# Presumed Ocular Histoplasmosis

## III. Epidemiologic Characteristics of People With Peripheral Atrophic Scars

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**Histoplasmin skin tests and dilated funduscopic examination for presumed ocular histoplasmosis were carried out on 842 individuals, aged 13 years and older, from Walkersville, Md. Seventy percent of the male and 51% of the female population were sensitive to the histoplasmin skin test; among reactors, males had a mean diameter of induration of 11.6 mm, and females had a mean induration of 9.7 mm. Histoplasmin sensitivity was most frequent in the third to the sixth decade, and mean induration size was largest in the third to the fifth decade.**

**Twenty-one individuals were identified as having only peripheral atrophic scars of presumed ocular histoplasmosis. The frequency of these scars was 2.5% and was similar in both sexes and at all age groups. One case of a disciform lesion was identified by the survey, giving a prevalence of about 0.1% in the community and a prevalence of about 4.5% among those with peripheral atrophic scars. All cases of presumed ocular histoplasmosis were histoplasmin-positive; male cases had a mean induration of 15.0 mm, and female cases had an induration of 10.7 mm.**

Woods and Wahlen,[1] in 1959, described a specific ocular disease characterized by an acute macular or paramacular elevated disciform-appearing lesion in the presence of more peripheral atrophic punched-out scars. Because persons with this fundus picture tended to be sensitive to the histoplasmin skin test, they felt that this disease resulted from systemic infection with *Histoplasma capsulatum*.

In describing epidemiologic characteristics of individuals with presumed ocular histoplasmosis, most attention has been given to the disciform lesions.[2-6] Two studies have commented on characteristics of persons with peripheral scars,[7,8] but only one has concentrated on them.[9]

Evidence is accumulating that the proliferative macular disease probably arises in individuals who have such peripheral atrophic scars already present in their fundi.[10,11] Therefore, it becomes important to try to predict which persons with peripheral scars are likely to develop the more serious vision-impairing disciform lesion.

The ideal method of accomplishing this would be to observe a large group of persons with peripheral scars for a long period of time and to compare the characteristics of those who developed the disciform process with those who did not. A quicker, though less precise method, is to compare persons with peripheral scars, most of whom will never develop the relatively rare disciform lesion, with persons with the disciform lesion. If, as in this study, the two groups of cases come from different populations, they will reflect, in part, differences inherent in the source populations. However, major characteristics differentiating peripheral scars from disciform lesions might still emerge.

### Materials and Methods

Characteristics of persons with the disciform lesion were collected from several published series.[2-7] Opportunity to evaluate characteristics of people with only peripheral scars resulted from a community-wide survey designed to test the association of positive histoplasmin skin tests and fundus scars of presumed ocular histoplasmosis. In early 1970, this survey was conducted in Walkersville, a small village located in Frederick County, Maryland. Details of the study are given in previous papers.[12-14]

Only individuals aged 13 years and older were selected for the study because of limitations imposed by the ophthalmic exam. To determine the number of people who would be eligible for the survey, a private census was conducted. A self-ad-

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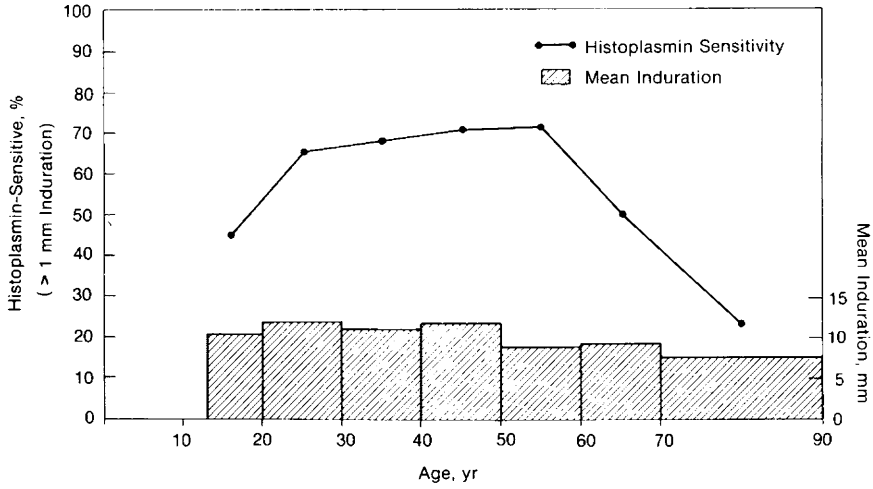


Histoplasmin sensitivity and mean induration by age for Walkersville, Md population (842 subjects, age 13 and older).

ministered questionnaire was distributed at the time of examination. Participants were then skin-tested on the volar surface of the left forearm with 0.1 ml of histoplasmin, lot H-42, diluted in a solution with a ratio of 1:100. The skin tests were read 48 hours later by two observers who had no knowledge of the ocular findings. The frequency distribution of histoplasmin reactions was clearly bimodal, with a sharp antimode at 2 mm of induration.[12] On the basis of this finding, a positive histoplasmin reaction was defined as 2 mm or more of induration.

External and dilated funduscopic examinations were carried out at the time of skin testing by members of the resident, attending, and full-time staff of the Wilmer Institute. Individuals with any lesions that might possibly represent presumed ocular histoplasmosis were referred to the Wilmer Institute for final examination by two members of the full-time staff with experience in the field of uveitis. Of those individuals who were considered as possibly having ocular histoplasmosis, 91% were examined by the uveitis experts who had no knowledge of the skin test results or of the other expert's evaluation. Subjects considered by these two ophthalmologists as having definite or highly suspect scars of presumed ocular histoplasmosis form the basis of this report.

At a later date, screening 70-mm photofluorograms were offered by the Frederick County Tuberculosis Association to people from the Walkersville community who participated in the survey. One of us (G. W. C.), who had no knowledge of the ocular status or histoplasmin sensitivity of the individuals, read the photofluorograms for the presence of pulmonary calcification. To obtain a comparable series of readings for pulmonary calcifications in individuals with the disciform lesions, chest roentgenograms from a sample of the people described by Van Metre and Maumenee[3] were reviewed by the same reader, using the same criteria for classification, again without knowledge of the ocular status or histoplasmin sensitivity of the individuals.

## Results

Seventy-four per cent of the total eligible population (1,144 individuals) of Walkersville, Md, over the age of 13 years, participated in this survey. Participation was slightly better among females (75.7%) than among males (71.1%). The reactivity of the tested population to the histoplasmin skin test is given in Table 1. More males (69.7%) than females (51.0%) were sensitive to histoplasmin; among those with measurable induration, males had slightly larger reactions than females. Response by age to the histoplasmin skin test is shown in the Figure. The proportion of positive reactors was less among teenagers than in those in the succeeding decades. Thereafter, histoplasmin sensitivity remained relatively constant at about 65% until age 60, and was then less in the older ages. Among those who reacted to the test, mean reaction sizes were greatest between the ages of 20 and 50.

Among the 842 individuals examined in the survey, 22 were described by the uveitis experts as having fundus scars consistent with presumed ocular histoplasmosis. One of these 22 had peripheral atrophic scars and an active proliferative macular disciform lesion. This one case gave an estimated prevalence of 0.1% in the community and 4.5% among individuals with peripheral atrophic scars. The remaining 21 individuals had peripheral atrophic scars only and form the basis of this report.

The prevalence of people with only peripheral scars in the Walkersville community was 2.5% (Table 2). Among persons with a positive histoplasmin skin test, the prevalence was 4.2%; the prevalence was slightly, but not significantly, higher among female reactors (4.6%) than among male reactors (3.8%). There was no tendency for the prevalence rate of peripheral scars to change with age, but among histoplasmin reactors, the rate was slightly greater in the oldest age group (Table 3).

All of the 21 persons with peripheral scars reacted to histoplasmin on the initial test; among males, the mean induration reaction size was 15.0 mm, while among females it was 10.7 mm, contrasted with mean reaction sizes among reactors in the total study population of 11.6 mm for

Table 1.—Individuals Reactive to Histoplasmin Antigen

| | No. Tested | Histoplasmin Reactors* | | Mean Diameter of Induration Among Reactors, mm |
|---|---|---|---|---|
| | | No. | % | |
| Male | 379 | 264 | 69.7 | 11.6 |
| Female | 463 | 236 | 51.0 | 9.7 |
| **Total** | **842** | **500** | **59.1** | **10.6** |

* > 1 mm of induration.

Table 2.—Prevalence of Peripheral Scars of Presumed Ocular Histoplasmosis

| | No. With Peripheral Scars | Total Population | | Histoplasmin-Positive | |
|---|---|---|---|---|---|
| | | No. | Prevalence/100 | No. | Prevalence/100 |
| Male | 10 | 379 | 2.6 | 264 | 3.8 |
| Female | 11 | 463 | 2.4 | 240 | 4.6 |
| **Total** | **21** | **842** | **2.5** | **504** | **4.2** |
| | | $\chi^2$ (1 df) = .06; $P > .75$ | | $\chi^2$ (1 df) = .2; $P > .1$ | |

males and 9.7 mm for females.

Largely because chest photofluorograms could not be offered at the same time as the other survey examinations, x-ray films were taken of only 52% of the initial surveyed population. Two of 16 persons (12.5%) with peripheral scars had pulmonary calcifications consistent with healed pulmonary histoplasmosis. This was similar to the finding of 15.3% pulmonary calcifications observed among the population without fundus scars who had x-ray films taken (Table 4). However, among the chest x-ray films which we reviewed from the study by Van Metre and Maumenee,[3] pulmonary calcifications were observed in 60% of individuals with disciform scars. The frequency of pulmonary calcification among their controls (12.2%) was similar to that in Walkersville (Table 5).

Table 3.—Age Distribution of People With Peripheral Scars of Presumed Ocular Histoplasmosis

| | Total Population | | | Histoplasmin-Positive Population | | |
|---|---|---|---|---|---|---|
| Age, yr | No. in Study | No. With Peripheral Atrophic Scars | Prevalence/100 | No. Positive | No. With Peripheral Atrophic Scars | Prevalence/100 |
| 13-19 | 188 | 4 | 2.1 | 87 | 4 | 4.6 |
| 20-39 | 265 | 9 | 3.4 | 177 | 9 | 5.1 |
| 40-59 | 265 | 5 | 1.9 | 189 | 5 | 2.6 |
| 60+ | 124 | 3 | 2.4 | 49 | 3 | 6.1 |
| **Total** | **842** | **21** | **2.5** | **502** | **21** | **4.2** |
| | | $\chi^2$ (3 df) = 1.4; $P > .5$ | | | $\chi^2$ (3 df) = 1.9; $P > .5$ | |

## Comment

A comparison of characteristics of persons with macular disciform scars, as compiled from the literature,[2-7] with characteristics of persons with peripheral atrophic scars is given in Table 6. The age distribution cannot be compared because age at onset can be determined only for macular disciform lesions, which are found too infrequently in general populations to determine prevalence by age. Case series suggest that disciform lesions are very seldom encountered in blacks. In Asbury's study,[9] the prevalence of peripheral scars was twice as high among blacks as whites, a finding all the more impressive in view of the general finding of similar histoplasmin sensitivity among blacks and whites.[15] The available evidence suggests that males are more likely to develop disciform lesions than females. Pulmonary calcification and peripapillary scarring are much more frequently associated with disciform lesions than with peripheral scars. Bilateral occurrence of peripheral scars does not seem to predispose to disciform lesions.

Gass and Wilkinson[10] have recently pointed out that, in individuals who already have a disciform macular scar in one eye, if the disciform process occurs in the second eye, it frequently begins in or around an atrophic peripheral scar located in the macular or paramacular area. Schlaegel[11] found that when atrophic scars were present in this area of the second eye, that individual had about a tenfold risk of developing a disciform lesion as compared to those individuals without such scars. It seems reasonable to presume that the disciform lesion in the first eye might also arise from such a preexisting atrophic lesion.

Woods and Wahlen[1] originally noted that there was no sign of activity in any of the peripheral scars at the time of onset of the hemorrhagic macular lesions. They concluded that the atrophic scars must have occurred some time earlier in the course of the ocular disease. Schlaegel believes that these peripheral lesions develop around the time of first exposure to *H capsulatum*. This is borne out by the experimental evidence of Wong et al[16] who could produce these peripheral lesions by intravenous injection of the organisms into rabbits, but only before the animals had developed immunity to the fungus. The failure of Asbury[9] and the present study to find a clear-cut increase in the prevalence rate of peripheral scars with age is also consistent with the belief that these lesions are most likely to have occurred at the time of first infection.

In the Walkersville community, about 65% of the total tested population had been infected with histoplasmosis by the age of 20-24 years. It seems likely that most peripheral atrophic lesions occurred at about the same age. In the various case series, the age of onset for the disciform lesions ranges from 20 to 60, with median age of onset at age 30 to 39.[6] The combination of these two findings suggests that if the disciform process does arise from an atrophic peripheral scar, then it would seem to occur from 10 to 30 years after the initial

Table 4.—Presence of Pulmonary Calcification on Chest X-ray Films of People With Peripheral Scars of Presumed Ocular Histoplasmosis

| | | X-ray Films Taken | | Presence of Pulmonary Calcification | |
|---|---|---|---|---|---|
| | | No. | % | No. | % |
| People with presumed ocular histoplasmosis | 21 | 16 | 76.2 | 2 | 12.5 |
| General population | 821 | 425 | 51.8 | 65 | 15.3 |
| **Total** | **842** | **441** | **52.4** | **67** | **15.2** |
| | $\chi^2$ (1 df) = .1; | | $P = .75$ | | |

Table 5.—Review of Pulmonary X-rays of Sample of Patients With Disciform Scars and Controls*

| | No. Reviewed | Pulmonary Calcification | |
|---|---|---|---|
| | | No. | % |
| Disciform scars | 15 | 9 | 60.0 |
| Controls | 49 | 6 | 12.2 |
| | $\chi^2$ (1 df) = 14.71 | | $P < .001$ |

* From study of Van Metre and Maumenee; specific ocular uveal lesions in patients with evidence of histoplasmosis.[3]

Table 6.—Epidemiologic Attributes of Individuals With Presumed Ocular Histoplasmosis

| Attributes | Ocular Histoplasmosis: Macular Disciform Scars | Ocular Histoplasmosis: Peripheral Atrophic Scars: Present Study | Ocular Histoplasmosis: Peripheral Atrophic Scars: Asbury[9] |
|---|---|---|---|
| Age | Fourth decade, median age of onset; age range, 20-59 yr[2-6] | 14-83 yr; uniform age distribution* | Age 20+; uniform age distribution* |
| Race | Frequency,[4,5,11]† | ... | Prevalence, |
| Black | 1.1% | | 2.5% |
| White | 98.9% | | 1.3% |
| Sex | Frequency,[2,3,5,6]† | Prevalence, | Prevalence, |
| Male | 54.0-72.4% | 2.6% | 1.8% |
| Female | 27.6-46.0% | 2.4% | 1.2% |
| Prevalence | 0.1%[12] | 2.5% | 1.6% |
| Pulmonary calcification | 81%[4] | 12.5% | ... |
| Peripapillary scarring | 85%[5,7] | 28.5% | 18.0% |
| Bilateral peripheral scars | 52%[4] | 62% | ... |

* Age of onset of peripheral scars has not been conclusively determined.
† Prevalence of disciform lesions has not been determined for race and sex; these figures refer to frequency in case series.

systemic infection and the development of the peripheral lesion.

Woods and Whalen[1] have also suggested that the disciform lesion might be the result of hypersensitivity to histoplasmin. The age of onset of the disciform lesions occurs during the period of greatest reactivity to the histoplasmin skin test, as found in this survey. Weber and Schlaegel[17] have shown a similar age pattern of sensitivity to various skin tests among their uveitis patients. Compared to controls with other ocular inflammatory diseases, their disciform cases were more reactive to delayed skin tests in general,[17] and most reactive to purified protein derivatives (PPDs) prepared from atypical mycobacteria.[18] The higher frequency of bilateral disciform lesions among males[6] might be related to the tendency found in this survey for males to have larger reactivity to histoplasmin than females.

The high frequency of pulmonary calcification found among individuals with the disciform disease is in direct contrast with the low frequency found in the Walkersville community, both in the general population and in individuals with only peripheral scars. Pulmonary calcification is most likely to develop following lung infections that occur in early childhood,[19] although such calcification has been reported to occur after the onset of the disciform lesion in at least one instance.[1] It is not known whether the high frequency of calcification among disciform cases represents early childhood exposure to the organism or whether both calcification and the disciform lesion result from hyperreactive cellular immune response to *H capsulatum*.

In any case, the presence of pulmonary calcification in people with peripheral atrophic scars would appear to be associated with an increased risk of developing disciform macular disease. The risk would appear to be increased still further if the individual were male, white, aged 20 to 60 years, strongly reactive to histoplasmin, and had peripheral atrophic scars located in the macular, paramacular, or peripapillary areas of the choroid. Fluorescein angiography might be necessary to demonstrate such lesions,[8,10,20] and should be strongly considered if atrophic scars are detected elsewhere in the fundus.

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**Key Words.**—Ocular histoplasmosis; epidemiologic survey; chorioretinitis; histoplasmin sensitivity; pulmonary calcification.

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