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Amblyopia☆

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AMBLYOPIA

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When the eye is developing after birth, it has to be stimulated in certain ways in order for it to develop properly, just like any other organ in the body. It is simply not good enough to have the eye stimulated with light, because light alone is not sufficient for adequate eye development. One of the things the visual system needs are figures - such as parallel lines or lines perpendicular to each other. We call this "form vision." The light must also be properly focused on the back of the eye. Therefore, when you are born, your eyes have to be optically perfect or near perfect for them to develop properly. Amblyopia is *cortical* maldevelopment, not eye maldevelopment, and it occurs when the eye does not receive this necessary "form vision" or when there is an unequal ability of the eyes to focus.

Amblyopia is generally defined as a unilateral or bilateral decrease in visual acuity caused by form vision deprivation, abnormal binocular interaction, or both, for which no organic cause can be detected by the physical examination of the eye and which, in some cases, is reversible by therapeutic measures.¹ It often occurs as the result of congenital conditions that do not permit both eyes to focus simultaneously. For example, if there is congenital strabismus (squint), and the child utilizes one eye only, the unused eye will become amblyopic. The same holds true for congenital opacification of the ocular media, (that is, the cornea or the lens, which are normally clear), as in cataract or anisometropia (unequal refraction between eyes of the same individual). The reason for the reduction in vision appears to be a lack of proper connections from the retinal ganglion cells to other neurons in the central nervous system during postnatal development.

When you look into the eye of people with amblyopia, they have normal eyes. They look absolutely normal. But their visual acuity, that is, their ability to resolve objects in space or on paper or wherever, is poor in that eye. It often occurs as a result of congenital (at birth) improper lining up of the eyes. You've probably seen people who have an eye that goes in or out. When it goes in, we call that esotropia. When it goes out, it's exotropia. When you have that kind of a situation that persists beyond birth for a significant period, then the eye that is not being used by the child becomes

amblyopic. Regardless of how good it looks clinically or physically, the unused eye will then not be able to focus properly, making the patient essentially blind in that particular eye.

The other thing that may happen is that a child may be born with a unilateral cataract, or a scar in the cornea. That prevents the eye that's affected from receiving proper form vision. Even if treated properly later - with cataract surgery, for example -- at some later period in life during adolescence or adulthood, that eye will still not be able to see properly, even though it looks good, because the connections to the brain were never properly made. And that seems to be the major problem with amblyopia. It is not a problem in the eye itself, but rather, that the eye wasn't stimulated properly so that the brain did not receive the proper input when the cells that go from the eye to the brain developed.

In the last 30 years or so, there has been considerable experimental work aimed at trying to understand the processes which lead to amblyopia, by using nonhuman animals. Cats and nonhuman primates have been the most studied, but chickens and tree shrews also have been used. Experimental manipulations have included: suturing the eyelids closed; removing an eye; causing artificial strabismus (the shifting or crossing or uncrossing of the eye), either surgically or through the use of prisms, so that the world the animal sees is wrong in the eye that has the prism; or, rendering the ocular media opaque by either injecting substances into the cornea or creating artificial cataracts. There have been numerous assertions by those presently doing this sort of work that these manipulations have led to a significantly greater understanding of amblyopia and that the results have been used to develop treatment methods for affected humans. We need to examine this hypothesis.

There are major differences in the development and structure of the visual systems of humans and nonhuman animals.^{2,5} The cat, who is widely used, does not have a macula or fovea, two regions of the retina (located in the back of the eye and which functions like the film in a camera) of primary importance for human vision. These areas account for essentially all useful vision occurring in the human and it is the development, or lack thereof, of their connections in the brain that are of the utmost importance in amblyopia.¹

Because a cat does not have a fovea or a macula, it is not at all analogous to compare humans to cats. Although there are some general similarities between humans and cats with respect to neuroanatomy, the differences are so great that the results obtained in this work do not appear to have had any meaning for the human situation, as evidenced by the fact that reports on human clinical conditions do not reference this work. The

cat "model" cannot predict what changes may occur in humans when vision is deprived either monocularly or binocularly. Furthermore, the experimental situation in the cat and other nonhuman animals is entirely artificial, a perturbation of an otherwise normal animal. Spontaneously occurring visual deprivation in human children, however, often is associated with other developmental defects which tend to modify and confound the situation.

Although there are many structural and physiological similarities between certain nonhuman primates and humans, there may still be problems in extrapolating the information to the human situation. In some cases, for example with myopia, or nearsightedness, there is considerable difference between similar nonhuman primate species with respect to the results, following similar experimental manipulations.⁶ When atropine was used in one eye of either rhesus or stump-tailed macaques, different results were obtained with respect to the production of myopia. There was also a difference between these otherwise similar primates in the effects of artificially closing one eye. The obvious question is, if you have different results between closely related nonhuman primates, how do you know which of those nonhuman primates might mimic the human situation? Because of the considerable similarity to humans, the use of nonhuman primates also raises greater ethical concerns for many people, concerns that may make the use of these animals inappropriate.

There has been considerable concern expressed by vision scientists other than just myself that the experimental work is either not relevant or may be misleading with respect to the human condition and its treatment.^{1,7-12} Hoyt⁷ reported that nonhuman animal work had suggested that binocular patching, as done in phototherapy of jaundiced children, might be harmful. The data from children, however, suggested that binocular patching was not harmful. Marg⁸ pointed out that the results of examination of amblyopic children were at odds with some of the experimental work and that, along with the conflicting findings between nonhuman animal species, this seemed to demonstrate that one could not extrapolate nonhuman animal results to children with confidence. He stated that the nonhuman animal "models" were not entirely valid for children.

Metz⁹ noted that the type of occlusion done in experimental work was different from that used therapeutically in children with amblyopia. He was concerned because the experimental work done on cats could be interpreted to suggest that amblyopic children should not be patched. Such an interpretation, based on nonhuman animal studies, would be most unfortunate for amblyopic children.

Von Noorden and Maumenee¹² were critical of the classic work of Wiesel

and Hubel because of the substantial difference in neuroanatomy and neurophysiology between cats and humans (Hubel received a Nobel Prize for this). Von Noorden, who is one of the most famous vision scientists in the field of sight deprivation, later commented on how data from nonhuman animals could not be directly applied to humans, and that there were differences between monkeys and cats in the various studies done.¹ It is important to stress that this is from a vision scientist who strongly supports vision deprivation experiments. Yet, he recognizes that there are serious problems as far as extrapolation to people. In his Jackson Memorial Lecture¹¹, one of the more prestigious honors in the United States, he was again critical of nonhuman animal experiments with regard to infantile esotropia (convergent strabismus, or the inward motion of the eye or crossing of the eye shortly after birth). He pointed out that the monkey work was not analogous. He concluded that there is no animal "model" for infantile esotropia, despite all the work that had been done making infant monkeys strabismic, or cross-eyed.

When evaluating the claims for the importance of nonhuman animal work, one also must bear in mind that this work is largely neurophysiological, dealing with recordings of single cells in the brain. It does not measure vision, which has a large psychological component in people, and actually has little to do with vision in terms of behavior and function. This is even alluded to by some vision science researchers in their own publications.¹³ You cannot adequately study vision in nonhuman animals because you cannot communicate with them, and putting electrodes into single cells in the brain does not tell you whether and how the animals see. But, of course, that's not important to these researchers. Their interest, in many cases, is in single cell recordings.

In addition, some of this work has involved some rather serious suffering on the part of the nonhuman animals. For example, in one study, monkeys were deprived of sight in one eye for periods up to five years.¹⁴ In at least one case, one monkey was deprived of her or his sight in *both* eyes for a period of one year.¹⁵ In many cases, the eyes themselves have been removed in these and other sentient creatures.¹⁶

Animals also have been subjected to neuromuscular blocking agents such as gallamine triethiodide, sometimes with what appeared to be inadequate attention to anesthesia. These agents paralyze most of the muscles in the body, but leave the animal conscious and able to feel pain and anxiety even though they cannot respond by moving. In some cases, the experimenters did not appear to be aware that these agents *do not* provide any anesthesia or analgesia. In a letter to Richard Whitehead, dated 8 June 1987, Colin

Blakemore, who uses gallamine triethiodide extensively in his work, made the following statement: "there is the possibility that muscle relaxants themselves may have some anaesthetic or analgesic action . . ." This, of course, is preposterous in that it has been known for many decades that these agents have no anesthetic or analgesic properties.¹⁷

Blakemore, who is one of the leading defenders of experimental work involving nonhuman animals, has made the claim in a document entitled "A reply to criticism of experiments involving visual deprivation," dated September 1987, and written and distributed by Blakemore, that amblyopia "was poorly understood until about 25 years ago when experimental research involving animals began to tackle the question of its origin . . . in the absence of any real knowledge of the cause of the disease there was no single agreed (upon) method of treatment." This is at serious odds with the available facts. Treatment for, or prevention of, amblyopia had been successfully accomplished many years before the experimental work was even considered.^{12,18-21}

Cibis²⁰ recounted that Paulos of Aegina, in the seventh century, was the first to attempt what is now considered rational treatment of strabismus and amblyopia by using masks in an attempt to force the deviated eye to look straight ahead. She also pointed out that this concept was improved upon by von Graefe, Donders and other influential ophthalmologists in the nineteenth century because they correctly believed that strabismus caused amblyopia. Abraham,¹⁸ an ophthalmologist, noted that Claud Worth, a nineteenth century ophthalmologist, was recommending early treatment of anisometropia, or the unequal refraction ability between the two eyes, because he knew this condition would lead to strabismus and amblyopia. In a symposium on the subject, Peter and others,²¹ in 1932, years before experimental work, recommended early treatment of strabismus or anisometropia, and early patching of the problem eye to prevent amblyopia. They also cautioned that *the good eye cannot be continuously patched or else the amblyopia would transfer to it*. They, therefore, recommended alternate patching of the normal and abnormal eyes, which is still being done today. If you patch only one eye alone and do not patch back and forth, you'll cause blindness in the other eye and do no service to the child.

There is no evidence that there has been any improvement in the treatment or prevention of amblyopia since the early part of this century. Abraham¹⁸ made the following comments concerning Claud Worth, who retired from practice almost 50 years before experimental work began: "It is surprising how little . . . has been added to the major store of knowledge as he presented it, at least from the practical viewpoint . . . Worth's emphasis on *early* treatment of the error of refraction and the amblyopia is still the

keynote of the most rational approach to the treatment of the strabismic child . . ."

In 1987, Blakemore claimed, "before the animal research began it was not known whether squint could *cause* amblyopia or whether the existence of poor vision in one eye *causes* the squint." This simply is not true. For example, Claud Worth had made the proper association in the nineteenth century.¹⁸ Even as early as the 18th century, George Louis Leclerc de Buffon pointed out that amblyopia leads to strabismus.⁸ It is immodest and irreverent of modern day experimenters to take credit for something that was known hundreds of years ago.

Blakemore also stated that there was "no clear view about the time of onset or duration of the period of sensitivity to the disease," the implication being that the nonhuman animal work had provided the answer. This is not true, because this sensitive period is species-specific and is very different in nonhuman primates, cats or humans, both qualitatively and quantitatively.^{1,8,10,19,21,22} Experimental work on nonhuman animals could not shed light on the human situation. The sensitive period of a cat happens to be a few months, of a monkey, a year or so, of a human being, up to six years. You cannot learn the sensitive period of a human by studying cats. Furthermore, the fact that earlier ophthalmologists had been recommending early correction of strabismus, and early diagnosis and correction of anisometropia, indicates that they had known and understood the concept of a sensitive period long before the experimental work using nonhuman animals.

When you review the situation of amblyopia, you find that all the work that has been done on nonhuman animals has been on the basis of information derived from human observations.^{12,18-21,23,24} All the hypotheses so far examined by experimental work were known by physicians in this field years before the experimental work was done. The available history also seems to indicate that there has been essentially no change in concepts or in treatment methodologies over the last 100 years or more. Therefore, modern day experimental work appears to have had no significant effect on how amblyopia is managed today.

Can we continue to learn more about amblyopia without resorting to nonhuman animal experimentation? Keep in mind that any information we obtain from experimental work must still be confirmed in humans. By carefully studying the human situation in the first place, we not only derive information that is more meaningful in caring for human patients, we also save the resources that would have been expended on nonhuman studies and we prevent suffering and loss of life of the animals that would have been used.

Many of the hypotheses based upon observations of spontaneous cases of amblyopia or other similar vision disturbance in people have since been confirmed in contemporary studies of human patients.^{12,25-35} With some examples, it will become clear that we see the "human model" all the time. We see "experiments of nature" all the time. All we have to do is study them and we will learn something.

Awaya and others reported in 1973²⁵ about a study on people who had had occlusion of vision in one eye due to eyelid problems soon after birth, such as swelling or tumors of the eyelid. These people had developed stimulus or form vision deprivation amblyopia. Here's a perfect accident of nature, if you will, right there for us to study.

Cerny reported in 1987²⁶ about a group of infants who had cataracts. Those who were operated on before 8 weeks of age, and fitted with corrective lenses after the surgery, did far better in terms of behavioral, mental and visual skill development than those who were operated on after 8 weeks. It was an epidemiological study. We learned a tremendous amount. We know now that we want to operate on the child with cataracts as soon after birth as we can safely do so.

Hoyt and others reported in 1981²⁷ their study of infants that had had unilateral eyelid closure. These children developed monocular or unilateral axial myopia, nearsightedness, as a result of this early attenuation of pattern vision, this lack of form vision that I mentioned earlier. Now this was something that was uncertain from the non-human animal studies done in cats, in particular by von Noorden and Crawford, for example. We learn more from studying these children with a naturally occurring problem than we do from studying cats.

Johnson and others, in 1982,²⁸ took advantage of identical twins, one of whom had a unilateral cataract since birth that was then removed many years later. Again, a beautiful controlled experiment, if you will. They found that there was reduced visual acuity in the eye that was deprived through the cataract. This patient, then, can go on to be used, in an ethical way, to study further and find out more about amblyopia.

Moran and Gordon in 1982²⁹ studied a patient who had a unilateral cataract removed at 19 years of age. This cataract was present since birth. After surgery, they found that this individual had amblyopia in that eye. Again, another experiment of nature.

Von Noorden and others, in 1983,³³ were able to obtain the brain of a patient who had had amblyopia since birth or soon after birth. By studying this brain, they learned what actually happened in a human being. Of course, they got this brain not by killing the person, but rather, the person died and

willed his brain to research. They found that there was a decrease in the size of the cells in the brain in certain areas. Why do the work in normal cats when you can study it in abnormal people and see precisely what has happened?

Demer and others in 1988³⁵ used positron emission tomography (PET) to study the cerebral (brain) blood flow and metabolism in amblyopic vs. normal people. They found that PET was feasible for investigating brain function in these people and that its greatest value might be in locating and characterizing the poorly understood, extra striate areas of vision in humans. They concluded that this technique had great potential for research.

These types of studies provide the necessary conditions to understand how vision develops in human beings. You cannot study how vision develops in an animal with whom you cannot communicate. There are many aspects of amblyopia that are absolutely dependent upon our ability to communicate with the patient. For instance, there's a situation in amblyopia where people who have an amblyopic eye can read a smaller line on the Snellen chart -- the visual acuity chart -- if you put the letters further apart. For some reason, and it is not understood why, if the letters are closer together, they have difficulty reading them. How could you possibly learn anything about that studying a monkey or a cat who cannot read our language? You have to be able to speak with the individuals in order to learn what is happening. To me, vision isn't simply sticking electrodes into the brain and seeing what happens when you stimulate the brain with various stimuli. Vision is a cognitive process, a psychological process, and we're not going to learn what we have to learn by doing that.

By taking advantage of these "experiments of nature," it is not unreasonable to predict that we will continue to improve our understanding of amblyopia and similar conditions. By studying people who have lost an eye early in life, who have had untreatable or untreated opacifications of the ocular media early in life, or who have had other perturbations of their developing visual system for reasons unrelated to the eye, we can learn a tremendous amount. In addition to the references to human studies already cited, there have been other studies utilizing contemporary technology to further our understanding of vision in volunteers.^{36,37}

These situations are not uncommon and they provide the necessary conditions to understand how vision develops in the human being. These, not the experimental studies in nonhuman animals, have led, and will continue to lead, to the most important information on how to manage vision disorders in people.

Questions

Question: What are the arguments of the vivisectionists regarding the experiments performed on cats in order to study amblyopia?

Answer: Well, as I understand the question, I believe I've elaborated on that to some degree, but let me summarize it. The arguments are that by studying the cat, you can understand in a more simplistic manner what is happening. And by the reductionist theory, which, I believe, was amply argued against this morning, you can learn something and then build on that to a more complex animal, such as the human. The problem is that if the cat doesn't respond the way the human does, all the building you're doing may be going in the wrong direction. You may be building X while the blueprint calls for Y. And so you end up with a building that looks considerably different from what your blueprint was to begin with. I don't think there's much relevance there. Again, I come back to this serious problem of lack of communication between us and the nonhuman animals that are being used.

Q: If it is totally unscientific, why isn't there any denouncement expressed loudly by scientists?

A: Well, I didn't want to say it too loudly because I was afraid I'd hurt your ears, but I think I am expressing this very loudly. It is pure nonsense to be studying visual deprivation in nonhuman animals, particularly when we have all the material we need in human animals. And I'm not saying that we should go out and make humans deprived of vision. That happens naturally on a daily basis. What we need to do is to use all our technology to study those people who have been unfortunate enough to have these conditions. By studying them, we're going to learn a tremendous amount. History has shown that we've learned everything with regard to the production of amblyopia, and to its management or prevention, from studies on people. The experimental work has come after the fact, not before the fact.

Incidentally, I'm not the only vision scientist who is objecting to these types of experiments. There are many vision scientists doing that throughout the world. I happen to be just one who was invited to speak to this issue.

Q: If there is a scientist who is doing such experiments on animals, and it's totally wrong, how can this scientist continue being treated as a scientist around the world? When it comes to conferences abroad, everybody should

point a finger at him and say "This is the scientist who is doing unscientific things." I didn't hear about those things happening.

A: Well, I think the problem is one of inculturation. If you spend the whole early part of your life, as an example, thinking that the world is flat, then you're going to work for the rest of your life thinking that the world is flat. If your whole training in physiological sciences, as an example, has been by using or resorting to nonhuman animals as the proper way to study things, when you get out and you start doing your own work, along with the rest of the millions or thousands of other peers, you're going to try to answer questions you have by doing that type of thing. The people who are going to fund you, the funding agencies, for instance in the United States, the National Institutes of Health, made up of all these people who have learned everything they've learned using nonhuman animals, will be making decisions based on their perception of what is important. And because they learned on nonhuman animals, they're going to use that as the paradigm. They're going to fund only those projects that they think fit the paradigm. I think Dr. Heimlich mentioned that very well with his own experience when he went to, I think it was the National Cancer Institute, and he had an idea. They said, well, if you're going to try it in some animals, nonhuman animals, we'll fund you. The implication being that we're not interested otherwise. And it's a mindset. It's a mindset we have to break. And the reason why it continues is because the mindset right now is prevailing. And I hope that by more and more physicians and veterinarians and others challenging this mindset, we'll start to shift it in a different direction.

Q: Is there any general information one can learn from the experiments on the cats which can serve indirectly to promote human science?

A: Well, the answer, of course, is yes, indirectly. But is the information appropriate? You will not know until you study the human. That's the key problem. You can come up with all the hypotheses you want, from studying cats or monkeys or tree shrews or chickens, but until you see what happens in the human being, you can't say whether your hypothesis is correct. But once you've seen it in a human being, what's the point of the nonhuman animal studies?

Q: Is discovery of onset of sensitivity the primary justification for continued experimental work? Obviously, there has to be some justification offered by vivisection for the continued experimental work. You mentioned before that

there was an experiment where the vivisectors argued that the onset of sensitivity was a justification, that there were no clear criteria for determining the onset of sensitivity. I'm wondering what other justifications they have given in light of what seems to be a massive amount of work that has been done in this century and prior.

A: Well, the problem is that as human beings we're very curious and we're not willing to let well enough alone, even if we find the answer to preventing something. And so we can prevent amblyopia right now quite adequately, and we don't need to spend millions and millions of dollars a year on studying how it develops at the cellular and subcellular level, because we know what happens. And we can simply take these children with cataracts or with strabismus, or whatever, and treat them at a very early age, and they don't become amblyopic, for the most part. That's not sexy, though. It's much more exciting if you can delve into the single cell recording situation, and show different patterns of responses and whatever, and map out the different parts of the brain that respond to different stimuli and what have you. It means nothing with respect to vision, but it's exciting and it's fun and it gets a lot of grants and lots of papers get published and notoriety occurs as a result of that. There really isn't any justification other than just understanding it. And prior to the situation being challenged, there really wasn't much emphasis on how this information was going to be applied to people, but rather, simply, that we're understanding things.

It's knowledge for knowledge's sake. John Orem is an example of this mindset. He's a physiologist in Texas studying sleep deprivation in cats. His laboratory was raided. The information was taken from his laboratory and brought to the public's attention. All of a sudden, people who were defending Orem said that his work was very important for Sudden Infant Death Syndrome, which claims many thousands of children every year. It's interesting, though, that even after the raid, Orem has been quoted as saying "I don't like this, the way these people are trying to make my work clinically relevant. I never thought it was clinically relevant. I just want to learn about what's happening in the brain when you deprive animals of sleep." I mean, that's basically what he said.

Q: I think it was an amazing essay for just that reason. That was the first time in many years that I've seen a vivisector say "Why does my work have to be useful? Isn't it enough that I am generating data which may have no use whatsoever but which adds to the store of knowledge?"

A: It's basic science.

Q: I would have thought that in these experiments you're talking about, they would at least have tried to make it look like there would be some application for it. If amblyopia can be prevented, it seems that whatever measures one gets on the cellular level are largely irrelevant. You can't even promise any sort of clinical application.

A: But that isn't the way science works. Another example is at my own institution. We have a behaviorist who routinely mutilates goats, cats and rats by taking out parts of their brains. And when I was on the animal use committee there, I would object to these types of experiments on the basis that we learn nothing, and so we would challenge him. Allegedly what he said, through the campus veterinarian, is "If I had to provide clinical relevance for my work, I would be laughed out of the circles in which I work." I think that's a profound statement. I mean, if he can't justify his work on any practical level, or if his colleagues in the behavioral sciences would laugh him out of the circle of behavioral science because he would try to apply it clinically, I think that is a sad state of affairs.

Q: I understand that the problem of amblyopia can be solved by working strictly on human beings. But, for instance, could the problems of cataract removal, and also lensectomy [removing the lens] have been solved working on human beings from the word go, taking a person who has a cataract and just doing the surgery on that human being without experimenting on cataract removal or lensectomy on animals as a means of developing a safe way of doing these procedures in a human being?

A: The answer is clearly yes. Cataract surgery was being performed thousands of years before any work was attempted on nonhuman animals. Cataract surgery was developed in Egypt, and in the Native Americans in the United States, etc. in terms of correcting and understanding what is happening with cataracts, long before we even started vivisection. Also, the actual surgery itself was developed using people, not nonhumans.

Q: Are there any conclusions we can make from experiments in animals, at least one success which would justify experiments, a model which works for certain kinds of experiments; you could, therefore, say that this model works from animals to humans?

A: I can't think of any, because you can always study it in a human in some way.

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