THE STATUS OF PRESUMED OCULAR HISTOPLASMOSIS: INCLUDING A REPORT OF A SURVEY

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HISTOPLASMOSIS as a rare cause of severe systemic disease was first described by Darling in 1906.[1] Since then, the etiologic agent, pathogenesis, varied clinical pictures, diagnostic tests, and epidemiology have been extensively studied. Schwarz and Baum[2] prepared an excellent historical summary of the first 50 years of histoplasmosis research, emphasizing the important contributions that have resulted in a remarkably complete understanding of this disease. It has been established that *Histoplasma capsulatum* is a fungus that is worldwide in distribution but is most frequently encountered in the Mississippi Valley area of the United States. The fungus appears in the animal body as a slightly ovoid cell 1–5 microns in diameter, but grows as a mold on artificial media at room temperature. The infection is common in man and many animals, and the organism has been recovered from soil, water, and air. There is good evidence that the disease is acquired by inhaling spore-contaminated dust.

Most cases of histoplasmosis are almost asymptomatic, but the disease may manifest itself as a very mild upper respiratory infection, clinically appearing as an influenza-like illness lasting one to four days. Slightly more severe infections causing fever, cough, and mild chest pains lasting up to two weeks may be diagnosed as atypical pneumonia, the true etiologic agent going undetected.[3] Severe infections may be divided into three groups:[4]

1. Acute histoplasmosis, frequently occurring in epidemics as a severe disease, is characterized by marked prostration, fever, and occasional chest pain with or without pulmonary symptoms even when X-rays show severe disseminated pneumonitis. The illness may last from one week to six months and is almost never fatal.

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2. Acute progressive histoplasmosis, usually fatal within six weeks, is manifested by fever, cough, loss of weight, prostration, ulcers of the mucous membranes of the oropharynx, splenomegaly, hepatomegaly, and occasionally generalized involvement of all internal organs. This form of the disease, seen especially in infants and children, may resemble lymphoma and must be differentiated from Hodgkin's disease, acute leukemia, and lymphosarcoma. Uveitis occasionally occurs in this group.

3. Chronic progressive histoplasmosis that continues for years is usually seen in older patients and must be differentiated from pulmonary tuberculosis, though it is well to remember that both diseases may be present. The lungs show progressive changes, often with cavitation. In the end stages, other organs of the body may be involved in addition to the lungs. Uveitis is occasionally seen in this group also.

Recently the use of amphotericin B (Fungizone®) has proved helpful in many cases of severe systemic infection, especially if treatment has been started early and nephrotoxicity has been minimal. General supportive measures are indicated just as in tuberculosis. At post mortem *Histoplasma capsulatum* is often abundantly present in tubercle-like nodules of epithelioid cells found in the liver, spleen, and bone marrow. The organisms have also been found in calcific lesions of the lungs,[5] spleen, and liver[6] in a high percentage of subclinical cases examined at post mortem.

Following the recognition by Christie and Peterson[7] of subclinical benign histoplasmosis, the population distribution of this form of the disease has been verified by numerous observers.[8–10] The results of skin test surveys for histoplasmosis have been summarized by Edwards and Palmer,[8] who showed that infection with *Histoplasma capsulatum* occurs in up to 90 per cent of the population in the Eastern Mississippi River basin and has a lower incidence elsewhere (e.g., less than 1 per cent in the Pacific Northwest).

THE CURRENT STATUS OF PRESUMED OCULAR HISTOPLASMOSIS

Ocular histoplasmosis as the cause of a distinctive type of posterior choroiditis has become a popular diagnosis since the 1959 report of Woods and Wahlen.[11] Prior to this time, only scattered reports[12,13] suggested histoplasmosis as a possible cause of uveitis. In 1942, Reid, *et al.*[14] published a report of a fatal case of systemic histoplasmosis in which small tubercle-like choroidal nodules had been observed in each eye prior to death. *Histoplasma capsulatum* was recovered from

many body organs, but the eyes unfortunately were not obtained for autopsy. Woods and Wahlen noted the occurrence of choroidal depigmented areas associated with certain types of macular lesions, a positive skin test to histoplasmin, hilar lung calcifications, and anergy to the tuberculin skin test. Their original description of the central and peripheral lesions has since been confirmed by other observers.[15–17]

The central lesions are in or very near the macula and most frequently begin as a small subretinal cyst with a halo of edema or subretinal serous exudate causing symptoms of metamorphopsia. The cystic area enlarges and may become a serous detachment of the entire macula. A collarette of hemorrhage around the cystic lesion occurs in approximately 50 per cent of cases and represents a more violent reaction. Sooner or later the edematous process subsides, and if no hemorrhage has occurred, little or no permanent scarring results. If hemorrhage has occurred in the active phase, scarring occurs which conforms to the criteria for serous and hemorrhagic disciform detachment of the macula as defined by Maumenee.[18] The inflammatory process remains confined mainly to the choroid, so that exudation into the vitreous does not occur. Extensive macular lesions may occasionally evoke a slight vitreous haze near the active lesion at the height of the inflammation. The central lesion nearly always is unilateral at onset, with the fellow eye eventually becoming involved in about 25 per cent of cases.

Nearly all cases having characteristic central lesions of presumed ocular histoplasmosis demonstrate peripheral lesions of discrete, focal atrophic chorioretinitis. These areas measure ⅓ to 1/10 disk diameter and appear as "punched out" areas of the choroid, often with little or no pigment. Figures 1–14 demonstrate a wide variety of these lesions, hereafter referred to as "histo" spots* for simplicity. Histo spots are also frequently observed in the fellow eyes of persons with unilateral central lesions, and occur infrequently in persons with no other abnormal ocular findings.

Woods and Wahlen theorized that the peripheral choroidal lesions represent the ocular manifestation of subclinical dissemination of the infection which causes widespread focal lesions in many body organs. It has been established that *Histoplasma capsulatum* is a potent tissue sensitizer, and these investigators therefore reasoned that a later uveal

*The term "histo" spot will be used hereafter as a convenient synonym for healed foci of choroiditis of presumed ocular histoplasmosis. Understandably, some authorities object to the term since the etiology has not been confirmed. The only slightly less awkward term "punched out" choroidal foci of presumed histoplasmosis could also be used.

hypersensitivity reaction could occur, triggered by a circulating antigen originating either from spores liberated from a peripheral uveal area or from some other remote systemic source. Another possible explanation for this hypersensitivity reaction is that it arises from re-infection with *Histoplasma capsulatum*. In either event, the active lesion most often affects the macula. The process can subside with little or no permanent damage, but if the lesion is complicated by hemorrhage, scarring causes some permanent loss of vision.

Several experiments support this hypothesis. In 1949 Day[12] showed that direct inoculation of *Histoplasma capsulatum* into the interior chamber of the rabbit caused focal uveitis lesions which were well healed after several months. The organisms were recovered in the first several weeks following inoculation, but not thereafter. Okudaira and Schwarz[19] demonstrated that in previously immunized rats intraocular challenge with living or killed *Histoplasma capsulatum* or histoplasmin produced an ophthalmitis compatible with the clinically observed delayed type of hypersensitivity reaction. Single intraocular injections of histoplasmin or heat-killed *Histoplasma capsulatum* produced no inflammatory reaction in non-immunized rats. A recent study by Sethi and Schwarz[20] demonstrated that the pigeon eye reacts with a granulomatous iridocyclitis to injection of *Histoplasma capsulatum* into the anterior chamber. The organism was cultured from these eyes as well as from the lungs, liver, and spleen, demonstrating that dissemination from primary ocular infection is common under experimental conditions. Smith and Singer[21] also described ocular histoplasmosis in the rabbit, and Salfelder, Schwarz, and Akbarian[22] produced granulomatous uveitus in dogs by injecting *Histoplasma capsulatum* intravenously.

Several reports have appeared recently on large groups of patients with choroiditis presumed to be due to histoplasmosis.[15–17] The diagnostic criteria of ocular histoplasmosis vary slightly from group to group, but in general can be summarized as follows:

1. The presence of a macular lesion which may become hemorrhagic, unassociated with any vitreous exudate.

2. The presence of the small "punched out" healed foci of choroiditis (histo spots) in the choroid, as well as characteristic peripapillary findings (Figure 8). The peripapillary lesions appear as atrophic areas adjacent to the optic disk. Pigmentation is minimal, but a fine rim of pigment may line the outer extent of the lesion. The entire circumference of the disk may have adjacent choroidal changes usually

extending irregularly less than ½ disk diameter peripherally but at times being much larger.

3. A positive skin test to histoplasmin (0.1 ml. of 1:100 dilution intradermally).

4. Some authorities feel that other evidence of systemic involvement such as hilar adenopathy or splenic calcification should be present. Anergy to tuberculin, emphasized by Woods,[11] is no longer generally considered a significant diagnostic criterion.

It is always difficult to establish the cause of any case of uveitis. Pathogenic organisms have been demonstrated on microscopic examination or culture of uveal tissue obtained from enucleated eyes, but—except in the case of *Toxoplasma*—none has proved to be a common cause of uveitis. Rarely, pathogenic organisms have been isolated from anterior chamber and vitreous fluids *in vivo*, but only an occasional rare cause of uveitis such as leptospirosis or herpes simplex has been established by this method. The frequent occurrence of uveitis in association with ocular infections of known cause such as herpes zoster or herpes simplex keratitis has been interpreted to mean that the infection is also the cause of uveitis even in the absence of direct cultural or microscopic proof obtained from the eye. Finally, at least two types of uveitis of unknown etiology but with characteristic pathology—sarcoidosis and sympathetic ophthalmia—have been identified by the distinctive microscopic appearance of enucleated or postmortem eyes.

None of the above evidence has been adduced for histoplasmosis, so that the evidence, though accumulating, is still circumstantial since *the organism has not been recovered from the uveal tract of man*—not even from fatal systemic infection.

It seems appropriate to digress briefly to consider the evolution of toxoplasmosis as an established cause of uveitis. The sequence of events leading to the identification of toxoplasmosis as a common cause of posterior uveitis is a useful model of how such a clinical pathologic correlation can evolve. Comparison of this course with the current status of presumed ocular histoplasmosis in order to evaluate the likelihood that *Histoplasma capsulatum* can cause uveitis seems particularly appropriate when one remembers that *Toxoplasma gondii* is the only common confirmed cause of posterior uveitis. (See Table 1)

Although the discovery of toxoplasmosis preceded that of histoplasmosis by several years, our knowledge of the life cycle of *Toxoplasma gondii* remains incomplete. In 1923 Janku identified the first

TABLE 1. SUMMARY OF COMPARISON OF TOXOPLASMOSIS AND HISTOPLASMOSIS AS RELATED TO CAUSATION OF POSTERIOR UVEITIS

Characteristics	Toxoplasmosis	Histoplasmosis
Type of organism	Not definitely classifiable by present categories; parasitic	Definitely a fungus
Knowledge of life cycle	Known only *in vivo*	Completely known
Relationship to systemic disease	Known cause	Known cause
Uveitis associated with systemic disease	Frequent in congenital disease; probably rare in adults	Circumstantial evidence for occasional uveitis in overwhelming systemic infection
Presumed or established clinical picture of uveitis	Characteristic	Characteristic
Organisms identified in histologic section of uveal tract	Yes	No
Indirect evidence indicating causal relationship of organism and posterior uveitis, correlating characteristic clinical picture with other reliable evidence that disease is present	Good evidence[30]	Good evidence[15]

case of what is now considered to be congenital human toxoplasmosis and is credited with the first description of the associated retinochoroiditis.[23] The parasite was isolated post mortem from the brain, spinal cord, and eyes of an infant with congenital toxoplasmosis for the first time in 1939.[24] Since then the parasite has been demonstrated many times at autopsy in infected ocular tissue of infants dying from congenital toxoplasmosis. Wilder was the first to demonstrate *Toxoplasma gondii* in histologic sections of enucleated eyes from adults with retinochoroiditis.[25] The eyes of these patients all showed focal exudative posterior uveitis clinically, and the organism was found in the retinal lesions. On the basis of the histologic reconstruction of the lesions in which the *Toxoplasma* organism has been found both in histologic specimens and in the culture of these specimens, it has been established that the primary lesion in ocular toxoplasmosis is retinitis.[26] Toxoplasmic retinochoroiditis has been produced by Hogan in rabbits[27] and by Frenkel in hamsters,[28] satisfying Koch's postulates as well as can be done for an organism that can only be grown *in vivo*.

Once toxoplasmosis was established as a definite cause of uveitis, it was still necessary to prove that it is a common cause. Except in a few

isolated instances, it has not been possible to recover the organism directly from ocular tissue either by anterior chamber puncture or by obtaining biopsy material from the posterior segment of the eye. Rarely, it has been possible to isolate organisms from the blood of a patient with uveitis. Although the inflammation can be severe, it usually runs a self-limiting course, subsiding without gross destruction of the globe and frequently allowing a return of useful visual function.

Confirmatory laboratory evidence of toxoplasmosis can be ascertained by the measurement of circulating antibody levels. The Sabin-Feldman dye test,[29] one of the early techniques, remains the best today, with high titers indicating the presence of toxoplasmosis infection. There is some disagreement about low titers, as the test is not absolutely specific, but a rising titer is diagnostic of active toxoplasmosis infection. The toxoplasmin skin test has definite limitations in confirming present or past infection, mainly because of difficulties in standardizing antigens and because of cross-reactions with other types of infection.

In establishing toxoplasmosis as a cause of a given case of active choroiditis, the two most important diagnostic points are the ophthalmoscopic appearance of the lesions and the interpretation of the Sabin-Feldman dye test. The active lesion is characteristic and is usually found in the posterior pole of the eye in or near the macula. In the active stages the lesion appears white through a very hazy vitreous. As healing begins, pigment can be seen around the border of the lesion after several weeks. If healing progresses without relapse, pigment is deposited throughout much of the lesion, particularly around its borders, with the white sclera showing through destroyed choroid and retina on ophthalmoscopy. Relapses are common, and active lesions appear adjacent to healed lesions.[27]

A series of 344 consecutive patients with uveal tract disease studied by Van Metre, Knox, and Maumenee[30] revealed 73 with focal exudative retinal choroiditis and 271 with other lesions. A toxoplasmin skin test was positive in 94 per cent and the Sabin-Feldman dye test positive in 92 per cent of the focal exudative retinal choroiditis cases, as compared with 23 per cent with positive skin tests and 32 per cent with a positive Sabin-Feldman dye test in the other ocular lesions studied. This is strong evidence that toxoplasmosis is a common cause of posterior focal choroiditis.

By analogous reasoning we should be able to elucidate the possible role of histoplasmosis in uveitis by comparing it with toxoplasmosis. Ironically, more is known about the epidemiology of generalized histoplasmosis than of toxoplasmosis. As already stated, the organism

is definitely classifiable as a fungus and its life cycle is much more clearly delineated than that of *Toxoplasma*. *Histoplasma capsulatum* has worldwide distribution, with at least one major endemic area of infection in the United States (the Mississippi Valley) as well as areas in South America, Africa, and Indonesia.[3]

The specific clinical picture of presumed ocular histoplasmosis has been well defined, and is much more common in areas endemic for histoplasmosis than in other areas. The chorioretinitis of presumed ocular histoplasmosis is much less marked than that of toxoplasmosis and never causes major destruction of the globe or severe endophthalmitis which might justify enucleation and possible isolation of the organism.

If the theory proposed by Woods and Wahlen[11] is valid, it is obvious that it will be very difficult to fulfill Koch's postulates for ocular histoplasmosis from material obtained from macular lesions, since these active central lesions are believed to be due to hypersensitivity rather than direct infection. It might be possible to recover the organisms from a peripheral lesion, but such areas are rarely seen even in routinely sectioned eyes in endemic areas. The organisms may well disappear from these lesions in a relatively short time, as did the organisms from the lesions produced experimentally in rabbits by Day.[12]

Serologic complement fixation tests for histoplasmosis do show high or rising titers in the presence of confirmed active systemic infections, but most reports on series of cases of presumed ocular histoplasmosis indicate no significant diagnostic support from serologic studies.[11,16,31] The histoplasmin skin test has proved to be a reliable indication of previous infection by *Histoplasma capsulatum*.[8] In a study paralleling the one on toxoplasmic retinochoroiditis cited previously, Van Metre and Maumenee[15] have reported on 251 consecutive patients with uveal tract disease in which 61 had the ocular lesion of presumed histoplasmosis whereas 190 had other chorioretinal lesions which justified their inclusion in the uveitis survey of the Wilmer Institute. In the patients in whom it was possible to diagnose histoplasmosis on the basis of clinical observation only, the incidence of positive histoplasmin skin tests was 94 per cent compared to 25 per cent in the others studied. A higher incidence of positive histoplasmosis complement fixation tests, a higher incidence of residence in areas endemic for histoplasmosis, and a higher incidence of fibrocalcific lesions on chest X-ray were also recorded in the 61 cases of presumed ocular histoplasmosis than in the other 190 patients in the survey who served as the control

group. Although such a control group leaves something to be desired since all of the patients had other ocular diseases, Van Metre and Maumenee's study constitutes a strong argument for histoplasmosis as the cause of the distinctive lesion described, much as their similar study did for toxoplasmosis.[30]

Any observant ophthalmic clinician in the endemic area of histoplasmosis will agree that we are observing a distinct clinical picture as described in several reports.[11,15–17] Even persons with these distinctive lesions have not always had positive skin tests to histoplasmin. This does not definitely rule out histoplasmosis as the cause, however, since it is well known that the skin test can change from positive to negative, particularly in older women.[32] It seems reasonable to conclude from the foregoing discussion that *Histoplasma capsulatum* is the likely etiologic agent of presumed histoplasmosis. Definite validation of this inference will ultimately depend upon (1) identification of the organism on histologic section of peripheral or central lesions in the eye; (2) recovery of viable organisms from such lesions; (3) production of lesions by injection of culture material into experimental animals; and (4) passage of the disease to human volunteers by injection of material taken from the lesions of sacrificed animals. Until this has been done, however, it is appropriate to apply other indirect methods of study to further clarify this relationship. The following survey was undertaken with this purpose in view.

REPORT OF A SURVEY

Since direct microbiologic evidence for the possible role of histoplasmosis in uveitis is at present inconclusive, the attempt should be made to establish or rule out this possibility on the basis of epidemiologic studies. Theoretically, a survey of the total population in an endemic area would be an ideal method of correlating presumed clinical ocular histoplasmosis lesions with the most reliable criteria for the presence of the disease. It has been established that the delayed reaction to intradermal histoplasmin is reliable evidence that histoplasmosis infection has occurred some time previously.[8] A survey of the total population in an endemic area, correlating healed foci of choroiditis (histo spots) with skin test results, would yield valuable statistical data which could be used to evaluate histoplasmosis as a potential cause of uveitis. A total survey is impossible, but a survey of a sizable cross-section of the well population is the next best approach. It is

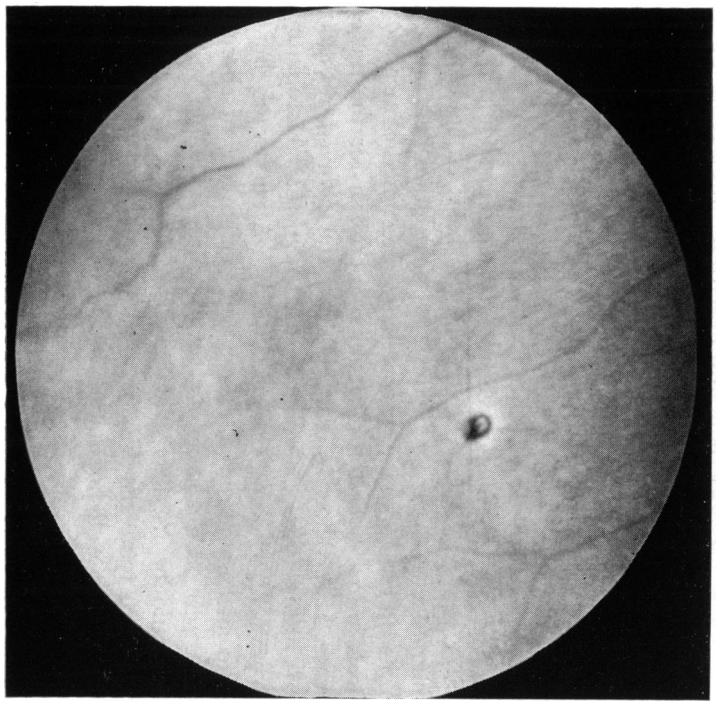

FIGURE 1. CASE 12.
Right eye with single ideal spot. Several similar lesions left eye. Rated ++++.

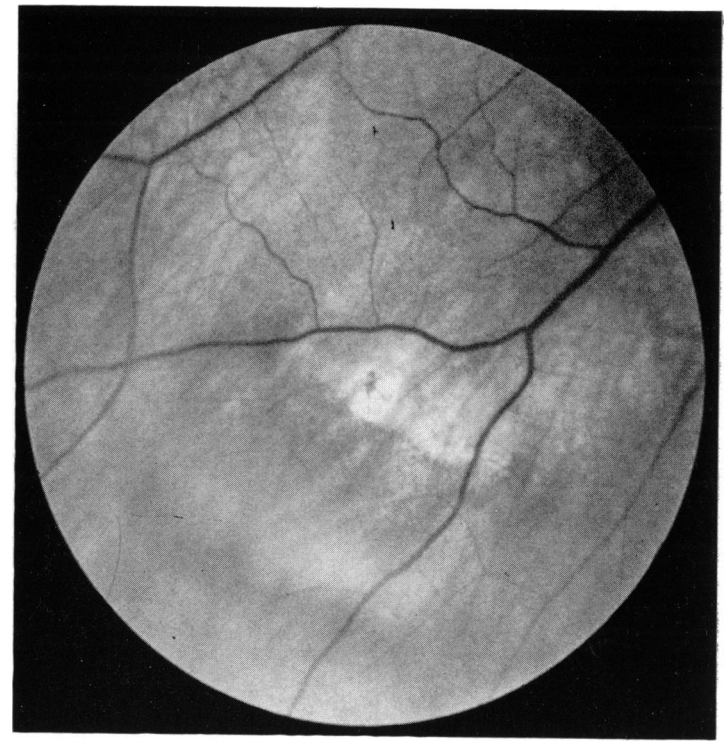

FIGURE 2. CASE 12.
Left eye showing one of several "punched out" lesions seen. Rated ++++.

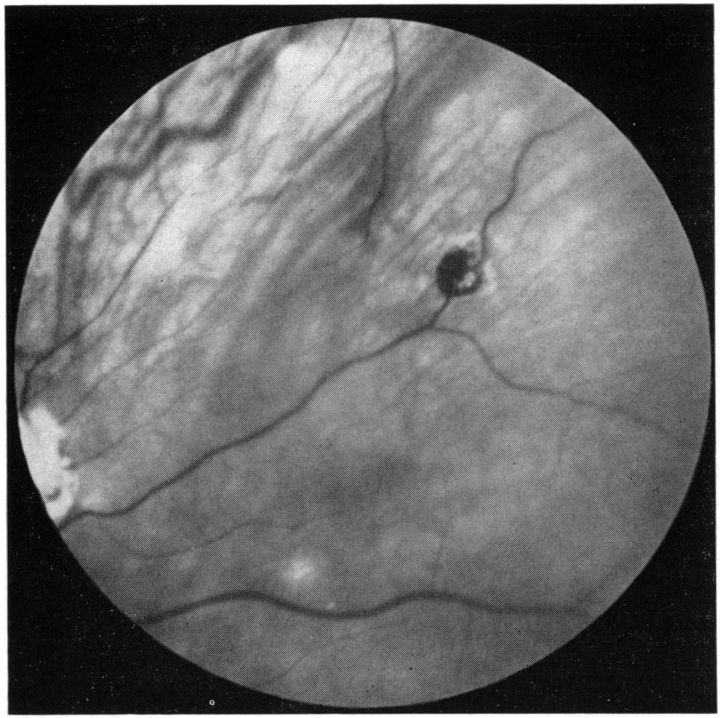

FIGURE 3. CASE 15.
Right eye with single lesion and considerable pigmentation.

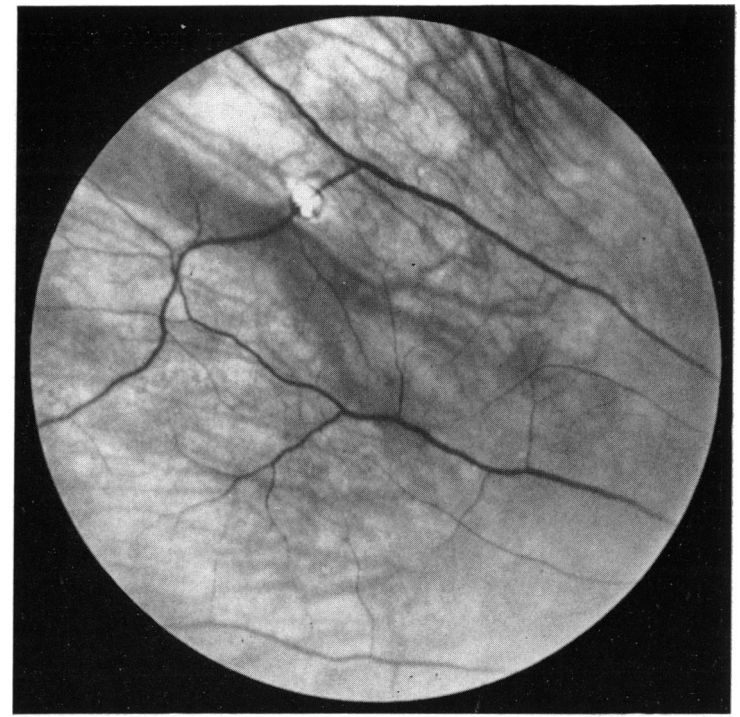

FIGURE 4. CASE 15.
One of several scattered "punched out" lesions seen in left eye. Rated ++++.

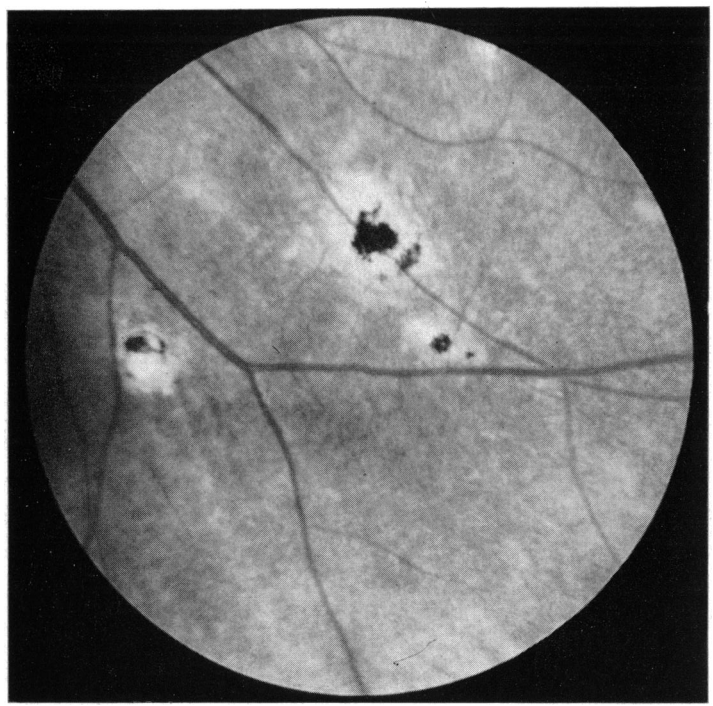

FIGURE 5. CASE 2.

Ideal peripheral lesions (histo spots) showing "punched out" choroidal areas with some central pigmentation. Rated +++; would be ++++ if lesions were bilateral.

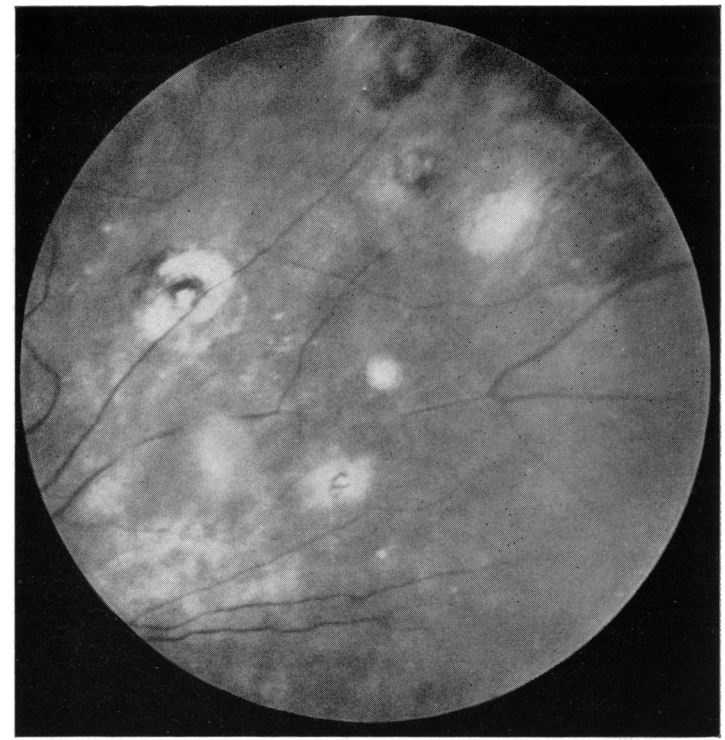

FIGURE 6. CASE 7.

Multiple typical lesions of left eye. Rated +++ because of unilaterality.

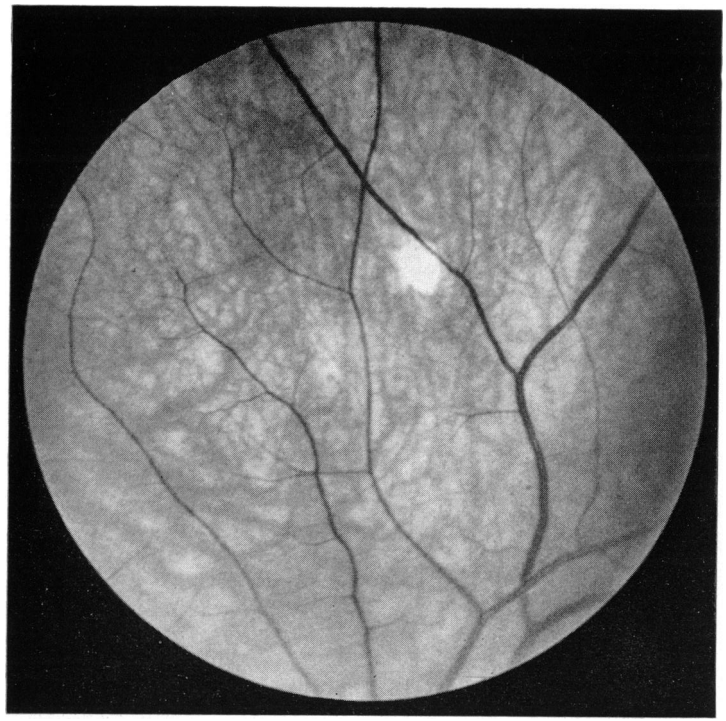

FIGURE 7. CASE 13.
Right eye showing single "punched out" spot. Similar single lesion left eye. Rated +++.

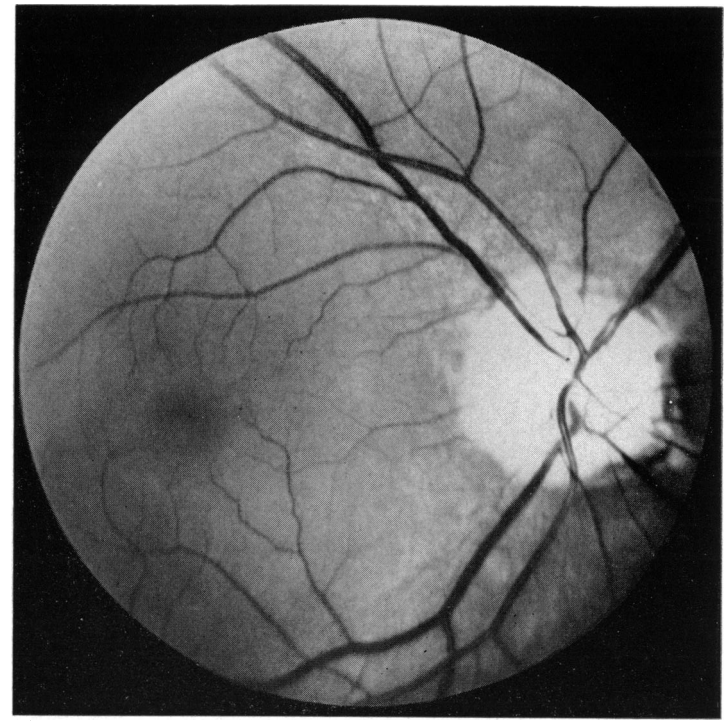

FIGURE 8. CASE 13.
Right eye showing typical peripapillary changes.

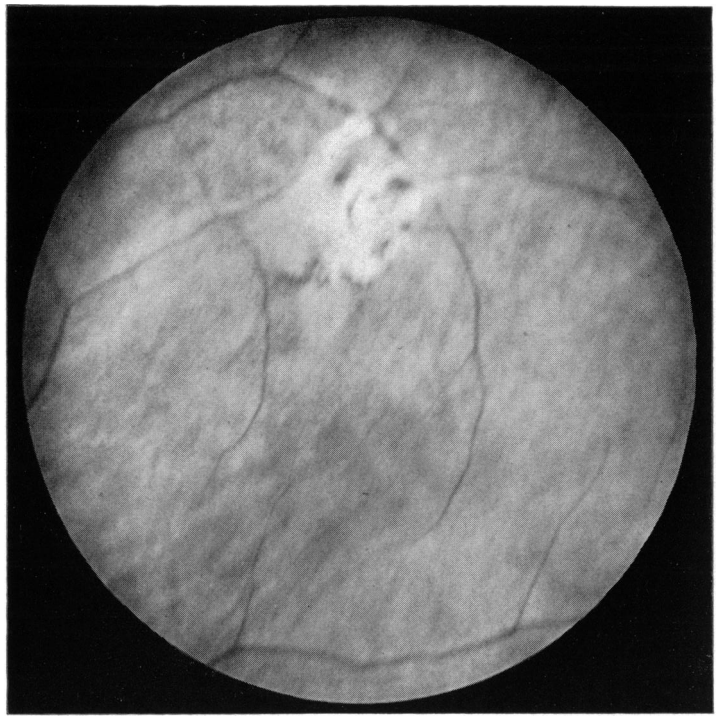

FIGURE 9. CASE 3.
Left eye showing lesion larger than ideal. Large lesion also present in the right eye. Rated ++.

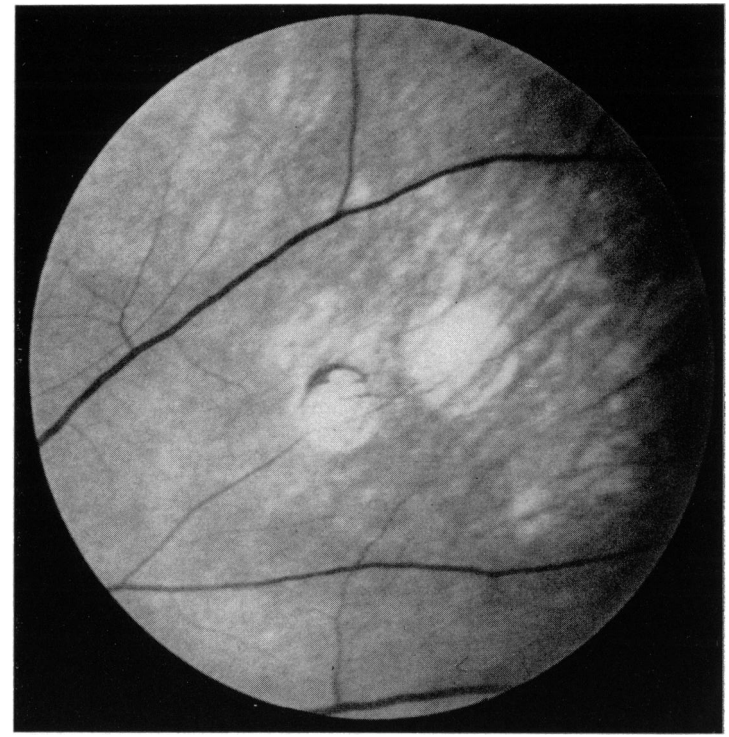

FIGURE 10. CASE 4.
Two lesions left eye. Lesions would be more typical if choroidal vessels not present in them. Rated ++.

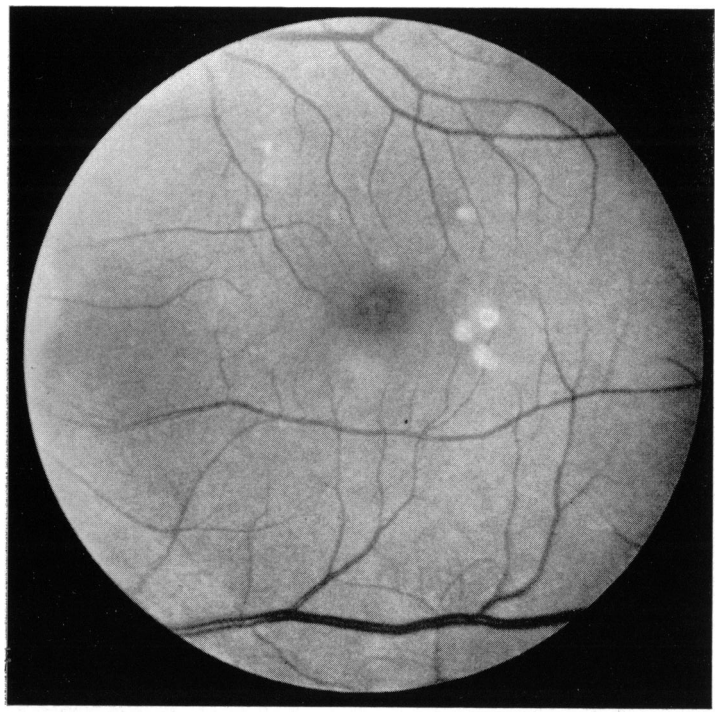

FIGURE 11. CASE 9.

Three small "punched out" spots ideal except for location near macula. Rated ++.

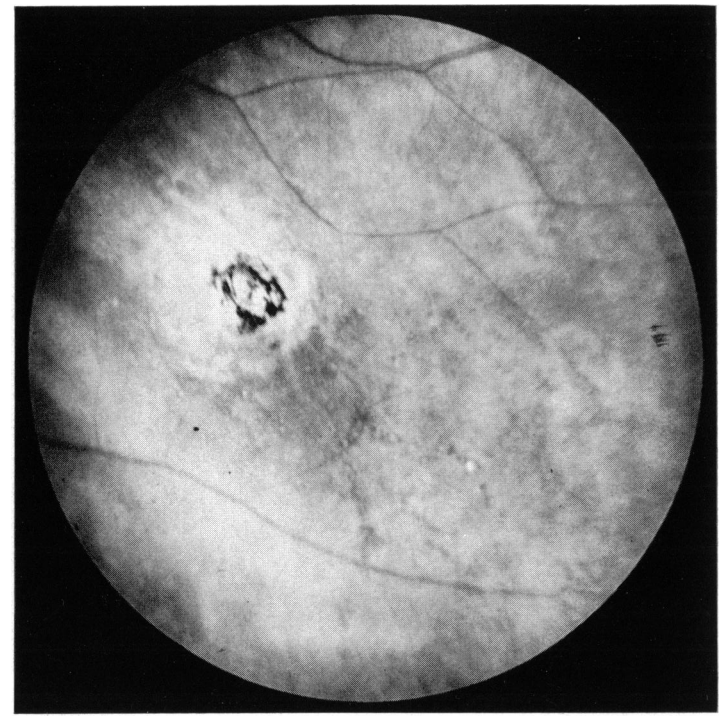

FIGURE 12. CASE 11.

Good lesion left eye but somewhat large to be ideal. Rated ++ because of size and unilaterality.

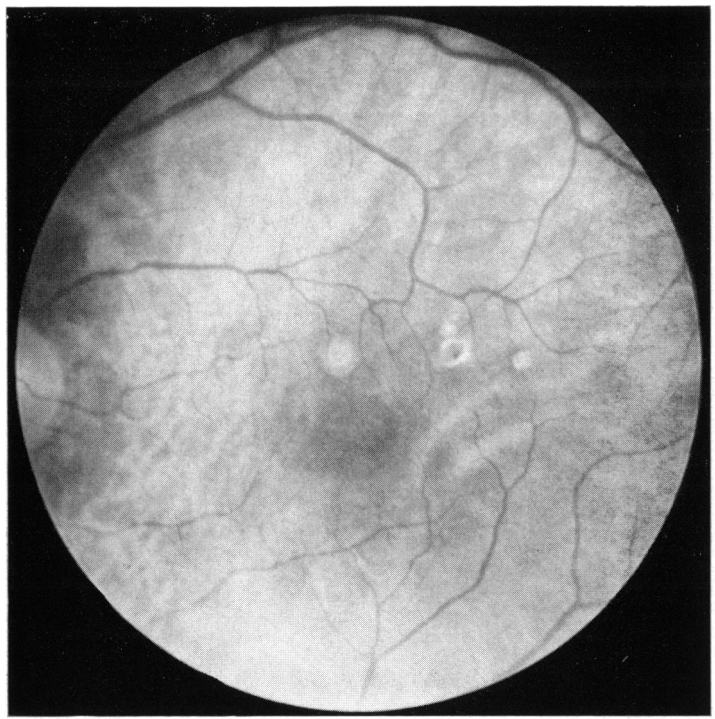

FIGURE 13. CASE 1.

Left eye shows four paramacular lesions. Patient rated only + because no other lesions are present in the left eye, and no lesions present in the right eye.

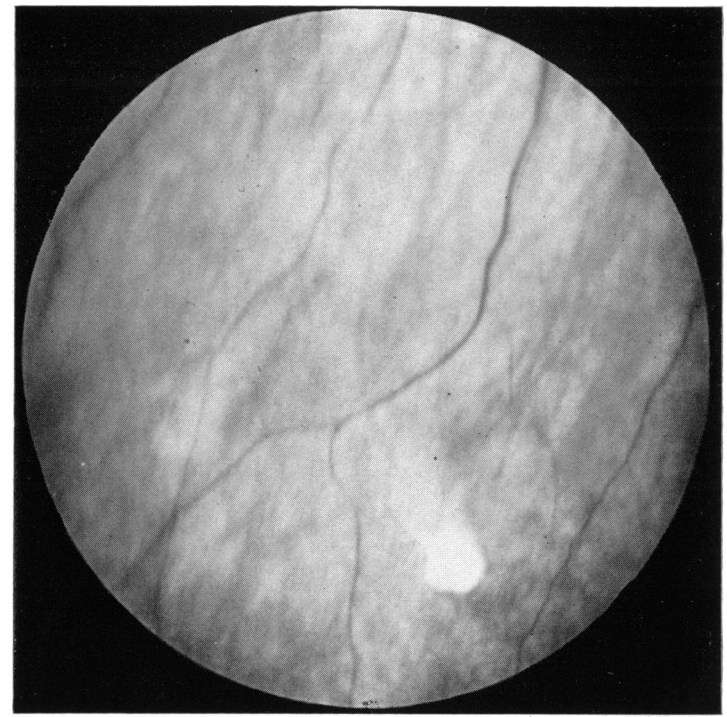

FIGURE 14. CASE 18.

One "punched out" lesion with no pigment in the right eye. Unilateral. Rated +.

difficult to find large groups of healthy persons who are willing to submit to skin tests and intensive ophthalmoscopy. Hospital populations are unsatisfactory since the presence of other disease would certainly prejudice the results.

In the survey reported here, therefore, all available co-operative inmates of Longview State Hospital, Cincinnati, Ohio, are included. This population consists of 1219 persons of all age groups, but mostly adults (only 22 persons being under age 21). An additional 198 male inmates of the Cincinnati Workhouse are also included. While all persons surveyed were not born in the endemic area, nearly all have resided in the endemic area for many years. What follows, then, is a report and analysis of findings on these 1417 persons, all in apparent good physical health.

Methods

Eight residents of the Department of Ophthalmology, College of Medicine, University of Cincinnati, along with nursing and clerical assistants, worked as a team with the author.

SKIN TESTING

A histoplasmin skin test was done on the right forearm of each individual. All skin tests were done by a registered nurse who had been carefully instructed in the proper technique of intradermal injection. This technique is important since the results are less apt to be positive if the injection is made subcutaneously. Histoplasmin antigen was obtained from the clinical laboratory of the Jewish Hospital, Cincinnati, Ohio. Fresh dilutions of histoplasmin were prepared for each day's survey, and the material was kept refrigerated until used. The 1:100 dilution of this antigen is comparable to the histoplasmin which was used in the same locality in 1953 to survey 7000 school children who proved to have an 80 per cent incidence of positive skin tests at age 18.[9] All skin reactions were carefully measured with a millimeter rule at 48 hours. For a test to be considered positive, an area of induration of not less than 5 mm. in diameter was necessary. Most of the positive reactions measured 10–15 mm., whereas a few ranged up to 25 mm., but in no instance was there any slough of dermal tissue. There was no known instance of activation of a focal choroidal or macular lesion, a complication first reported by Woods and Wahlen[11] and observed by others.

TECHNIQUE OF OPHTHALMOSCOPY

Cyclopentolate (Cyclogyl®), 2 per cent, and phenylephrine (Neosynephrine®), 10 per cent, were instilled in both eyes and all persons were examined with the indirect ophthalmoscope, supplemented at times by examination with the direct ophthalmoscope. Verification of the lesions was always done by several observers, including the author; when possible, fundus photographs were taken of those lesions which were judged to fall within the category of histo spots. Some individuals originally considered to have histo spots were eliminated on subsequent study when their lesions failed to conform to the established criteria. Since the skin test was applied on the same day as ophthalmoscopy was performed, its result was not known to the examiners.

In all, 22 individuals were found to have lesions compatible with histo spots. It was possible to obtain satisfactory photographs of 20 of the 22 patients; in the other two, the lesions were too peripheral for fundus photography. One of the more common incidental findings on such examination was the presence of a healed chorioretinal lesion characteristic of toxoplasmosis. As a matter of interest, 45 of the 1417 patients showed such lesions—almost exactly double the number of persons with lesions characteristic of presumed histoplasmosis.

RATING OF LESIONS

A qualitative rating system was established for the evaluation of the lesions, with ++++ indicating lesions of healed foci of choroiditis ideally conforming to the criteria for presumed ocular histoplasmosis and +++, ++, and + indicating that the criteria are fulfilled to a lesser degree. These ratings are based solely on the appearance of the lesions without reference to the age of the subject or the skin test result. Table 2 lists the findings of the 22 persons in which histo spots were found.

Criteria for Rating

++++ Bilateral multiple small lesions considered to be ideal histo spots, size $\frac{1}{5}$ to $\frac{1}{10}$ disk diameter, "punched out" appearance, with or without pigment, and located away from the macula; typical peripapillary changes also frequently present (Cases 10, 12, 14, 15, 16)

+++ 1. Bilateral lesions not rated ++++ because they are less numerous or because they are larger than ideal (Cases 13, 20)

2. Ideal unilateral lesions (Cases 2, 6, 7, 19, 21, 22)

TABLE 2. SUMMARY OF 22 CASES WITH HISTO SPOTS

Case	Age	Race	Sex	Skin test	Fundus photo	Description histo lesion	Rating	Explanation of rating
1	65	C	F	—	Yes	Right: none Left: 4 small lesions near macula; little pigment (Fig. 13)	+	4 typical lesions but unilateral and near macula
2	55	C	F	+	Yes	Right: 4 peripheral spots; some pigment (Fig. 5) Left: none	+++	Would be ++++ except unilateral
3	34	C	M	+	Yes	Right: 1 large confluent peripheral area Left: 1 histo spot; slight pigment (Fig. 9)	++	Right: suggestive of degeneration; too large to be ideal Left: typical lesion, somewhat too large to be ideal
4	64	N	F	+	Yes	Right: none Left: 2 lesions; slight pigment (Fig. 10)	++	2 typical unilateral lesions. Would be better except choroidal vessel pattern partially present in 1 spot
5	73	N	M	+	Yes	Right: 3 small pigmented spots Left: none	+	Unilateral; more pigment than ideal
6	70	C	M	—	Yes	Right: none Left: 4 histo spots	+++	Typical multiple lesions but unilateral
7	69	C	F	—	Yes	Right: none Left: several histo spots with pigment and some areas of myopic degeneration (Fig. 6)	+++	Unilateral, typical histo spots
8	71	C	F	+	Yes	Right: 1 large pigmented spot Left: 2 spots near macula	++	Bilateral but only 1 large spot right; 2 lesions left near macula
9	74	N	F	−	Yes	Right: 1 small depigmented spot near disk Left: 3 small depigmented spots near macula (Fig. 11)	++	Bilateral but all lesions close to macula
10	67	N	F	+	Yes	Right: peripheral superior lesion Left: several lesions	++++	Bilateral typical lesions

TABLE 2. SUMMARY OF 22 CASES WITH HISTO SPOTS (*Concluded*)

Case	Age	Race	Sex	Skin test	Fundus photo	Description histo lesion	Rating	Explanation of rating
11	74	C	F	−	Yes	Right: none Left: lesion slightly large to be ideal (Fig. 12)	++	Typical lesion except slightly large
12	68	C	M	+	Yes	Right: 1 spot, pigmented (Fig. 1) Left: several peripheral spots (Fig. 2)	++++	Bilateral typical lesions
13	39	C	M	+	Yes	Right: 1 depigmented spot (Fig. 7) Left: 1 depigmented spot	+++	Would be ++++ if a few more lesions. Typical peripapillary appearance (Fig. 8)
14	40	C	M	+	No	Right: many small typical lesions Left: many small typical lesions	++++	Bilateral typical lesions
15	59	C	M	−	Yes	Right: 1 pigmented lesion (Fig. 3) Left: Several scattered lesions; typical peripapillary changes (Fig. 4)	++++	Bilateral typical lesions
16	28	C	M	+	Yes	Right: 2 pigmented spots Left: 2 pigmented spots	++++	Bilateral typical lesions
17	39	C	M	+	Yes	Right: none Left: 1 spot, somewhat large	+	Only one unilateral spot present
18	21	C	M	−	Yes	Right: 1 lesion, no pigment Left: none	+	Only one unilateral spot present
19	56	N	M	+	No	Right: multiple typical lesions in inferior fundus Left: none	+++	Would be ++++ if bilateral
20	41	N	M	−	Yes	Right: 1 lesion Left: 1 lesion	+++	Would be ++++ if more lesions
21	35	N	M	+	Yes	Right: none Left: several pigmented lesions	+++	Would be ++++ except unilateral
22	43	C	M	+	Yes	Right: several pigmented lesions (Fig. 14) Left: none	+++	Would be ++++ except unilateral

++ 1. Only one or two typical lesions, whether unilateral or bilateral (Cases 3, 8, 9)
2. Unilateral lesions considered less than ideal in size, number, appearance, or location (Cases 4, 11)

\+ 1. Single unilateral lesion (Cases 5, 17, 18)
2. More than one typical lesion but only present in the macular area (Case 1)

Table 3 summarizes the skin test results by race. The over-all incidence of 52.8 per cent positive skin tests covering all age groups in an endemic area correlates well with previously reported series.[8,10]

TABLE 3. RESULTS OF HISTOPLASMIN SKIN TEST BY RACE

	Total tested	Positive	Percentage positive
Caucasian	1140	578	50.7
Negro	277	170	61.4
TOTAL	1417	748	52.8

A higher percentage of positive skin tests was found in the Negro group (61.4 per cent) than in the Caucasian group (50.7 per cent). Some other reports[10,32] have shown a higher percentage of positive skin tests to histoplasmin in the Caucasian, but at least one authority has found a higher percentage among Negroes.[33] Table 4 summarizes by race the skin test results of those 22 persons who were found to have histo spots. Nine of the 15 Caucasians and five of seven Negroes are positive, both races having an incidence about 10 per cent higher than that of the total population studied.

TABLE 4. SKIN TEST RESULTS OF 22 PERSONS WITH HISTO SPOTS BY RACE

	Total found	Positive	Percentage positive
Caucasian	15	9	60
Negro	7	5	71
TOTAL	22	14	63

Table 5 summarizes the skin test results by sex of those 22 persons who were found to have histo spots. A higher percentage of males were observed to be positive, again approximately in the same ratio as in the over-all survey. In both sexes a somewhat higher incidence of positive skin tests occurred in persons with histo spots than in the others in the survey.

TABLE 5. SKIN TEST RESULTS BY SEX OF 22 PERSONS WITH HISTO SPOTS IN FUNDI

	Total found	Positive	Percentage positive
Male	14	10	71
Female	8	4	50
TOTAL	22	14	63

Tables 6 and 7 summarize the skin test results by age groups. The males show a significantly higher percentage of positive tests (59.9 per cent) than do the females (44.3 per cent). It has been established that the percentage of positive skin tests reaches a peak in the late

TABLE 6. RESULTS OF HISTOPLASMIN SKIN TESTS BY AGE GROUPS, MALES

Age group	Total tested	Negroes tested	Total positive	Negroes positive	Percentage positive
Under 20	11	2	7	1	63.6
20–29	114	33	78	20	68.4
30–39	116	36	80	24	69.0
40–49	128	26	84	18	65.6
50–59	150	32	91	22	60.7
60–69	129	22	66	13	51.2
Over 69	128	17	58	13	45.3
TOTAL	776	168	464	111	59.9

TABLE 7. RESULTS OF HISTOPLASMIN SKIN TESTS BY AGE GROUPS, FEMALES

Age group	Total tested	Negroes tested	Total positive	Negroes positive	Percentage positive
Under 20	11	1	5	0	45.5
20–29	15	1	7	1	46.7
30–39	66	13	37	7	56.1
40–49	111	22	59	14	53.1
50–59	165	30	83	17	50.3
60–69	150	26	62	14	41.3
Over 69	123	16	31	6	25.2
TOTAL	641	109	284	59	44.3

teens and declines slowly but steadily thereafter, with the decline being particularly noticeable in postmenopausal women.[32] (Figure 15) The percentage of positive skin tests in Tables 6 and 7 correlates well with these previous observations.

Table 8 summarizes the frequency of positive histoplasmin reactions among the tested population by age, race, and sex. Table 9 summarizes the skin test results of the 22 persons with histo spots also by age, race,

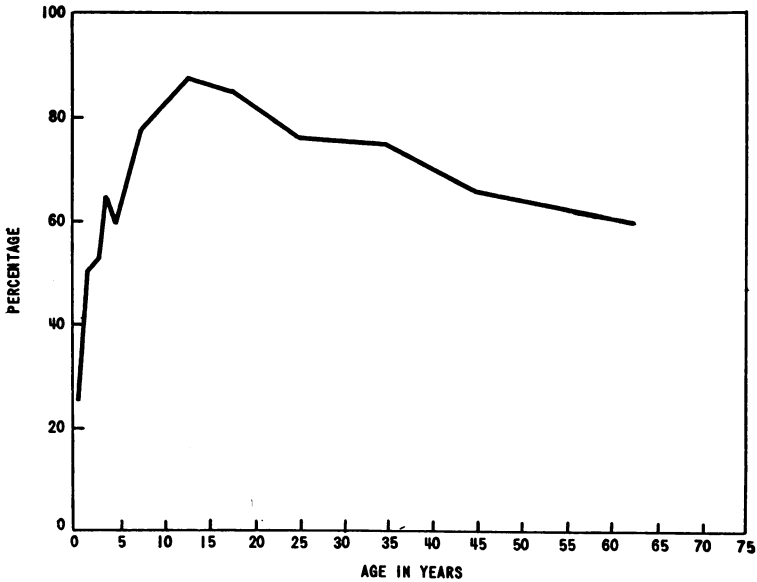

FIGURE 15

Percentage of persons positive to histoplasmin by age, Williamson County, Tennessee, August, 1945–July, 1950.

and sex. Table 10 is derived from Tables 8 and 9 to show the expected number of positive histoplasmin skin tests among the 22 persons with histo spots. By multiplying the percentage of positive reactors by the number of persons with histo spots for each category, the figures for Table 10 are derived. From these calculations, 12.5 positive reactors would be expected among the 22 persons, whereas 14 were actually found. The expected does not vary greatly from the number found in any age group (see last two columns of Table 10).

TABLE 8. FREQUENCY OF POSITIVE HISTOPLASMIN REACTIONS AMONG TESTED POPULATION BY AGE, RACE, AND SEX (PERCENTAGE OF POSITIVES DERIVED FROM TABLES 6 AND 7)

Age	Caucasian male	Caucasian female	Negro male	Negro female
Under 20	67	50	50	—
20–29	72	43	61	—
30–39	70	57	67	54
40–49	65	51	69	64
50–59	58	49	69	57
60–69	50	39	59	54
Over 69	41	23	76	38

TABLE 9. SKIN TEST RESULTS OF 22 PERSONS WITH HISTO SPOTS IN FUNDI BY AGE, RACE, AND SEX

	Total				Histoplasmin Positive			
	Caucasian		Negro		Caucasian		Negro	
Age	Male	Female	Male	Female	Male	Female	Male	Female
Under 20	0	0	0	0	0	0	0	0
20–29	2	0	0	0	1	0	0	0
30–39	3	0	1	0	3	0	1	0
40–49	2	0	1	0	2	0	0	0
50–59	1	1	1	0	0	1	1	0
60–69	1	2	0	2	1	0	0	2
Over 69	1	2	1	1	0	1	1	0
ALL AGES	10	5	4	3	7	2	3	2

TABLE 10. EXPECTED NUMBER OF POSITIVE HISTOPLASMIN SKIN TESTS AMONG THE 22 PERSONS HAVING HISTO SPOTS BASED ON PERCENTAGES OF TABLE 8

Age	Caucasian male	Caucasian female	Negro male	Negro female	Totals expected all groups	All groups observed
Under 20	—	—	—	—	—	—
20–29	1.4	—	—	—	1.4	1
30–39	2.1	—	0.7	—	2.8	4
40–49	1.3	—	0.7	—	2.0	2
50–59	0.6	0.5	0.7	—	1.8	2
60–69	0.5	0.8	—	1.1	2.4	3
Over 69	0.4	0.5	0.8	0.4	2.1	2
Totals Expected, ALL AGES	6.3	1.8	2.9	1.5	12.5	14
OBSERVED	7	2	3	2	14	

Table 11 summarizes the percentage of histo spots found in the survey population by age, and by race and sex. There is remarkably little variation by age group. The rate of occurrence is nearly twice as high in Negroes as in Caucasians, possibly only by chance. The incidence for all males is 1.8 per cent and for females 1.2 per cent—probably an insignificant difference.

Discussion

Since our understanding of ocular histoplasmosis is incomplete at this time, the findings of this survey are being presented as completely and objectively as possible so that re-evaluation of these data will be possible as additional information accumulates.

TABLE 11. PERCENTAGE OF HISTO SPOTS FOUND IN SURVEY POPULATION

By age		By race and sex	No./Total	Percentage	
Under 20	—				
20–29	1.6%	Caucasian males	10/609	1.6	1.3
30–39	2.2%	Caucasian females	5/532	0.9	
40–49	1.3%	Negro males	4/168	2.4	2.5
50–59	0.6%	Negro females	3/109	2.8	
60–69	1.8%				
Over 69	2.0%	TOTAL MALES	14/777	1.8	
ALL AGES	1.6%	TOTAL FEMALES	8/641	1.2	

One of the most important findings of the survey is that histo spots are relatively uncommon (22 out of 1417, or 1.6 per cent) in persons living in an area where histoplasmosis is known to be endemic. The incidence of positive histoplasmin skin tests in this survey is about the same as previously reported in other surveys. The incidence of positive skin tests in the 22 cases having histo spots is not much higher than the over-all average (63 per cent as compared to 52.8 per cent). Table 10 shows that 12.5 persons would be expected (on the basis of calculation) to have positive skin tests, and this does not vary significantly from the 14 persons observed. When broken down into age groups, the "expected" totals are remarkably similar to the totals actually observed. Thus, *based solely on the correlation of positive skin test results and histo spots*, this survey does not support the current concept of ocular histoplasmosis.

However, further investigation of the eight persons with histo spots in which histoplasmin skin tests were negative led to findings which can be interpreted as supporting the current concept of ocular histoplasmosis. Five of these individuals were age 65 or over, and the other three were 21, 41, and 59. Four of the group aged 65 and over were females. It has been previously noted that known positive skin tests may become negative in later life, particularly in females,[32] and it is possible that all or most of the negative group over 65 were at one time positive. In hopes of finding other evidence of previous infection with histoplasmosis, the eight persons whose skin tests were negative received chest X-rays and abdominal X-rays in an effort to demonstrate hilar and splenic calcifications. It is interesting, but perhaps only coincidental, that in all eight cases the chest plates showed "evidence of healed histoplasmosis or tuberculosis"* by the appearance of hilar

*From report of radiologist, Longview State Hospital, Cincinnati, Ohio.

calcifications (Figure 16), although no evidence of splenic calcifications typical of histoplasmosis[6] could be demonstrated.

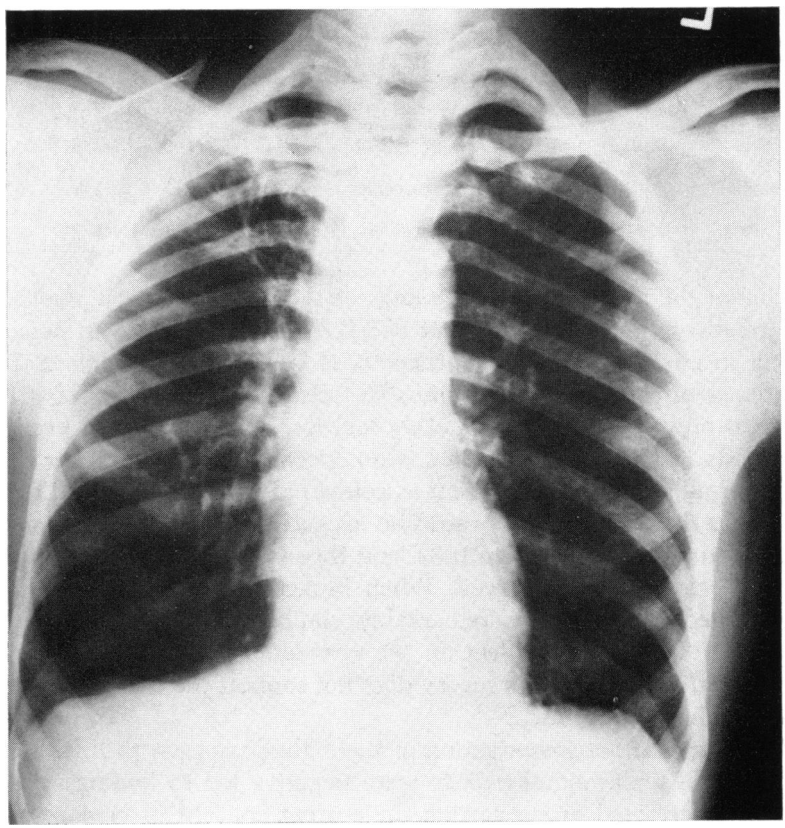

FIGURE 16. CASE 20.
Chest X-ray showing typical pulmonary findings of hilar calcifications compatible with histoplasmosis.

It is certainly not unreasonable to say, therefore, that all 22 persons with histo spots present possible evidence of previous infection with *Histoplasma capsulatum*. At the same time it must be remembered that these persons reside in an endemic area where a high percentage of the population would be expected to show such evidence. It was not possible to search for radiographic evidence of hilar or splenic calcifications in all persons with negative skin tests, but it is probable that a high percentage of this group also would show pulmonary hilar

calcification compatible with previous pulmonary infection with *Histoplasma capsulatum* or the tubercle bacillus.

It must also be explained that serologic tests such as the complement fixation test would not have been helpful since serologic changes are only present during active disease. Serologic tests have been of little or no diagnostic value even in cases demonstrating active macular lesions;[11,16,31] this is not unexpected since this aspect of ocular histoplasmosis is presumed to be due to hypersensitivity. Although some epidemiologists have utilized the technique of quantitative analysis in evaluating skin tests by making calculations based on measurements of the size of the induration area, it was felt that such analysis would not contribute to the interpretation of the results of this survey. (Only one negative skin test reaction had any measurable induration, and a high proportion of the positives measured 12–15 mm. in diameter.)

The author's experience in private practice and at the Department of Ophthalmology, College of Medicine, University of Cincinnati, is similar to that of others reporting from university centers in the endemic area.[16,17,31] This experience could be summarized by stating that a distinct clinical entity, including the macular lesions, peripapillary changes, and histo spots, occurs in persons who in most cases react positively to the histoplasmin skin test. Histo spots without macular involvement are also seen in numbers which correlate well with the 1.6 per cent incidence encountered in this survey. I certainly feel that we are dealing with a specific clinical entity. The evidence for histoplasmosis as the cause of this entity is gradually becoming more convincing. Perhaps the strongest single supporting fact is that it occurs almost exclusively in areas where histoplasmosis is endemic or in persons who have lived in endemic areas.

Conclusions Based on Reported Survey

1. The incidence of peripheral histo spots in adults in an endemic area is less than 2 per cent (1.6 per cent in this survey).

2. Fourteen of the 22 cases with healed foci of choroiditis of presumed histoplasmosis had positive histoplasmin skin tests. The other eight cases showed radiographic changes in the lungs compatible with pulmonary histoplasmosis or tuberculosis. Thus, all 22 persons present findings that can be interpreted as evidence of previous histoplasmosis infection.

3. The incidence of histo spots in Negroes was double that in Caucasians in this survey (2.5 *vs.* 1.3 per cent).

4. The incidence of histo spots did not vary significantly by sex or age group (Table 11).

5. Healed toxoplasmosis-like chorioretinal lesions are approximately twice as common as histo spots in the general adult population in an area endemic for histoplasmosis.

Summary

One thousand four hundred and seventeen physically well persons, mostly adults living in a histoplasmosis endemic area, were surveyed. All persons were given a standard histoplasmin skin test, and the fundi of both eyes were examined with the indirect ophthalmoscope through dilated pupils. The over-all incidence of positive skin tests using freshly prepared histoplasmin was 52.8 per cent. The incidence was higher in Negroes (61.4 per cent) than in Caucasians (50.7 per cent) and higher in males (59.9 per cent) than in females (44.3 per cent), particularly in the age group 69 and over (45.3 *vs.* 25.2 per cent). Twenty-two persons surveyed had histo spots in their fundi, and 14 of these reacted positively to histoplasmin. The eight histoplasmin negative individuals all had radiographic lung field changes which were consistent with previous pulmonary *Histoplasma* or tuberculous infection, although none of the eight demonstrated the splenic calcifications on abdominal films which have been considered characteristic of past histoplasmosis infection.

There was an over-all incidence of 1.6 per cent histo spots in those surveyed as compared to a 3.2 per cent incidence of healed toxoplasmosis-like chorioretinal scars in the same group. Negroes had a 2.5 per cent incidence of histo spots as compared to a 1.3 per cent incidence in Caucasians, while the rate for all males was 1.8 per cent as compared to 1.2 per cent for females. The incidence rate was remarkably constant for all age groups.

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