Variations in acute multifocal histoplasmic choroiditis in the primate

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Experimental histoplasmic choroiditis was produced in primates by intracarotid injections of living H. capsulatum organisms. The severity of the choroiditis varied with inoculum size, as well as with site of injection (common carotid vs. internal carotid artery). A reproducible model of histoplasmic choroiditis in primates was produced with an internal carotid injection of 5,000 to 10,000 organisms/lb. The clinical and histopathological course of this acute choroiditis over the first 30 days is presented.

Key words: ocular histoplasmosis, primate model, intracarotid injection

Presumed ocular histoplasmosis is a clinical syndrome consisting of hemorrhagic macular disciform lesions with associated peripapillary and peripheral atrophic choroidal scars.1-2 Clinical and epidemiological evidence exists for an association between this characteristic syndrome and previous exposure to Histoplasma capsulatum.4-6 The exact pathogenesis of the macular lesion, however, remains unknown. Late development of subretinal neovascularization7-9 and/or an inflammatory component10 has been implicated.

Many attempts have been made to establish an animal model of ocular histoplasmosis.12-14 Since the presence of a macula is the sine qua non for the establishment of an appropriate model, the primate is one of the few animals which can be used.

We will describe the development of a primate model for studying acute histoplasmonic multifocal choroiditis. Variations in the acute phase of the disease will be discussed.

Methods

Animals. The Macaca speciosa (stumptailed macaque) was selected for initial experiments because of its size (17 to 32 lb.) and because of our previous experience in the use and management of this species. In a later phase of our work, the Macaca mulatta (rhesus monkey) was also employed.

Fungus. H. capsulatum, strain Campbell G184B, from the Mycology Laboratory, Department of Immunology and Microbiology, University of California, Los Angeles, was used in these experiments.10-16 This same organism was used in earlier rabbit studies.14 Stock cultures of H. capsulatum in the yeast cell phase were kept in a refrigerator and transferred at monthly intervals on blood-glucose-cysteine agar.17

Inocula for injecting animals were prepared as follows. The fungus was grown on slants of blood-glucose-cysteine agar incubated at 37° C for 48 hr. The growth was washed from the slants with a salt solution of low ionic strength (STM) consisting of 0.01M KCl, 0.0024M NaCl, and 0.0025M MgCl₂. The yeast cells were washed twice in STM and finally suspended in 0.15M NaCl. The concentration of the cells was determined by hemocytometer count, and the number was adjusted to the desired level (10⁶ to 10⁷ yeast cells/ml in most experiments). The adjusted saline suspensions were then injected intracarotid.
Table I. Relation of inoculum size to severity of clinical course in animals injected by common carotid artery

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<th>Organisms (×10^6/lb)*</th>
<th>Clinical course†</th>
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*One primate injected at each dose level.
†Clinical grades: 0 = No clinical evidence of ocular lesions; 1 = less than 5 discrete choroidal foci, with clear vitreous; 2 = multiple (greater than 5) isolated foci, with clear vitreous; 3 = multiple discrete foci, with some confluent foci of choroiditis and/or localized discrete serous detachment; 4 = diffuse confluent patches of choroiditis with or without hazy media, hypotony.

were kept in an ice bath until transport to the Doheny/USC Vivarium. Animals were injected within 2 hr of preparation of the inoculum, and the viability at the time of injection was ascertained in random samples by dye exclusion (Janus green B).\textsuperscript{18} Tested inocula contained yeast cells of greater than 80% viability. Immediately after completion of the surgical procedures described below, a sample of the remaining material was subcultured onto a slant of blood-glucose-cysteine agar which was incubated at 37° C and onto a plate of blood agar and Sabouraud’s glucose agar, both of which were incubated at room temperature. This was performed as a final test of viability of organisms.

Baseline primate evaluation. All subjects were kept for the standard 30-day quarantine in the USC Vivarium and underwent tuberculin skin tests, stool tests for ova and parasites, and routine hematological studies. Only animals with negative tuberculin skin tests and normal laboratory examinations were utilized in this study.

Prior to intracarotid injection, all primates were weighed, had an external eye examination, and the fundus was examined with the binocular indirect ophthalmoscope. Utilising the Zeiss fundus flash III camera, we performed fundus photography and fluorescein angiography (0.7 cc of 5% fluorescein sodium). Histoplasmin skin tests (Parke-Davis & Co., Detroit, Mich.) were administered to all animals. One animal was excluded because of retinal abnormalities noted on baseline examination. All prestudy histoplasmin skin tests were negative.

Surgical technique. After overnight fasting, animals were given intramuscular phencyclidine hydrochloride (Sernylan), 1 mg/lb, or ketamine hydrochloride (Ketaset), 3.33 mg/lb, with atropine sulfate, 1.33 mg/lb, intramuscularly and then removed from their cage after appropriate sedation was induced. There were no deaths due to anesthesia in this study.

Primates were immobilized in the supine position with limb restraints and firm neck extension. The chest and neck were shaved and scrubbed with Betadine. The skin of the neck was opened with a midline incision from the angle of the jaw to the angle of Louis. Blunt dissection was then employed to dissect the fascial and muscular planes overlying the trachea. The common carotid artery alongside the trachea was exposed by blunt dissection to release its fascial sheaths as well as adherences to the vagus nerve and jugular venous plexi.

Table II. Relation of inoculum size to severity of lesions in animals injected by the internal carotid artery

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<th>Organisms (×10^6/lb)*</th>
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*One primate injected at each dose level.
†See explanatory note Table I.
Common carotid artery injection. A loop of cotton suture was placed around the caudal portion of the common carotid artery, and gentle elevating pressure was applied to stop blood flow. The inoculum of \textit{H. capsulatum} suspension was then introduced with a tuberculin syringe and 25-gauge needle into the common carotid artery rostrally to the occlusion. Injection was completed and the cotton suture simultaneously released, restoring normal blood flow to the carotid system. Total inoculum size was usually 0.1 to 1.0 ml, depending on the experiment.

Firm pressure on the puncture site stopped the small amount of bleeding from the injection. After application of an antibiotic solution, 2% nitrofurazone (Furacin), in the wound, closure was accomplished with two layers of interrupted 4.0 chromic gut suture. A plastic aerosol bandage (Rezifilm) was applied at the end of the procedure. There were no wound dehiscences or wound abscesses related to \textit{H. capsulatum} noted throughout the experiments.

Internal carotid artery injection. Inoculation of the internal carotid artery was employed to provide more direct flow to the ipsilateral eye (the first branch of the internal carotid artery is the ophthalmic artery). The following technique was used. After common carotid artery isolation (as previously described), further blunt dissection was carried out rostrally in order to visualize the carotid bulb, the site of the branching of the internal and external carotid arteries. The two branches were separated from one another to allow clamping of the external branch. Once the external carotid artery was clamped, the common carotid was injected as described above. A few pulsations later, the vascular clamp was released. Although much more difficult to carry out technically, the injection of the internal carotid artery was accomplished without major complication or fatality related to the procedure. The remaining surgical procedures after release of the external carotid artery clamp were the same as described above.

Follow-up examination. Most primates were restudied with fluorescein angiography and fundus photography at 4 and 7 days after injection and at weekly intervals thereafter for the first month after surgery. (This report deals with results during the first month after inoculation.) Lesions noted on early examinations were specifically monitored in later studies. Histoplasmin skin testing was usually repeated within the first month after injection, but the antigen became unavailable during the study.

Animals were fasted overnight and sedated as described for injection. After induction of anesthesia with sodium pentobarbital or sodium thiopental (Surital), 7 mg/lb, all eyes were diluted with Neo-syneprine hydrochloride (10%) and tropicamide (1% Mydriacyl). Studies including external examination, binocular indirect ophthalmoscopy, fundus photography, and fluorescein angiography were performed.

Animals were sacrificed and/or enucleations were performed at various time intervals following
injection. Cultures of fresh ocular tissues were carried out in the operating suite by dissecting a portion of retina and choroid from the enucleated globe. Materials were placed on Sabouraud's dextrose agar, blood agar plates, and blood-glucose-cysteine agar. Lung, liver, and spleen were also cultured in the same way at the time of sacrifice of the animals.

The portion of the eye not utilized for culture was placed immediately in 10% neutral, buffered formalin solution and submitted for histopathological examination to the Eye Pathology Laboratory at the Estelle Doheny Eye Foundation. Serial sections through areas of abnormality noted on gross pathological examination were prepared and stained for fungi by periodic acid-Schiff (PAS) and Gomori methenamine silver (GMS) methods.

Results

Common carotid artery injections (Campbell strain). Twelve animals received common carotid artery injections with strain G184B. (See Table I.) Dose ranged from $3.75 \times 10^7$ to $2.90 \times 10^8$ organisms/lb. Ten primates developed ipsilateral ocular lesions. In general, the larger the inoculum size, the more multifocal and severe the acute choroiditis. On the other hand, two of the four largest inocula produced almost no ocular disease, indicating much variability with this injection site. Larger inocula usually resulted in a more diffuse choroiditis and, in some instances, overlying serous detachments of the retina. More severe disease exhibited scattered foci of retinitis but only overlying areas of diffuse choroiditis. Retinitis was the exception rather than the rule. Eyes with severe, diffuse choroiditis also had ciliary body and iris inflammation. Some animals developed a red external eye, with crusting, severe anterior chamber reaction, and some

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Figs. 2, 3, and 4. Clinical course of a typical grade 2 or 3 histoplasmic choroiditis.

Fig. 2. Three days after internal carotid injection, lesions are hardly visible by clinical examination (A, arrow) but multiple lesions are detected on fluorescein angiography (B and C). Arrows point to areas of apparent choroiditis which are obvious as filling defects initially on the fluorescein pass (B) and stain later in the fluorescein pass (C). Figs. 3 and 4 show the later phases of these same lesions.
eyes became hypotonous, giving the appearance of endophthalmitis. This was found to be a diffuse uveitis (choroiditis, iritis, cyclitis) rather than an endophthalmitis, even in the most severe cases (see discussion of histopathology). The infiltration of cells and organisms extended to involve the iris and ciliary body, as well as choroid in such cases.

By reduction of the inoculum size, a much less violent, acute histoplasmic choroiditis was produced. At doses from 9.40 to 2.90 x 10^8 organisms/lb, scattered foci of multifocal histoplasmic choroiditis developed without involvement of retina or the remainder of the uveal tract. The eyes remained quiet, with clear vitreous. During the first month following injection, most lesions gradually decreased in size, becoming quite discrete and, in some instances, disappearing altogether on clinical examination.

When histoplasmin skin tests were performed on seven of these primates after at least 9 days after injection, six converted their initial negative tests to positive.

Fig. 3. Six days after injection (3 days after the findings in Fig. 2) A and B, Multiple foci of choroiditis are seen at the posterior pole with a small serous detachment just inferior and temporal to the nervehead. C, Fluorescein angiography reveals early blockage of the fluorescence. D, Later in the fluorescein pass these areas stain.
Fig. 4. Twenty days after injection (2 weeks after the clinical findings from Fig. 3). A, Some of the previously observed lesions are less obvious. B, Serous detachment observable on fluorescein angiography is less pronounced.

Internal carotid artery injection (Campbell strain). The responses following internal carotid artery injection of Campbell G184B organisms are shown in Table II. Twenty-four of 25 injections resulted in ipsilateral ocular lesions.

At high doses of organisms (1.2 × 10^6 to 1.0 × 10^4/lb) a diffuse pattern of multifocal and often confluent choroiditis developed, occasionally with associated involvement of the ciliary body and iris as noted with high doses in common carotid injections. At lower doses (3,000 to 5,000 organisms/lb) a reproducible pattern of discrete, multifocal choroiditis developed in 16 primate eyes (Table II). Severity of eye disease was correlated with inoculum size. No eyes developed frank endophthalmitis. Eyes with a grade 4 response developed hazy media related to hypotony rather than endophthalmitis. Yet, at doses below 1 × 10^6/lb, the media eventually cleared. The diffuse uveitis (choroidi-
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tis, cyclitis, iritis) resulting from the high-dose inoculation began clinically as a confluent mottling of the choroid within 3 to 4 days after injection. Progression to a more diffuse confluent choroiditis with, at times, iridocyclitis, focal retinitis, and serous detachments, occurred over the next week. By reduction of the inoculum size below $1.0 \times 10^4$/lb, a reproducible, acute, multifocal histoplasmic choroiditis was observed without the development of diffuse uveitis, hypotony, or serous detachments (Fig. 1). Eyes were not red and had no evidence of vitreous inflammation. No evidence of involvement of the contralateral side was found by clinical examination. Ocular lesions could be visualized easily at all times during the 30 days after injection.

Clinically, choroiditis lesions at the 3,000 to 5,000 yeast cells/lb inoculum size began as a subtle mottling of the fundus, which was barely visible by fundus photography but could be noted as early as 3 days after injection by fluorescein angiography (Fig. 2). These foci developed into more discrete areas of multifocal choroiditis with marked involvement of the posterior pole, including the peripapillary and macular areas (Figs. 3 and 4). On occasion, confluent areas of choroiditis in the macular area developed, overlying localized macular serous detachments very soon after injection (Figs. 5 and 6). Serial examinations during the first month after injection disclosed that the serous detachments resolved, with flattening of the retina and the beginning of atrophic choroidal scars. Active foci, and later atrophic scars, occurred throughout the fundus periphery as well but were far more difficult to document photographically. Fortunately, the majority of lesions seemed to occur at the posterior pole, making them readily available for follow-up examination.

Histoplasmin skin tests were done on nine primates, 3 weeks to 1 month after injection. Eight became positive. Further tests could not be done because standardized histoplasmin skin test material was no longer commercially available.

**Fluorescein angiography.** Fluorescein angiography of acute multifocal histoplasmic choroiditis (grades 2 to 3) revealed initial blocking of the fluorescein dye, with subsequent rapid leakage of dye into the area of acute choroiditis (Figs. 2 to 4). Residual staining of these patches was seen late in the fluorescein pass. Late staining was quite profound in the few instances of acute serous detachments (Figs. 5 and 6). Occasionally evidence of acute choroiditis could be detected by fluorescein angiography before other clinical signs (Fig. 2).
Fig. 7. For legend see facing page.
Histopathology and culture. The histopathology of lesions occurring via either the common carotid or internal carotid technique was similar and correlated well with the clinical grade (0 to 4).

Grade 4 lesions, i.e., diffuse, confluent choroiditis with hazy media, hypotony, serous detachments, etc., had a remarkably thickened choroid, packed with mononuclear inflammatory cells and *H. capsulatum* organisms (Fig. 7). Organisms could be cultured and seen histopathologically by special stains from such severe lesions for the entire 30-day period following injection (the duration of current study). Scattered foci of acute retinitis with small retinal hemorrhages were present with associated organisms. The ciliary body and iris were similarly involved in severely affected eyes at high doses. Sections did not reveal vitreous involvement (and rarely any retinal lesions) despite massive and diffuse choroiditis. No true "endophthalmitis" was found.

In clinical grades 2 and 3 lesions, the acute foci of histoplasmic choroiditis consisted of discrete patches with lymphocytic infiltrates and organisms localized to the choroid (Fig. 8). In most instances, the retinal pigment epithelium was intact. However, with larger foci or confluent areas of choroiditis, the retinal pigment epithelium was sometimes disrupted, and in some instances, cells and organisms appeared to have broken through Bruch’s membrane and the retinal pigment epithelium into the subretinal space (Fig. 9). Such inflammatory foci were found at the posterior pole, including the macula and foveal and peripapillary areas. The retina,
Fig. 9. Histopathology of an acute focus of histoplasmic choroiditis shows organisms (arrow) and inflammatory cells breaking through Bruch's membrane and the retinal pigment epithelium into the subretinal space. (H&E; x600.)

ciliary body, iris, and vitreous were not involved in the inflammatory lesions with rare exception of a focus of retinitis overlying a large area of confluent histoplasmic choroiditis.

Findings in the eye opposite the injection. There were four instances of fundus lesions observed in the contralateral eye after injection. Three occurred after large-inoculum common carotid artery injections. One animal developed an area of choroiditis adjacent to the disc in the contralateral eye 25 days following injection of 1 million organisms per pound in the internal carotid artery. In the most reproducible and clinically important type of lesions with internal carotid injections (grades 2 and 3), however, no contralateral lesions were observed.

Systemic disease. One animal died due to systemic histoplasmosis. This primate was the first injected with Campbell strain organisms and received a very large dose ($3.7 \times 10^6$ yeast cells/lb). The animal expired in 18 hr. No other monkey was lost as a result of anesthesia, surgery, or systemic histoplasmosis. In addition, there was no manifestation of significant systemic disease such as pneumonitis. In early cases, cultures were taken of nasal secretions, but no organisms were found.

We examined lungs, livers, and spleens in three animals sacrificed. Cultures of these organs done within the first weeks after injection were positive for $H.\ capsulatum$. Histopathology revealed infiltration of the liver with organisms, especially at larger inoculum sizes.

Comment

A primate model of ocular histoplasmosis is important in the study of the ultimate pathogenesis of the late macular disciform
lesion in humans. It is now generally assumed that reactivation of small, inactive, asymptomatic paramacular or peripapillary atrophic scars late in life results in hemorrhage and loss of central vision. The question remains as to whether this "reactivation" of small scars is related to the nonspecific development of subretinal neovascularization or an inflammatory (immunologic) event. A primate model is crucial, since it has a macula similar to man's. The model described in this report offers an advantage because multiple small scars develop in the macular area following acute multifocal histoplasmic choroiditis. This model presents the opportunity for long-term studies on reactivation.

Other animal models of ocular histoplasmosis have been described. Day first produced ocular histoplasmosis in 1949 by injecting mycelial-phase H. capsulatum into the anterior chamber of rabbit eyes, producing a violent granulomatous iridocyclitis. Since these original experiments, investigators have studied the experimental ocular disease in a variety of models. Living and dead Histoplasma organisms, usually the yeast phase, have been injected into all parts of the eye—cornea, anterior chamber, vitreous, suprachoroidal space, and retrobulbar space. Intravenous and intracarotid routes have also been utilized. Of significance is the fact that none of these models has approximated the clinical syndrome as encountered in humans, i.e., a focal choroiditis with minimal involvement of the retina, no anterior segment disease, and a later macular lesion. Smith and Singer first produced a choroiditis in rabbits and then primates following intravitreal injection of living H. capsulatum. None of the primates developed macular disease, and this model was less than satisfactory, since it involved direct injection of organisms into the eye.

The dissemination of organisms to the eye during the course of acute systemic histoplasmosis was first demonstrated by Salfelder et al. who found granulomatous histoplasmic choroiditis and iridocyclitis in the eyes of dogs following intravenous injection of organisms. These animals had experimentally induced valvular heart disease, and the role of this in the production of ocular disease (via septic emboli from vegetation on the valves) was not assessed. Wong and Green injected Histoplasma spores intravenously into rabbits and produced areas of focal choroiditis. Smith et al. also produced multifocal histoplasmic choroiditis in rabbits, using yeast-phase organisms injected into one carotid. The intravascular injection of yeast-phase H. capsulatum closely approximates the proposed mechanism for dissemination of organisms in systemic infection. In these cases inhalation of airborne mycelial-phase organisms (spores) occurs as a primary event. The spores are engulfed by the reticular endothelial system in the lungs, and the organism is transformed into the yeast phase ("tissue phase"). It then disseminates hematogenously to various other organs. The intravascular injection of yeast-phase H. capsulatum therefore more closely simulates the usual route of dissemination following primary lung infection.

Animal models to date involve animals without a macula (rabbit), with no possibility for later macular disease. The only reported primate studies to date have utilized direct intravitreal injection. Wong and Green produced a few areas of choroiditis in primates by intravenous injection of spores, but only peripheral lesions were observed (W. R. Green, personal communication, 1977). Therefore a primate model with multiple foci of choroiditis is necessary in order to produce numerous paramacular and peripapillary histoplasmic scars which might later be activated to produce macular disease.

During the development of the primate model described in this paper, variations in acute histoplasmic choroiditis were observed. Inoculum size seemed to be crucial, and marked variations were seen with changes in total number of organisms injected. With as few as a total of 150,000 organisms, scattered foci of choroiditis with very little confluence occurred, whereas with $1 \times 10^6$ total organisms, a diffuse histoplas-
mic choroiditis, cyclitis, and iritis occurred, often with exudative, serous retinal detachment.

The internal carotid route seemed to result in more reproducible foci of choroiditis with less variability than did the common carotid route (Tables I and II). Organisms given in the common carotid are spread through the external carotid as well as the internal carotid with a dilution effect, perhaps accounting for the variability following common carotid injection. Direct injection of the internal carotid would seem to provide a more direct route to the ophthalmic artery and the eye.

The variations occurring in the first month following injection were also dependent upon inoculum size. With larger inocula a diffuse uveitis (choroiditis, cyclitis, and iritis) with occasional associated serous detachments of the retina persisted for a month, but at no time did frank endophthalmitis develop. Only occasional foci of retinitis ever occurred, and these were seen only with severe, diffuse choroiditis. The vitreous cavity remained free of inflammation. With smaller inocula, scattered, less confluent foci of choroiditis developed, with no anterior uveal involvement.

Of considerable interest was the observation that small active foci, well documented by fluorescein angiographic studies, were sometimes observed to become barely visible or invisible to clinical examination later in the first month after injection. Histopathologically, foci of inflammatory cells could be seen in the choroid in these instances. The significance of this in relation to human disease may be related to the occurrence of small acute foci without significant disturbance of the retinal pigment epithelium, and therefore such areas may not be visible by routine examination techniques after the acute phase. Late development of "de novo" active macular disease may, in fact, be related to reactivation of such clinically inapparent old foci.

At lower inoculum sizes, given via the internal carotid artery (5000 organisms/lb), a reproducible model of multifocal histoplastic choroiditis was established. Over the first month, these lesions began to resolve into atrophic-appearing scars reminiscent of those seen in human disease. One of the goals of future studies will be to determine the natural course of this model and, specifically, to determine how long organisms remain within these lesions and how long inflammatory cells, without organisms, remain.

In studies of these lesions over the initial 30-day period, multiple foci of inflammatory cells could still be found histopathologically. In instances of severe disease, organisms could still be cultured and demonstrated after 1 month.

In a few instances, damage to Bruch's membrane was observed (Fig. 9), creating a possible site for late ingrowth of subretinal neovascularization. This, of course, is speculation but emphasizes the importance of long-term follow-up studies of this model.

Aside from the possible long-term significance of this model for human presumed ocular histoplasmosis, the findings of localized exudative serous detachments in the macular zone, overlying areas of confluent choroiditis, is interesting. Detailed studies of the exact source of this fluid and its passage through the retinal pigment epithelium into the subretinal space are planned.

In summary, we have successfully produced experimental acute ocular histoplastic choriditis in the primate. The extent and severity of the choroiditis vary with inoculum size and route of injection. With the use of internal carotid injections and a dose range of 5000 to 10,000 yeast phase organisms per pound, a reproducible model of multifocal choroiditis results. Scattered foci of choroiditis at the posterior pole, including the peripapillary and macular areas, result in the development of small scars in these areas, reminiscent of peripapillary and peripheral atrophic scars which characterize the human ocular disease. Future studies will be directed toward the natural course of this model with attempts to reactivate small atrophic peripapillary and macular scars.

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REFERENCES


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