearing and bilateral lid-suture produces less severe deficits than monocular deprivation, likewise recovery is more likely. Recovery is most marked after dark-rearing [Cynader et al, 1976; Kalil, 1978; Cynader, 1979]. After bilateral lid-suture, recovery is sometimes fairly limited [Wiesel & Hubel, 1965b] or substantial [Chow & Stewart, 1972], with more recovery involving visual behaviour [Smith et al, 1980a].

Most studies of reversal dealt with monocular deprivation. These will be discussed in the following pages.

### A. KITTENS

Wiesel & Hubel [1965b] found that in all kittens deprived monocularly or binocularly during their early postnatal life had slight behavioural recovery during the first

3 months; but animals remained severely handicapped and never learned to move freely using visual cues. There was no morphological improvement in the lateral geniculate nucleus and few cells recovered in the visual cortex to be driven by the deprived eye. They concluded that the animal's capacity to recover from the effects of early monocular or binocular visual deprivation, whether measured in terms of behavioural, morphological or in single cell cortical physiology is severely limited, even for periods of recovery of over a year. In 1970 these authors reported only very limited recovery in cortical physiology, with no obvious recovery in lateral geniculate nucleus after a period of binocular severity extending up to 5 years following 3 months of monocular deprivation since birth. Closing the normal eye, though necessary for behavioural recovery, had no detectable effect on cortical physiology. The amount of possible recovery in the visual cortex was probably no greater if the period of eye closure was limited to 7 weeks, but after a 5 weeks closure period there was a definite enhancement of the recovery, even though it was far from complete [Hubel & Wiesel, 1970]. This was similar to the findings of Ganz and Fitch [1968], who reported poor behavioural recovery after monocular deprivation; though Ganz et al [1968] reported a considerable percentage (38.5%) of cortical cells driven by the initially deprived eye. Better behavioural recovery was reported after closure of

the good eye than occurred on simple binocular viewing, but this was not accompanied by an increase in the ability of the deprived eye to drive cortical cells [Dews & Wiesel, 1970].

Recently other authors reported better recovery than reported previously. Chow & Stewart [1972] demonstrated recovery after reverse closure in visual behaviour, lateral geniculate nucleus cell size and cortical physiology except for cortical dominance patterns. In addition, an extremely prolonged period of reverse suturing can lead to some recapture of the cortex by a deprived eye, even in adult cats. Mitchell et al [1977] and Olson & Freeman [1978] also reported significant recovery from the effects of early unilateral eye closure after a period of reverse closure. Behavioural recovery was nearly the same after binocular viewing or after reversal of deprivation. Physiological recovery was more pronounced after reverse closure than simple viewing, with significant recovery on binocular viewing alone. They concluded that there was considerable recovery of function, even with binocular viewing; thus the competitive effect of visual deprivation was not the only factor operative in the interrelation between the two eyes. Giffin and Mitchell [1978] also reported some recovery of patterned vision in all deprived animals after monocular lid-suture over a period of 2-3 months. The extent of this

recovery became progressively less as the period of deprivation was prolonged, although the acuity that was eventually attained by the reverse sutured animals was always slightly higher. The recovery observed after reverse suturing was reasonably well correlated with changes in the ocular dominance of the visual cortex under similar circumstances. They also postulated an additional non-competitive mechanism of recovery. On the other hand, adult cats showed no recovery from earlier effects of visual deprivation after binocular viewing or after up to 3 years of reversed closure [Hoffmann & Cynader, 1977].

1) Recovery of the cortical effects Blakemore and van Sluyters [1974], in an excellent article, showed the exact time course for physiological recovery after reversal in the monocularly deprived kittens (Fig. 9). Reverse suturing at 5 weeks caused complete switch in ocular dominance. Resuturing at 14 weeks, however, had almost no further effect on ocular dominance. Animals reverse-sutured at intermediate ages had cortical neurons strongly dominated by one eye or the other, but the animal never went through a stage of high binocularity. These cells were organised into clear columnar groups according to ocular dominance. Between 5 weeks and 4 months, there appeared to be a period of declining sensitivity to both the effects of

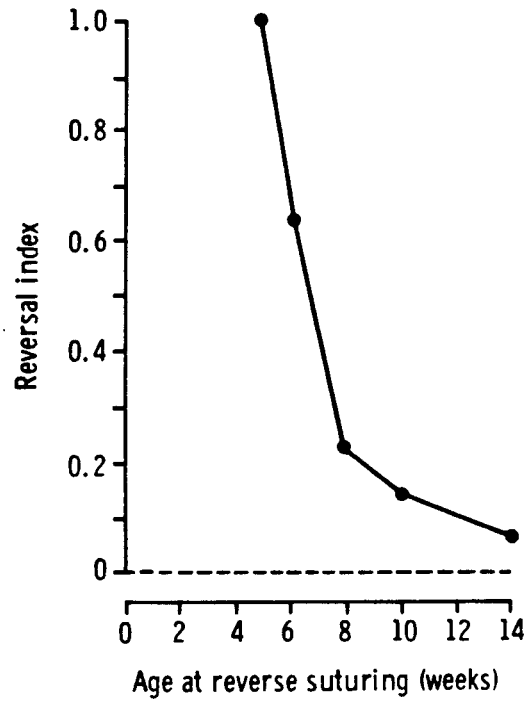



Fig. 9 Recovery according to age after reverse lid suture as measured by the reversal index in previously monocularly deprived kittens. The reversal index is the ratio of the number of neurons dominated by the more recently experienced right eye to the total number of visually responsive cells, and thus provides an indication of the degree to which the initially deprived eye recaptured cortical cells [Blakemore & van Sluyters, 1974].

an initial period of monocular deprivation and the reversal of those effects by reverse-suturing. They suggested this period to be a period of neuronal plasticity during which the afferent connections of cortical cells were utterly plastic; it might be a period of synaptic liability and not just a capacity for

selective degeneration [Blakemore, 1978].

Movshon [1976a] also studied the reversal of physiological effects of monocular deprivation on the kitten's visual cortex. Kittens had monocular deprivation for a period of 4-7 weeks of age. Reverse closure reversed cortical dominance, but had no effect on binocularity. This switch was most rapid following reverse-suturing at 4 weeks of age. Delaying the age of reverse-suturing reduced the rate and extent of cortical dominance reversal. There were also changes in the relative sizes of ocular dominance columns. The columns devoted to the initially deprived eye were very small in animals with brief periods of reverse-suture, but they were larger with longer periods of reverse-suturing. No kitten reverse-sutured at the age of 6-7 weeks showed complete reversal of deprivation effects. He suggested that the sensitive period for cortical binocular development consists of two phases. First, all cortical neurons may be modified by experience; secondly, an increasing number of cortical neurons become fixed in their properties, while some remain modifiable to a later date.

There is a general agreement that once cortical binocularity is lost it cannot be reversed. But Levitt & van Sluyters [1982] were able to reverse binocularity after a short period of optically-induced strabismus.

2) Lateral geniculate nucleus - Morphological recovery

Reversal of the morphological effects of monocular deprivation in the kitten's lateral geniculate nucleus was studied by Dürsteler et al [1976]. These authors monocularly deprived kittens until the age of between 5-14 weeks, after which they reverse-sutured such animals for a varying length of time. When reverse lid closure was done at the age of 8-14 weeks, the mean cell size was still smaller in the laminae connected to the initially deprived eye, but reverse suture at 5-6 weeks of age produced reversal of interlaminar size differences. Even within 3 days of reverse lid closure, most morphological effects of the initial lid-suture had been abolished, and they were fully reversed within 12 days. These results compared well with the physiological changes in the visual cortex of these and similarly reared animals (Fig. 10). These findings were supported by the findings of Cragg et al [1976], who also have demonstrated that the originally deprived cells in the lateral geniculate nucleus were able to recover their normal size if reverse suturing occurred at 3-6 weeks of age. However, no recovery occurred after 14 weeks of monocular closure since the first week after birth.

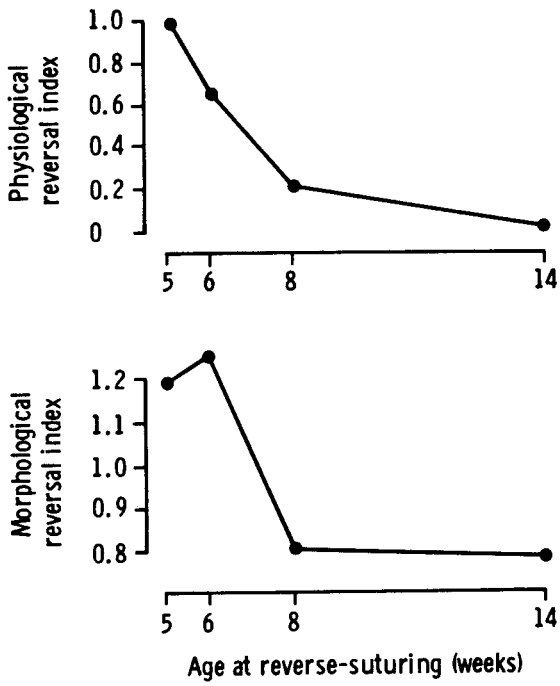



Fig. 10 Reversal of morphological effects on the lateral geniculate nucleus as related to the age of reverse-closure. This is compared well with the reversal of the physiological effects on the visual context [Dursteler et al, 1976].

3) Behavioural recovery In their work, Wiesel & Hubel [1965b] and Dews & Wiesel [1970] reported limited recovery of the visual function of deprived kittens after extended periods of monocular deprivation if done during the sensitive period, but shorter periods of deprivation caused a less marked effect, though equally permanent. The behavioural recovery observed in animals deprived monocularly to the age of 4-6 weeks

was excellent - the only residual effect was on lowering visual acuity. Better recovery was possible after reverse closure than simple viewing. Other authors reported better recovery, especially after reversed lid-suture [Chow & Stewart, 1972; Blakemore & van Sluyters, 1974; Mitchell et al, 1977; Giffin & Mitchell, 1978].

Movshon [1976b] deprived kittens until the age of up to 7 weeks, after which reversal lid-suture was performed. Following the opening of their initially deprived eye, all kittens appeared behaviourally blind when forced to use that eye, in agreement with previous findings. After a period of reverse-suture, performance when using the initially deprived eye had improved, while that through the initially open eye deteriorated. This reversal occurred most rapidly in kittens with reverse-suture at the age of 5 weeks, but less rapidly when this was delayed until 6-7 weeks of age. Most kittens showed gross abnormalities of interocular alignment and exhibited marked exotropia or esotropia. The results of changes in the visual behaviour correlated well with the changes seen in the cortical ocular dominance in the same animals.

Wilkinson [1980] studied monocular visual acuity reversal in kittens after reverse-suture. He found that sensitivity to reversal varies as a function of

age when the amount of visual experience is held constant. Sensitivity declined steadily throughout the critical period if reversal occurred on or before 57 days of age (8 weeks). The initially deprived eye was able to gain superiority over the initially exposed eye. By 14 weeks of age, the effects of reversal were negligible (Fig. 11).

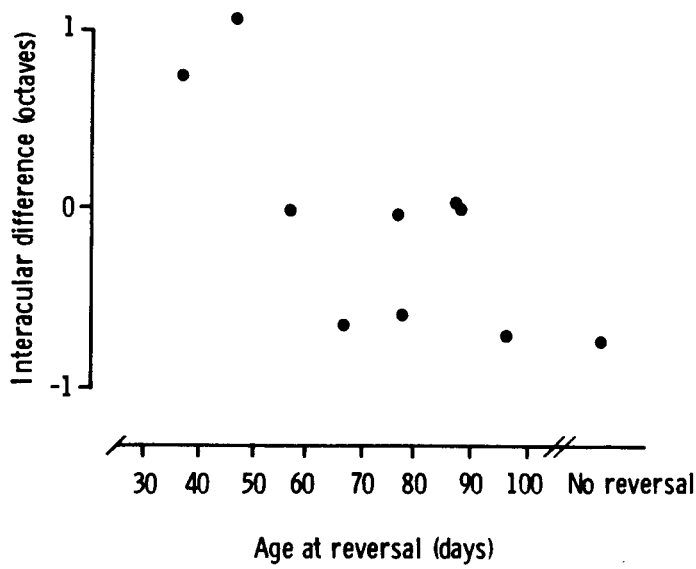



Fig. 11 Size of the interocular acuity difference in octaves plotted against reversal age. Each circle represents a cat. A positive interocular difference represents superior acuity in the initially deprived (reversal) eye, whereas a negative value indicates superior acuity in the initially exposed eye [Wilkinson, 1980).

## B. MONKEYS

Earlier studies again demonstrated no or limited recovery in the effects of visual deprivation if the animal was deprived within the sensitive period.

Little or no recovery occurred after monocular deprivation [von Noorden et al, 1970a; von Noorden & Crawford, 1978a], artificial strabismus [von Noorden & Dowling, 1970; Crawford & von Noorden, 1979a] or artificial anisometropia [Boothe et al, 1982]. Most recorded recovery occurred in the cortical dominance, none in the lateral geniculate nucleus cell-size and only partial recovery in vision after strabismus.

Later it became clear that there is more marked recovery from the effects of monocular deprivation if reverse monocular closure is performed within the sensitive period.

1) Reversal of cortical effects Monkeys deprived by monocular lid-suture within the sensitive period showed shrinkage of the ocular dominance columns subserving the deprived eye [Levay et al, 1980; Swindale et al, 1981]. Reverse-suture is associated with re-expansion of the stripes belonging to the originally deprived eye, if this is performed within the sensitive period.

Physiological recovery occurred also after reverse closure, whereby the originally deprived eye gained

dominance over the cortical cells, provided this was done before 9 weeks of age. Simple re-opening of the deprived eye produced no effect [Blakemore et al, 1978, 1981].

2) Reversal of morphological changes in the lateral geniculate nucleus In the lateral geniculate nucleus, the reversal of the cell size difference between the deprived and the non-deprived laminae can be achieved by reverse-suture. This can be achieved within 6 days of reverse-suture performed at the age of one month. No reversal occurred by the age of nine weeks. Simple re-opening of the closed eye has little or no effect on the lateral geniculate nucleus recovery. These morphological results in the lateral geniculate nucleus correlated closely with the changes in the width of ocular dominance "columns or stripes" in layer IVc of the visual cortex of such animals [Vital-Durand et al, 1978; Garey & Vital-Durand, 1981].

3) Visual recovery Contrasted with the recovery in cortical physiology and lateral geniculate nucleus cell size, no recovery occurred in the visual behaviour [Wiesel, 1977]. This is also confirmed by earlier studies.

## C. RECOVERY AFTER ENUCLEATION OF THE GOOD EYE

Some authors, rather than performing reverse lid-suture to assess the degree of recovery of the deprived eye, enucleated the experienced eye after early monocular deprivation, long after the sensitive period to determine whether the deprived eye retained any connection with the visual cortex. In kittens this resulted in a rapid increase in the proportion of cells that could be actively excited from the deprived eye in the visual cortex [Kratz et al, 1976; Blakemore & Hawken, 1982]. Up to 39% of neurons came to be driven by the deprived eye immediately after enucleation or soon after. There was no further increase in the number of responsive cortical cells over a period of more than a year.

These findings were supported by Spear [1977], who reported 34% of the striate cortex cells to be driven by the originally deprived eye following enucleation of the experienced eye after the sensitive period. This occurred within 20-30 hours. After that he found no further improvement for more than a year. Receptive fields were abnormal in directional and orientational selectivity. Visual experience after enucleation made no difference. On the other hand, Hoffmann and Cynader [1977] found a much lower yield of cortical units driven by the deprived eye and these were localized in small isolated clusters, but there was a recovery of Y-cells in the lateral geniculate nucleus

to normal proportion.

Recovery was also reported in the size of the lateral geniculate neurons after 14 weeks of deprivation, since before the eye opening, i.e. after the end of the sensitive period. This occurred after crushing of the optic nerve of the viewing eye [Cragg et al, 1976]. Recovery of the visual acuity of the deprived eye also occurred after the critical period when the retina of the open eye was removed [Hendrickson et al, 1977].

This fast recovery after removal of the experienced eye could be possibly caused by neuronal sprouting from the deprived eye axons in the lateral geniculate nucleus or visual cortex occurring in normal kittens [Hickey, 1975; Kalil, 1972, 1973], but this only occurred in kittens younger than 20 days of age. Another possible mechanism by which this improvement in cortical drive can occur is via release of inhibition by projections from the normal eye. It was possible that monocular deprivation resulted in tonic inhibitory imbalance, which ultimately resulted in suppression of the response to stimulation of the deprived eye [Kratz et al, 1976; Spear, 1977; Smith et al, 1978; Rauschecker & Singer, 1979]. The locus of inhibition would principally be in the striate cortex. It was possible that some inhibition could occur in the lateral geniculate nucleus contributing to the marked decrease in the number of cells in the deprived laminae which have a Y-type response

property [Sherman et al, 1972]; or it occurred by denervation hypersensitivity occurring in the lateral geniculate nucleus, or visual cortex hyperexcitability following enucleation [Fentress & Doty, 1971]. Others found little evidence of that [Kasamatsu & Adey, 1974; Kratz et al, 1976]. The first two were the most likely explanations.

## D. MECHANISM OF RECOVERY AFTER REVERSE DEPRIVATION

Many authors put forward different explanations for the actual cause of recovery of the deprived eye. Some stated it might be the result of a process of regeneration by an innate tendency for the growing fibres to return to the innervation sites they once occupied, or to which they were originally allocated [Mitchell et al, 1977]. Blakemore et al, [1978] suggested that the axons of the deprived afferent pathways might retain their cortical distribution, but simply had their post-synaptic influence suppressed. Reversed closure, if done within the sensitive period is associated with re-expansion of the formerly shrunken ocular dominance columns belonging to the deprived eye [Le Vay et al, 1980]. It was possible that small clusters of units driven exclusively by the deprived eye did survive in monocularly deprived but were more difficult to record [Stryker & Shatz, 1976]. Kratz et al [1976] stated that the normal eye held the deprived eye in check by tonic inhi-

bition but Blakemore and Hillman [1977] did not find any response from the deprived eye, at least not within minutes, when the viewing eye was blinded, so the effect might not be due to a change in the properties of individual cells that are normally dominated by the experienced eye, but be caused by the simple increased detectibility from the other surviving units dominated by the deprived eye, when the massive cortical activities originating in the normal eye became absent. There was chemical evidence to support the active inhibition theory [Duffy et al, 1976; Burchfiel & Duffy, 1981]. These authors reversed the activity of the cortical cells subserving the amblyopic eye after monocular deprivation by intravenous injection of bicuculline; this acts by reducing the inhibitory mechanisms mediated by Y-amino butyric acid (GABA), acting as a GABA-receptor blocker.

The improvement of function on simple binocular viewing might be incompatible with binocular competition, it might represent a recovery to the original form or level of damage. Genetic factors are presumably largely responsible for the basic pattern of geniculate terminals in the ocular dominance columns, since very young kittens and monkeys seem to possess columns that were qualitatively similar to adult animals, although perhaps were not fully formed [Hubel et al, 1977; Rakic, 1977]. In addition, reversal procedures by lid suture or enucleation of the experienced eye do not

extend the period in development during which cells in striate cortex can be modified by experience. Rather they may simply release those cells already receiving anatomical connections from the deprive eye from a tonic inhibition mediated by the experienced eye [Smith et al, 1978].

E) Summary:

Recovery from the histological, physiological and behavioural effects occurs after simple re-opening, but more strongly after reverse deprivation, provided this is done within the sensitive period. Little recovery is recorded in the monkey's visual behaviour and no recovery in cortical binocularity once lost, except, perhaps, at very early stages.

After enucleation of the good eye in monocularly deprived kittens, the deprived eye came to be driven approximately by 35-40% of the cells of the visual cortex; this occurred within a short period. It might indicate that the deprived eye does not lose its connections with the visual cortex, but these are kept in check by active inhibition by those belonging to the normal eye.

## VI. SUMMARY

In this chapter we have seen that young experimental animals, especially kittens and monkeys, possess a sensitive period during which the visual system is affected by visual deprivation. In kittens it extends between 3-12 weeks of life, and between 0-12 weeks of life in monkeys. This sensitive period coincides well with the period of post-natal anatomical growth and functional and physiological maturity, reflecting the importance of normal function for normal development.

The effects of visual deprivation occur at the behavioural, anatomical and physiological levels. The behavioural effects essentially manifest as poor vision and poor spatial behaviour. The anatomical effects affect primarily the cell size and/or cell communication channels. These changes most markedly involve the lateral geniculate nucleus. They also involve the visual cortex and the retina to a varying degree. The physiological effects occur mainly at the cortical level. Cortical binocularity and ocular dominance are most markedly affected. On the whole, these changes are more marked after monocular than binocular deprivation. This occurs possibly because, in monocular deprivation, the normal eye in a compensatory mechanism, takes over the function of the deprive eye, exaggerating the functional separation. This is not possible under conditions of binocular deprivation, where

only pure deprivation effects are operative. In addition, the visual cortex and lateral geniculate nucleus seem to be more susceptible to visual deprivation than lower centres, i.e. retina.

These effects are essentially reversible, especially after reverse deprivation, provided this is done early enough within the sensitive period. Reverse deprivation after the sensitive period produced little or no recovery. Nevertheless, the deprived eye does not lose its cortical connection in adult life. This is unmasked by enucleation of the good eye. This might represent a basic compensatory or plastic capacity of visual function.

# PART TWO

## EVIDENCE FOR THE PRESENCE OF A SENSITIVE PERIOD OF DEVELOPMENT FOR THE VISUAL SYSTEM IN HUMANS

- REVIEW -

"The nervous system shows two stages of development: an early period of intrinsic growth and self differentiation and a later period of growth that is dependent upon functional activity" [Roux, 1895].

## I. INTRODUCTION

From the previous chapters it is now established that animals, including monkeys and kittens, have a definite period in their post-natal life, during which the visual system is susceptible to alterations in visual experience. A few days of visual deprivation during the period of heightened sensitivity can produce a permanent or long-lasting effect on the structure and function of the visual system.

In man the situation is less clear. It has long been suspected, based on clinical experience, that a sensitive period exists, similar to that found in experimental animals. Hyvärinen [1982] quoted Locke's view in an essay concerning human understanding [1690] ("Suppose a man born blind, and now adult, and taught by his touch to distinguish between a cube and a sphere of the same metal. Now the blind man was made to see, would he be able at first sight, without touching them, tell the difference between them?"). Instances of this kind have occurred. Less than 100 cases have been documented in the literature. Studies of such congenitally blind emphasised the importance of early visual experience for vision and understanding spatial relations and active movements. The weight of evidence overwhelmingly supports the conclusion that the visual system is not innately, without visual experience, capable of extracting the meaning of visual signals.

Few investigators studied anatomical and biochemical effects of visual deprivation in early childhood Donaldson [1891] described the brain of a 60 year old man who lost his sight in the left eye at two years of age, but the right eye survived with very reduced vision until the age of 8 years. He was also a deaf mute. There was a difference between the two sides of the occipital cortex, the left being more atrophic. He said, "The conservation value for the nerve centres of even weak stimuli has long been recognised and it is but natural, therefore, that the occipital lobe chiefly concerned with the right eye should be better preserved than the other, whose development presumptively arrested earlier during the years most important for growth. The persistence of vision in the right eye, though in defective form, is still of great importance to the full development of the visual cortex. The disturbances in the cortex are probably to be looked upon much more due to an arrest of growth following the removal of normal stimulation than to a continuation of the degeneration into the hemispheres." In remarking on the changes in the auditory cortex of this brain, the same writer said, "The disturbance here is most probably due to early and long continued lack of normal excitation, for the cortical cells in the sensory area are peculiarly dependent for their proper development on the special sense with which they are associated". Hechest [1933] described the brain of 3 patients, 49, 52 and 62

years of age, who had corneal opacities since childhood. He found the optic nerve to be reduced by two-thirds and atrophy of the lateral geniculate body, but there were no changes in the visual cortex. Recordon & Griffitsh [1938] studied a 2 month old patient with congenital absence of both eyes and found no optic nerves, the lateral geniculate nucleus was absent, superior colliculus and the visual cortex seemed to be normal.

Clinical experience in ophthalmology, indicated that many ocular diseases occurring during infancy and childhood might interfere with normal functioning of the visual system, resulting in permanent amblyopia. These include form deprivation amblyopia which results from interference with the quality of visual image, e.g. congenital and traumatic cataracts, corneal opacities, lid swellings, etc. Strabismic and anisometropic amblyopia are also well known clinical entities occurring secondary to strabismus and anisometropia in childhood. Sometimes deprivation amblyopia can be prevented or reversed, at least in its early stages, by patching of the good eye, thus forcing the use of the "lazy" eye putting it at a functional advantage. Amblyopia secondary to occlusion therapy is known to occur after treatment for strabismic and other forms of amblyopia. It is also known to occur exclusively in the young. Analysis of these types of visual deprivation might throw some

light on the sensitive period in man, during which these conditions can lead to amblyopia.

It is known that the newborn human visual system is not fully developed at birth but will continue to develop, both anatomically and physiologically post-natally. This period of post-natal anatomical growth and physiological maturity will be correlated with the sensitive period derived from clinical experience.

Summary

The evidence for the sensitive period in man is derived from autopsy studies of the visual system in patients deprived of vision since their early childhood. But the main evidence is derived from clinical situations affecting children in their early years of life, preventing normal formation of the retinal image or binocular cooperation. This can lead to amblyopia which sometimes is associated with secondary strabismus. Analysis of the age at which amblyopia has been produced under different conditions and the age at which it could be reversed might help to outline the sensitive period for the visual system development in man when visual deprivation could still affect its function. This will be correlated with the period of post-natal anatomical and physiological growth of the visual system.

## II. GROWTH AND DEVELOPMENT OF THE VISUAL SYSTEM IN MAN

The newborn eye and visual systems are unlike those of the adult. Many structures are incomplete or under-developed and many physiological functions are still immature. These will continue to develop in a few months to a few years in the post-natal period [Hickey, 1977a; Gardiner, 1982]. A good summary of the visuo-sensory development of the child was compiled by Amigo [1972].

### A. ANATOMICAL DEVELOPMENT

#### 1. The Eye

The newborn eye is much smaller than that of the adult; it is only about threee-quarters of its size. Its axial length is 17.9mm and it is 1.5dioptre hypermetropic. The cornea and lens are strongly curved. The adult size of the cornea is not reached until between 1-2 years of life [Mann, 1931; Doggart, 1950; van Alphen, 1961]. The axial length of the eye reaches approximately 23mm at 3 years of age It reaches adult value of 24mm by 13-14 years of age [Larsen, 1971]. On the whole, dimensions almost equal to those of adults are reached by 3 years of age after a phase of rapid and extensive growth [Sorby et al, 1957, 1961].

The fovea is not fully developed until at least 6 months of age [Duke-Elder, 1973 {p.69}]. In addition, maturation of the macula is subject to a considerable individual difference; nevertheless, cell densities in the

macula approach those of the adult range at 2-2$\frac{1}{2}$ years of age [Streeten, 1969].

2. Visual pathways:

The optic nerve is incompletely myelinated at birth, its myelination is completed by 2 years of age [Magoon & Robb, 1981].

Hickey [1977a,b] examined 53 human autopsy brains ranging in age from newborn to 40 years. He found that the smaller parvocellular layer in the lateral geniculate nucleous (X-cells) reached adult size near the end of the first year and the larger magnocellular layer (Y-cells) require at least 24 months before reaching adult size. In all cases, geniculate cell growth in humans is either complete or nearing completion by the end of the second postnatal year.

Conel's [1939, 1941, 1947] studies of the development of cerebral cortex demonstrated that the sensory cortex, including the visual cortex, has less dendritic arborization and therefore fewer cellular interconnections at birth than primary motor cortex. The dendritic density increases in the sensory cortex with age and this precedes the increase in the sensory association area (Fig. 12).

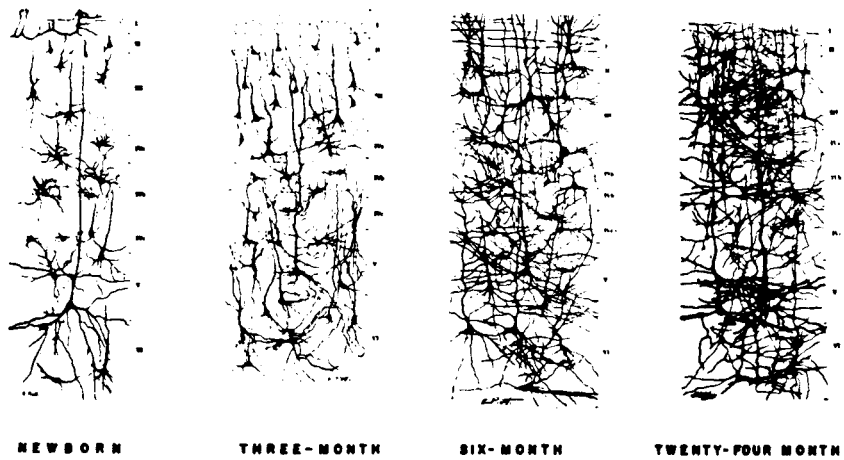



Fig. 12 Development of dendrites in the human visual cortex [Conel, 1939, 1941, 1947]. [After Mendelson & Ervin, 1962].

On the whole, connections of the peripheral organs with the occipital cortex and the fibre system which belongs thereto have been more or less completed by about the end of the second year [Keiner, 1951 {122}]. So it appears the visual system is anatomically mature by the age of 2 years [Haith, 1978].

3. Brain

The brain, of which the visual system is essentially both a part and its major sensory input, continues to grow over the first six years of life. The newborn child has a brain mass of 350gms; at one year it reaches 500gms. The brain grows rapidly in the first few years of life. It reaches 75% of adult weight by $2\frac{1}{2}$ years of age and 90% by 6

years of age [Rose, 1976; Sagan, 1977]. The typical adult brain weight is 1375gms. Dobbing & Sands [1970] illustrated two major periods of cellular multiplication in the human brain - one from 15-20 weeks of gestation and one which commences at 25 weeks of gestation. The second period probably ends in the second year of post-natal life.

## B. PHYSIOLOGICAL DEVELOPMENT

### 1. Visual acuity

The infant's visual acuity reaches adult value of 6/6 by six months of age [Fantz et al, 1962; Marg et al, 1976; Dobson & Teller, 1978]. Atkinson & Braddick [1982a] showed that acuity develops very rapidly over the first few months of life, but at 6 months is still clearly less than adult values. By 3-4 years acuity is 6/6 or better with grating targets and then approximates the adult value; i.e. acuity is effectively mature by the age of $3\frac{1}{2}$ years. But at five years of age 'crowding' effects (inability to discriminate symbols that are crowded together closely) may still impair performance on practical acuity tests more than for the adult. On the other hand, Teller [1981] found that acuity levels in human infants reached adult standard (resolving grating of about 30 cycles per degree, using preferential looking technique) at about 30 months of age (Fig. 13). The earlier view that 6/6 visual acuity or so is not achieved until 5-8 years of age was not only the result of inadequate testing techniques, but also a failure to distinguish between the post-natal development of the basic visual functions and the relatively slow development of visual learning, involved in object recognition and in visually guided behaviour [Ordy et al, 1965]. Thus acuity develops much earlier than behavioural discrimination.

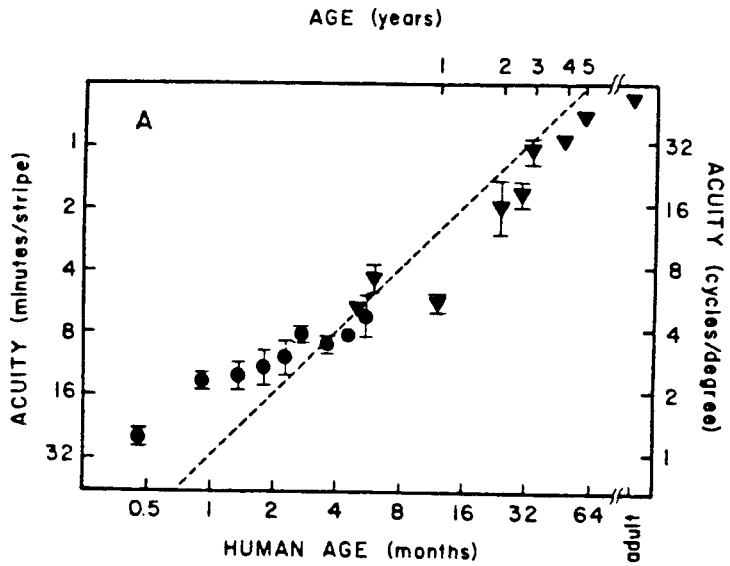



Fig. 13 Development of acuity in human infants. Acuity is plotted against age. The ordinates are logarithmically scaled, both in the number of minutes subtended by each black or white stripe of the acuity grating (left ordinates), and in the number of cycles of the grating per degree of visual angle (right ordinates). Age is also plotted logarithmically, in months for the human infants. Circles: PL techniques; Triangles: operant techniques. The error bars show ±1 standard error of the mean, with the number of subjects per group being 4 to 10 The dotted lines illustrate the mnemonic that acuity, in cycles per degree, is approximately equal to age in months. The acuity values given are the extrapolated cut-off frequencies of spatial contrast sensitivity functions measured at different ages. [Teller, 1981].

## 2. Development of binocularity and stereopsis

Stereopsis has been documented to be present as early as two months of age [Hyvärinen & Lindstedt, 1981], 3 months [Polak et al, 1964], $3\frac{1}{2}$-6 months [Fox et al, 1980] or four months [Held et al, 1980; Braddick & Atkinson, 1982]. But good stereoscopic acuity is not reached until about $3\text{-}5\frac{1}{2}$ years of age [Amigo, 1972]. This is supported by the findings of Romano et al [1975] who found that the lower limits of stereo acuity compatible with normal binocular

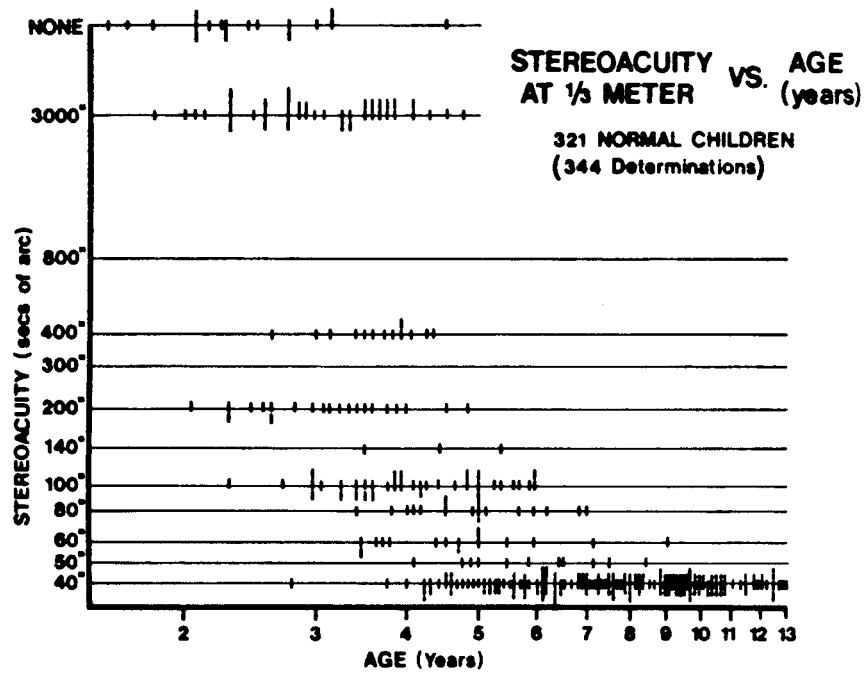



Fig. 14 Scattergram plot of Titmus Stereoacuity test scores for 321 children with normal binocular single vision by other factors. There is a gradual improvement in scores with advancing age until age 9, after which a normal score of 40 seconds of arc is consistently obtained. Marks not directly on a line indicate a score on the nearest line [Romano et al, 1975].

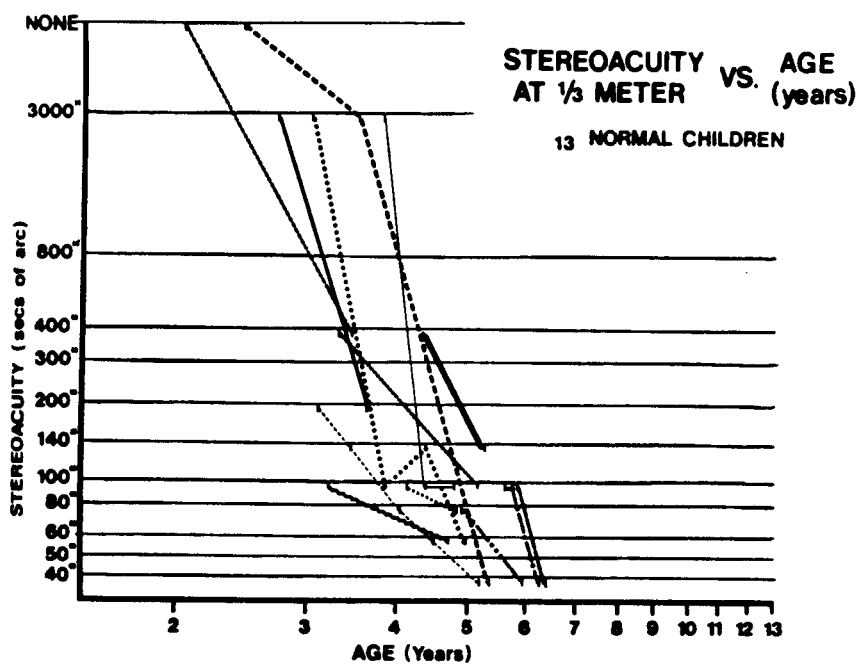



Fig. 15 Titmus Stereoacuity test scores on 13 children with normal binocular single vision by other factors, tested more than once at intervals of three months or more. These individual cases demonstrate the same type of gradual improvement with advancing age as the group as a whole in Figure 14. The slightly steeper slope is probably the result of experience or training from multiple testings [Romano et al, 1975]

single vision were first present at $3\frac{1}{2}$ years of age. The development of stereopsis is complete at 8 [Kitao, 1960] or 9 years of age [Sachsenweger & Junker, 1956; Romano et al, 1975] (Fig. 14).

Figures 14 and 15 represent the development of stereoacuity between $1\frac{1}{2}$-13 years of age. Few patients did not obtain 40" acuity after 7 years of age.

By six months of age, fusion reflexes are well developed, but the process of directing and linking the two eyes is normally complete at the age of about 18 months [Keiner, 1951 {204}]. This is supported by Jampolsky [1978], who concluded that the critical period for establishing bifoveal fixation and stereoscopsis ends at 18 months to 2 years.

3. Physiological development - Electrophysiological evidence

Visual evoked responses (VER) have been used as a reliable estimate for measuring visual acuity in infants [Dobson & Teller, 1978; Linksz, 1973]. They can also give valuable information on the development of vision in man [Harter & Suitt, 1970; Sokol & Jones, 1979]. In post-mortem Golgi preparations performed on premature infants, VER development was found to be correlated with the degree of dendritic formation in the visual cortex [Purpura, 1976]. Using the visual evoked response it is generally agreed that the visual system in humans undergoes rapid maturation in

the first year of life and the visual acuity approximates adult level by 24 months of age. In the same way the amplitude and wave-form of VER change to the adult configuration by 24 months of age [Arden & Barnard, 1979]. However, Sokol and Jones [1979] reported that minor changes in VER wave-form continued until the age of five to six years and there was little change after seven years (Fig. 16). Harter et al [1977], furthermore, found that the

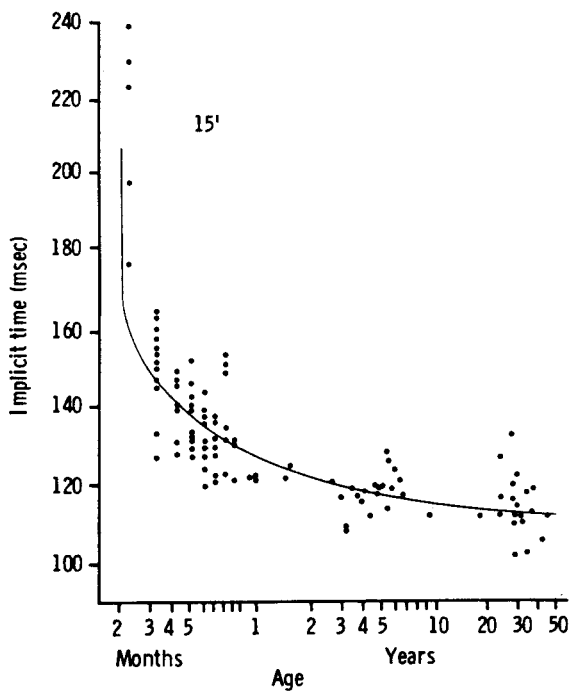



Fig. 16 Implicit time of $P_1$ component in the VER for 15' checks as a function of age from infancy to adulthood. The curve was fitted to the data by the method of least squares [Sokol & Jones, 1979].

latency of the first wave of the VER is not adult-like until 3 years of age when tested with fine check-patterns. Arden and Barnard [1979] using VER found that the plasticity of the visual system was retained in the age of 5-11 years.

Petrig et al [1981], on the other hand, found that the infant begins to produce stereoscopically evoked potentials at the age of 10 to 19 weeks, several weeks after showing the classical checker board evoked potentials. They suggested that the onset of cortical binocularity precedes stereopsis. This might indicate the beginning of the sensitive period for the development of cortical binocularity. This is supported by the findings of Braddick & Atkinson [1982] who, using VER, found evidence of cortical binocularity in almost every infant aged 3 months and in some younger infants.

Interocular transfer (IOT) of the tilt after effect was used to assess binocularity. It is highly correlated with stereopsis, which is a common clinical index of binocular function. By relating the degree of IOT of the tilt after effect to the date at which strabismus was first seen and corrected, the strabismus was found to have maximum effect on this measurement between one and three years of age and continues with exponentially decreasing strength until the age of eight years [Banks et al, 1975] (Fig. 17).
These authors suggested that immediate corrective surgery is not necessary to maintain cortical binocularity when the

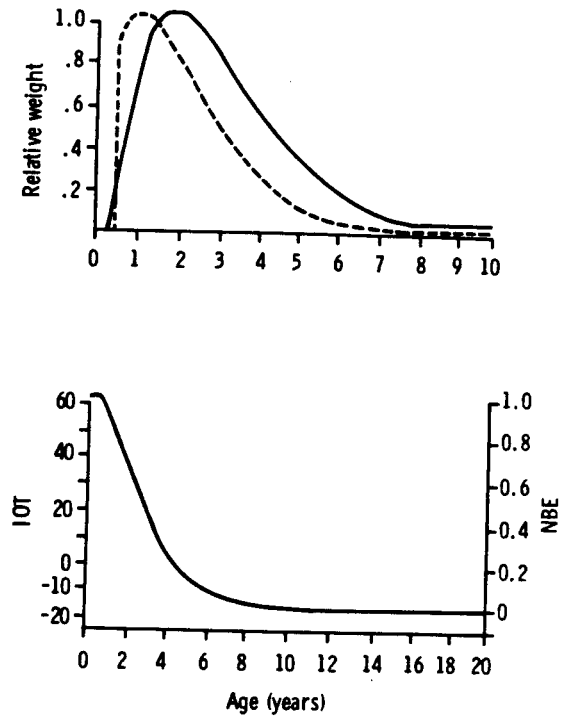



Fig. 17 Method for describing the sensitive period for the development of binocularity. (a) reflects the relative importance of abnormal binocular experience from birth to age 10 years. (b) point plot of the interocular transfer values as a function of the age at corrective surgery for each of 12 cases of congenital esotropia [Banks, Aslin & Leston, 1975].

(IOT = interocular transfer, NBE = normal binocular experience).

esotropia is of late onset, of four years and over. Also, by measuring IOT in children whose squint developed at different ages but was corrected by surgery, the end of the critical period for the development of binocular vision in humans was found to be about 2-2.6 years [Hohmann & Creutzfeldt, 1975] (Fig. 18).

Finally, it appears that individuals vary in the rate of maturation of visual functions and other sensory and somatic development with eventual development of normal capabilities [Mellor & Fielder, 1980; Illingworth, 1982; Hoyt et al, 1983].

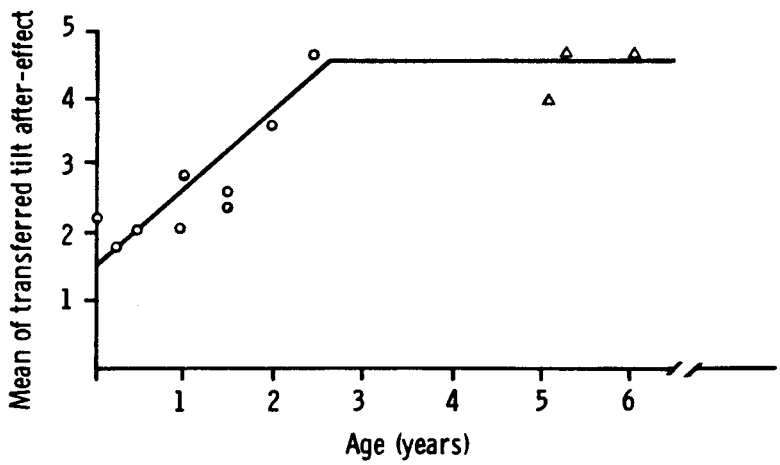



Fig. 18 Binocular transfer of tilt after-effect in operated strabismic children, whose squint developed at different ages [Hohmann & Creutzfeldt, 1975].

## 4. Milestones in the brain physiological development

The first two years of life are devoted to acquisition of many perceptual motor coordinations. Speech is a complex brain function. During the second year of life an average child is capable of imitating speech sounds and forming simple words, but not until he is about two years old, does he seem capable of sustaining true symbolic processes [Miller, 1962].

The critical age for learning speech is probably about the age of 1-2 years. A deaf child if identified before the age of 1 year can be prepared, by suitable auditory stimulation, to use his residual hearing better for learning speech at the age of 2 or 3 years than if he does not start being stimulated until the age of 2 or 3 years. And if a deaf child is left unattended until the age of 6-7 years, he can be taught to speak only with great care and difficulty [Hirsch, 1970]. In addition, a child starts to walk well between 18-24 months [Sheridan, 1973]. Thus it is apparent that during the first two years of life major milestones in development of brain function occur.

## C. SUMMARY

The human visual system is not fully developed at birth, either anatomically or physiologically. On the whole, the adult dimensions of the eye ball are not reached until 2-3 years of age, and the macula is matured by 2-$2\frac{1}{2}$ years of age.

The optic nerve is fully myelinated by 2 years of age. By this time the cell growth in the lateral geniculate body is complete and the second major period of cellular multiplication in the human brain is at its end.

Furthermore, channels of communication between cells, dendrites and synapses are not fully formed at birth but continue to develop until at least the first 2 years of

life. It may well continue to a later date, hence the brain as a whole, continues to grow when it reaches 90% of adult value by 6 years of age. Increases in the channels of communication might account for this growth. This might turn out to be the great variable, depending on information gained by learning and sensory experience.

The visual acuity, however, rapidly develops in the first 6 months of life. It is effectively mature by $3\frac{1}{2}$ years of age, but full sophistication is probably not achieved until 5-6 years of age. Fusional reflexes are present in the first few months, but are not complete until 18 months of age. Furthermore, though stereopsis is present early, good stereoscopic acuity is not reached until the age of $3\text{-}5\frac{1}{2}$ years and is maximal by the age of 8 years.

Electrodiagnostic tests also throw some light on the physiological development of the visual pathways and visual processes, e.g. visual evoked response development can be correlated with the degree of dendritic formation in the visual cortex. It is not adult in configuration until 2-3 years of age, though minor changes in configuration might continue to a later date. In addition, interocular transfer indicates that binocularity is affected greatly by the strabismus under 2-3 years of age, decreasing in its effect until the age of 8 years. Individual variation in the rate of growth and maturity must also be taken into account.

## III. EFFECTS OF VISUAL DEPRIVATION

Different aspects of visual deprivation are well studied in animals experimentally. In man the available evidence is derived mainly from clinical situations. Children affected by obstacles to their vision during early childhood developed amblyopia with or without secondary strabismus.

Amblyopia is Greek for "dullness of vision". It is defined clinically as unilateral or bilateral decrease of the visual acuity either by form deprivation or from abnormal binocular strabismus interaction or both, for which no organic cause can be detected by physical examination of the eye [von Noorden, 1978a; Van Balen, 1981], in other words purely functional disturbance of visual acuity. Physiologically, Ikeda [1980] has suggested, based on her findings from experimental animals, that amblyopia is a peripheral defect. This might be due to an arrest in the development of the sustained-X-cells function in the retina and lateral geniculate nucleus. These cells subserve the area centralis in the retina and are most adapted for fine spatial discrimination and high levels of visual acuity.

This developmental amblyopia may result from different aetiological factors. In this section I will review the clinical experience of many authors with such conditions emphasising the age at which amblyopia can be produced and the age at which it is reversible. The production of

amblyopia by conditions interfering with normal visual stimulation, unilateral or bilateral, is analogous to the monocular and binocular visual deprivations in animals produced experimentally. Moreover, reversal of amblyopia in man by therapy, mainly occlusion of the good eye, is essentially similar to the reversal of the effects of visual deprivation after reverse closure in experimental animals. Determination of the age at which amblyopia can be produced or reversed would outline the sensitive period in man as it has in experimental animals.

## A. STIMULUS DEPRIVATION AMBLYOPIA

### 1) Cataract

Cataracts in children have long been known to be associated with amblyopia in spite of successful surgery and meticulous optical correction.

a) Unilateral congenital cataract:

In unilateral congenital cataract, one eye has the advantage of normal vision while the other is deprived by the cataract, a situation similar to monocular deprivation in experimental animals. It is generally accepted that poor vision and amblyopia is the end result, with little improvement after cataract surgery and optical correction [Arlt, 1853; Stellwag, 1864; von Hofe, 1936; Costenbader & Albert, 1957; Hiles & Waller, 1977; Ryan & Maumenee [1977]; Helveston et al, 1980]. Recent advances in understanding the mechanisms of deprivation amblyopia in animals, the improvements in surgical techniques, and in contact lens technology, led to early surgery and good results have been obtained [Enoch & Rabinowicz, 1976; Campos et al, 1978; Vaegan & Taylor, 1979; Stark et al, 1979; Francois, 1979; Beller et al, 1981; Jacobson et al, 1981]. Thus, surgery performed early in life followed by immediate optical correction and amblyopia therapy might result in a favourable visual outcome in such patients. Poor visual results were reported to occur

in children if operated upon at the age of six months or later. Vaegen & Taylor [1979] found that if deprivation after uniocular cataract occurred between 6-30 months of age, "counting fingers" was the best visual acuity achieved. If deprivation commences between 3-10 years visual acuity is decreased at a slower rate and is more likely to respond to full time occlusion. Beller et al [1981] reported good results in eight patients with monocular congenital cataract operated upon in the first six weeks of life with immediate contact lens correction. These patients had a mean follow-up period of 2.8 years, using Snellen or 'E' visual testing, five patients had a visual acuity of 6/9 or better, the remaining three had a visual acuity of 6/24 or better in their aphakic eyes.

b) Traumatic cataract

This also results in amblyopia, similar to unilateral congenital cataract, if it occurs in children [Juler, 1921; Black, 1943: Braendstrup, 1944]. This may be a more accurate guide to the age at which cataract can lead to amblyopia, because the onset is usually known exactly. Klein [1900] reviewed cases with traumatic cataract and concluded that amblyopia only developed if unilateral cataract had occurred before the age of three years of life. Juler [1921] found that

cataracts before the age of six years resulted in exceedingly poor vision and in most cases only "hand movement" or "counting fingers" - so the risk of amblyopia extends to the sixth year of life. Braendstrup [1944] summarised the status of unilateral cataract and analysed 77 cases with such conditions (29 congenital and 48 traumatic). He concluded that if cataract occurred between 2-7 years of age the visual results are bad. Better function occurred fairly suddenly at the age of eight years (Fig. 19). Only two

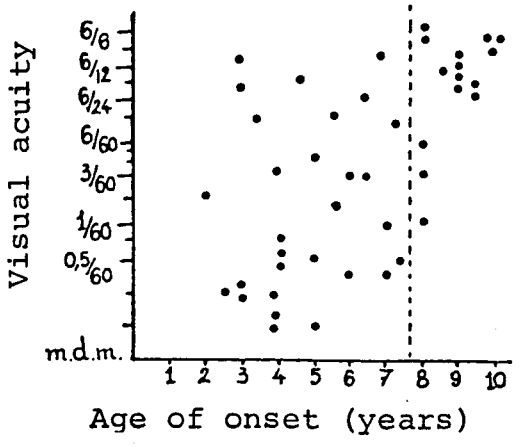



Fig. 19 Functional results after operation for unilateral traumatic cataracts in function of age at the beginning of the cataract [after Braendstrup, 1944].

patients out of 72 who had unilateral cataract after the age of 10 years had a visual acuity of 6/24 or 6/36, the remainder obtained a visual acuity of 6/18 or better. McKinna [1961] studied 26 patients with trau-

matic cataract before the age of six years; only one developed vision of 20/30 after surgery and correction, while seven out of 26 had vision of 20/30 or better when it occurred after six years of age. Frey et al [1973] found five patients out of 22 with unilateral traumatic cataract in children had poor vision; All had injury under five years of age, and none of the patients who had the injury under six years of age had a visual acuity better than 20/70. In 21 patients with unilateral congenital cataract only three patients had good visual acuity. Two of these had surgery and refractive correction in the first four months of life with a visual acuity of 20/40. Daniel [1974] obtained stereopsis in 27% of 181 cases of unilateral traumatic aphakia between 2-5 years of age who were corrected with contact lenses after surgery. Fifty-six per cent attained fusion while 22% remained non-binocular. On the other hand, Shapiro et al [1978] demonstrated visual acuity of 6/15 or more in traumatic cataract cases only if the lens opacity occurred after the age of 5 years. Amblyopia was thought to occur from birth to the end of five years of life. It rarely occurred in children as old as seven years [von Noorden & Crawford, 1979].

c) Bilateral congenital cataract

The situation in bilateral congenital cataract is similar to binocular deprivation in experimental animals; in this case starting from birth. This can lead to amblyopia affecting both eyes [Owens & Hughes, 1948; Bagley, 1949; Leinfelder, 1963; Francois, 1963; Ryan et al, 1965; von Noorden et al, 1970b].

Some authors reported that early surgery for removal of the cataracts resulted in worse results than later surgery [Owens & Hughes, 1948; Bagley, 1949:; Ryan et al, 1965]. The age of onset was not available in these later studies, nor the exact time between surgery, clear pupil and full optical correction which is of importance especially if surgery is done in the first six years of life. Others advised early surgery and correction for better results [von Noorden et al, 1970b; Davies & Tarbuck, 1977; Jacobson et al, 1981; Pratt-Johnson & Tillson, 1981]. Others advised early surgery - for details see Francois [1963]. Taylor et al [1979] concluded that amblyopia secondary to congenital cataract was largely preventable and even treatable. For this early treatment and optical correction are essential, since the effects of deprivation start at about 4 months of age and continue to a cumulative but decreasing degree throughout the first decade of life. The sensitive period in humans ap-

pears to begin at about 4 months, rise to its zenith at 7 or 8 months and then decline gradually over the first decade. So Taylor [1980] advised lensectomy as the choice of operation in the first 12-18 months for congenital cataract. Rogers [quoted by Scott, 1980] operated upon 9 bilateral cases at less than 6 months of age - 3 patients with surgery at less than 3 months of age all developed normal acuity; 6 patients operated on after 3 months had vision of less than 20/200. In addition, Scott [1980] reviewed 122 cases with congenital cataract (47 unilateral and 75 bilateral) and concludes that all cases with vision of $\leq$ 20/200 had surgery after 3 months of age. Furthermore, patients with bilateral cataracts operated upon prior to 8 weeks of age seemed to have normally developing vision [Rogers et al, 1981. This is supported by Gelbart et al [1982] who advised surgery for bilateral cataracts before 8 weeks of age with short intervals between the two operations (48 hours or less), to minimize the functional and competitive advantage of the operated, and corrected, eye over the non-operated eye. On the other hand, Francois [1979] stated that when a patient affected by total congenital cataract was operated on after the age of 7 years, often no functional improvement was observed, even if the anatomical results were perfect.

TABLE 4

Cataract in children as an indication for the presence of a sensitive period

(Assaf, 1983)

| | Period of enhanced sensitivity | Period of low sensitivity (years) | Upper end (years) | Authors |
|---|---|---|---|---|
| Unilateral cataract | | | 3 | Klein 1900 |
| | | | 6 | Juler 1921 |
| | | | 7 | Braendenstrup 1944 |
| | | | 6 | McKinna 1961 |
| | | | 6 | Frey et al 1973 |
| | | | 5 | Shapiro et al 1978 |
| | First 2 | 2-7 | 7 | von Noorden 1978, |
| | 0-5 years | | 7 | von Noorden & Crawford, 1978, 1979 |
| | 4 months - 3 years | 3-10 | 10 | Vaegen & Taylor, 1979 |
| Bilateral cataract | | | 7 | Francois 1979 |
| | 4-8 months | | 10 | Taylor et al 1979 |
| | First 12-18 months | | - | Taylor 1980 |
| Early Surgery | Advised to avoid amblyopia | | | |
| | a) Unilateral cataract<br>First 6 weeks [Beller et al 1981]<br>First 3 months [Jacobson et al 1981] | | | |
| | b) Bilateral cataract<br>First 3 months [Rogers, 1980; Scott, 1980, Parks, 1982]<br>First 2-4 months [Jacobson et al 1981; Mohindra et al 1983]<br>First 8 weeks [Gelbart et al 1982] | | | |

Bilateral congenital cataracts are sometimes associated with nystagmus. Parks [1982] found all patients except one out of 15 with bilateral cataracts had nystagmus by the age of 3 months. He suggested

that the critical period for development of fixation reflex in both unilateral and bilateral deprivation disorders is between 2-4 months of age. The onset of nystagmus in bilaterally deprived infants probably marks the end of the critical period.

Table 4 summarizes the ages at which amblyopia, after cataract in children, can be produced or reversed as reported by different authors.

2) Corneal opacities:

Corneal opacities occurring in early childhood can also result in amblyopia [von Noorden & Maumenee, 1968; Awaya, 1978]. Singh and Das [1978] investigated 42 cases of corneal grafts in 2 groups of patients who developed corneal opacities either before or after 5 years of age. A severe irreversible form of amblyopia with eccentric fixation was observed in cases of unilateral corneal opacity when the anomaly occurred before the age of 5 years, and corneal grafting was delayed until the 2nd or 3rd decade of life. If the opacity was bilateral, although the onset was before the age of 5 years, the improvement in visual acuity after corneal grafting occurred in the relatively better eye with foveal fixation. Good visual results were seen after corneal grafting when the offending opacity occurred after the age of 5 years. Foveal fixation was also observed in most of these cases. They concluded that corneal opacities

after 7 years of age have no significant effects on the development of amblyopia and fixation patterns after keratoplasty. Keratoplasty was also advised before the age of three to avoid permanent amblyopia [Picettie & Fine, 1966]. These authors performed keratoplasty in children and found that amblyopia could be prevented in patients operated under the age of 4 years. But when corneal opacity occurred before the age of 4 years and surgery was delayed until after 7 years of age, amblyopia limited the improvement in vision. They suggested that optical keratoplasty must be considered before the age of 3 years if permanent disabling amblyopia is to be avoided. Surgery performed at the age of 6 or 7 years will in the majority of instances fail to prevent amblyopia (Table 5).

**TABLE 5**

**Corneal opacity as an indication of the sensitive period**

(Assaf, 1983)

| Condition | Authors |
|---|---|
| Sugery to be done before 3-4 years of age to avoid amblyopia | Picattie & Fine 1966 |
| Opacities after the age of 7 years had no effect on amblyopia and fixation patterns | Singh & Das 1978 |

3). Other Forms of Stimulus Deprivation

Occlusion or monocular visual deprivation of the viewing eye is a well-known method of treatment for various forms of amblyopia, especially used for strabismic amblyopia. Sometimes occlusion results in a transference of amblyopia to the newly occluded eye, called occlusion amblyopia, which is a form of stimulus deprivation amblyopia. This is known to occur up to the age of 5-6 years [Peter, 1932]; 6 years [Hardesty, 1959]; $4\frac{3}{4}$-5 years [von Noorden, 1973a, 1976]. There is a high risk of occlusion amblyopia during the first 2 years, but during this period it is usually reversible.

Awaya et al [1973] reviewed 19 cases of amblyopia with the history of unilateral occlusion of the eye (mostly for about one week following lid surgery). Sixteen cases were less than 13 months of age. The remaining three were within 36 months of age. In another article, Awaya et al [1979a] reviewed a total of 100 cases of deprivation amblyopia after entropion or other minor lid surgery, after unilateral congenital or traumatic cataract or with small punctate posterior polar cataract or linear scar of the corneal endothelium and found no irreversible decrease in visual acuity in patients who had short term deprivation after 18 months of age, with a peak effect between six and nine months. For longer periods of occlusion the critical period may extend to 24 months of age. When occlusion

treatment of the sound eye was started before the ninth year of age, visual recovery was poor in approximately 50% of cases and all the patients who started occlusion of the sound eye after nine years of age had showed a poor recovery of their visual acuity. (See also Awaya [1978], and Awaya et al [1979b]).

Amblyopia can also occur in congenital ptosis if it is severe enough to cover the pupil and obstructs the visual axis [von Noorden, 1967; Anderson & Baumgartner, 1980]. Hemangiomas affecting the lids can also cause stimulus deprivation amblyopia [de Venecia & Lobeck, 1970; Awaya et al, 1973; Stigmar et al, 1978; Kushner, 1982] in addition to a variety of lid affections that cause lid swelling and encroach on the line of sight, e.g. burns, etc. [Awaya et al, 1973].

Von Noorden [1981] analysed 11 cases with stimulus deprivation amblyopia of different aetiology and concluded that amblyopia occurring after monocular deprivation began between birth and $5\frac{3}{4}$ years. As a rule, improvement in visual acuity can be expected in patients whose visual deprivation began after the age of 30 months. In those patients whose visual deprivation began at birth or during infancy, treatment was unsuccessful when started after the age of $2\frac{1}{2}$ years (Table 6).

**TABLE 6**

**Other causes of deprivation amblyopia as an indication of the sensitive period**

(Assaf, 1983)

| Period of enhanced sensitivity | Upper end | Authors |
|---|---|---|
| Birth - 18 - 24 months | 8 years | Awaya et al 1979 |
| Birth - 30 months | $5\frac{3}{4}$ years | von Noorden 1981 |

Congenital glaucoma can result in amblyopia secondary to the corneal oedema and other factors which prevent proper eye usage [Clothier et al, 1979; Biglan & Hiles, 1979].

Bilateral ocular patching in newborns for 1-10 days as part of the treatment of neonatal jaundice produced no difference from normal, when reviewed at 5 years of age, in the incidence of strabismus or loss of stereoacuity [Hoyt, 1980].

4) Summary:

Stimulus deprivation amblyopia results from prevention of the image formation on the retina, either unilateral or bilateral. The most common cause is cataract, unilateral or bilateral, congenital or traumatic.

In unilateral congenital cataract early surgery is advised within the first 6 weeks - 3 months if secondary amblyopia is to be prevented. Unilateral traumatic cataract, if it occurs in children, produces amblyopia up to 7 years of age. In bilateral cataract early surgery is also advised before 2-4 months to prevent secondary ambly-

opia and nystagmus.

Corneal opacities can result in stimulus deprivation amblyopia if it occurs up to the age of 7 years. For this reason keratoplasty is advised before the age of 3 years.

Analysis of the 100 or so cases of Awaya and his co-workers [1973, 1979a,b] showed that the sensitive period for the production and reversal of amblyopia in such cases extended up to 8 years of age, with a critical period lasting from birth until 18 to 24 months of age.

Von Noorden [1981] also analysed 11 cases with stimulus deprivation amblyopia and concluded that amblyopia after monocular occlusion occurs between birth and $5\frac{3}{4}$ years of age, and the critical period might extend up to the age of 30 months.

## B. STRABISMUS AND STRABISMIC AMBLYOPIA

The occurrence of "primary" strabismus itself may be a factor in estimating the susceptibility of the visual system during its development. Once visual development and maturation is achieved and the patient has reached a certain age, the occurrence of squint is unlikely, unless secondary to some pathology. Thus the incidence of squint as related to age may be an indication of the duration of the "sensitive period". Strabismus can also help to outline the sensitive period by analysis of the age at which strabismic amblyopia can be produced by the strabismus, and reversed by therapy.

### 1) Prevalence of strabismus

Worth [1903] stated that strabismus occurred most often between the 2nd - 4th years of life, [see also Cashell, 1952], but more recent publications tend to give a younger age. Keiner [1951, {47-60}] found that 18.4% of strabismus cases occurred soon after birth, 53.9% in the first year, and 78% by the end of the second year. Only occasionally does strabismus start after the age of 4 years and after the 7th year hardly any new cases of strabismus occur (Fig. 20). Scobee [1951] and Nordlow [1953] found also about 50% occurred in the first year of life, and Scobee showed that the majority occurred before the age of six years (Fig. 21) These findings were supported by other authors. Nordlow [1964] found that the onset of constant convergent

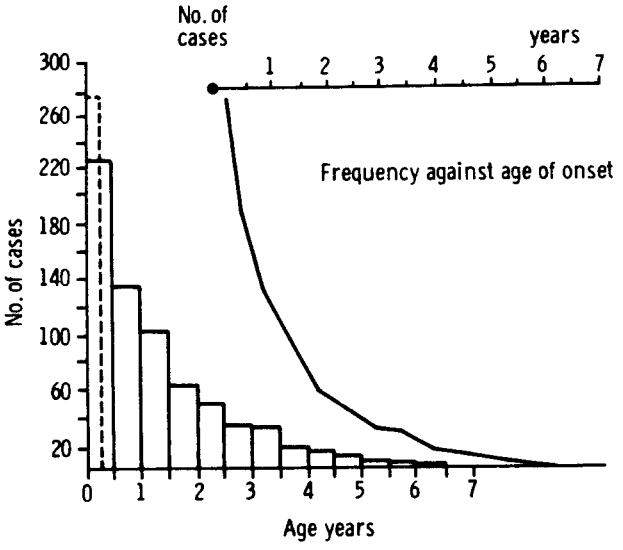



Fig. 20 Graphic representation of 656 cases of convergent strabismus. Frequency against age of onset [Keiner, 1951].

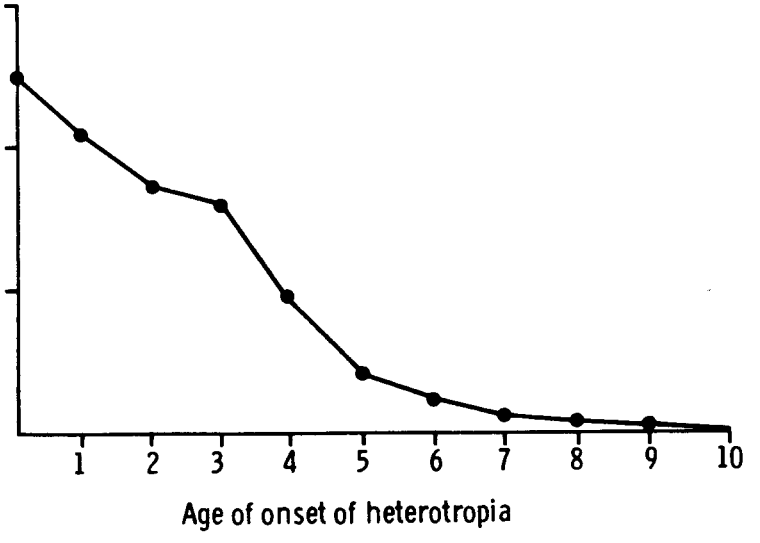



Fig. 21. A study of the age at which heterotropia was first noted in 524 consecutive patients [Scobee,1951].

strabismus is most frequent during the first year of life. It then decreases quickly, to cease at the age of 7 years. Crone and Velzeboer [1956] found 75-81% of all strabismus cases occurred before four years of age: and Flom [1970] stated that it rarely starts beyond 5-6 years of age.

2) Production of Strabismic Amblyopia

In constant monocular strabismus, one eye is used for fixation and one is deviating. As in experimental animals, the deviating eye usually becomes amblyopic. Amblyopia develops in about 50% of untreated strabismus cases [Worth, 1903; Harms, 1938; Crone & Velzeboer, 1956], and is always unilateral.

Amblyopia occurs particularly in convergent strabismus, but less commonly in divergent strabismus. Many patients with convergent squint are hypermetropic, the eye with the higher refractive error being the deviating eye. The image is relatively out of focus in the eye with higher refractive error, active suppression to avoid confusion and diplopia is also a factor. After the age of 9 years the child's capacity to suppress is much reduced [Bishop, 1981; Gardiner, 1982].

Chavasse [1939] coined the term 'amblyopia of arrest', implying that the turning and the associated disuse of the squinting eye resulted in the arrest of the development of visual acuity, i.e. the visual acuity remains at the level

at the time of onset of squint. It is less likely to occur after 6 years of age. This is also supported by Linksz [1952]. These are in accordance with the findings in experimentally-produced strabismus in kittens, which resulted in an arrest in the development of spatial vision at the age of onset of the strabismus [Jacobson & Ikeda, 1979]. Costenbader et al [1948] showed that the duration of strabismus is more closely related with the appearance of amblyopia than to the age of the child at the time the squint appeared. But it appears that the age of onset-duration is of paramount importance in the production of amblyopia. The duration varies with age. Strabismus with earlier age of onset needed shorter periods to result in amblyopia. Amblyopia does not occur if strabismus appeared after the 7th year [Peter, 1932; Braendstrup, 1944], or 51 months of age [von Noorden & Dowling, 1970]. On the other hand, strabismic amblyopia had been detected within the first year of life. There was a significant difference between the acuity of two eyes, using forced-choice preferential looking techniques, in esotropic infants as young as 5-6months [Mohindra et al, 1979].

3) Response to therapy in strabismic amblyopia

According to Flom [1970], Worth [1903] reviewed 985 children with constant convergent strabismus whom he had examined and followed during a 10 year period. Of the

children who had onset of strabismus before 1 year of age and who were treated immediately, approximately 90% ultimately obtained normal visual acuity of 20/20. If treatment was delayed by three months, but no longer, only 50-65% of children ultimately obtained normal acuity. If treatment was delayed by more than three months, none of them obtained normal acuity and few achieved 20/30 - 20/20 acuity, most had poorer than 20/200 acuity or lost the ability to fixate monocularly with the amblyopic eye. If the onset of strabismus was between one and three years of age and treatment was delayed by no more than three months, about 90% obtained normal acuity. If management was delayed by 3-12 months, a reasonable number of children obtained normal or nearly normal acuity. If this was delayed by more than a year, most children did not obtain good visual acuity and approximately 40% lost the ability to obtain monocular fixation. If strabismus occurred after three years of age and management was delayed by as much as seven months, about 85% obtained normal acuity. Even if treatment was delayed for four years or more, many children obtained moderate recovery of acuity and only small proportions lost the ability to fixate. Stanworth [1949] found that patients with an age of onset of squint of 3 years or more had a better chance of developing fusion or stereopsis post-operatively. Most of the patients with strabismus who had no binocular vision after therapy had an

age of onset before 4 years and very few after 6 years [Houlton, 1952]. Lyle et al [1949] and Lyle & Jackson [1953] reported that after 7-8 years of age improvement with occlusion is much slower, becoming progressively more so towards adult life. This coincided with Peter's view [1941], which stated that improvement with occlusion for strabismic amblyopia is greatest in children under 7 years of age, but it is observed in adolescence and early adult life. Nordlow [1956] advised early surgery in squint cases, with age of onset at 6 months or later, to obtain better binocular fixation. The age of onset influences both the incidence and intractability of amblyopia. Squints under two years of age mostly had poor vision; squints after that had better vision [Naylor & Wright, 1959]. Thomas et al [1979] demonstrated dramatic improvement of visual acuity with a short period of occlusion in infants with strabismus within the first year of life, and demonstrated extreme liability of the infant's visual system to binocular differences. In addition, Lennerstrand et al [1982] showed that normal levels of visual acuity were reached after quite short occlusion periods in $2\frac{1}{2}$ year old children with strabismic amblyopia.

Improvement of visual acuity after occlusion therapy in strabismic amblyopia occurred maximally before the age of four years and this treatment became increasingly less

effective between the ages of 4-9 years. It was almost ineffective after that age [Bishop, 1981]. Using flash therapy to the macular region of the amblyopic eye some authors reported recovery of vision in patients with life time strabismus up to 58 years of age [Allen, 1978]. Others found considerable improvement in the amblyopic eye after occlusion in children over five years of age [Scobee, 1951], after eight years [Dowling, 1942; Brown & Edelman, 1976], and over 25 years [Kasser & Feldman, 1953]. Until seven years of age most cases can be restored to normal vision with proper methods of management according to Peter [1934]. From 7-12 the recovery is slightly lower and from 12-21 years of age the possibilities are only fair.

4) Results of therapy in congenital esotropia

There is disagreement concerning the outcome of the management of congenital esotropia which occurs in the first six months of life. Some authors opposed early surgical correction on the basis that the final results are functionally poor, regardless of timing of management, therefore it is safer to defer surgery to a later date; e.g. Fisher et al [1968] found that surgery for congenital esotropia between 6-12 months of age does not lead to significantly better functional results or better alignment of the two eyes than does surgery performed between 12 and 24 months. Others argued that logic, on the evidence from

other clinical situations and on animal visual deprivation experiments, is on the side of early surgery, which seemed necessary if any good functional result is to be achieved. Some authors failed to obtain binocular single vision in a series of patients with congenital esotropia operated upon after two years of age. Houlton [1952], Doggart [1950], and Gunderson [1970] all reported poor binocular single vision results. Leahey [1960] felt that extremely early surgery can often be of invaluable help, but considered the duration of the squint and the age of the child to be very important in indicating which cases are favourable for early surgical correction. On the other hand, Chavasse [1939 {p.519}] argued that if the various obstacles to fusion development could be overcome and deviation fully eliminated before the age of two years, good results could be achieved. This is supported by other authors who had favourable results through the use of very early surgery, before two years of age [Taylor, 1963, 1972, 1976; Ing et al, 1966]. Taylor [1972] operated on 102 patients with congenital esotropia after two years of age. None was converted to phoria. Of fifty patients who were operated upon between $3\frac{1}{2}$ - 23 months of age, 30 were converted to phoria with stereopsis ranging from 40-400 seconds of arc. Foster et al [1976] concluded that bifoveal fixation was greater in patients operated upon before 2 years of age, but was still obainable when surgery was performed as late as 6

years of age. Parks [1981] and Zak & Morin [1982] found that congenital esotropia had an excellent prognosis for development of single binocular vision for eyes brought to within 10 prism diopter of straight within the first year of life, good up to 2 years, then diminished rapidly thereafter, becoming hopeless after 4 years. This was supported by Ing [1983] who reviewed, in a multi-centric study, 106 patients with congenital esotropia and who were aligned by surgery. Surgical alignment was considered to be achieved

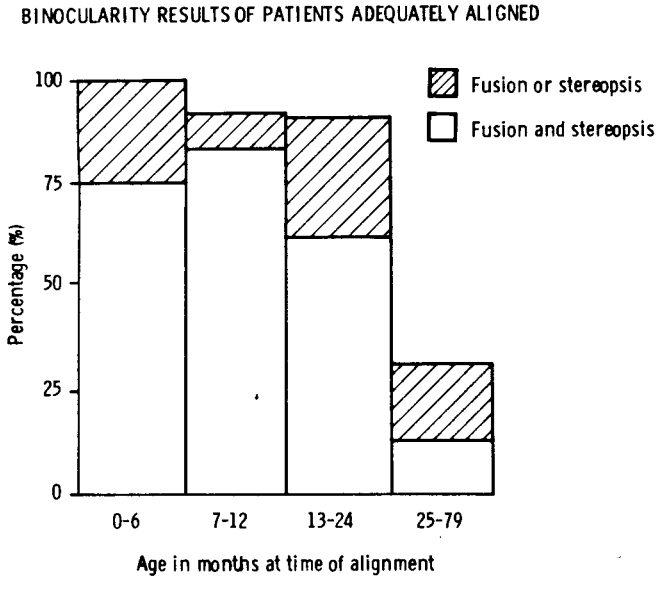



Fig. 22 Presence of binocular single vision in patients with congenital esotropia plotted against the age of surgical alignment. Alignment is achieved to within 10 prism diopters of orthophoria for a minimum of six months [Ing, 1983].

when the strabismus was brought to within 10 diopters of orthophoria for a minimum of 6 months. The results of sensory testing, using Bagolini striated glasses, worth 4

lights and polaroid Titmus stereotest, showed that all patients aligned by the age of 6 months showed evidence of binocularity and those aligned by the age of 12 months or 24 months had a high percentage of binocularity. Of the few aligned after 24 months of age, only two showed both fusion and stereopsis and both had been aligned before the age of 3 years (Fig. 22).

Summary:

Strabismus also can act as an indicator for the sensitive period in many ways. The production of strabismic amblyopia, reversal of such amblyopia, the age of onset of "primary" strabismus and therapy of congenital esotropia.

Amblyopia in strabismus can be detected as early as 5-6 months of age and is less likely to occur after 6-7 years of age.

Improvement in visual acuity after occlusion and the fusion potential after surgery is better in squints with age of onset after 3 years. On the other hand, improvement is dramatic after short periods of occlusion in the first year of life, occurs maximally before 4 years of age and is less likely after 7 years of age.

Occurence of strabismus might reflect the maturation of fixation reflex and oculomotor system, since if the system is mature it is less likely to develop faults unless secon-

dary to some pathology, but errors are more likely to occur during the laying out, maturation and "learning process".

It is evident now that patients with congenital esotropia if corrected early, within the first 2 years of life and brought to within a few prism diopter angle can achieve some degree of binocular single vision with good prognosis for vision (Table 7).

**TABLE 7**

**Evidence for the presence of sensitive period - Strabismus**

(Assaf, 1983)

1. Development of strabismic amblyopia

   - Rarely develops after the seventh year of age [Peter, 1932]
   - Less likely after 6 years of age [Chavasse, 1939; Peter, 1941]
   - Does not occur after 51 months of age [von Noorden & Dowling, 1970]
   - Can be detected as early as 5-6 months of age [Mohindra et al, 1979]

2. Strabismus prevalence

   - Majority between 2-4 years of age [Worth, 1903]
   - Occurs only occasionally after 4 years and hardly after 7 years [Keiner, 1951]
   - Majority before 6 years of age [Scobee, 1951]
   - 75%-81% before 4 years of age [Crone & Velzeboer, 1956]
   - Onset ceases after 7 years of age [Nordlow, 1964]
   - Rarely occurs beyond 5-6 years [Flom, 1970]

3. Response to therapy

   - Strabismus with age of onset after 3 years has better visual acuity [Worth, 1903] and better fusion and stereopsis [Stanworth, 1949] after therapy, and mostly those with poor binocular single vision result had their age of onset before 4 years of age [Houlton, 1952].
   - Improvement is greatest before 7 years of age [Peter, 1934, 1941]
   - Less likely to respond to occlusion after 7-8 years of age [Lyle et al, 1949; Lyle & Jackson, 1953]
   - Better vision after occlusion if the age of onset is after 2 years [Naylor & Wright, 1959]
   - Dramatic improvement occurs after short periods of occlusion in the first year of life [Thomas et al, 1979]
   - Improvement occurs maximally before the age of 4 years and less effectively between 4-9 years of age [Bishop, 1981]

4. Results of therapy in congenital esotropia

   Patients brought straight to within 10 prism diopters during the first 2 years of life produced good prognosis for vision and binocular single vision [Taylor, 1972; Foster et al, 1976; Parks, 1981; Ing, 1983]

## C. REFRACTIVE AMBLYOPIA

Anisometropia occurs when there is a difference in the refractive power of the two eyes. There are differences among various authors on what actually constitutes anisometropia, but most agree that a difference of 1-1.50 DS or 1.00 DC or more is enough to be labelled as such [Bishop, 1957; Stevens, 1960].

The association between amblyopia and anisometropia is well known in the literature [Worth, 1903; Lagleyze, 1913; Costenbader et al, 1948; Lyle, 1950; Horwich, 1964; Ingram, 1979; Mets & Price, 1981; Kivlin & Flynn, 1981]. Furthermore there is an increased incidence of strabismus and/or amblyopia associated hypermetropia and/or astigmatism or anisometropia [Ingram, 1973, 1977; Ingram et al, 1979]. The term anisometropic amblyopia was suggested for wider use by Phillips [1959]. Anisometropia can result in unequal image sizes presented to the two retinas. The unequal images cannot be fused into a single image beyond a certain range of size difference. Amblyopia of the anisometropic eye often results. In addition, if the patient is hypermetropic he is more likely to develop amblyopia [Jampolsky et al, 1955; Sen, 1980]. This occurred in the more hypermetropic eye because normally the accommodative state of the two eyes is well matched. In anisometropia the patient uses his more nearly emmetropic eye to determine his state of accommodation, the other retinal image will be habitually

defocussed and blurred by an amount equal to the difference in refractive error in the two eyes [Ikeda & Tremain, 1978a]. So anisometropia can act as a mild version of monocular occlusion. A similar situation can be produced in animals. On the other hand, patients who have a slight to moderate myopia tend not to develop amblyopia; this is possibly due to the later age of onset of myopia. If the myopia is not too high, the myopic eye is at focus some distance in front of the patient, which the child can use to view near objects.

Some authors observed that the degree of amblyopia varies with the degree of anisometropia [Copps, 1944; Lyle, 1950; Sen, 1980; Bradley & Freeman, 1981]. Others disagreed and stated what is actually needed to achieve a certain level of anisometropia to trigger the development of amblyopia. The final depth of amblyopia depends on unknown factors [Helveston, 1966; Malik et al, 1968]. Malik et al [1968] suggested that the depth of amblyopia is related to the age of onset rather than the amount.

It has been widely recognised that treatment of anisometropic amblyopia produces good results if started early [Hurtt et al, 1977]. And it has been generally held that treatment of anisometropia beyond the age of 10-13 years gives poor results {McMullen, 1939; Bishop, 1957; Phillips, 1959; Sullivan, 1976]. But Sen, [1982] found

possible improvement up to the age of 20 years. Probably the determining factor for improvement is the age of onset and hence the depth of amblyopia and its reversibility, in addition to the age of presentation for treatment, hence the duration, and possibly the amount of anisometropia. This might explain the difference in results of treatment at different ages.

Many astigmatic patients, after correction of this refractive error, continue to see lines of one orientation less clearly than others [Martin, 1890; Luedde, 1922]. This astigmatic amblyopia can occur in patients who develop high astigmatism, unilaterally or bilaterally, during their infancy or early childhood as a result of long-standing unequal focus of the image on their retina. Almost all humans who have uncorrected early astigmatism suffer from some degree of "meridional amblyopia" which persists after correction of their refractive error [Freeman et al, 1972; Mitchell et al, 1973; Mitchell & Wilkinson, 1974; Freeman & Thibos, 1975]. Freeman & Thibos [1973] showed that human subjects, who had reduced resolution for a pattern of a particular orientation secondary to astigmatism, showed a decreased evoked potential response elicited by a target of the same orientation. These authors concluded that deficiency of a specific feature in the early visual input can alter the organisation of the visual pathways. On the other hand, if the astigmatic patient receives optical cor-

rection by roughly three years of age, then when tested as an adult with lines or gratings of various orientations, he displays normal visual acuity for all axes. Astigmatic amblyopia, though resulting from blurring of the retinal image, most likely occurs at the cortical level [Freeman et al, 1972; Freeman, 1977; Mitchell, 1979]. This situation is analogous to kittens raised with artificial astigmatism.

At about 6 months of age 50% of normal infants showed astigmatism of one or more diopters (only 5-10% in adults). By the end of one year the majority had lost or reduced their astigmatism [Held 1977; Thomas et al, 1979; Fulton et al, 1980; Atkinson & Braddick, 1982b]. In spite of that, it had been demonstrated that large amounts of astigmatism present during early infancy do not result in amblyopia in the first year of life. This meridional amblyopia must develop after one year of age [Held, 1977]. Others also found an extremely high incidence of astigmatism (of 1D or more) during the first year of life [Mohindra et al, 1978; Howland et al, 1978], which does not decline towards the adult incidence until after 2 years of age, or between 1 and $3\frac{1}{2}$ years [Ingram & Barr, 1979]. The earliest age at which meridional amblyopia has been detected is just prior to three years [Mohindra et al, 1978]. This was supported by Fulton et al [1980], who found that during the first

three post-natal years the incidence of astigmatism and distribution of spherical equivalents and anisometropia did not distinguish normal patients from most of those with esotropia and amblyopia.

Bilateral high refractive errors can also result in some form of residual impairment of visual acuity after correction if it occurs early enough during the sensitive period [Ikeda & Wright, 1974]. This has been proved to occur in experimental animals raised with bilateral defocus during their sensitive period [Ikeda & Tremain, 1978a].

Summary:

Many authors suggested that amblyopia after refractive errors is not detected before 3 years On the other hand, reversal of this amblyopia extends to a later age than stimulus deprivation or trabismic amblyopia. This is possibly due to the later age of onset and hence, in general, is less dense and could be reversed more easily (Table 8).

**TABLE 8**

**Refractive amblyopia as an indication of the sensitive period**

(Assaf, 1983)

| Condition | Age | Authors |
|---|---|---|
| Incidence of amblyopia | Not detected prior to 3 years of age | Mohindra et al 1978<br>Fulton et al 1980 |
| Response to therapy | Up to 10-13 years of age | McMullen 1939; Bishop 1957; Phillips 1959; Sullivan 1976 |
| | Up to 20 years of age | Sen 1982 |

## IV. THE SENSITIVE PERIOD

The wide interest in the presence of a sensitive period for the visual system in man has been reawakened by the findings in experimental animals in the sixties and early seventies. Man likewise appears to possess a sensitive period, the exact details of which are unknown No major study, as far as I am aware, has been attempted to gather and analyse the evidence from all its aspects.

Based largely on the data of Worth [1903] on strabismic amblyopia and Juler [1921] on amblyopia after traumatic cataract in children, the sensitive period in man has generally been regarded as lasting until the age of 6 years [Duke-Elder, 1949].

Von Noorden & Maumenee [1968] suggested the term "stimulus deprivation amblyopia" to describe amblyopia where the formation of images on the macula is prevented by opacities of the ocular media, a situation similar to the effects of stimulus deprivation in experimental animals. They suggested that if these opacities occurred at or soon after birth, the capacity for central fixation and normal vision never develops, even though the opacities were removed later in life. A milder and usually reversible form of amblyopia may occur in children up to the age of 4-5 years.

In the early seventies, von Noorden and his co-workers extended the animal work on stimulus deprivation and stra-

bismic amblyopia to monkeys. These authors attempted to correlate their findings with similar clinical situations in man. Von Noorden et al [1970a] suggested that amblyopia after form deprivation occurs in the first 2-3 years of life. Later it was thought that amblyopia after unilateral visual deprivation can occur up to the age of 51 months [von Noorden, 1973a, 1974], or in the first 5 years of life [von Noorden & Crawford, 1977]. A more recent opinion suggested that the sensitive period might extend from birth to approximately 7 years of age with sensitivity greatest in the first 2 years of life [von Noorden, 1978b]. In another article, von Noorden and Crawford [1979] suggested that the plastic age in most children extends from birth to the end of the 5th year of life, the sensitivity declining as the child grows older. Awaya and his co-workers [Awaya et al, 1973; Awaya, 1978; Awaya et al, 1979a,b] studied a total of 100 cases of form deprivation amblyopia, which mostly occurred after occlusion following surgery for entropion. These authors concluded that the period of vulnerability for binocular function may last until 36 months of age. On the other hand, the critical period for uniocular visual acuity may last only until 18 months of age for short periods of occlusion, with a peak effect between 6-9 months of age. For longer periods of occlusion, this extended to 24 months of age and the oldest age at which amblyopia occurred after deprivation is 4 years. But the

exact upper limit for the production of amblyopia is uncertain.

Vaegen & Taylor [1979] and Taylor et al [1979] analysed patients with infantile and juvenile cataracts and concluded that in unilateral congenital cataract correction before 4 months of age produces less visual loss. Deprivation between 3-10 years reduces vision at a slower rate and is more likely to respond to full time occlusion. For bilateral visual deprivation the amblyopic effect starts at about 4 months of age, rises to its zenith at 7-8 months and then declines gradually over the first decade of life.

Von Noorden [1981] analysed 11 cases with stimulus deprivation amblyopia and concluded that amblyopia after monocular visual deprivation begins from birth and extends up to the age of $5\frac{3}{4}$ years. As a rule improvement of the visual acuity can be expected in patients whose visual deprivation began after the age of 30 months. In those patients who had visual deprivation which began at birth or during infancy, treatment was unsuccessful when started after the age of $2\frac{1}{2}$ years.

Furthermore, evidence discussed previously from the development of the visual system and other authors reports on many clinical situations involving visual deprivation in childhood, reinforces the presence of a sensitive period (Tables 4,5,6,7,8). It is now accepted by most authors that the first 2 years or so represent a stage of high

susceptibility. The sensitive period appears to start from birth with good chances of complete recovery if deprivation is removed before the age of 3 months. The upper limit is still controversial, but the evidence suggests that a significant sensitivity is essentially over by the age of 5-8 years.

Summary:

Man appears to possess a sensitive period. The evidence is mainly derived from clinical situations. In addition, evidence from the development of the visual system indicates a stage of post-natal growth and maturity. It is known, from work on experimental animals, that the sensitive period largely coincides with the period of post-natal growth and maturity.

Based on data from these two sources, it appears that the first two years or so represent a stage of high susceptibiity - the critical period. The sensitive period might start from birth, but sensitivity appeared to be greater after the first 3 months of life. By 5-8 years of age sensitivity to visual deprivation is essentially over.

## V. RECOVERY FROM THE EFFECTS OF VISUAL DEPRIVATION

Again, the main observations on recovery after visual deprivation in man are concerned with function, not anatomical studies, and even that is not fully documented.

The functional effects of visual deprivation on the visual system mainly involve the visual acuity, with the production of amblyopia, and loss of binocularity, sometimes with secondary strabismus. It is obvious that once binocularity is lost it is not regained - a situation similar to the loss of binocularity in experimental animals.

Improvement in visual acuity is the main concern, since it is more connected with the practical ocular function. Occlusion of the sound eye, which is a form of reversal of deprivation, has long been used in the treatment of different types of amblyopia. DeBuffen [1743] first advocated this form of treatment. Later this was abandoned for a time, but revived later. Occlusion is a well-accepted and most beneficial way of improving vision in the amblyopic eye by forcing it into use and giving it a competitive advantage over the non-deprived eye.

Earlier studies reported little or no improvement after various types of stimulus deprivation amblyopia. Better results were obtained after strabismus and anisometropic amblyopia. For more details see Chapter II of this section.

It has been known that response to occlusion depended

on age [Duke-Elder, 1949; Catford, 1967; Schapero, 1971; van Balen, 1981; Frysakova & Vymazal, 1982]. Improvement is more likely in the very young infant. This becomes progressively more difficult after the age of 5 years and unusual after the age of 7 years. It is generally accepted that amblyopia responds best when occlusion is started before the age of six years [Dowling, 1942; Duke-Elder & Wyber 1973]. Greater improvement in vision occurred with full time occlusion [Catford, 1967]. On the other hand, Massie [1965], Gokhale & Gokhale [1969], Malik et al [1970], Brown & Edelman [1976] and Allen [1977] all had good results after occlusion in children over 7 years of age. It is probably the age of onset, not only the duration, which may determine the response to occlusion. The age duration factor is of over-riding importance in the prognosis for reversal of abnormal visual development [Schapero, 1971; Jampolsky, 1978]. In addition, anisometropic amblyopia, without strabismus, tended to respond to occlusion at a later date than strabismic amblyopia, because anisometropic amblyopia is not detected until the third year of life. In general, the younger the age of onset, the less likely that therapy would be successful [Peter, 1932; Chavasse, 1939 {311}].

From this, it will be seen that amblyopia can be reversed if the cause of deprivation can be removed and reverse occlusion started early enough within the sensitive period.

Some authors argued that permanent damage to the visual system could be produced by only a few days of visual deprivation occurring during the critical period [Awaya et al, 1973, 1979a]. Others argued for spontaneous recovery on return to normal stimulation [Hartwig et al, 1976; Odom et al, 1981]. They suggested that the plasticity of the visual system of infants aged 1 year or less seems to work both ways, i.e. rapid depression of visual acuity on deprivation and a bouncing recovery on return to normal stimulation. But in cases in which deprivation lasted for more than one month, no recovery of function took place if deprivation occurred before 30 months of age [von Noorden, 1981]. Jacobson et al [1983] studied recovery in patients with unilateral visual deprivation after reverse deprivation or by simple cessation of deprivation. They suggested that the effect of monocular deprivation on vision was not permanent. Recovery of vision after binocular deprivation from birth reached normal levels after therapy if started before 2 months of age. At 4-6 months of age, treatment resulted in reduced visual acuity, but recovery subsequently occurred [Mohindra et al, 1983].

Among these conflicting findings, it seems most likely recovery occurs at an early stage. This depends on the type of visual deprivation, age of onset and its duration.

Finally, the maximum recovery is not revealed until the

experienced eye is enucleated. It is well known from pubished literature that if a patient had an amblyopic eye and his good eye became blind or lost, for one reason or another, the vision in the amblyopic eye might improve to a certain extent, depending on the cause of poor vision, providing there was no anatomical defect. It takes this drastic measure to unmask fully the potential for recovery. A situation similar to this can be produced in experimental animals [Kratz et al, 1976; Spear, 1977].

Summary:

The degree of recovery of the functional effect of visual deprivation during the sensitive period is still controversial. Many factors affect this recovery, including the type of visual deprivation, age of onset and its duration. At an early stage complete recovery is possible, but after prolonged deprivation permanent defects are the rule.

## VI. SUMMARY

As seen, the visual system in humans is not fully developed at birth, but continues to develop both anatomically and physiologically post-natally. Analysis of the age of production and the age of reversal of amblyopia can outline the sensitive period in man. It could be said that there is a rough correspondence between the anatomical and physiological growth and the development and reversal of amblyopia; i.e. the growing system is susceptible to outside influences mostly during its period of growth and maturation. In man it appears that in the first 2-3 years marked anatomical growth and maturity occurs in the visual system, along with the development of many visual physiological processes. These physiological processes mature probably up to the age of 5-8 years. This second period is also associated with a reduced rate of anatomical growth. There is probably a range of normal variation in the rate of development and maturity among various individuals.

There is multidirectional evidence from many sources for the presence of a sensitive period. This corresponds well with the period of anatomical growth and physiological maturity. The first two years or so might represent the critical period. The sensitivity to functional deprivation declines to negligible levels by the age of 5-8 years. Recovery from the effects of visual deprivation can occur,

depending on the age of onset, types of visual deprivation and its duration.

## PART THREE

# INVESTIGATIONS TO DETERMINE THE SENSITIVE PERIOD IN MAN BY ANALYSIS OF PATIENTS WITH TRANSFER, OR REVERSAL, OF FIXATION AFTER OCCLUSION FOR STRABISMIC AMBLYOPIA

Fixation characteristics are most important and are more important to the clinician examining the young developing visual system than is the examination of the visual acuity [Jampolsky, 1978].

## I. INTRODUCTION

The oculomotor system is a position-coded system [Robinson, 1970]. Its function is to transfer the field of vision into the field of fixation to bring the image of the object of attention on to the fovea and to keep it there, and to position the eyes so that at all times they are properly aligned [von Noorden, 1974].

The term, fixation, is used to indicate the seemingly steady maintenance of the image of the object of attention on the fovea. If one eye fixates this is called monocular fixation; if both eyes fixate it is then called binocular or bifoveal fixation. In normal development bifoveal fixation follows the establishment of unifoveal fixation [McNeer, 1978]. Fixation results from a complex motor act in which a number of movements contribute and is ultimately comparable to the hardly perceptible motions of the body of a person standing strictly to attention [von Noorden, 1980]. As mentioned, the aim of fixation is to place the image of the visual object attracting attention on the fovea which is the retinal area of highest acuity and to keep it there.

The major abnormal motor disorder is misalignment. We are born with approximately straight eyes and a yoked motor system and we must learn to use them together normally. The fixation mechanism of the better eye stably fixes an otherwise unharnessed roving yoked eye movement system [Jampolsky, 1978]. Two essential features of the

oculomotor system are necessary for normal binocular coordination, equal bilateral inputs and equal bilateral ouptuts.

Fixation and visual acuity are the two major motor and sensory functions of the visual system. Fixation characteristics are most important and more important to the clinician examining the young developing system than is the examination of the visual acuity. Which is the cart and which the horse? The acuity-fixation consideration has not always been clear. A child with amblyopia or arrested vision has arrested fixation mechanism and thus poor visual acuity [Linksz, 1952 - after Jampolsky, 1978]. In strabismic amblyopia the fovea is no longer the area of optimal retinal fixation and with eccentric fixation an extra foveal retinal area becomes the new reference point of the oculomotor system. In general, an amblyopic eye may lose its ability to fixate normally [Srebro, 1983] and an eye which cannot fixate may become amblyopic.

It occasionally occurs that infants and young children having occlusion treatment for strabismic amblyopia not only demonstrate improvement in the visual acuity of the amblyopic eye, but also switch fixation to that eye, sometimes with suppression and amblyopia of the originally sound eye. This had been recognised for a long time [Peter, 1932; Costenbader et al, 1948; Keiner, 1951 {144}]. Peter

[1932] stated that the deviation and 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 reverse the amblyopia. Different authors reported or reviewed similar cases after occlusion, though in general not in great numbers (Table 9). Goodier [1969] reviewed 21

**TABLE 9**

**Patients with occlusion amblyopia and/or transfer of fixation as reported by different authors**

(Assaf, 1982b)

| Author | Year | No. of Patients | Maximum patient age reported |
|---|---|---|---|
| Costenbader, Bair and McPhail | 1948 | 1 | 1 year |
| Costenbader | 1958 | 2 | 2 years |
| Hardesty | 1959 | 1 | 2 years |
| Burian | 1966 | 1 | 3 years |
| Goodier | 1969 | 21 | 5 years |
| Von Noorden | 1970 | 2 | 4 years |
| Roper Hall | 1970 | 8 | 3 years |
| Thompson | 1971 | 1 | 3 years |
| MacLellan *et al* | 1979 | 22 | 5 years & 5 months |
| Assaf | 1981 | 115 | 7 years |

patients over three years of age, none were older than five years. Similarly, Maclellan and co-workers [1979] reviewed

22 patients - none were older than 5 years and 5 months. Lyle and Jackson [1953] emphasized the importance of frequent checking of patients while under occlusion because of the danger of occlusion amblyopia. Gibson [1955] suggested that the danger of inducing amblyopia in the sound eye was remote. Should it occur, however, experience had shown that vision was rapidly regained on cessation of occlusion. Hardesty [1959, 1970] stated that over six years of age there was probably no danger of producing occlusion amblyopia of a marked degree by patching for several months. Occlusive amblyopia after occlusion therapy for strabismus can develop up to the age of $4\frac{3}{4}$-5 years and is as a rule reversible [von Noorden, 1973a, 1976]. This susceptibility is greatest in the first 2 years of life. Switching of fixation, after occlusion, may occur suddenly with change of dominance [Jampolsky, 1978]. A remarkably similar dominance switch is seen after enucleation; this might result from a release from inhibition by the now absent input from the normal eye [Kratz et al, 1976; Spear, 1977].

The fact that a switch of fixation occurred at all, especially if it either required occlusion for its reversal (temporary) or was not affected by such occlusion (permanent switch), implied that the neurological mechanisms of fixation must be of sufficient plasticity in those patients

to permit considerable change. It is well known that this plasticity was greater in young children who required less occlusion than older children to produce a switch of fixation, but could nevertheless be present sufficiently in some children up to the age of 5-6 years. Analysis of the production and reversal of human amblyopia, especially the stimulus deprivation type has been widely investigated to indicate the age of susceptibility. Little or no consideration was given to the behaviour and development of fixation under conditions of visual deprivation. Moreover, the sensitive period for such effects is not clear. The present study attempts to illustrate such importance. Patients who totally switched fixation, with or without amblyopia, to the originally deviating eye were analysed in an attempt to define the sensitive period in man. This might be important for the future management of strabismus, and other forms of amblyopia. The age of switch of fixation, provided other factors are held constant, might reflect the sensitivity to occlusion, i.e. visual deprivation. Other factors related to the transfer of fixation, such as visual acuity, binocular single vision; refractive errors, etc., are also analysed.

## II. PATIENTS AND METHODS

All the patients recorded under the heading of strabismic amblyopia in the Orthoptic Department of the Sheffield Area Health Authority (Teaching) were reviewed.

A total of 2649 patients were listed under this heading but notes for only 1904 were found. These patients attended during the period 1941-1978, when the study was commenced. A few were still attending at the time of review, but the final outcome of occlusion could be determined.

Out of the 1904 patients reviewed only 115 patients had switched fixation after different forms of occlusion for strabismic amblyopia. These patients were selected on the following criteria :

1. Before occlusion a measurable strabismus had been present without alternation of fixation.
2. Occlusion had been either:
   a) Total continuous occlusion of light and form (as a patch);
   b) Intermittent or partial physical occlusion, sometimes with periods of total continuous occlusion.

   Patients who had other than physical occlusion at any stage were not included in the analysis, but in view of the particular interest of those in whom the transfer of fixation was not reversible, one such patient who

had had atropine occlusion during part of his occlusion period is mentioned in the analysis; another patient in whom the type of occlusion was unknown is discussed under category 'b'.

3. After occlusion there was transfer of fixation, without alternation, to the non-occluded eye for either a limited period or until the patient was discharged. The age of first attendance for these patients ranges between 7 months, and five years and ten months. There was a male to female ratio of 7:5 (67/48). Fifty-two per cent of the patients had a family history of strabismus. This was common im immediate relatives. The right and left eyes were affected equally and prematurity occurred in 11% of the cases. The selected patients were grouped according to whether the transfer of fixation was :

a) Transient: In this group of patients the originally fixing eye either regained its dominance on fixation or alternated fixation with the originally squinting eye. This occurred without any further occlusion of the newly fixing eye during the subsequent visit or visits;

b) Temporary: In this group of patients the originally fixing eye regained its dominance on fixation or alternated fixation with the originally

squinting eye. This occurred after various forms of occlusion of the newly fixing eye in the subsequent visit or visits;

c) Permanent: In this group of patients the originally fixing eye had not regained its dominance on fixation. But the originally squinting eye took over the dominance of fixation permanently. This occurred in spite of reversal of occlusion in which energetic occlusion of the newly fixing eye was performed.

Of the 115 patients who showed these criteria for transfer of fixation, 25 patients had transient switch of fixation, 75 patients had temporary switch and 15 patients had permanent switch.

Of the 75 patients with temporary switch, in 48 cases further occlusion was delayed until a further visit or visits which confirmed the transfer of fixation, but 27 patients were treated by immediate occlusion of the fixing eye; some of these might, if left without occlusion, have shown only transient switch of fixation, so the distinction between transient and temporary switch was somewhat blurred.

Of the 15 patients with permanent switch, only five never switched back or alternated in spite of reversed occlusion. The remainder switched back at some time to the originally squinting eye, and after further different types and methods of occlusion, they again switched to strabismus in the originally good eye for a few years before discharge.

## III. RESULTS

The 115 patients with switch of fixation were analysed and studied from different aspects which might affect the occurrence of switch of fixation.

1) Degree of Strabismus:

The majority were of moderate and slight/moderate degree, next were those of slight degree and the least common were those of moderate/marked degree as mentioned in the orthoptic notes.

It is a general policy of the department to consider strabismus of less than 15-20 prism diopters as mild, 20-40 as moderate, and marked if above 40.

2) Intermittency

As reported on first attendance, 47 patients had an intermittent history, 24 were constant and in 44 patients there was no clear history.

3)Age of Onset:

This ranged between birth and five years and seven months. There was no apparent difference between the three groups (Fig. 23). All patients had their age of onset under $3\frac{1}{2}$ years, except two of permanent switch and one with transient switch. These last three patients had visual acuities of 6/12 - 6/9 in the amblyopic eye. The median age for the age of onset for the whole group was 21 months.

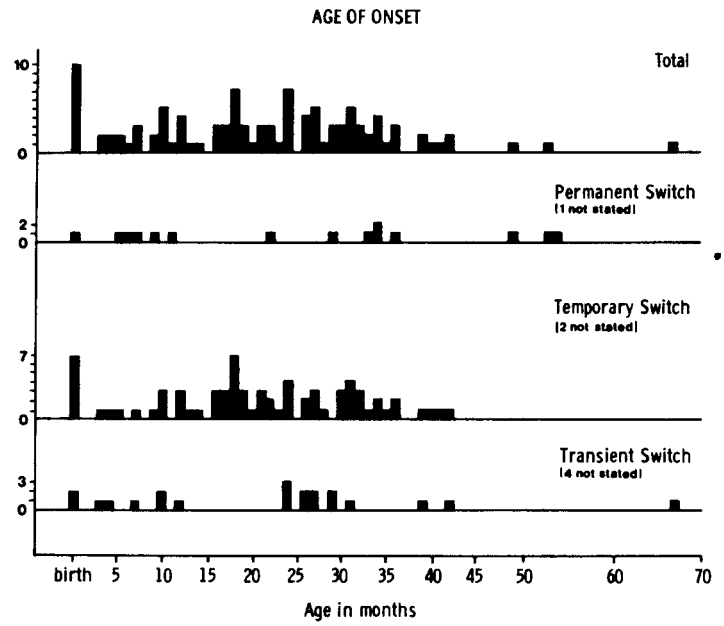



Fig. 23 Age of onset ranged between birth and five years and seven months. All except three were below 3½ years of age. These last three patients had good visual acuity in the amblyopic eye, which ranged between 6/12 and 6/9 [Assaf, 1982b].

4) Age on First Attendance:

This ranged between seven months and five years and 10 months, with a median of 30 months. The median for permanent switch patients was 25 months, for the temporary switch group was 28 months and 35 months for transient switch patients. The transient switch patients tended to be older on first attendance (Fig. 24).

This contrasts with the age of attendance in amblyopia and strabismus, which tend to occur in two peaks. One at

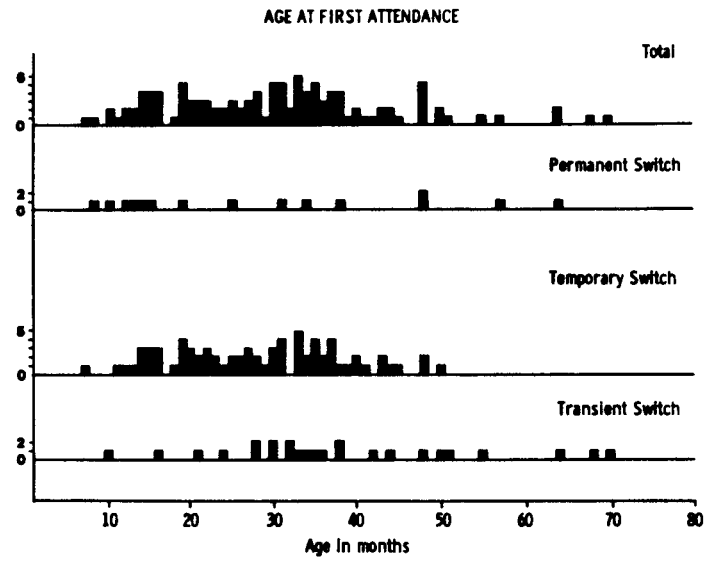



Fig. 24 Age of first attendance ranged between seven months and five years and 10 months. Permanent switch tended to occur among the youngest and transient switch among the oldest patients on attendance [Assaf, 1982b].

the age of 3-4 years, and the second at the age of 5 years when children first go to school [Ingram, 1977]. In addition, Katsumi & Uemura [1978] demonstrated the peaks of first attendance to be between the age of 3-5 years for patients with esodeviation and beteween 6-15 years of age for exodeviation.

5) Duration of Squint:

The maximum duration of the strabismus in patients with permanent switch had been about one year, except one patient with two years duration. Those with temporary switch had a maximum duration of three years. The longest duration was

in those with transient switch with an upper limit of $4\frac{1}{2}$ years (Fig. 25). The median for permanent switch patients was six months, for temporary switch seven months, and 12 months for transient switch. This difference in the duration is significant at the 5% level.

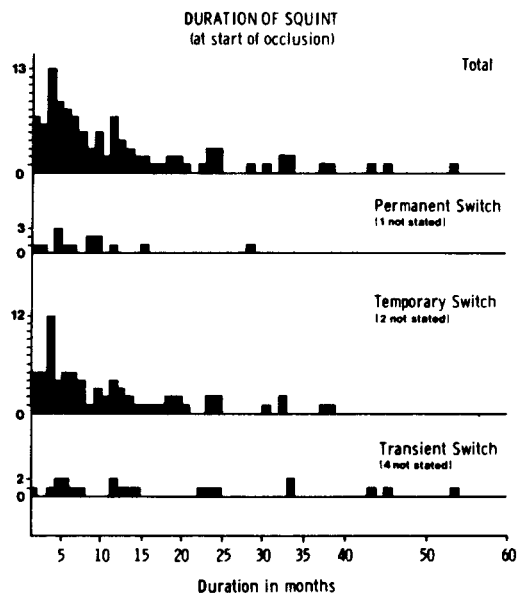



Fig. 25 None of the patients had a squint duration of over $4\frac{1}{2}$ years. For patients with permanent switch it was mostly under one year, for temporary switch under three years and $4\frac{1}{2}$ years for transient switch patients [Assaf, 1982b].

6) Type of Occlusion:

Transfer of fixation can follow either total continuous occlusion or various combinations of partial or intermittnt occlusion. The majority of the latter had a period of initial total continuous occlusion, then had a break in

occlusion or a change to milder forms. Younger patients tended to switch only after total continuous occlusion (Fig. 26). In addition, there is strong statistical evidence (significant at 0.1%) for permanent switch patients to follow partial and/or intermittent occlusion.

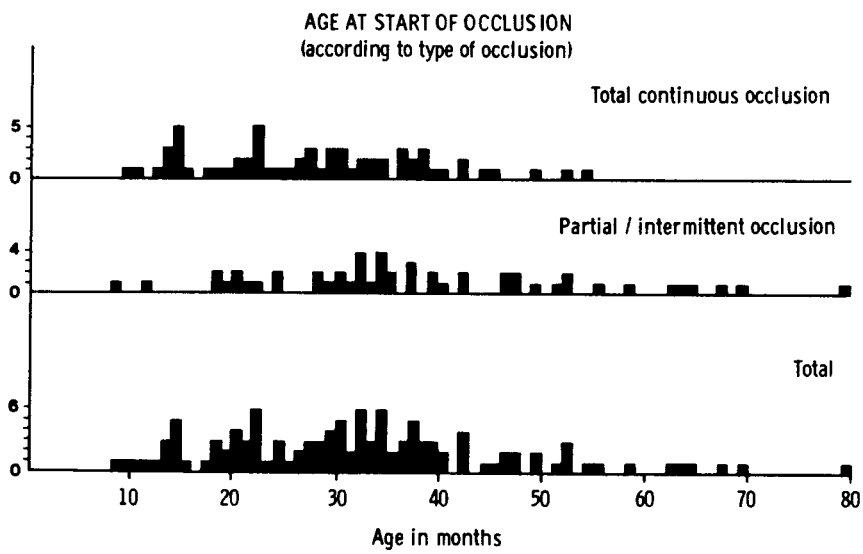



Fig. 26 Age of occlusion ranged between 9 months and 6 years and 8 months. Younger patients tended to switch after total continuous occlusion only. Most older patients either had an initial total continuous occlusion which was changed to a lesser form of occlusion after some response; or had an initial partial/intermittent occlusion because of the presence of good visual acuity and/or fixation at the start of occlusion [Assaf, 1982b].

In two patients in the temporary group and two in the permanent group transfer of fixation followed strabismus surgery on the originally fixing eye, the squint having become alternating. There were no surgical complications

and presumably the change in fixation was due to lid swelling, photophobia, changes in refraction or lid closure acting as a temporary form of occlusion. Refractive changes are reported to occur after routine strabismus surgery [Thompson & Reinecke, 1980; Marshall, 1936].

7) Age of Commencement of Occlusion

The age of occlusion of 115 patients ranged from nine months to six years and eight months (Fig. 27), with a mean of 33 months. Eighty-eight per cent of the patients had an

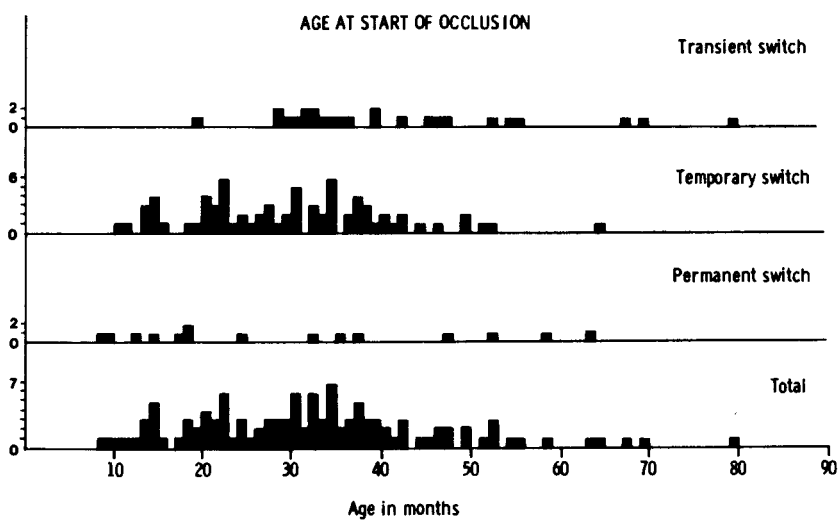



Fig. 27 Age at the start of occlusion for patients with transfer of fixation according to the type of switch. Most were under $5\frac{1}{2}$ years of age, and older patients tended to have transient switch. The number of the patients at the younger end of this figure is probably determined by the number of patients occluded at such an early age, rather than by sensitivity to occlusion [Assaf, 1982a].

age of four years or less. A total of 14 patients switched fixation when the start of occlusion was over four years. All except four had a visual acuity of 6/36 or better in the amblyopic eye at the start of occlusion, one of those four was aged five years and four months and had a permanent switch of fixation after seven successive months of mostly total continuous occlusion.

The age of occlusion for the patients with permanent switch of fixation ranged from nine months to five years and four months, with a mean of 25 months (Table 10). Patients with transient switch had a mean of 37 months (Table 11). Those with temporary switch had a mean of 31 months (Table 12). The transient group were an older age group as compared with the other two. This is significant at the 1% level if we consider the ages below and above 29 months.

8) Age of Transfer of Fixation

Patients were given different periods of occlusion after which they attended the orthoptic department for checking their visual acuity, state of fixation, etc. Sometimes transfer of fixation was demonstrated, with or without amblyopia, so the squinting eye was now the fixing eye and the originally fixing eye became the squinting eye. Switch of fixation could have occurred at any time during the period since the patient's preceding visit. The time between the last visit, during which switch of fixation was

TABLE 10

Patients with permanent transfer of fixation

(Assaf, 1983)

| Age of Occlusion (months) | Anisometropia (1.50D or more) | Visual Acuity 6/36 or Better | Good Fixation and/or Binocular Single Vision | Total Continuous Occlusion only |
|---|---|---|---|---|
| 9 | - | - | - ? | - |
| 10 | - | - | - | + |
| 13 | - | - | - ? | + |
| 15 | - | - | - ? | + |
| 18 | - | - | + | + |
| 19 | - | - | + | - |
| 19 | - | - | + | - |
| 25 | - | - | - ? | - |
| 33 | - | +6/18 6/9 | + | - |
| 36 | - | - | + | - |
| 38 | - | - | - | - |
| 48 | - | - | - | - |
| 53 | - | +6/12 6/6 | + | - |
| 59 | - | +6/9 6/6 | + ? | - |
| 64 | - | - | - | - |

TABLE 11

Patients with transient transfer of fixation

(Assaf, 1983)

| Age of Occlusion (months) | Total Continuous Occlusion only | Anisometropia (1.50D or more) | Visual Acuity 6/36 or Better | Good Fixation and/or Binocular Single Vision |
|---|---|---|---|---|
| 20 | + | - | - | - |
| 29 | + | - | - | - |
| 29 | - | + | - | - |
| 30 | - | + | - | - |
| 31 | - | - | - | + |
| 32 | - | + | - | - |
| 32 | - | - | - | + |
| 33 | - | - | - | - |
| 33 | - | - | - | - |
| 34 | + | - | +6/36 6/9 | - |
| 35 | - | + | - | - |
| 36 | - | + | - | - |
| 37 | + | - | - | + |
| 40 | + | + | - | - |
| 40 | - | - | - | - |
| 43 | + | - | 6/24? 6/36? | + |
| 46 | + | - | - | - |
| 47 | - | - | +6/18 6/9 | + |
| 48 | - | - | +6/9 6/36 | + |
| 53 | - | - | +6/12 6/9 | - |
| 55 | + | - | +6/12 6/36 | + |
| 56 | - | - | +6/12 6/36 | + |
| 68 | - | - | +6/12 6/18 | + |
| 70 | - | - | +6/6 6/12 | + |
| 80 | - | - | +6/6 6/9 | + |

**TABLE 12**

**Patients with temporary switch of fixation**

(Assaf, 1983)

| Age of Occlusion (months) | Total Continuous Occlusion only | Anisometropia (1.50D or more) | Visual Acuity 6/36 or Better | Good Fixation and/or Binocular Single Vision |
|---|---|---|---|---|
| 11 | + | - | - | + |
| 12 | - | - | - | - |
| 14 | + | + | - | - |
| 14 | + | - | - | - |
| 14 | + | - | - | - |
| 15 | + | - | - | - ? |
| 15 | + | - | - | - |
| 15 | + | - | - | - |
| 15 | + | - | - | - |
| 16 | + | - | - | - |
| 19 | + | - | - | - |
| 20 | - | - | - | + |
| 21 | + | - | - | - |
| 21 | + | - | - | - |
| 21 | - | - | - | - ? |
| 21 | - | - | - | - ? |
| 22 | + | - | - | + |
| 22 | + | - | - | + |
| 22 | - | - | - | - ? |
| 23 | + | + | - | - |
| 23 | + | + | - | - |
| 23 | + | - | - | + |
| 23 | + | - | - | - |
| 23 | + | - | - | - |
| 23 | - | - | - | - |
| 24 | + | - | - | + |
| 25 | + | - | - | - ? |
| 25 | - | - | - | - ? |
| 26 | + | - | - | - ? |
| 27 | + | - | - | - ? |
| 27 | + | - | - | - |
| 28 | + | - | - | - |
| 28 | + | - | - | - |
| 28 | + | - | - | - |
| 29 | - | - | - | + |

**TABLE 12** - cont'd

| Age of Occlusion (months) | Total Continuous Occlusion only | Anisometropia (1.50D or more) | Visual Acuity 6/36 or Better | Good Fixation and/or Binocular Single Vision |
|---|---|---|---|---|
| 30 | + | + | - | - |
| 30 | + | - | - | + |
| 30 | + | - | - | - |
| 31 | + | + | - | - |
| 31 | + | - | +6/36 6/6 | - ? |
| 31 | + | - | - | - |
| 31 | - | - | - | - |
| 32 | + | - | - | - ? |
| 33 | + | - | - | + |
| 33 | + | - | - | - |
| 33 | - | + | - | - |
| 34 | + | - | - | - ? |
| 35 | + | - | +6/18 6/9 | - ? |
| 35 | + | - | - | + |
| 35 | - | + | - | - |
| 35 | - | - | +6/36 6/9 | - ? |
| 35 | - | - | - | - |
| 35 | - | - | - | - |
| 37 | + | - | - | - |
| 37 | + | + | - | - |
| 37 | - | + | - | - |
| 38 | + | - | - | - |
| 38 | + | - | - | - ? |
| 38 | - | - | +6/18 6/9 | + |
| 39 | + | - | - | - |
| 39 | + | - | +6/36 6/6 | - ? |
| 39 | + | - | +6/36 6/6 | + ? |
| 40 | - | - | - | + |
| 41 | + | - | - | - |
| 41 | - | + | - | - |
| 42 | - | + | - | - ? |
| 43 | + | - | - | - |
| 43 | - | - | - | - ? |
| 45 | + | - | - | + |
| 48 | - | - | - | - |
| 50 | + | - | - | - |
| 50 | + | - | - | - ? |
| 52 | - | - | +6/9 6/5 | - ? |
| 53 | + | - | - | - |
| 65 | - | - | +6/36 6/5 | + |

demonstrated, and the immediately preceding one was undoubtedly variable.

The age of transfer of fixation was taken as the age at the mid-point of the period of occlusion during which the transfer occurred. This ranged from nine months to six years and 10 months (Fig. 28). The graph for the age of

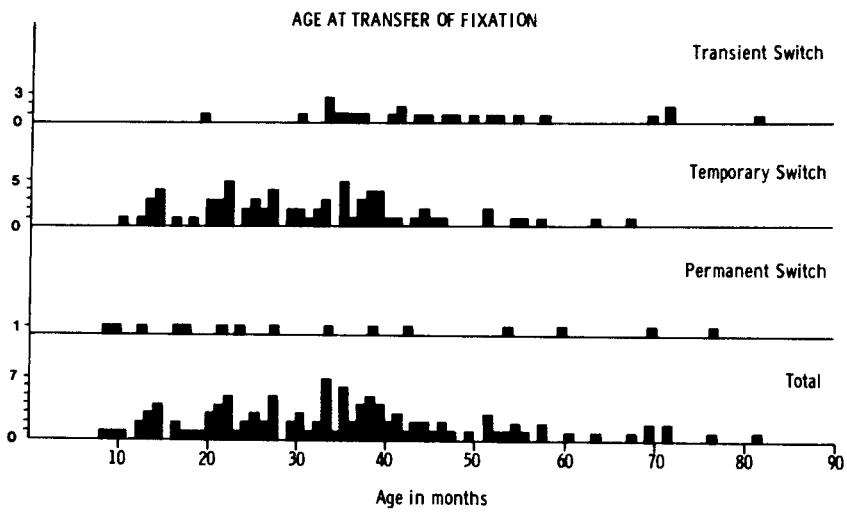



Fig. 28 Age at transfer of fixation taken as the age at the middle of the last period of occlusion immediately before the visit during which switch of fixation was demonstrated. Most patients were under 6 years of age [Assaf, 1982a].

switch of fixation (Fig. 29) shows that the peak of the permanent switch cases was in the second year of life, the temporary switch cases at the third year, and those of the transient switch at the fourth year of life. Fig. 28 shows that only one patient had transient switch of fixation below the age of 30 months and this patient at the age of 20

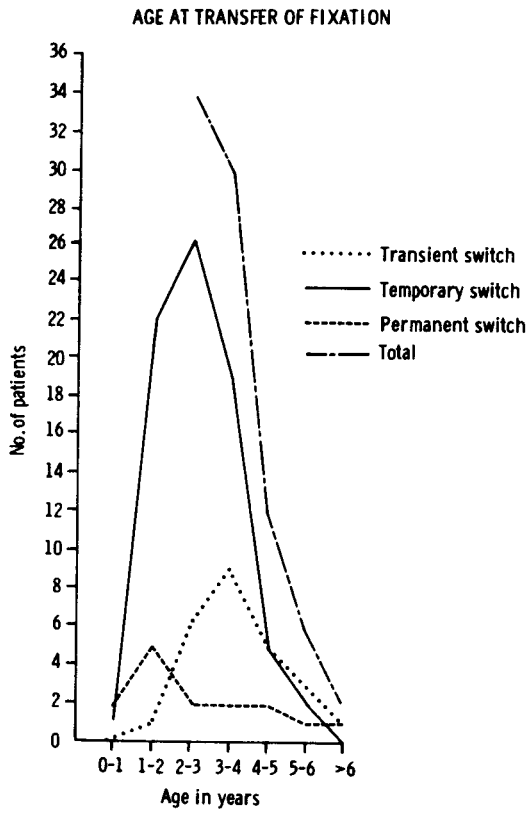



Fig. 29 Graph for the age at the transfer of fixation according to the type of switch. Notice patients with permanent switch of fixation had a peak age between 1-2 years. Temporary switch between 2-3 years and those with transient switch between 3-4 years of age [Assaf, 1982a].

months had only one week of total continuous occlusion. So younger patients tended, if they transferred fixation at all, to have at least a temporary, if not permanent, transfer. This difference in age is significant at the 1%

level. All three groups showed a decrease in the number of patients at the end of the fifth year of life.

9) Duration of Occlusion:

The relationship between the duration of occlusion and the age of occlusion, in the production of switch of fixation, cannot be usefully assessed in those patients who had various forms of intermittent and/or partial occlusion. The relationship in those who had continuous total occlusion is shown in Figs 28,29. The continuous line shows the period

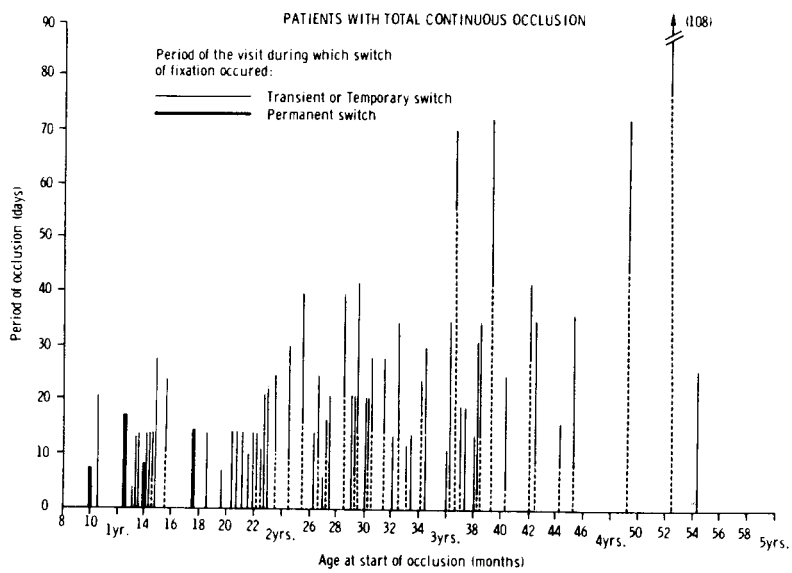



Fig. 30 Patients who switched fixation after total continuous occlusion only. Four under the age of 18 months had permanent switch, all other patients had either temporary or transient switch. The duration of occlusion increased with age, with variations which could be explained in most cases by the refractive state, visual acuity, and fixation prior to occlusion and the type of switch produced. None of the patients was older than $4\frac{1}{2}$ years [Assaf, 1982a].

of occlusion during which the switch of fixation occurred,

its upper end giving the total period of occlusion. Switch of fixation could have occurred at any time during this period. This figure shows a wide range of scatter, but this could be explained by variations in the state of visual acuity and fixation before occlusion, binocular single vision, refractive state, duration of squint and the type of switch produced in addition to how strictly the patient carried out the instructions for total continuous occlusion.

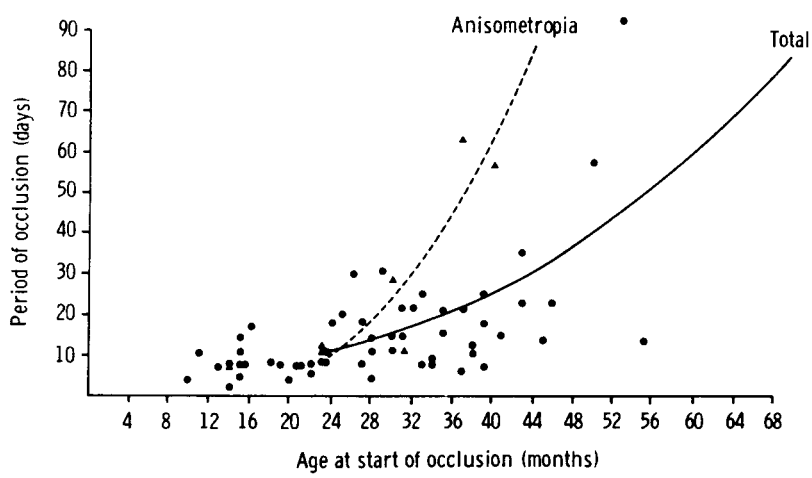



Fig. 31 This diagram represents patients who switched fixation after total continuous occlusion only. The dots represent the duration of occlusion up to the middle of the period between the visit during which switch of fixation was detected and the immediately preceding one. The length of this last period varied in different patients and switch of fixation could have occurred at any time during it. Patients with anisometropia leave the sequence of the main group at about 2 years of age, becoming more resistant to occlusion. By the age of $3\frac{1}{2}$ resistance to occlusion becomes very marked. After $3\frac{1}{2}$ to 4 years of age resistance to occlusion becomes more marked, especially in the presence of poor visual acuity and/or fixation. None of the patients was older than $4\frac{1}{2}$ years [Assaf, 1982b].

The fit of the curve impoves dramatically if the state of visual acuity and fixation prior to occlusion, type of transfer of fixation, and the presence of anisometropia were included in plotting the duration against the age of occlusion.

Nevertheless, there is an obvious relationship between the age at occlusion and the duration of occlusion, the reversal of fixation occurring quicker in the younger age group (statistical significance on regression analysis). The youngest patient to switch after total continuous occlusion was 10 months and the oldest was four years and seven months at the start of occlusion. Most of the patients below two years of age switched fixation after one period of total continuous occlusion and mostly within two weeks of occlusion. There is a noticeable increase in resistance to occlusion after this period, and resistance to occlusion reaches a high level after the age of four years.

Children with permanent switch of fixation are in many ways the most interesting, since it implies that permanent damage could be produced to fixation and visual acuity. All these patients had energetic occlusion in an attempt to reverse the transfer of fixation. The age of occlusion at which switch occurred in this group extended to 64 months of age (Fig. 32) and the age of transfer extended to 77 months. Patients under the age of 18 months needed a relatively short time of occlusion to transfer fixation. Four

patients with permanent transfer switched after total continuous occlusion only; all were below the age of 18 months.

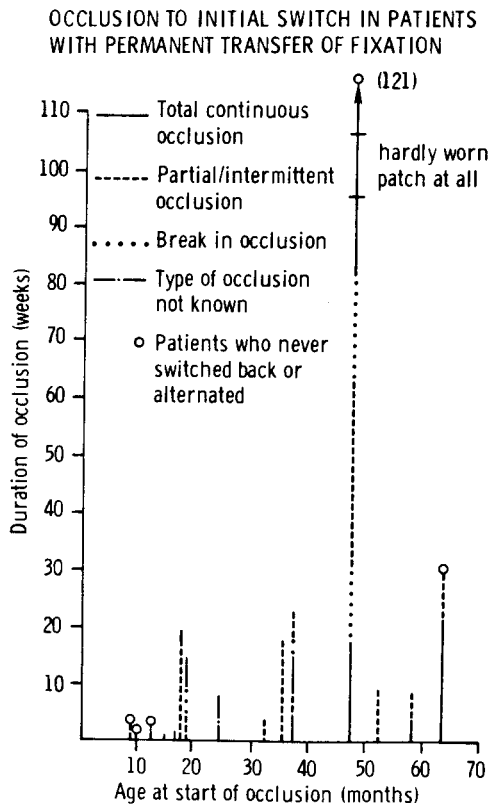



Fig. 32 Period of occlusion in patients with permanent switch of fixation. Patients under 18 months of age had relatively shorter periods of occlusion. Five patients never switched back or alternated. Three were under 13 months of age, and 2 had prolonged initial total continuous occlusion. None of the patients were older than $5\frac{1}{2}$ years of age at the start of occlusion [Assaf, 1982a].

Five of these patients never switched back or alternated after the initial transfer of fixation, in spite of reversal of occlusion, indicating considerable damage to the

fixation mechanisms. Three of these patients were below 14 months of age and two had prolonged periods of occlusion, one after about 7 months of mostly total continuous occlusion, and the second over 2 years of interrupted occlusion (Fig. 32).

10) Refractive Errors:

Anisometropia was considered 1.5 diopters difference or more between the two eyes. Seventeen patients had anisometropia (Table 13). It is of interest to find that none of the permanent switch patients had anisometropia of this amount and this had weak statistical significance (significant at 10% level). Relatively more anisometropic patients had transient rather than temporary switch.

TABLE 13

Patients with anisometropia of 1.5D difference or more as related to the type of switch

(Assaf, 1982b)

| | Transient | Temporary | Permanent | Total |
|---|---|---|---|---|
| Anisometropia | 6 | 11 | 0 | 17 |
| No anisometropia | 19 | 64 | 15 | 98 |
| Total | 25 | 75 | 15 | 115 |

The only patients in whom the relation between the sensitivity and duration of occlusion can be assessed with some accuracy are those who had total continuous occlusion only. By analysing such patients (Fig. 31) it will be seen that sensitivity to occlusion for patients with anisometropia leaves the curve for the whole group at about two years of age at the start of occlusion, showing that they become more resistant to occlusion. By the age of $3\frac{1}{2}$ years, resistance to occlusion reaches a much higher level. No anisometropic group switched fixation in the total continuous occlusion patients beyond the age of 40 months. Only two patients switched fixation beyond this age in the whole group, one at 47 months and the other at 63 months. Both of these patients had previous occlusion at the ages of 33 and 42 months respectively, i.e. had intermittent occlusion. This last patient was the oldest patient with anisometropia to switch fixation in the whole group, with an age of $3\frac{1}{2}$ years at the start of occlusion.

11) Visual Acuity and Fixation at the start of Occlusion:

The visual acuity at the beginning of occlusion was often not recordable with high accuracy. Relatively more patients with a visual acuity of 6/36 or better, binocular single vision, as measured by stereoacuity and intermittent or good fixation in the squinting eye were in the transient and permanent switch groups as compared to those of temporary

switch (Table 14). Also less eccentric or poor fixation patients were present in the transient group (8/25) than in the temporary switch group (42/75). These differences were significant at the 5% level. This was possibly due to patients

**TABLE 14**

**Visual acuity, binocular single vision and fixation before occlusion**

(Assaf, 1982b)

| | Transient | Temporary | Permanent |
|---|---|---|---|
| - Visual acuity of 6/36 or better | 6 | 8 | 3 |
| - Binocular single vision present at times | 5 (13) | 2 (20) | 2 (7) |
| - Central/good fixation | 2 | 10 | 2 |
| - Slow to fix/unsteady/poor fixation | 3 | 25 | 4 |
| - Eccentric fixation | 5 | 17 | 0 |
| - Not stated | 4 | 13 | 4 |
| - Total | 25 | 75 | 15 |

with transient switch being older at the start of occlusion and unlikely to switch fixation if they had poor or eccentric fixation. None of the patients with eccentric fixation was present in the permanent switch group. In 21 patients the state of fixation was not recorded.

In Figure 28, for patients who had total continuous occlusion only, five patients had an age of occlusion of

over 43 months. Those patients with ages of 45 and 55 months had visual acuity of 6/36 in the amblyopic eye at the start of occlusion, but the last patient had only transient switch. The patient with an age of 46 months had poor visual acuity, but had transient switch. Only the patients with the ages of 50 and 53 months had poor visual acuity and temporary switch. It is apparent that under the age of about $3\frac{1}{2}$ years patients switch fixation in less than about one month of total continuous occlusion if they are to switch readily. Beyond that age there is a marked increase in the duration of occlusion required to produce switch of fixation in patients with poor visual acuity and/or poor fixation at the start of occlusion.

A total of 14 patients switched fixation at the age of occlusion of over 4 years. Ten had a visual acuity of 6/36 or better, 4 did not. One of these 4 was a 5 years and 4 months old child at the start of occlusion and had permanent switch of fixation after 7 successive months of mostly total continuous occlusion. Of these 14 patients, 8 had transient switch, 3 temporary and 3 had permanent switch.

12) Visual Acuity versus Fixation immediately after Switch:

In many cases it is apparent that switch of fixation occurred before any decrease in visual acuity in the occluded eye. It occurred in spite of the presence of equal or worse visual acuity in the originally deviating eye

which is now the fixing eye. This is more apparent in patients who had intermittent/partial occlusion (Table 15), presumably with more chance of seeing the patient at an

**TABLE 15**

**Visual acuity immediately after switch in patients who had switch of fixation in spite of the presence of worse or equal visual acuity in the originally squinting eye**

(Assaf, 1982b)

| Original Strabismus | Visual acuity and strabismus after switch | | | | | Type of occlusion |
|---|---|---|---|---|---|---|
| RCS | 6/12 | 6/9 | LCS | | | Partial and/or intermittent occlusion |
| LCS | 6/6 | 6/12 | RCS | | | |
| LCS | 6/6 | 6/6 | RCS | | | |
| RCS | 6/12 | 6/6 | LCS | | | |
| LCS | 6/6 | 6/6 | RCS | | | |
| RCS | 6/12 | 6/12 | LCS | | | |
| LCS | 6/5 | 6/5 | RCS | | | |
| RCS | 6/9 | 6/9 | LCS | | | |
| RCS | 6/6 | 6/9 | LCS | -> 6/6 | 2/60 | |
| | (in one month without further occlusion) | | | | | |
| LCS | 6/9 | 6/9 | RCS | | | |
| LCS | 6/9 | 6/9 | RCS | | | |
| RCS | 6/12 | 6/12 | LCS | | | |
| RCS | 6/6 | 6/6 | LCS | | | |
| LCS | 6/9 | 6/9 | RCS | | | |
| LDS | 6/9 | 6/9 | RDS | | | |
| RCS | 6/9 | 6/5 | LCS | | | |
| RCS | 6/6 | 6/6 | LCS | | | |
| RCS | 6/9 | 6/6 | LCS | | | |
| RCS | 6/12 | 6/9 | LCS | | | |
| LCS | 6/18 | 6/18 | RCS | -> 6/24 | 6/18 | Total continuous occlusion |
| LCS | 6/9 | 6/9 | RCS | | | |
| LCS | 6/9 | 6/9 | LCS | -> 6/18 | 6/6 | |
| | (in three months without further occlusion) | | | | | |
| RCS | 6/12 | 6/9 | LCS | -> 6/9 | 6/12 | |
| | (in seven months) | | | | | |
| LCS | 6/12 | 6/18 | RCS | | | |
| RCS | 6/12 | 6/12 | LCS | | | |
| RCS | 6/9 | 6/6 | LCS | | | |
| RCS | 6/18 | 6/12 | LCS | | | |
| LCS | 6/18 | 6/18 | RCS | | | |
| LCS | 6/6 | 6/9 | RCS | | | |

early stage of switch before any change in the visual acuity. In one patient visual acuity in the newly deviating eye dropped from 6/9 to 2/60 in one month without any further occlusion.

13) Visual Acuity on Discharge:

It is interesting to note that patients with permanent switch of fixation had the best outcome of visual acuity in the worst eye followed by temporary switch patients as compared to patients with transient switch (Table 16). (There was no statistical difference between the three groups).

TABLE 16

Visual acuity on discharge

(Assaf, 1982b)

| Visual acuity in worst eye | Transient | Temporary | Permanent |
|---|---|---|---|
| 6/9 or better | 16 (64%) | 55 (73%) | 13 (87%) |
| 6/12 or worse | 9 | 20 | 2 |
| Total | 25 | 75 | 15 |

14) Binocular Single Vision on Discharge:

Only two patients in the whole group had good binocular single vision on discharge. These were occluded at the ages of 33 and 43 months of age and belonged to the transient switch group (Table 17).

TABLE 17

Binocular single vision on discharge

(Assaf, 1982b)

| | Transient | Temporary | Permanent |
|---|---|---|---|
| Good (100" or better) | 2 | 0 | 0 |
| Moderate (up to 400") | 4 | 4 | 3 |
| Gross (above 400") | 3 | 5 | 2 |
| Negative | 13 (3 alternate suppressions) | 63 (17 alternate suppressions) | 9 |
| Not stated | 3 | 3 | 1 |
| Total | 25 | 75 | 15 |

## IV. THE SENSITIVE PERIOD

The sensitive period in man has recently received increasing interest following the findings in experimental animals. These results are still not reflected widely in the practice of paediatric ophthalmology. Amblyopia can be prevented and treated if obstacles to normal visual function are removed early enough within this period, thus allowing normal development to be resumed. The period during which the developing visual system is affected by alteration in the visual function is called the sensitive period. There is some confusion in the literature about the difference between the critical period and the sensitive period, sometimes they are used interchangeably. But the term critical period should be reserved for the most sensitive part of the sensitive period, when brief periods of visual deprivation can produce marked effects on the visual system.

We have seen in Part 2 how the visual system develops post-natally and how clinical situations which interfere with normal development by visual deprivation or by preventing normal binocular co-operation result in amblyopia. The age at which amblyopia can be induced and reversed may indicate the limits of the sensitive period. Switch of fixation produced in response to monocular occlusion might also be used to delineate the limits of the sensitive period. This may reflect the maturity of the fixation

mechanism. The development of this mechanism on the other hand is a separate process from the development of many other visual functions and its process of maturation may or may not reflect the general maturation of the visual system. Nevertheless, some conclusions can be drawn.

The period of susceptibility to switch of fixation after occlusion was found to extend between 9 months and 6 years and 10 months. The lower limit is probably determined, in this study, by the small number of patients occluded at such an early age rather than by the sensitivity to occlusion. Analysis of the number of patients switched at different ages and the type of switch produced showed that sensitivity during this period varied greatly as a function of age. From this analysis, the sensitive period, for transfer of fixation could be classified into stages :

**A. CRITICAL PERIOD**

This is the part of the sensitive period with most susceptibility to visual deprivation. During this period as little as one or two weeks of total continuous monocular occlusion (deprivation) can produce switch of fixation and amblyopia, sometimes permanent, especially if not treated by reverse occlusion. It extends up to 18 months of age with patients under 14 months being more vulnerable. It declined gradually to 24-30 months of age [Assaf, 1982a]. These conclusions were drawn from the following

observations:

1. The three patients under 14 months of age in the permanent switch group, switched fixation after a short period of occlusion and never switched back or alternated.

2. The four patients who had permanent switch of fixation after total continuous occlusion were under 18 months of age.

3. Those patients below 18 months of age in the permanent switch group needed relatively shorter periods of occlusion to switch.

4. Most of the patients under two years old in the total continuous occlusion patients switched fixation with one period of total continuous occlusion and mostly within two weeks of occlusion.

5. The peak of the permanent switch group was in the second year of life.

6. Transfer of fixation below 30 months of age was permanent or temporary rather than transient.

These conclusions support other studies on the development of the visual system and different clinical situations with visual deprivation in childhood:

The supportive evidence from the anatomical and physiological growth includes :

1) The dimensions of the eyeball are essentially similar to the adult by two years of age [Sorby et al, 1956, 1961; Mann, 1931; von Alphen, 1961].

2) Cell densities in the macula approaches those of adult range at 2-2$\frac{1}{2}$ years of age [Streeten, 1969].

3) Optic nerve myelination is completed by 2 years of age [Magoon & Robb, 1981].

4) Cellular growth in the lateral geniculate nucleus is complete by 2 years of age [Hickey et al, 1977a,b].

5) The critical age for the development of binocular vision in humans was found to be about 2-2.6 years of age [Hohmann & Creutzfeldt, 1975].

6) Visual evoked responses reached adult configuration by 24 months of age [Arden & Barnard, 1979].

This indicates that the visual system is essentially anatomically mature by two years of age. The end of significant anatomical growth coincides with the end of the critical period. In addition, indirect supportive evidence can be drawn from the growth of the brain in general. The brain reaches 75% of its adult weight by 2$\frac{1}{2}$ years of age [Rose, 1976]; in addition, a second major period of cellular multiplication in the human brain ends in the second year of post-natal life [Dobbing & Sands, 1970].

Furthermore, within the first two to three years of life, complex brain functions, such as walking and language,

develop [Miller, 1962; Hirsch, 1970].

The supporting evidence derived from stimulus deprivation amblyopia include :

1) Awaya et al [1979a] found that the critical period in man extends up to 18-24 months of age.

2) Von Noorden [1981] concluded that the critical period in humans extended up to 30 months of age. This is similar to the present findings [Assaf 1982a]. The supporting evidence from studies on strabismus cases is mainly derived from cases with congenital esotropia. Such patients, if brought to within 10 prism diopters of orthophoria during the first 2 years of life may have good prognosis for vision and binocular single vision [Taylor, 1972; Foster et al, 1976; Parks, 1981; Ing, 1983].

Anisometropic patients are different from the rest of the group only after 2 years of age [Assaf, 1982b]. This concurs with other authors who found no astigmatic amblyopia during the first year of life [Held, 1977; Atkinson & Braddick, 1982b] and only detected it during the third year of life [Mohindra et al, 1978; Fulton et al, 1980].

B. **STAGE OF CONSIDERABLE SENSITIVITY**

During this period, a few weeks of total continuous monocular deprivation can cause switch of fixation and amblyopia. This period extended up to $3\frac{1}{2}$ years of age [Assaf, 1982b]. This is supported by the following:

1. Only three patients switched fixation with an age of onset beyond $3\frac{1}{2}$ years. These three patients had good visual acuity in their amblyopic eye.
2. No anisometropic patients of 1.5D or more switched fixation beyond $3\frac{1}{2}$ years of age at the start of occlusion.
3. From analysing patients who switched fixation after total continuous occlusion, it will be seen that patients with poor visual acuity had a marked increase in resistance to occlusion after $3\frac{1}{2}$ years of age (Figure 30).
4. The peak of the temporary switch group was in the third year of life.

As seen, the development of many visual functions occurs along with marked anatomical growth within the critical period, which is followed by a period of consolidation and maturity. This, probably, is largely achieved within this stage and extending into the next stage to approximately the age of $5\frac{1}{2}$ years. Thus, the visual acuity is effectively at adult levels by $3\frac{1}{2}$ years of age [Atkinson &

Braddick, 1982a]. In addition, good stereoscopic acuity is not achieved until about 3-5$\frac{1}{2}$ years of age [Amigo, 1972; Romano et al, 1975]. Furthermore, binocularity is more or less firmly established by this age [Banks et al, 1975]. Thus, patients whose age of onset of strabismus is after 3-4 years, have better visual acuity and stereopsis results after therapy [Worth, 1903; Stanworth, 1949; Banks et al, 1975]. Picetti & Fine [1966] advised keratoplasty for corneal opacities before the age of 3-4 years if amblyopia is to be avoided. Similarly, occlusion for cases of monocular cataract is most effective before 4 years of age [Vaegan & Taylor, 1979].

## C. STAGE OF REDUCED SENSITIVITY

This extended from 3$\frac{1}{2}$ years up to the age of 5$\frac{1}{2}$ years [Assaf, 1982a]. In a patient with poor visual acuity in the amblyopic eye, a few months of total continuous occlusion is usually needed before switch of fixation and amblyopia can occur. This is supported by:

1. Few patients (seven) switched fixation beyond 5$\frac{1}{2}$ years.
2. Few patients (two) switched fixation with short periods of total continuous occlusion after 4 years of age.
3. All patients with permanent switch of fixation were aged 5$\frac{1}{2}$ years at the start of occlusion.
4. Older patients, over four years of age, tended to have transient switch and have good visual acuity of 6/36 or

better before occlusion, in their amblyopic eye.

5. The peak of the transient switch group was in the fourth year of life.

At this stage visual functions are firmly rooted, especially those affecting visual acuity and binocularity. Only prolonged total monocular deprivation, over a few months, can affect these functions. This is supported by the findings of many studies on strabismus and deprivation amblyopia [Juler, 1921; Frey et al, 1973; Shaprio et al, 1978; von Noorden, 1981]. Finally, strabismus rarely occurs after the age of 5-6 years. Predictably, strabismic amblyopia rarely develops after the age of 6 years, and when present is less likely to respond to occlusion after that age.

## D. STAGE OF LOW SENSITIVITY

This extended from about $5\frac{1}{2}$ years to approximately the end of the 7th year of life [Assaf, 1982a]. Deprivation effects at this stage tended to be transient except in cases of prolonged deprivation. This is supported by the findings in congenital and juvenile cataracts [Braendenstrup, 1944; Francois 1979; von Noorden & Crawford, 1979], or other forms of stimulus deprivation amblyopia [Pitcatti & Fine, 1966; Singh & Das, 1978; Awaya et al, 1979a]. In addition, strabismus rarely starts, if at all, after the age of 7 years and strabismic amblyopia in

general rarely responds to occlusion beyond this age.

By the 7th year of life, it is quite unlikely that visual deprivation can affect visual function to any permanent degree. By this time, visual acuity, visual evoked potential, binocularity and stereopsis are adult in character [Amigo, 1972; Banks et al, 1975; Romano et al, 1975; Sokol & Jones, 1979; Bishop, 1981; Gardiner, 1982; Atkinson & Braddick, 1982a;]. Furthermore, the brain as an organ matrues, reaching 90% of adult weight by the age of 6 years.

In spite of the clinical findings on the recovery of visual function after occlusion, the full potential of the recovery from the effects of visual deprivation can only be unmasked by enucleation of the experienced eye. From clinical experience, such recovery can still occur well into adulthood. This is probably an essential part of the inherited plasticity of brain functions. Furthermore, there must be individual variations, within a normal range, in the rate of growth and maturity, reflecting different individual sensitivity at different ages.

## V. REVERSAL OF THE EFFECTS OF VISUAL DEPRIVATION

As noted previously, there is still controversy about the reversibiity of the amblyopia which results from visual deprivation in man, particularly that occurring during the critical period. Some state that short periods of deprivation during the critical period can produce permanent effects which are not reversed by reverse closure [Awaya, 1973; Awaya et al, 1979]. Others maintain that such an effect is transient and there is speedy recovery after a return to normal function [Hartwig et al, 1976; Odom et al, 1981; Jacobson et al, 1983].

In the present study it was possible to assess the recovery of fixation and visual acuity in some patients.

### A. RECOVERY OF FIXATION

Only 15 patients had permanent switch of fixation. Of these, only 5 never switched back or alternated. The remainder switched back after reverse occlusion, but after further various forms of deprivation switched back to fix with the originally squinting eye for a few years before discharge. Of those patients who never switched back or alternated, 3 were under 14 months of age and switched after a fairly short period of occlusion. One patient, occluded at the age of 9 months with 3 weeks of occlusion "as much as possible". A second patient occluded at the age of 10 months for one week of total continuous occlusion and the

third was 13 months of age and switched after 17 days of total continuous occlusion. The other two had obvious prolonged occlusion (Fig. 32). One patient occluded at the age of 4 years for 121 months with total continuous and interrupted or part-time occlusion. The last period of occlusion extended for approximately 3 months of constant occlusion and switched the balance from visual acuity of 6/12 (R) 6/9 (L) and suspected left convergent squint (the patient had right convergent squint) to 6/6 (R) 6/36 (L) with constant left convergent squint. The second patient was occluded at the age of 64 months (5 years and 4 months) and occluded for 7 months of mostly total continuous occlusion. These patients had energetic occlusion in the hope of producing reversal, but continued to fix with the originally deviating eye. From this it is concluded that it is possible to produce permanent damage to the fixation mechanism with short periods of occlusiion, especially during the critical period. Prolonged periods of visual deprivation can also produce permanent damage to fixation as late as 5 years and 4 months at the start of occlusion, but the period of deprivation has to be continuous and extend over a period of a few months.

## B. RECOVERY OF THE VISUAL ACUITY

Only two patients had significant irreversible amblyopia in the newly deviating eye. These were among those

with a permanent switch of fixation. One had a visual acuity of 6/24 and was occluded at 10 months of age. The second was occluded at 4 years of age and was discharged with a visual acuity of 6/36. Both had energetic occlusion aimed at reversal. In addition, only 3 patients had a visual acuity difference of two lines, being 6/5 in one eye and 6/9 in the originally fixing eye. These patients, as expected, were among the permanent switch group and were occluded at the ages of 9 months, 15 months and 64 months. Thus, in the whole group all patients occluded under 15 months of age had residual amblyopia and permanent switch of fixation. One patient occluded at 13 months of age had a divergent squint to start with, and was discharged with 6/9 visual acuity in either eye. The two older patients (4 years, 5 years and 4 months) had prolonged periods of occlusion.

Thus, it is apparent that permanent damage to visual acuity can occur and is a sequel to damage to the fixation mechanisms.

It may be noted that occlusion produced transfer of fixation before any changes in the visual acuity (Table 15). This could indicate either that the drop in the visual acuity in the occluded eye is secondary to the transfer of fixation, or lowered visual acuity has a less rapid onset, perhaps following structural changes which may occur in the

visual centres on visual deprivation during the sensitive period [Assaf, 1982b]. The first is the most likely explanation, since it has been shown that monkeys with surgically-induced esotropia had normal visual acuity until 4 weeks post-operatively. After this period amblyopia began to develop. The deviated eye showed poor acuity at every subsequent age tested [Kiorpes & Boothe, 1980]. Similar findings were reported in kittens with esotropia, where there was a period of continued normal development of 2-3 weeks duration after the onset of esotropia, before acuity differences between the two eyes became apparent [von Grunau, 1979].

## C. RECOVERY OF BINOCULAR VISION

Of the whole group, only two patients had stereoscopic acuity of 100 seconds of arc or better. These two patients, with ages of occlusion of 33 and 43 months, were among the transient switch group. This is presumably because these patients tended to have a fairly good visual acuity and possessed some binocular single vision and were thus occluded less severely.

It might be concluded that switch of fixation is something clinically undesirable or difficult to reverse, but this was evidently not the case. It was much easier to under-occlude than to over-occlude, thus stopping short of the best possible improvement of visual acuity in the

amblyopic eye. Patients with permanent transfer of fixation very rarely had damage to the fixation and visual acuity severe enough to result in permanent marked amblyopia in the occluded eye. Comparatively, these patients with permanent switch had relatively the best outcome of visual acuity in the worst eye. The least improvement in visual acuity was in the transient group, which is probably due to the fact that relatively larger numbers of these patients had good visual acuity, binocular vision or good fixation at the beginning of treatment and hence were occluded with milder forms of occlusion. Most had partial/intermittent occlusion. It may be added that these patients were older and therefore probably less responsive to occlusion.

## VI. SUMMARY

Patients who had occlusion of the fixing eye in the course of treatment for strabismic amblyopia and developed switch of fixation were analysed. Out of a total of 1904 cases occluded only 115 patients switched fixation. They were analysed in order to determine the sensitive period for that occurrence. This was found to extend between 9 months, to the end of the 7th year of life. The beginning is approximate because of the few patients occluded at such an early age.

The period of greatest sensitivity, the critical period for switch of fixation extended to 18 months, declining gradually to about 30 months of age. During the critical period as little as one or two weeks of total continuous occlusion can produce switch of fixation. A period of considerable sensitivity to occlusion extended to $3\frac{1}{2}$ years of age, when a few weeks of deprivation are needed to switch fixation. Beyond that, sensitivity to occlusion declined considerably extending up to the age of $5\frac{1}{2}$ years, when months rather than weeks of visual deprivation is needed to switch fixation. Beyond this age, switch of fixation can still occur, but it follows only prolonged monocular occlusion and tends to be transient (Fig. 33).

The critical period for switch of fixation corresponds well with the period of rapid post-natal anatomical growth

at different levels in the visual system. A later period with less susceptibility to occlusion coincided with the period of consolidation and maturity of the visual physiological processes laid down during the critical period. This period was also associated with a period of reduced anatomical growth.

It was noticed that switch of fixation in many patients preceded any deterioration of the visual acuity in the newly deviating eye. Moreover, permanent damage to fixation and visual acuity can occur after one or two weeks of occlusion during the critical period, and after a few months of successive total continuous occlusion in older patients up to $5\frac{1}{2}$ years of age. No recovery of binocular single vision occurred.

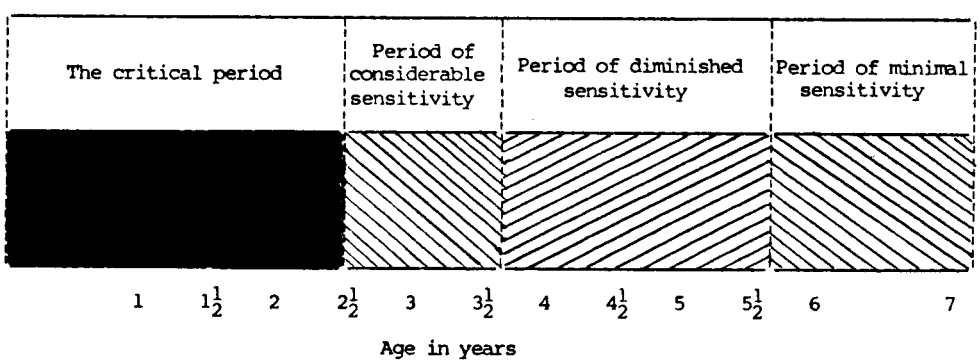



Fig. 33 The sensitive period for transfer of fixation in man extended up to 7 years of age. This period can be subdivided into intervals of decreasing sensitivity ranging from a critical period to a period of minimal sensitivity.

# GENERAL CONCLUSION

The term "Sensitive Period" is used to describe a period of intense post-natal development of the visual system. During this period, structural, functional and biochemical changes occur, leading to the ultimate emergence of stereoscopic vision. Visual deprivation during this period can drastically affect the function of the visual system.

Definition of the sensitive period of the visual system has been studied extensively in experimental animals, particularly the cat and the monkey, using a variety of techniques. The most widely used tool in these studies has been visual deprivation. Visual deprivation in animals can produce anatomical, physiological or biochemical changes in the visual system if it occurred within the sensitive period. The age at which visual deprivation effects can be produced and/or reversed is used to outline the sensitive period. The most pronounced effects of visual deprivation noted in monkeys and cats occur during the first 12 weeks of life. The sensitive period thus defined correlates well with the period of post-natal growth and functional maturity of the visual system. In both cats and monkeys there lies within the sensitive period an interval, the critical period, during which deprivation effects can be produced by brief periods of deprivation with more lasting effects. This critical period coincides with a period characterised by

intense anatomical growth in the visual system.

The sensitive period in children is inferred from finding the ages at which amblyopia can be both induced and reversed. This was thought to extend up to approximately 6 years of age, with the first 18 months to 2 years representing the critical period.

Another method was used by the author to indicate the sensitive period during which switch of fixation can be produced after occlusion therapy for strabismus amblyopia. The sensitive period, defined by switch of fixation, may be subdivided into intervals of decreasing sensitivity, ranging from the critical period to one of minimal sensitivity. It extended to 7 years of age, with the first 18-30 months representing the critical period. This period largely coincided with the period of post-natal anatomical growth and functional maturity of the human visual apparatus, with the critical period coinciding with the time of maximal anatomical growth and differentiation of the eye and its connections within the central nervous system. The sensitive period for switch of fixation also coincided with the period of development of stereoscopic vision, relative importance of abnormal visual experience, the age of onset of concomitant strabismus in children, and the age at which no permanent amblyopia is produced after unilateral traumatic cataract (Fig. 34).

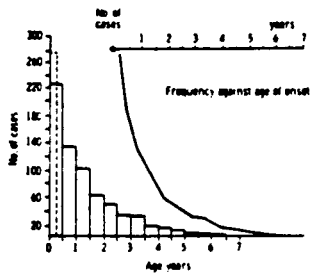
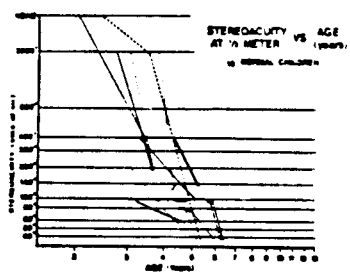
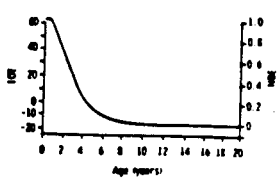
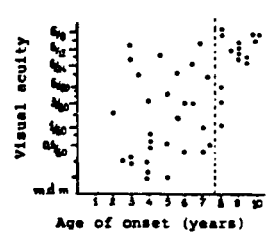
| Figure | Subject | Author |
|---|---|---|
|  | Age of switch of fixation | Assaf [1982a] |
|  | Age of onset in esotropia | Keiner [1951] |
|  | Development of stereopsis in young children | Romano et al [1975] |
|  | The relative importance of abnormal binocular experience from birth to 10 years of age | Banks et al [1975] |
|   | Function/Age of onset after unilateral traumatic cataract | Braendstrup (1944) |

**Fig. 34** Age of switch of fixation paralleled the age of development of stereopsis, age of onset of strabismus and the period of relative importance of binocular experience for the development of binocular vision in man. This is compared with the functional results after unilateral traumatic cataract in young children [Assaf, 1983].

In conclusion, it has been demonstrated that a period of diminishing sensitivity to visual deprivation occurs in children. It coincides with the period of normal postnatal anatomical and functional growth of the visual apparatus, which reaches its definitive form at around 7 years of age, with a normal range of individual variations. The clinical implications are well known. Unless obstacles causing visual impairment during this period are removed, it is clear that vision itself as well as its ultimate synthesis, stereopsis, will be damanged. The amount of damage will naturally depend on the time of development at which deprivation occurs, its type and duration, and indirectly upon the age at which therapy is undertaken. Hence, the treatment of strabismus and other conditions causing visual impairment which fall within the sensitive period, is a matter of urgency increasing inversely with the child's age.

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