Title
Review of grant application for the study of ocular histoplasmosis

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Review of Grant Application for the Study of Ocular Histoplasmosis

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I have reviewed the grant applications concerning the study of ocular histoplasmosis by Ronald E. Smith. In summary, I believe the studies are a waste of animal life and money because the animal "model" is of doubtful validity and most of the studies could relatively easily be carried out in people who live in areas endemic for *Histoplasma capsulatum*. Specific comments follow.

1. There have been only a few cases of human ocular histoplasmosis in which the organism was actually found, and even these reports are controversial. Thus, clinicians use the term "presumed ocular histoplasmosis," because a pathological association with histoplasmosis is rarely, if ever, found.

2. The disease in the monkey is not being produced in a "natural" manner. Normally, the organism would gain access to the subject via inhalation of the infective stage of the organism. After establishment in the lungs, there may be hematogenous (blood-borne) spread of some organisms to other parts of the body, including the eye. In stark contrast to this, the monkeys in this study are injected with massive numbers of the organism into the carotid artery which results in a large bolus of organisms reaching the ocular tissues.

3. Many people have a positive histoplasmin skin test, yet the majority of them have not been found to have "characteristic" ocular lesions. In fact, in endemic areas, it may be assumed that most people are exposed to the organism. Those who do develop disease may be on immunosuppressive drugs or have a faulty immune system. This is another major difference from the monkeys who are presumably immunologically and otherwise normal.

4. Much is made by the investigators of the macular involvement in humans. They state that this occurs some 10 to 20 years after the initial peripheral choroidal lesions. However, this assertion is largely speculative, because progression of the eye disease has not been shown to be due to the organism or its antigen.

5. Some of the lesions produced in the monkey are similar to those seen in the human syndrome. However, from an academic standpoint, I would not be surprised if other organisms, bacterial or fungal, produced similar lesions when introduced in this manner.

6. The following comments refer to the specific goals of the research for the period 2/1/86 to 1/31/87.

A) The study of the "natural" history of ocular histoplasmosis cannot be done with this protocol, because the animals are infected in an unnatural manner.

B) The detection of residual organisms or antigens could easily be done in humans.

C) The study of the immunopathology of reactivation is something that would be better studied in humans. It seems that by their own admission they have not seen reactivation in monkeys despite challenge. If they followed a population of humans showing the syndrome, they could do serial skin tests or other immunologic profiles and then correlate these with the appearance of the lesions. Perhaps then they could show a relationship between "reactivation" and antigenic stimulation.

7. Subretinal neovascularization, an important phenomenon in human presumed ocular histoplasmosis, has never been convincingly produced in the monkey "model" despite many years of observation. The investigators did report one monkey who developed subretinal neovascularization.[1] However, that study was flawed in several respects. It did not state the age of the monkey so it is not known if the retinal changes could have been related to age. Since the vascular lesion was not demonstrable with fluorescein angiography, it was possible that it may have been present as a clinically "silent"

lesion before the monkey was infected. The production of a visible scar in this area could therefore have been fortuitous, or the result of increased susceptibility of that area for localization of organisms, or a direct result of the organism. The investigators were not able to find any evidence of the organism or its cell wall remnants even after "...detailed ... examination..." They also did not examine the lesion by immunofluorescent techniques to see if *H. capsulatum* antigen was present.

The validity of this monkey "model" has also been questioned recently by others.[2] Because of their study of subretinal neovascularization, they felt that it is possible that the "...monkey is sufficiently different not to be a comparable and adequate animal model." They suggested that the membranes seen in the monkey may be "...related to age, myopia, or both as well as to histoplasmosis."

References:

1. Jester JV, Smith RE: Subretinal neovascularization after experimental ocular histoplasmosis in a subhuman primate. *Am J Ophthalmol* 1985;100:252-258.
2. Stafford TJ, Anness SH, Fine BS: Letter to the editor. *Am J Ophthalmol* 1986;101:132.

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